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APPLICATIONS OF PSYCHEDELIC-ASSISTED PSYCHOTHERAPY ACROSS PERSONALITIES AND PSYCHOPATHOLOGIES: AN INTEGRATIVE LITERATURE REVIEW WITH META-ANALYSIS

A dissertation submitted to the Wright Institute
Graduate School of Psychology, in partial fulfillment of the requirements
for the degree of Doctor of Psychology

by
BRIAN C. PEACOCK
JULY 2022

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APPLICATIONS OF PSYCHEDELIC-ASSISTED PSYCHOTHERAPY ACROSS PERSONALITIES AND PSYCHOPATHOLOGIES: AN INTEGRATIVE LITERATURE REVIEW WITH META-ANALYSIS

by
Brian C. Peacock

Psychedelic-assisted psychotherapy is reemerging in clinical practice following promising results from clinical trials for disorders such as major depression, PTSD, and death anxiety. There are many factors to consider in deciding whether a psychedelic-assisted treatment is appropriate for a patient, especially when their presentation does not fit a single diagnostic label. This study provides a practical heuristic for planning psychedelic-assisted treatments. A translational research approach was taken. Basic (T1) research in pharmacology, neuroscience, phenomenology, and psychological change were reviewed. These findings were then synthesized with applied (T2) literature regarding risks, therapy techniques, and clinical research. A systematic literature search was performed using 128 topic keywords covering topics across these literature domains. These keywords were searched in combination with the names of eight major psychedelics—mescaline, LSD, psilocybin, DMT, ayahuasca, MDMA, ketamine, and ibogaine—for a total of 1024 separate Google Scholar searches. From this search, 1,164 references were included in this review. A preliminary meta-analysis was performed to normalize effect sizes across treatments for comparison. Findings were synthesized into

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summary tables to represent the literature, allow for comparison of psychedelics, and serve as clinical references. From this, a process was developed for planning evidence-based psychedelic-assisted treatments to maximize treatment efficacy while minimizing risk. Translational insights emerged, including new treatment opportunities, patient assessment criteria, and directions for future research. Finally, this study substantiates the need for legal reform to allow medical access to an expanded range of psychedelic medicines due to their unique and valuable properties.

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Using This Dissertation

As this is an extensive review, it seems prudent to guide the reader on using this dissertation by providing some likely use cases. To ease navigation, be sure to make use of the bookmarks in the PDF document.

If you are making clinical decisions regarding a psychedelic treatment… Then proceed to Chapter 13 "Planning Psychedelic-Assisted Therapies," which provides an overview of summary tables relevant to clinical decision-making and instructions for using the treatment planning worksheet in Appendix C.

If you are looking to compare psychedelics… Then proceed to the Table of Tables and find the summary table(s) relevant to what you wish to compare. These tables provide an overall symbolic comparison of the psychedelics, with sections from the respective chapter supporting each symbol. Therefore, if you are looking for more detail about a summary table finding, look for the corresponding section in the chapter.

If you are studying a single psychedelic across multiple literature domains… Then begin by examining the summary tables (see Table of Tables). Each summary table column represents the literature found on a psychedelic. Next, skim through the chapters relevant to your study and look for the sub-headings that match the psychedelic in which you are interested.

If you are studying a specific aspect of a psychedelic… Then proceed to the Table of Contents to identify the chapter relevant to your field. Most topics have separate sub-sections for each psychedelic covered.

If you are looking for a general summary of findings… Then proceed to Chapter 14 "Discussion and Conclusion."

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Chapter 1: Introduction

Statement of Problem

Psychedelic-assisted therapies have shown substantial promise in treating a variety of psychological conditions, with efficacy often exceeding what can be done with standard treatments. For this reason, psychedelic treatments are returning to mainstream practice as FDA trials near completion and legal psychedelics such as ketamine gain widespread use. As psychedelics re-emerge into medicine, clinicians face complex decisions in choosing optimal psychedelic treatments. Psychedelic drugs are unique in that they produce striking changes across all levels of the human system–molecular, neurological, phenomenological, affective, and cognitive. Psychedelic effects propagate through time, resulting in changes to mind, brain, body, and behavior lasting from hours up to a lifetime. The complexity of this process is further compounded by the existence of different psychedelic compounds and enumerable environmental variables that affect psychedelic experience. Clinicians face the task of choosing between psychedelics, therapeutic techniques, and treatment sequences to maximize treatment efficacy while minimizing risk. With the field of modern psychedelic medicine in its infancy, no systematic methodology exists to support clinicians in this task.

Historical and Professional Context

Early Research

As early as 1925, there were Western accounts of indigenous mescaline use (Shonle, 1925). For the most part, however, Western medicine did not become aware of psychedelics until 1949, when Sandoz Pharmaceuticals began manufacturing and distributing lysergic-acid diethylamide (Novak, 1997). LSD showed great promise to

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clinicians, who found the drug useful in treating psychiatric disorders as varied as alcoholism, schizophrenia, depression, and neuroses (Chandler & Mortimer, 1960; Osmond, 1957; Pennes, 1954; Sandison, 1954; Sloane & Doust, 1954). In the 1960s, psychedelic drugs entered the American public consciousness when proponents like Timothy Leary advocated their use as a societal panacea. Problems arose as psychedelic drugs were used indiscriminately, and their use was perceived as a threat to the established social order. Concerns about widespread psychedelic use led to prohibition by congress in 1968 (Public Law 90-639, 1968). Following prohibition, psychedelic research was severely constricted, and much of the early clinical research was suppressed. Commentary on psychedelics was no longer permitted within the mainstream of clinical psychology.

Psychedelic Renaissance

In the past 10 years, there has been a resurgence of clinical research into psychedelics. Randomized controlled trials aimed at obtaining FDA approval have demonstrated the efficacy of both MDMA- and psilocybin-assisted psychotherapy in the treatment of post-traumatic stress disorder (PTSD) and end-of-life anxiety, respectively (Griffiths et al., 2016; Mitchell et al., 2021; Ot'alora G et al., 2018; Ross et al., 2016). MDMA-assisted psychotherapy has been designated by the FDA as a "Breakthrough Therapy" for PTSD, with the U.S. Department of Veterans Affairs (VA) sponsoring much of the research (Amoroso & Workman, 2016; Mitchell et al., 2021; Ot'alora G et al., 2018). Further, there is a breadth of research on ketamine, which has remained legal for medical use (Grady et al., 2017; L. Li & Vlisides, 2016; Nutt et al., 2013). In addition to clinical trials, there is new research taking place in the U.S. and abroad with

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- LSD (Carhart-Harris, Muthukumaraswamy, et al., 2016; Lebedev et al., 2016; Ly et al., 2018; F. Müller et al., 2018; F. Müller & Borgwardt, 2019; Pokorny et al., 2019; and others),
- DMT (L. P. Cameron et al., 2019; Ly et al., 2018; Nardai et al., 2020; Nemes et al., 2019; and others),
- 5-MeO-DMT (Davis et al., 2019; Sepeda et al., 2019; Timmermann et al., 2019; Uthaug et al., 2020; and others),
- ayahuasca (da Silva et al., 2019; de Almeida et al., 2019; Katchborian-Neto et al., 2020; Zeifman et al., 2019; and others), and
- ibogaine (Marton et al., 2019; Mash et al., 2018; Noller et al., 2018; Z. Zhao et al., 2019; and others).

The acknowledged medical utility of psychedelics is expanding to include the treatment of other psychological disorders. There are also solid arguments for administering psychedelics to healthy people for personal and spiritual growth(Elsey, 2017; C. P. Müller & Schumann, 2011). With such promising research, the use of psychedelic-assisted psychotherapy is poised to expand in the coming years, both in the scale of operations and range of potential patients. While clinical trials have demonstrated results targeted at specific DSM diagnoses, there is a critical limitation to this kind of diagnosis-targeted research as actual patients rarely fit into neat diagnostic categories (McWilliams & Lingiardi, 2017). Given that clinical trials target specific diagnoses by excluding participants with co-occurring disorders, there is a lack of understanding of how psychedelics interact with more complex patients. These combined factors

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demonstrate a gap in understanding regarding when and how psychedelic-assisted therapies should be applied.

Legal Status

As of 2022, most psychedelics are listed by the United States Drug Enforcement Agency (DEA) as Schedule I drugs except for ketamine, which is listed as a Schedule III drug and is therefore available for medical use. The DEA scheduling system is summarized as follows (United States Drug Enforcement Administration, n.d.):

- **Schedule I:** "Drugs with no currently accepted medical use and a high potential for abuse."
- **Schedule II:** "Drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence."
- **Schedule III:** "Drugs with a moderate to low potential for physical and psychological dependence."
- **Schedule IV:** "Drugs with a low potential for abuse and low risk of dependence."
- **Schedule V:** "Drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics."

Schedule I drugs may not be prescribed by medical professionals but can be administered by those granted DEA licenses for research (United States Department of Justice, n.d.). Schedule II, III, IV, and V drugs can be obtained by prescription.

In 2018, the DEA published a press release announcing a streamlined application process for research with Schedule I drugs (United States Drug Enforcement Administration, 2018). This new process included a web portal for submitting applications with applicants' "…qualifications, research protocol, and institution where

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the research will take place." The press release stated that the DEA approved more than 590 researchers as of December 2017 to study Schedule I drugs. Further, the press release stated, "Every researcher who has submitted a valid research proposal has been approved." Combined with the growing body of recent human psychedelic studies performed in the United States, this indicates a less restrictive governmental stance toward psychedelic research.

Changes in the legal status of psychedelic drugs are already progressing due to rigorous medical research demonstrating their efficacy. MDMA and psilocybin will likely be available for widespread medical use in the next 2 to 5 years. Medicalization occurs through the Food and Drug Administration (FDA) drug development pipeline, a tedious but linear path toward approval. In addition, several states and cities in the U.S. have passed legislation decriminalizing psychoactive plants, with some having passed specific provisions for psychedelic-assisted therapies (dos Santos et al., 2021).

Significance of Study

This study provides a comparative review of eight different psychedelics across biological, psychological, and clinical domains. To date, the author is aware of no other study of this breadth on psychedelics that has used a systematic approach to ensure coverage of the literature. By comparing psychedelics across many research domains, unique translational insights have been uncovered, as described in Chapter 12 and Chapter 14. Further, the comprehensive nature of this review has yielded an extensive set of tables summarizing the properties of psychedelics. A methodology has been described to use these tables to support patient assessment and evidence-based psychedelic

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treatment planning (see Chapter 13). Again, to the author's knowledge, this is the first such process described in the literature.

With various psychedelic-assisted therapies entering mainstream medical practice, systems for choosing the appropriate treatment or set of treatments for patients will be increasingly necessary. There is a particular challenge in translating clinical research that uses patients with "pure" DSM diagnoses to real-world patients whose presentations tend to be more mixed. This study provides a starting point for this decision-making by synthesizing the findings of clinical studies and general psychological change from psychedelics. It also examines the medical and psychological risk factors that may complicate treatment options for some patients. In addition, individual factors that can influence psychedelic experience and treatment outcomes are considered. Awareness of these factors is essential when planning individualized, evidence-based treatments designed to maximize effectiveness and minimize risk. Together, the outcome of this study represents a novel technique for planning psychedelic-assisted treatments with emerging relevance as these treatments return to use in clinical practice.

Finally, this synthesis of the existing psychedelic literature expands the scope of disorders that can be treated with psychedelic-assisted psychotherapy. It demonstrates the need for legal reform of medical access to psychedelic drugs, as the complexity of individualized treatment requires a range of treatment options to support a high standard of patient care. This research shows that each psychedelic has unique and useful properties that may be ideal for one patient and harmful to another. Access to the full range of psychedelic medicines supports the development of mental health treatments that can better meet patients' needs. Ultimately, the staggering effectiveness of

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psychedelic treatments represents a promising avenue toward meeting the systemic mental health challenges we face today. This study supports the need for legal access to psychedelic treatments while providing a structured approach to treatment decision-making and highlighting a wide array of future research directions.

Research Approach and Rationale

This study used an integrative literature review (ILR) methodology described by Torraco (2005, 2016). This approach was chosen due to the recent re-emergence of psychedelic research in medical contexts and the need to understand the rapidly developing body of research in this area to make effective clinical decisions. Because clinical decision-making spans many variables, universal guidance based on a single study is impossible. As such, an integrative review of the many studies in psychedelic science and therapy is more appropriate for developing a practical decision-making framework for the clinical application of psychedelic-assisted therapies. The research process began with a thorough literature search, followed by a summary and critical analysis of the literature, culminating in literature integration that yielded new insights relevant to clinical decision-making.

As the research questions address issues relevant to clinical practice, a translational research approach was used. Translational research as currently practiced evolved from a series of conferences in 2000 and 2001 that focused on bridging the gap between basic research and clinical practice (Fort et al., 2017). While the concept of translating basic research into clinical applications was not new, these conferences highlighted translation as a challenging problem, itself worthy of research attention (Maienschein et al., 2008). Fort et al. (2017) observed a shared series of translational

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phases across 33 studies. These phases span three levels: basic research (T1), clinical trials (T2), and studies of implementation and effectiveness (T3). In applying a translational approach, this study began with basic T1 research regarding psychedelics and progressed through the chapters to practical T2 clinical research. In the field of psychedelic-assisted psychotherapy, there is little research beyond clinical trials; therefore, T3 research was not covered.

Organization of Study

This study intends to cover the breadth of phenomena associated with psychedelics and their impact on people. Following the first two chapters introducing the topic and describing the methods of inquiry are chapters organized by domains of literature relevant to psychedelic-assisted psychotherapy as follows:

Part I: Biology

Chapter 3: Pharmacology (T1). This chapter introduces the eight psychedelics by providing their brief histories, molecular structures, pharmacokinetic properties, and impacts on neurotransmission.

Chapter 4: Neuroscience (T1). This next chapter provides a brief overview of contemporary psychedelic neuroscience. The effects of psychedelics on neuroplasticity, global brain function, and affect processing are included.

Chapter 5: Medical Risks (T1–T2). To conclude Part I, the medical risks associated with each psychedelic are summarized. This chapter aims to assist clinicians in assessing each psychedelic's acute and long-term medical risks. In addition, medical concerns relevant to a person’s stage of life are also discussed.

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Part II: Psychology

Chapter 6: Phenomenology (T1). The phenomenology of psychedelic experience is diverse and complex. This chapter focuses on quantified aspects of phenomenology rather than narrative case reports. As is expanded upon in the following chapters, some of these quantifiable phenomena mediate the effect of psychological change and symptom improvement from psychedelics.

Chapter 7: Psychological Change from Psychedelics (T1–T2). This chapter summarizes psychological changes following psychedelics. Findings are expressed mainly through tables rather than paragraphs. Factors of change examined include personality traits, coping skills, interpersonal functioning, well-being, mindfulness, spirituality, and clinical syndromes.

Chapter 8: Neuropsychology and Cognition (T1–T2). This next chapter describes the acute, subacute, and long-term impacts of psychedelics on neuropsychological and neurocognitive functions. Domains addressed include intellectual functioning, attention, memory and learning, executive functions, and verbal and psychomotor abilities.

Chapter 9: Psychological Risks (T1–T2). To conclude Part II, the psychological risks associated with psychedelics are summarized. These include challenging experiences, psychosis, mania, suicide, injury, and violence, among other adverse outcomes. This chapter aims to help clinicians evaluate the risk of negative outcomes across psychedelic treatments and account for individualized risk factors.

Chapter 10: Factors Influencing Psychedelic Experience (T1–T2). Factors such as mindset, environment, and dose are all known to influence psychedelic

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experience. Individual factors, including gender and personality traits, also impact psychedelic phenomena. Given that some experiences mediate the outcomes of psychedelic treatments, it is important to understand what factors impact the occurrence of these phenomena. Thus, this chapter summarizes these different factors.

Part III: Treatment

Chapter 11: Techniques of Psychedelic Therapy (T2). Here, the study shifts to translating foundational knowledge of psychedelics described in earlier chapters to the practice of psychedelic-assisted psychotherapy. This chapter describes the various techniques used to date in psychedelic therapies.

Chapter 12: Targets for Psychedelic-Assisted Therapies (T2). This chapter contains the bulk of the synthesized outcomes of this study. It is organized by clinical syndrome, describing different psychedelic treatments applicable to each syndrome. Further, translational findings from prior chapters relevant to each clinical syndrome are included. These translational findings are used to derive new insights into the potential utility of psychedelic-assisted psychotherapies in domains yet to be tested in clinical trials.

Chapter 13: Planning Psychedelic-Assisted Therapies (T2). This brief but essential chapter provides a framework for applying the findings of this synthesis to guide decisions about psychedelic-assisted therapies.

Chapter 14: Discussion and Conclusion (T2). To conclude, this chapter comments on the research process, outcomes, and limitations, as well as directions for further research.

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Each chapter is separated into sections by topic. Within each section, individual psychedelics are addressed as separate sub-sections, except when limited research is available for a topic or when no research was found for a psychedelic. At the end of most chapters, findings are synthesized into summary tables comparing the psychedelics and their properties. These tables provide an overview of literature findings to support clinical decision-making regarding psychedelic treatments, as described in Chapter 13. A list of the summary tables can be found in the Table of Tables.

Delimitations and Scope

As the scope of this study is broad, covering all domains relevant to psychedelic-assisted treatment, it was necessary to carefully delimitate which research was included. When available, meta-analyses and reviews were used to represent their respective knowledge domains. High-quality research methodologies like randomized controlled trials (RCTs) were prioritized above lower-quality methodologies. Psychedelic narratives and case studies were excluded, except when illustrative of phenomena not available quantitatively. To further limit the scope, treating organic disorders such as epilepsy and traumatic brain injury was not covered. Finally, animal studies were only included in basic research domains and when human studies were unavailable. Detailed exclusion criteria are provided in Chapter 2 under “Inclusion and Exclusion Criteria.”

Definition of Major Constructs

Psychedelic. A psychedelic is a drug that induces dramatic changes in perception and cognition (Masters & Houston, 1966). Psychedelic mind-states are categorically different from ordinary consciousness and can result in a rapid, lasting psychological change from a single experience (Lebedev et al., 2016). Humphry Osmond coined the

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term *psychedelic* in a 1956 letter to Aldous Huxley (Huxley & Osmond, 2018, p. xxi). The word is a composite of the Greek psykhē (ψυχή) "mind," and dēloun (δηλοῦν) "[to] make visible, reveal," or "mind manifesting" (Pollan, 2018; Sciolist, n.d.).

Classical Psychedelic. Classical psychedelics are serotonin 2A receptor (5-HT_{2A}) receptor agonists, including mescaline, LSD, psilocybin, and DMT (M. W. Johnson, Hendricks, et al., 2018). Ayahuasca is sometimes considered a classical psychedelic as it contains DMT combined with a monoamine oxidase inhibiter (MAOI).

Psychotherapy. Psychotherapy is a process by which an organism is changed in behavior, cognition, and affect through the skilled influence of another, the therapist. This process involves change through relational influence (Drisko, 2018; D. N. Stern et al., 1998), correction of cognitive distortions (Sacks, 2007), facilitating insight (Gibbons et al., 2007), direct sharing of knowledge (Bäuml et al., 2006; Colom & Lam, 2020). The cognate *psychotherapeia* was defined in 1853 medical writing as "remedial influence of the mind" (Dendy, 1853). The early roots of talk psychotherapy come from J. Breuer and Freud's *Studies on Hysteria* (1895). This work was substantially influenced by Jean-Martin Charcot, with whom Freud studied (J. Breuer & Freud, 1956, ca. 1883; L. Oliveira et al., 2018).

Psychedelic-Assisted Psychotherapy. For this study, psychedelic-assisted psychotherapy includes any form of psychotherapy facilitated by psychedelic drugs. This therapy is often accompanied by traditional psychotherapy (Mithoefer, 2017). The method of psychotherapy used during the psychedelic experience may vary from minimal therapeutic intervention (as in Griffiths et al., 2016) to more intensive engagement with the patient (as in Gasser, 1994; Grof, 1975). In addition to individual therapy,

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psychedelic-assisted group therapies have also been used (see Chapter 11 “Group Psychedelic Therapies”).

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Chapter 2: Methods

Research Questions

The methodology of this study was formulated to provide answers to the following research questions:

- What are the indications for different psychedelic-assisted therapies?
- When is it appropriate to use a psychedelic-assisted therapy?
- In what circumstances are psychedelic therapies contraindicated?
- Based on the current research, what new applications exist for psychedelics in mental health treatment?
- What psychodynamic changes do psychedelic drugs induce?

Methodology

This study used an integrative literature review (ILR) methodology as described by Torraco (2005, 2016). A summary of the method is as follows:

1. Determine whether an ILR is necessary for the topic. ILRs are most appropriate to address either mature topics or new and emerging topics.
2. Develop a conceptual structuring for organizing literature relevant to the topic. This conceptual structuring will become the basis for organizing the text of the ILR. Torraco stresses the importance of forming a coherent conceptual structure early in the process since altering the structure becomes more difficult as the writing progresses.
3. Describe the process by which the review will be conducted, using the conceptual structure as a template. Torraco likens this to the methodology of an empirical study asserting that “The literature is the data of an integrative literature review”

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(Torraco, 2005, p. 360). How the literature will be obtained is crucial to the literature review. The keywords and databases used must be described in detail, along with the inclusion and exclusion criteria.

4. Perform a critical analysis of the literature. The critical analysis involves "…carefully examining the main ideas and relationships of an issue and providing a critique of existing literature" (Torraco, 2005, p. 361). A critique should identify "…the strengths and key contributions of the literature as well as any deficiencies, omissions, inaccuracies, and other problematic aspects of the literature" (Torraco, 2005, p. 362). Through this process, the existing literature's limitations are identified, as are areas where knowledge can be improved by integrating new developments on the topic.
5. The final step in an ILR is synthesizing new knowledge on the topic. As described by Torraco, "Synthesis integrates existing ideas with new ideas to create a new formulation of the topic" (Torraco, 2016, p. 17). It is emphasized that synthesis "…is a creative activity that produces a new model, conceptual framework, or other unique conception informed by the author's intimate knowledge of the topic" (Torraco, 2005, p. 362). This synthesis draws on the deep knowledge of the topic obtained through the literature review. The success of this synthesis and the ILR as a whole rests on its "*provocativeness* or *fruitfulness,*" i.e., "…its capacity to generate new ideas and directions for the field" (Torraco, 2005, p. 364).

The justification for using an ILR method is described in Chapter 1, "Statement of the Problem." The conceptual structuring, method of literature review, and method of

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synthesis are described in the remainder of this chapter. The chapters following contain the completed literature review and critical analysis.

Conceptual Structuring

This study used an integrative literature review methodology to aggregate the results of many studies regarding psychedelics and psychedelic-assisted psychotherapy. A coherent conceptual structure was essential to complete a review of this scale. A translational research approach was used, as the research questions address issues relevant to clinical practice. Translational research bridges the gap between basic research and clinical practice through a series of three translational phases: (T1) basic research, (T2) clinical trials, and (T3) implementation and effectiveness studies (Fort et al., 2017).

Eight major psychedelics were covered by this review: mescaline, LSD, psilocybin, DMT, ayahuasca, MDMA, ketamine, and ibogaine. These eight psychedelics were chosen either because they are commonly used in psychedelic-assisted psychotherapy (LSD, psilocybin, ayahuasca, MDMA, ketamine, and ibogaine) or because they are foundational in the psychedelic literature (mescaline and DMT).

This review was organized into chapters around different academic domains of psychedelic research, further divided into subdomains. Within each subdomain, sections were written for each of the eight psychedelics. In the proposal for this study, the chapter structure was as follows:

> The first four chapters will cover basic (T1) psychedelic research: Phenomenology; Personality Change; Pharmacology and Neuroscience, and Psychedelics and Human Development. The next three chapters will focus on applied research (T2) in psychedelic-assisted psychotherapy: Techniques of

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Psychedelic Therapy, Clinical Research, and Risk Management with Psychedelic-Assisted Psychotherapy. The final chapter will discuss the findings of this study as well as future research directions.

However, as the review progressed, a different conceptual structuring emerged based on three major domains of psychedelic research that were further subdivided into chapters:

- **Part I: Biology**
  - Chapter 3: Pharmacology (T1)
  - Chapter 4: Neuroscience (T1)
  - Chapter 5: Medical Risks (T1–T2)
- **Part II: Psychology**
  - Chapter 6: Phenomenology (T1)
  - Chapter 7: Psychological Change from Psychedelics (T1–T2)
  - Chapter 8: Neuropsychology and Cognition (T1–T2)
  - Chapter 9: Psychological Risks (T1–T2)
  - Chapter 10: Factors Influencing Psychedelic Experience (T1–T2)
- **Part III: Treatment**
  - Chapter 11: Psychedelic-Assisted Therapies (T2)
  - Chapter 12: Targets for Psychedelic-Assisted Therapies (T2)
  - Chapter 13: Planning Psychedelic-Assisted T (T2)

Within each chapter, further conceptual structuring was identified post hoc and used to organize the text. Approximate chronological ordering was used when describing literature relevant to a specific concept.

Literature Search Method

Keyword Matrix

A matrix approach was used to obtain literature representing the breadth of research relevant to the eight psychedelics investigated. This approach combined a set of

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topic keywords with the names of the eight psychedelics to ensure coverage of that topic across each psychedelic. For instance, with the topic keyword “auditory processing,” eight searches were performed: “mescaline auditory processing,” “LSD auditory processing,” “psilocybin auditory processing,” et cetera. The complete set of searches conducted for this review is found in Appendix A.

Topic Keyword Generation

Before beginning the literature search, the author had assembled approximately 200 papers in an ad hoc fashion and from the bibliography of the recently published non-academic review of psychedelic research, *How to Change Your Mind* (Pollan, 2018). The author then organized those papers into categories and sub-categories. These categories and sub-categories were used as the starting set of topic keywords for the literature search. After beginning the literature search, additional relevant topic keywords were discovered. These keywords were added to the search matrix, with each new topic keyword being searched against the eight psychedelics studied.

Literature Search

Google Scholar was chosen as the primary search engine for this study, as psychedelic research spans several academic fields, including psychology, medicine, anthropology, biology, and neuroscience. Each keyword combination was searched in Google Scholar, and the first 10–50 results were reviewed for relevance against the inclusion and exclusion criteria defined below. The search date, number of results returned, number of results reviewed, and number of relevant references were recorded in Appendix A. When there was the possibility that a paper met inclusion criteria, it was by

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default selected to be further evaluated for inclusion or exclusion during the literature review process.

Inclusion and Exclusion Criteria

Appendix B summarizes the literature included in this study. The inclusion and exclusion criteria below were used to filter articles during the search and literature review phases.

General Criteria

Throughout the study, only sources available in English were considered as this is the first language of the author. Publications that meet the criteria below were included regardless of the academic discipline. As the breadth of this study is wide, secondary syntheses and meta-analyses were used when available to limit the study's scope.

Domains of Inclusion

Based on a preliminary review of the literature, several domains of literature were identified that were relevant to the research questions. The included domains were intended to span basic research to applied clinical research, consistent with a translational approach. The proposed content of this study was as follows:

- **Pharmacology and Neuroscience:** The pharmacology of psychedelics was summarized in brief. The secondary neurotransmitter effects were included when available, as these effects may have significance to theoretical clinical applications. The available neuroscience research was to be summarized in brief, including fMRI studies, animal models, and in vitro studies. However, post hoc exclusions were made in this area, as described in Chapter 4.

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- **Psychedelics and Human Development:** Studies addressing changes in developmental trajectory following psychedelic administration were reviewed. In addition, studies that address administration to sensitive populations such as children, elderly people, and pregnant people were summarized.
- **Phenomenology:** The phenomenology of each psychedelic was summarized based on the available quantitative phenomenological studies. Narrative reports were not included.
- **Personality Change:** Research on personality change following psychedelic administration was reviewed. Only studies able to establish causation were included.
- **Techniques of Psychedelic Therapy:** The state of the art of psychedelic-assisted psychotherapy was described. Different techniques used were compared, and their known applications were reviewed.
- **Clinical Research:** The available clinical research was reviewed in brief. This research included modern randomized clinical trials as well as historical studies using less robust methodologies, as clinical research into psychedelics has been significantly stunted by prohibition.
- **Risk:** The known risks of psychedelic-assisted psychotherapy were summarized along with techniques for mitigating this risk.

Domains of Exclusion

Due to the breadth of this study, it was important to limit the depth of literature reviewed to ensure the feasibility of the project (see preliminary literature search below). For this reason, a representative sampling methodology was chosen for this study

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(Torraco, 2016). Representative sampling involves choosing publications that best represent the current state of knowledge on a topic. For instance, in a mature research domain, a meta-analysis or meta-meta-analysis would best represent the topic, while primary sources could be excluded. In a less mature domain, there may only be a few publications, all of which would be chosen to represent the topic. To further limit the scope of this study, several domains of psychedelic research were explicitly excluded:

- **Narrative Phenomenology:** The phenomenology of psychedelic drugs is extraordinarily diverse and complex. This study focuses on the pharmacology, neuroscience, and clinical research of each psychedelic, with no attempt to classify the phenomenology. Phenomenology was considered when correlated in a generalizable sense with neuroscience and clinical research. This is consistent with a neuropsychology approach (Kolb & Whishaw, 2015).
- **Cultural and Spiritual Significance of Psychedelics:** While there is significant cultural and spiritual significance to many psychedelics, these aspects of psychedelic phenomena were excluded from this study to limit scope[1].
- **Studies of Characteristics of Psychedelic Users:** Studies examining the characteristics of psychedelic users within the general population do not provide information about the effects of a drug but rather information about the people who are drawn to use the drug. This results in an inability to differentiate the causative effects of psychedelics from the characteristics of those who choose to use them. Therefore, these studies were excluded.

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[1] Some post hoc modification was made to this exclusion as the importance of spiritual experience to psychological change became clear. Further, the traditional use of psychedelics was at times included as data regarding safety and possible effectiveness.

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- **Case Studies:** Case studies were excluded except when no substantive research with a larger sample was available for a given topic.
- **Patents:** As patents can be written without research to support the invention, patents were excluded from this study.
- **Studies using psychedelics to manipulate other variables:** Studies were excluded where psychedelics are used to manipulate a dependent variable based on the known properties of the psychedelic. Such studies do not provide new information about a psychedelic. For example, Haleem et al. (1988) used 5-MeO-DMT—known to reduce forepaw treading and tremors in rats via the 5-HT_{1A} receptor—to test the stress response of rats following restraint.
- **Organic disorders:** Treatment of organic disorders such as epilepsy, headaches, Tourette syndrome, and traumatic brain injury with psychedelics were not covered as this review focuses on psychological disorders.
- **Unavailable Literature:** Papers where the full text was not available through open access, The Wright Institute Library, or The University of California Berkeley Library, were excluded from the study except in rare cases where a study was deemed so important as to warrant interlibrary loan. The author estimates that approximately 5%–10% of papers found via Google Scholar were excluded for this reason, most published before 1970.

Post Hoc Exclusions

As the review progressed, it was necessary to make additional exclusions to limit the scope of the study. Specific post hoc exclusions made during the literature review

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process are described at the start of each chapter. Across chapters, the following post hoc exclusions were made:

- **Broad Non-Metanalytic Reviews:** Since this study was intended to be a broad review of the literature, other broad reviews were excluded with the assumption that the content of those reviews is included from more primary sources.
- **Behavioral Animal Studies:** The literature involving behavioral experiments with animals administered psychedelics was extensive. This literature was excluded except when uniquely relevant to a specific topic reviewed.
- **Psychedelic Microdosing:** Studies of psychedelic microdosing were excluded to limit the scope, particularly because research in this area is emergent and conflicting.

Literature Review and Critical Analysis

Critical analysis was performed for all literature included in this study. According to Torraco (2016), "Critical analysis of literature involves carefully examining the main ideas and arguments presented in the literature through a critical lens" (p. 16). The critical analysis for this study includes the following aspects described by Torraco:

1. Identifying strengths of the literature.
2. Examining weaknesses of the literature, including methodological problems.
3. Reviewing findings to "distinguish between assertion and evidence" (p. 4).
4. Examining social, cultural, and environmental influences on the literature.
5. Exposing contradictions within the literature.
6. Identifying gaps in the literature.

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The product of critical analysis is critique. Critique identifies the missing, incomplete, or poorly understood aspects of a topic as well as contradictions within the literature (Torraco, 2016). Critiques of each domain of literature were used to develop a literature synthesis and generate new theoretical insights.

Statistical Normalization

In this review, three primary statistics were of concern and are reported throughout the text:

1. ***N*:** The total number of participants in the study. *n* is used to refer to a subset of participants in a study.
2. ***p*:** The *p* statistic represents the probability of falsely rejecting the null hypothesis, thus mistakenly claiming an effect when there is none. Typically, *p* must be less than 0.05 to be considered significant, though 0.01 is preferred.
3. **Effect Size:** Effect size is a measure of a phenomenon's magnitude. For most studies, the effect size quantifies the difference in outcome measures between treatment groups and controls. For this purpose, Cohen's *d* is used as the preferred statistic. When a study did not provide Cohen's *d*, it was calculated by the present author provided that sufficient data was available. Other measures of effect size, such as Glass' Δ or Hedges' *g*, were reported instead of Cohen's *d* when those were the only measures provided. Each of these statistics compares means in terms of the number of standard deviations between them, though the computation of pooled standard deviation between the two outcomes varies between measures.

The combination of these three statistics represents both the statistical power of an experiment (*N* and *p*) and the magnitude of an observed phenomenon (Cohen's *d*). For

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example, an experiment could have high statistical power ($p < .01$; "statistically significant") but detect a small magnitude of effect (Cohen's $d < 0.2$). While this would be reported as "statistically significant" in scientific literature, the small effect size may make such a finding clinically insignificant. Conversely, a study could report a large effect size (Cohen's $d > 0.5$) with low statistical power ($p > .05$; "not statistically significant" [NS]). In these cases, a statistically significant effect might be found by a study with more statistical power. Such findings are referred to as "approaching significance" ($p = .05–.1$).

Descriptive Labeling Conventions

The following conventions were used to describe statistical power:

- $p < .05$: "statistically significant"
- $p = .05–.1$: "approaching significance"
- $p > .1$: "not significant" [NS]

Qualitative descriptors were also used to describe effect size as follows:

- Tiny: Cohen's $d < 0.05$
- Small: Cohen's $d = 0.05–0.2$
- Moderate: Cohen's $d = 0.21–0.5$
- Large: Cohen's $d > 0.5$
- Very Large: Cohen's $d > 1.0$

Effect Size Calculation and Labeling Conventions (post hoc)

As the review progressed, it became clear that normalizing effect sizes required various computational methods. In most cases, the methods described by Borenstein et al.

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(2009) were used, with other methods noted below. These methods were implemented post hoc, as were labeling conventions to designate what technique was used:

d = Cohen's d as reported in the original study.

d_c = Cohen's d computed from means and standard deviation (SD) or standard error of measurement (SEM).

d_g = Effect size is represented by Hedge's g instead of Cohen's d.

d_r = Cohen's d calculated from the correlation coefficient, r.

d_n = Cohen's d calculated from norm-referenced data by dividing the difference in scores by the standard deviation of the norm sample.

d_{OR} = Cohen's d calculated from a reported odds ratio using the method described by Susan (2000).

$d_{\eta 2}$ = Cohen's d computed from eta-squared using a web tool by W. Lenhard and A. Lenhard (n.d.).

d_{SMD} = Effect size reported as standardized mean difference.

When effect sizes are included in tables, these same subscripts follow values to indicate how they were computed (e.g., "0.21_c"). If no subscript follows a value, then it is the published Cohen's d from the study.

p-Value Calculation and Labeling (post hoc)

Occasionally, p-values were not provided by a study, but the data needed to perform a basic t-test was provided. For these cases, p-values were sometimes computed when judged to be valuable in translating research findings. The labeling conventions were used as follows:

p = p-value as reported in the original study

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p_t = Computed p-value using a 2-tailed t-test

p_Q = p-value for Cochran's Q statistic, an indicator of the heterogeneity or homogeneity of a set of studies included in a meta-analysis (Cochran, 1954). In general, $p_Q < .1$ indicates that the studies are heterogeneous and therefore measure different things. However, some studies use different cutoffs for p_Q.

Integration and Synthesis

The integration and synthesis sought to provide answers to the research questions based on the literature reviewed. The knowledge assembled in the literature review was used to formulate an understanding of the effects of each psychedelic drug. Initially, a neuro-psychoanalytic perspective (Solms & Turnbull, 2002) was to be used to link the basic science domains of neuroscience and pharmacology to the psychological domains of phenomenology, personality, and psychotherapy. Neuro-psychoanalysis unites neuroscience with the rich understanding of subjective experience described by psychoanalysis, leaning on research demonstrating that psychoanalytic concepts correlate with functional neuroscience (Axmacher et al., 2014; Solms, 2018).

While the principles of neuro-psychoanalysis were held throughout the synthesis, in the end, this body of theory was not a dominant organizing principle. Rather, findings from different domains of literature were integrated with a pragmatic approach, drawing on various theoretical systems to link together concepts. By focusing throughout the literature review on empirical data, theoretical concepts took a back seat for much of the writing process. Instead, findings were organized and normalized for comparison, allowing for the synthesis of vast amounts of data in summary tables. These summary

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tables became a map of the literature, describing the combined findings and allowing for easy reference.

In the later chapters on treatment, theoretical concepts were then applied in translating basic research into clinical insights. This later translational process was like what had been proposed, integrating knowledge gained about psychedelic actions with findings from clinical research across the range of clinical presentations. The review culminates in a summary table mapping the degree of indication of each psychedelic drug to each clinical presentation based on what is known from clinical trials (highest reliability) to what is inferred from basic research (lower reliability, prime for further research). This summary of findings can then be used to guide psychedelic-assisted treatment, especially when a patient's presentation deviates from a single DSM diagnosis as is studied in clinical trials.

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Chapter 3: Pharmacology

The pharmacology of psychedelics is a broad and thoroughly studied topic in the literature. This chapter provides a brief overview of the chemical structures, dosages, and pharmacokinetics of different psychedelics. The impacts of psychedelics on neurotransmission are also described in detail. Rather than an exhaustive literature review, references were chosen to provide a basic overview of these topics. As a starting point, the DARK Classics in Chemical Neuroscience series of articles in *ACS Chemical Neuroscience* were selected as representative reviews of psychedelic pharmacology when available (L. P. Cameron & Olson, 2018; Cassels & Sáez-Briones, 2018; Dunlap et al., 2018; Geiger et al., 2018; D. E. Nichols, 2018; Wasko et al., 2018). From there, more specific research was examined to elaborate on topics judged to be clinically relevant.

Pharmacological Properties

Summary Table 1 summarizes the pharmacological properties of the eight psychedelics studied herein. Sources for the properties shown in the tables are provided in the remainder of this chapter.

Psychedelics and Neurotransmission

The effects of each psychedelic on neurotransmission are described below. Throughout, binding affinities of drugs to different neurotransmitter receptors (*Ki*) are provided. Lower *Ki* values indicate a stronger binding affinity. Concluding this chapter, Summary Table 2 gives a comparative overview of neurotransmission effects across all eight psychedelics.

Summary Table 1

Pharmacological Properties

Property	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Formula	$C_{11}H_{17}NO_3$	$C_{20}H_{25}N_3O$	$C_{12}H_{17}N_2O_4P$	$C_{12}H_{16}N_2$	DMT + MAOI (beta-carbolines: harmine, THH, and harmaline)	$C_{11}H_{15}NO_2$	$C_{13}H_{16}ClNO$	$C_{20}H_{26}N_2O$
Active metabolite(s)	-	-	Psilocin	-	-	-	(*R,S*)-norketamine, (*R,S*)-dehydronorketamine, (*2S,6S*)-hydroxynorketamine, (*2R,6R*)-hydroxynorketamine	Noribogaine
Threshold dose	-	20 µg	-	0.1 mg/kg IV	-	-	-	-
Therapeutic dose	300 mg	100 µg	20–30 mg	0.2 mg/kg IV	0.5–1.0 mg/kg DMT	75–125 mg	0.1–0.5 mg/kg IV (non-anesthetic)	6–30 mg/kg
Onset	3.5–4 hr	18-60 min	15-30 min	2 min	30 min	-	5 min IN	-
Peak effects	-	2.5–2.8 hr	1.5 hr	90–120 s	1.5–2 hr	1–2 hr	21 min IN	-
Duration	-	8–12 hr	4–7 hr	30 min	4–6 hr	-	112 min IN	>24 hr
Half-life	6 hr	2.2–3.4 hr	Psilocin: 3 hr	5–15 min	DMT: 259 min Harmine: 116 min THH: 532 min	8–9 hr at 100 mg	2–3 hr	Ibogaine: 7 hr Noribogaine: 27.6–49.7 hr

Note. Data sources are cited in the sections below. All doses are oral unless indicated otherwise. MAOI = monoamine oxidase inhibitor; IV = intravenously; IN = intranasally.

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Mescaline Pharmacology

Mescaline is a psychedelic compound that occurs naturally in North American peyote cacti, South American San Pedro cacti, and other species (Cassels & Sáez-Briones, 2018). It can also be artificially synthesized. Mescaline has the chemical formula $C_{11}H_{17}NO_3$ (National Center for Biotechnology Information, 2021c).

Dose and Pharmacokinetics

An active dose of mescaline is approximately 300 mg (Rickli et al., 2016). The onset of effects is approximately 3.5–4 hours when taken orally (Hermle et al., 1992). Mescaline is eliminated by urinary excretion with very little change to the molecular structure (Cassels & Sáez-Briones, 2018). It has a half-life of 6 hours and is eliminated almost entirely from the body after 48 hours (Cassels & Sáez-Briones, 2018). Tolerance to mescaline develops quickly, and it shows cross-tolerance with LSD and psilocybin (Appel & Freedman, 1968; Balestrieri & Fontanari, 1959).

Impacts on Neurotransmission

Serotonin. Mescaline is a 5-HT_{1A} and 5-HT_{2A} agonist, with 5-HT_2 antagonists known to block its effects (Cassels & Sáez-Briones, 2018). Despite being active on these sites, mescaline has relatively weak binding affinity for the 5-HT receptors (Rickli et al., 2016). It has its strongest binding affinity for the 5-HT_{1A} receptor [4.6 ± 0.4 μM], followed by the 5-HT_{2A} receptor [6.3 ± 1.8 μM], the 5-HT_{2C} receptor [17 ± 2.0 μM], and the 5-HT_{2B} receptor [>20 μM] (Rickli et al., 2016). It is also known to be more active on the 5-HT_{2C} receptors at high doses, which is hypothesized to contribute to the more sedating response at these doses (Cassels & Sáez-Briones, 2018). Mescaline has negligible affinity for the serotonin transporter [>30 μM] (Rickli et al., 2016).

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Dopamine. Mescaline has weak binding affinity for the dopamine receptors as an agonist (Rickli et al., 2016). It has its strongest binding affinity for the D_2 receptor [>10 μM], followed by the D_1 receptor [>14 μM] and the D_3 receptor [>17 μM] (Rickli et al., 2016). Mescaline has negligible affinity for the dopamine transporter (DAT) [>30 μM] (Rickli et al., 2016). Dopamine agonism by mescaline appears to be critical, as its behavioral effects in cats are blocked by pretreatment with the dopamine antagonist haloperidol (Trulson et al., 1983).

Norepinephrine. Mescaline acts directly as an agonist to the alpha-2A receptor (Cassels & Sáez-Briones, 2018). It has a much stronger binding affinity for the alpha-2A receptor [1.4 ± 0.2 μM] than the alpha-1A receptor [>15 μM] (Rickli et al., 2016). Mescaline has negligible affinity for the norepinephrine transporter [>30 μM] (Rickli et al., 2016). Mescaline initially increased norepinephrine metabolism in male rats up to 4 hours after administration (Stolk et al., 1974). However, following that time, norepinephrine showed higher concentrations than without mescaline.

Glutamate. Stimulation of the 5-HT_{2A} receptors is known to increase glutamate release in the neocortex (Aghajanian, 2000; Gewirtz & Marek, 2000). Indeed, an increase in glutamate was seen in the cortex of cats when mescaline with direct application of mescaline (Mison-Crighel et al., 1964).

GABA. No significant change in γ-aminobutyric acid (GABA) level was seen in applying mescaline directly to the cortex of cats (Mison-Crighel et al., 1964).

Acetylcholine. Mescaline caused a two-fold increase in acetylcholine (ACh) release in the prefrontal cortex of rats in vitro but no change in ACh in the hippocampus

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(Nair & Gudelsky, 2004). Mescaline decreased the release of ACh in vitro in frog legs, decreasing neuromuscular transmission (Ghansah et al., 1993).

Histamine. Mescaline has negligible affinity for the H_1 receptor [>25 μM] (Rickli et al., 2016).

Adrenal Steroids. Mescaline did not significantly alter cortisol excretion in healthy volunteers (Hollister, 1969), nor did it significantly alter whole-body cortisol levels in Zebrafish (Kyzar et al., 2012). However, 5-HT_{2A} and 5-HT_{2C} agonism is associated with increased production and release of adrenocorticotropic hormone, which stimulates the release of cortisol (Geiger et al., 2018).

Oxytocin. 5-HT_{2A} agonism is associated with increased production and release of oxytocin, though no mescaline-specific studies were found regarding oxytocin (Geiger et al., 2018).

Trace amine-associated receptors (TAARs). Mescaline has some binding affinity for the $TAAR_1$ receptor ranging from 3.3–11 μM in rats and mice, respectively (Rickli et al., 2016).

LSD Pharmacology

Albert Hoffman first synthesized lysergic acid diethylamide (LSD) in 1938 at Sandoz Laboratories in Basel, Switzerland (Hoffman, 1980). However, its psychedelic properties were not discovered until 1943. LSD has the chemical formula $C_{20}H_{25}N_3O$ (National Center for Biotechnology Information, 2021d).

Dose and Pharmacokinetics

LSD induces subjective effects with a dose as low as 20 μg (D. E. Nichols, 2018). A typical psychedelic dose is approximately 100 μg (Rickli et al., 2016). The onset of

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effects is 18–60 min following ingestion (Holze et al., 2019). Peak subjective effects occur after approximately 2.5–2.8 hours, with an overall duration of 8–12 hours (Dolder et al., 2015). LSD is converted into several inactive metabolites by the liver before excretion and has a half-life of 2.2–3.4 hours (Dolder et al., 2015; D. E. Nichols, 2018). Tolerance to LSD develops rapidly, and it shows cross-tolerance with mescaline and psilocybin (Appel & Freedman, 1968; Balestrieri & Fontanari, 1959).

Impacts on Neurotransmission

Serotonin. LSD acts as a serotonin receptor agonist with its strongest affinity for the 5-HT_{1A} receptor [0.003 ± 0.0005 μM], followed by the 5-HT_{2A} receptor [0.004 ± 0.0001 μM], the 5-HT_{2C} receptor [0.015 ± 0.003 μM], then the 5-HT_{2B} receptor [12 ± 0.4 μM] (Rickli et al., 2016). LSD has negligible affinity for the serotonin transporter [SERT, >30 μM] (Rickli et al., 2016). LSD's effects can be blocked by the 5-HT_{2A} receptor antagonist ketanserin (Kraehenmann, Pokorny, Vollenweider, et al., 2017).

Dopamine. LSD has moderate affinity as a dopamine agonist, though it is weaker than its affinity for the 5-HT receptors (Rickli et al., 2016). It has its strongest binding affinity for the D_2 receptor [0.025 ± 0.0004 μM], followed by the D_3 receptor [0.10 ± 0.01 μM], then the D_1 receptor [0.31 ± 0.09 μM] (Rickli et al., 2016). The agonist effect of LSD on D_2 receptors reverses at high doses, a process mediated by $TAAR_1$ agonism by LSD (De Gregorio et al., 2016). LSD has negligible affinity for DAT [>30 μM] (Rickli et al., 2016).

Norepinephrine. LSD has modest agonist binding affinity as an agonist to the alpha-2A receptor [0.012 ± 0.002 μM] and little affinity for the alpha-1A receptor [0.67 ± 0.18 μM] (Rickli et al., 2016). It also has some affinity as an agonist to the beta-

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adrenergic receptors (Dolphin et al., 1978). LSD has negligible affinity for the norepinephrine transporter (NET) [>30 μM] (Rickli et al., 2016). In rats, 2 mg/kg of LSD increased synaptic norepinephrine in the hypothalamus, while 1 mg/kg did not (Sugrue, 1969). Given that 1 mg/kg of LSD is an extremely high dose of LSD for human use, the effect of LSD on norepinephrine release appears to be negligible.

Glutamate. Stimulation of the 5-HT_{2A} receptors is known to increase glutamate release in the neocortex (Aghajanian, 2000; Gewirtz & Marek, 2000). Congruent with this, characteristic head twitch behaviors induced by LSD are eliminated in mGluR2 receptor knockout mice, indicating that secondary glutamate action from LSD is likely to be critical to its effects (J. L. Moreno et al., 2011). However, knockout studies are limited because producing mice with a single reliably altered gene produces other genetic modifications (Eisener-Dorman et al., 2009). This creates a "genetic background effect" that researchers attempt to breed out but cannot eliminate completely. This genetic background effect can produce phenotypic differences that are not due to the single knockout gene.

GABA. LSD did not affect the electrical inhibition of single neurons by GABA in decerebrate cats (Boakes et al., 1970).

Acetylcholine. In a live cat cortex, LSD had "no marked effect" on the release of ACh (Domino & Bartolini, 1972), nor did it deplete ACh in male rats (Domino & Wilson, 1972). In guinea-pig ileum, LSD reduced ACh release up to 45% (Pfeuffer-Friederich & Kilbinger, 1985). Together, findings on the impact of LSD on ACh are mixed.

Histamine. LSD has very weak binding affinity for the H_1 receptor [1.1 ± 0.2 μM] (Rickli et al., 2016).

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Adrenal Steroids. 5-HT_{2A} and 5-HT_{2C} agonism is associated with increased production and release of adrenocorticotropic hormone, which stimulates the release of cortisol (Geiger et al., 2018). In healthy humans [N=14, male] and Guinea pigs, LSD did not significantly alter cortisol excretion (Hollister, 1969; Nadel et al., 1957). In Zebrafish, LSD increased whole-body cortisol (p<.05) with significance in one experiment while approaching significance (p<.10) in two others (Grossman et al., 2010). The magnitude of this effect was an approximate increase of 50%–100%. Together, it is unclear whether LSD affects cortisol excretion in humans.

Oxytocin. 5-HT_{2A} agonism is associated with increased production and release of oxytocin, though no LSD-specific studies were found regarding oxytocin (Geiger et al., 2018).

TAARs. LSD has weak affinity for the $TAAR_1$ receptor, ranging from 0.45–10 μM in rats and mice, respectively (Rickli et al., 2016). However, the $TAAR_1$ receptor antagonist EPPTB blocks the inhibitory effect of high-dose LSD on dopamine neurons in the ventral tegmental area (VTA), indicating that LSD has $TAAR_1$ agonist properties (De Gregorio et al., 2016). Further, LSD strongly increased cAMP production through $TAAR_1$ receptor agonism, indicating that this weak affinity may have a large effect (Bunzow et al., 2001).

Psilocybin Pharmacology

Psilocybin is the active psychedelic compound in “magic mushrooms” of the genus *Psilocybe* and others (Geiger et al., 2018). Psilocybin has the chemical formula $C_{12}H_{17}N_2O_4P$ (National Center for Biotechnology Information, 2021f).

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Dose and Pharmacokinetics

A typical therapeutic dose for psilocybin is 20–30 mg/70 kg (Garcia-Romeu et al., 2021). The onset of psilocybin is approximately 15–30 min following ingestion (Geiger et al., 2018). Psilocybin reaches peak subjective effects at 1.5 hours, as rated by an outside monitor, while peak cardiovascular effects occur 1.5–3 hours following ingestion (Griffiths et al., 2011). Psilocybin typically lasts 4–7 hours, with dose-dependent aftereffects persisting up to 24 hours following (Geiger et al., 2018). Psilocybin is quickly converted in the liver to its active metabolite, psilocin, which can cross the blood-brain barrier and affect neurotransmission, unlike psilocybin (Geiger et al., 2018). The half-life of psilocin is approximately 3 hours (R. T. Brown et al., 2017).

Impacts on Neurotransmission

Serotonin. Psilocin has its strongest binding affinity for the 5-HT_{2A} receptor, where it acts as an agonist [0.049 ± 0.01 μM], followed by the 5-HT_{2C} receptor [0.094 ± 0.009 μM], the 5-HT_{1A} receptor [0.123 ± 0.02 μM], and the 5-HT_{2B} receptor [>20 μM] (Rickli et al., 2016). The subjective effects of psilocybin are blocked by a 5-HT_{2A} antagonist demonstrating that this receptor target is critical to its effects (Vollenweider, Vollenweider-Scherpenhuyzen, et al., 1998). This higher relative affinity for the 5-HT_{2C} receptor in psilocybin compared to LSD or mescaline may contribute to psilocybin's more sedating effects, given that 5-HT_{2C} agonism decreases activation of the mesocorticolimbic dopamine system (Di Matteo et al., 2001). Psilocin has weak affinity for SERT yet exhibits a moderate inhibiting effect on it [6.0 ± 0.3 μM] (Rickli et al., 2016). In rats, psilocin increased serotonin concentration in the medial prefrontal cortex

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(mPFC) (Sakashita et al., 2015). However, no changes in serotonin concentration were observed in the VTA or nucleus accumbens (NA).

Dopamine. Psilocin has little binding affinity for the dopamine receptors as an agonist (Rickli et al., 2016). It has its strongest binding affinity for the D_2 receptor [3.7 ± 0.6 μM], followed by the D_3 receptor [8.9 ± 0.8 μM] and the D_1 receptor [>14 μM] (Rickli et al., 2016). Psilocin has negligible affinity for DAT [>30 μM] (Rickli et al., 2016). In rats, psilocin increased dopamine concentration in the NA, decreased dopamine in the mPFC, and had no effect on dopamine concentration in the VTA (Sakashita et al., 2015). In humans, Vollenweider et al. (1999) found that psilocybin increased dopamine in the caudate nucleus and putamen [*N*=7, male, average age=27, race N/R].

Norepinephrine. Psilocin has moderate inhibiting effect on NET despite having a mild affinity for it [13 ± 1.7 μM] (Rickli et al., 2016). Psilocybin 50 mg/kg was found to increase norepinephrine in the rat hypothalamus 3 hours following administration (Sugrue, 1969). However, Stolk et al. (1974) psilocybin 25 mg/kg decreased brain norepinephrine in male rats for 20 minutes, 1 hour, 2 hours, and 6 hours following administration, but not 1.5 hours or 4 hours following. Psilocin has negligible affinity for the alpha norepinephrine receptors with 2.1 ± 0.01 μM to alpha-2A and 6.7 ± 1.1 μM to alpha-1A (Rickli et al., 2016).

Glutamate. Stimulation of the 5-HT_{2A} receptors is known to increase glutamate release in the neocortex (Aghajanian, 2000; Gewirtz & Marek, 2000). Mason et al. (2020) found that glutamate release due to psilocybin is regionally and phenomenologically dependent. Under psilocybin, there were higher levels of cortical glutamate and lower levels of hippocampal glutamate. A larger decrease in hippocampal glutamate was

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predictive of positively experienced ego dissolution, while a larger increase in medial prefrontal glutamate was predictive of negatively experienced ego dissolution.

Histamine. Psilocin has very weak binding affinity for the H_1 receptor [1.6 ± 0.2 μM] (Rickli et al., 2016).

Adrenal Steroids. 5-HT_{2A} and 5-HT_{2C} agonism is associated with increased production and release of adrenocorticotropic hormone, which stimulates the release of cortisol (Geiger et al., 2018). However, no studies of psilocybin's effects on cortisol release were found.

Oxytocin. 5-HT_{2A} agonism is associated with increased production and release of oxytocin, though no psilocybin-specific studies were found regarding oxytocin (Geiger et al., 2018).

TAARs. Psilocin has weak binding affinity for the $TAAR_1$ receptors, ranging from 1.4 to 17 μM in rats and mice, respectively (Rickli et al., 2016).

DMT Pharmacology

N,N-dimethyltryptamine (DMT) is produced endogenously in the brains of humans and other mammals and synthesized by many plants (L. P. Cameron & Olson, 2018). DMT has the chemical formula $C_{12}H_{16}N_2$ (National Center for Biotechnology Information, 2021e).

Dose and Pharmacokinetics

DMT becomes psychedelically active at a dose of approximately 0.1 mg/kg intravenously (IV), with the typical psychedelic dose of 0.2 mg/kg IV (Strassman et al., 1994). DMT is quickly metabolized by MAO-A, resulting in a half-life of 5–15 minutes (L. P. Cameron & Olson, 2018). DMT is metabolized so rapidly that it is not orally active

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due to breakdown in the gut and liver (L. P. Cameron & Olson, 2018). For this reason, DMT is typically smoked or administered intravenously in humans (L. P. Cameron & Olson, 2018). The onset of effects is within 2 minutes, peaking 90–120 seconds after administration and subsiding entirely after 30 minutes (Strassman et al., 1994; Strassman & Qualls, 1994).

Impacts on Neurotransmission

Serotonin. DMT is an agonist or partial agonist for all the serotonin receptors (L. P. Cameron & Olson, 2018). It has its strongest binding affinity for the 5-HT_{1A} receptor [0.075 ± 0.02 μM], followed by the 5-HT_{2A} receptor [0.237 ± 0.04 μM], 5-HT_{2C} receptor [0.424 ± 0.15 μM], and the 5-HT_{2B} receptor [3.4 ± 3.2 μM] (Rickli et al., 2016). DMT has negligible affinity for the serotonin transporter [SERT, 6.0 ± 0.6 μM], and DMT itself is transported by SERT (L. P. Cameron & Olson, 2018; Rickli et al., 2016).

Dopamine. DMT is a short-acting, potent MAO_A inhibiter that is purported to result in a brief accumulation of dopamine in the brain (Waldmeier & Maître, 1977). It has negligible affinity for DAT [22 ± 3.9 μM] (Rickli et al., 2016). Haubrich and Wang (1977) found up to a 42% reduction in dopamine concentration in the forebrains of rats 5 minutes following DMT administration. However, T. L. Smith (1977) found that DMT increased dopamine synthesis in the striatum. DMT appears to have different effects on dopamine release across different brain areas, but further research is needed for confirmation. DMT has weak affinity for the dopamine receptors as an agonist (Rickli et al., 2016). Its strongest binding affinity is for the D_2 receptor [3.0 ± 0.4 μM], followed by the D_1 receptor [6.0 ± 0.9 μM] and the D_3 receptor [6.3 ± 2.1 μM] (Rickli et al., 2016).

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Norepinephrine. DMT has weak affinity for the alpha receptors [α_{1A}: 1.3 ± 0.2 μM; α_{2A}: 2.1 ± 0.4 μM] and negligible affinity for NET [6.5 ± 1.3 μM] (Rickli et al., 2016).

Glutamate. Stimulation of the 5-HT_{2A} receptors is known to increase glutamate release in the neocortex (Aghajanian, 2000; Gewirtz & Marek, 2000). For this reason, DMT likely stimulates glutamate release just as other classical psychedelics do (Schmidt, 2012). However, no research directly measuring DMT's effects on glutamate was found.

Acetylcholine. DMT decreased ACh concentration in the corpus striatum of rats but did not change ACh concentration in the frontal cortex (Haubrich & Wang, 1977).

Opioid System. DMT elevates beta-endorphin levels in the blood (Strassman & Qualls, 1994).

Sigma Receptors. DMT is known to be a sigma-1 receptor agonist based on research in mice (Fontanilla et al., 2009). However, this affinity is 100 times less than for the 5-HT_{2A} receptors (L. P. Cameron & Olson, 2018).

Histamine. DMT has a strong binding affinity for the H_1 receptor [0.22 ± 0.03 μM] (Rickli et al., 2016).

Adrenal Steroids. 5-HT_{2A} and 5-HT_{2C} agonism is associated with increased production and release of adrenocorticotropic hormone, which stimulates the release of cortisol (Geiger et al., 2018; Strassman & Qualls, 1994). This elevated cortisol response is seen with DMT (Strassman & Qualls, 1994)

Oxytocin and Prolactin. 5-HT_{2A} agonism is associated with increased production and release of oxytocin, though no DMT-specific studies were found regarding oxytocin (Geiger et al., 2018). DMT elevates plasma prolactin (Strassman & Qualls, 1994).

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TAARs. DMT has weak affinity for the $TAAR_1$ receptor, ranging from 2.2–3.3 μM in rats and mice, respectively (Rickli et al., 2016). However, DMT was also found to strongly increase cAMP production through $TAAR_1$ receptor agonism, indicating that this small affinity may have a large effect (Bunzow et al., 2001).

Ayahuasca Pharmacology

Ayahuasca contains DMT combined with a monoamine oxidase inhibitor (MAOI) (Domínguez-Clavé et al., 2016). As MAO-A quickly breaks down DMT, MAO inhibitors greatly increase DMT's half-life (L. P. Cameron & Olson, 2018). In traditional Amazonian cultures, *B. caapi* vine is used as a source of MAO inhibitors, while *P. viridis* is used as a source of DMT (Domínguez-Clavé et al., 2016). *B. caapi* contains various tricyclic beta-carbolines that include harmine, tetrahydroharmine (THH), and harmaline, all of which inhibit MAO.

Dose and Pharmacokinetics

A typical dose of ayahuasca contains 0.5–1.0 mg/kg of DMT (Riba & Barbanoj, 2011). Ayahuasca's effects are typically felt 30 minutes after ingestion, with visual experiences beginning after 45–60 minutes (Domínguez-Clavé et al., 2016). While there tend to be waves of intensity throughout the experience, peak intensity tends to be reached after 1.5–2 hours, with a return to baseline 4–6 hours after ingestion (Domínguez-Clavé et al., 2016). The intensity of ayahuasca is dose-dependent, and a ceiling effect is observed (Domínguez-Clavé et al., 2016). The point of maximum subjective intensity (1.5–2 hours) appears to correspond with the maximum plasma DMT concentration, with the maximum concentration of beta-carbolines occurring 1.5–3 hours

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later (Riba et al., 2003; Riba & Barbanoj, 2011). The half-life of ayahuasca components is 259 min for DMT, 116 min for harmine, and 532 min for THH (McKenna et al., 1998).

Ninety-nine percent of the DMT in ayahuasca is excreted as metabolites, with 50% as indole-3-acetic acid, 10% as DMT-*N*-oxide, and the remaining as other MAO-independent compounds (Riba et al., 2012). Of the beta-carbolines, approximately 18% of excretions are harmalol, 9% harmaline, 7% tetrahydroharmine, 2% tetrahydroharmol, and less than 1% are harmol and harmine (Riba et al., 2012).

Impacts on Neurotransmission

Because ayahuasca consists of DMT potentiated by an MAO inhibitor, the effects of DMT on neurotransmission are likely shared by ayahuasca. Only studies specifically examining ayahuasca's effects on neurotransmission are reviewed in this section. In the summary table at the end of the chapter, findings from DMT research are synthesized with ayahuasca research.

Serotonin. An increase in serotonin release and utilization rate was found in rats treated with ayahuasca (de Castro-Neto et al., 2013). The effects of ayahuasca are blocked by pretreatment with the 5-HT_{2A} antagonist ketanserin (Valle et al., 2016). The beta-carbolines have SERT affinity, with THH inhibiting showing the greatest inhibiting effect on the serotonin transporter [ED_{50}=3.4 μM], followed by harmine [11 μM], then harmaline [15 μM] (Buckholtz & Boggan, 1977).

Dopamine. Harmine increased dopamine release in the NA shell in male rats (Brierley & Davidson, 2012). No changes in dopamine release were seen in the NA core, and no changes in dopamine reuptake were seen. Ayahuasca increased dopamine

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concentration in the amygdala but not the hippocampus (de Castro-Neto et al., 2013). Harmine has mild inhibitory DAT affinity [ED_{50}=16 μM] (Buckholtz & Boggan, 1977).

Norepinephrine. In rats treated with ayahuasca, norepinephrine concentration increased in the amygdala but not the hippocampus (de Castro-Neto et al., 2013). Harmine has mild inhibitory NET affinity [ED_{50}=22 μM] (Buckholtz & Boggan, 1977).

GABA. A decrease in GABA concentration was found in the amygdala of rats treated with ayahuasca, while an increase in GABA concentration was found in the hippocampus (de Castro-Neto et al., 2013).

Adrenal Steroids. Ayahuasca modulated awakening salvatory cortisol response in patients with hypocortisolemia associated with treatment-resistant depression, with cortisol returning to normal 1 day after ayahuasca (de Menezes Galvão et al., 2018). A possible mechanism for this effect is the association between 5-HT_{2A} and 5-HT_{2C} agonism and increased production and release of adrenocorticotropic hormone, which stimulates the release of cortisol (Geiger et al., 2018).

Oxytocin. 5-HT_{2A} agonism is associated with increased production and release of oxytocin, though no ayahuasca-specific studies were found regarding oxytocin (Geiger et al., 2018).

MDMA Pharmacology

3,4-Methylenedioxymethamphetamine (MDMA) was first synthesized by Merck in 1912 as a precursor to an appetite-suppressing drug (Freudenmann et al., 2006). MDMA has the chemical formula $C_{11}H_{15}NO_2$ (National Center for Biotechnology Information, 2021a). Because MDMA was not developed as a product, its pharmacological properties were not tested in animals until 1927 (Freudenmann et al.,

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2006). The first human use of MDMA is not known. Human trials may have occurred in 1959 when MDMA was re-synthesized at Merck, but there is no clear evidence regarding this. Illicit MDMA was first found in 1970 in tablets seized in Chicago. The first known human MDMA studies were performed by A. T. Shulgin and Nichols (1978) and G. M. Anderson et al. (1978).

Dose and Pharmacokinetics

A typical MDMA dose is 75–125 mg (Vizeli & Liechti, 2017). Peak subjective effects occur 1–2 hours following administration (Peiró et al., 2012). The primary metabolite of MDMA in humans is *3,4*-dihydroxymethamphetamine (HHMA), which is excreted as a conjugate of glucuronic acid (Dunlap et al., 2018). The half-life of MDMA is approximately 8–9 hours for 100 mg administered to human subjects, but its half-life increases with its dose (Dunlap et al., 2018).

A genetic CYP2D6 enzyme deficiency occurs in approximately 7%–10% of Caucasians, leading to slowed MDMA metabolism (J. Yang et al., 2006). This enzyme deficiency means that in poor metabolizers, MDMA peak plasma concentration is approximately 36% higher than in normal metabolizers given the same dose. Still, J. Yang et al. concluded that the poor metabolizer phenotype does not increase plasma concentration sufficiently to risk acute MDMA toxicity, as is supported by other studies (Gilhooly & Daly, 2002; O'Donohoe et al., 1998; Schwab et al., 1999). See Chapter 5 section titled "Neurotoxicity" for more information on MDMA neurotoxicity.

Impacts on Neurotransmission

Serotonin. MDMA binds to SERT and reverses its direction of flow, substantially increasing the concentration of extracellular serotonin (Dunlap et al., 2018). This effect

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appears to be critical to MDMA's effects, as rats with genetically deleted SERT do not show the same behavioral effects or drug discrimination in response to MDMA (Pettie et al., 2019). MDMA also has moderate affinity for the 5-HT_{2B} receptor as an agonist [0.5 μM] and weak affinity for the 5-HT_{2A} receptor as an antagonist [7.8 μM], along with very weak affinity for the other serotonin receptors (Dunlap et al., 2018). Agonism of the 5-HT_{2B} receptor appears to be critical to MDMA's effects, as 5-HT release and behavioral effects are blocked by 5-HT_{2B} antagonists and in 5-HT_{2B} knockout mice (Doly et al., 2008).

Norepinephrine. Like with SERT, MDMA binds to the norepinephrine transporter (NET) and reverses its direction of flow, thereby increasing extracellular norepinephrine (Dunlap et al., 2018). This effect is very large, similar in magnitude to the serotonin increase caused by MDMA (Dunlap et al., 2018). The stimulant effects of MDMA are reduced by pretreatment with a NET inhibiter (Hysek et al., 2011).

Dopamine. MDMA also binds to DAT, inhibiting its action by reversing the flow of neurotransmitters and therefore increasing extracellular dopamine (Dunlap et al., 2018). This effect is slightly weaker for dopamine than serotonin and norepinephrine.

Glutamate. MDMA releases glutamate as a secondary effect due to the increased stimulation of dopaminergic neurons (Anneken et al., 2013). It does not affect the uptake of glutamate (Dunlap et al., 2018).

GABA. While MDMA does not affect the uptake of GABA (Dunlap et al., 2018), it does increase extracellular GABA in the VTA (Bankson & Yamamoto, 2004).

Acetylcholine. MDMA was found to increase ACh concentration in the prefrontal cortex, the dorsal hippocampus, and the striatum in rats (Acquas et al., 2001; H. S.

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Fischer et al., 2001; Nair & Gudelsky, 2005a, 2005b). Seven days following MDMA, rats were seen to have less release of ACh (Nair & Gudelsky, 2006).

Opioid Receptors. The rewarding properties of MDMA are preserved in mu opioid receptor knockout mice, indicating that these rewarding properties are likely not due to mu opioid agonism (Robledo et al., 2004). Pretreatment with a delta opioid receptor antagonist blocks the effect of MDMA on increasing hyperlocomotion in mice (Belkaï et al., 2009) and increasing lever pressing in rats (Reid et al., 1996).

Sigma Receptors. MDMA has strong affinity for both the sigma-1 and sigma-2 receptors as an agonist (Dunlap et al., 2018). This affinity is similar in magnitude to its affinity for the monoamine transporters.

Histamine. MDMA may have weak affinity for the H_1 receptor as an antagonist, though research is mixed [2,138 to >14,400 μM] (Dunlap et al., 2018). It has negligible affinity for the H_2 receptor [>10,000 μM] (Dunlap et al., 2018).

Adrenal Steroids. Parrott, Montgomery, et al. (2014) reviewed studies of MDMA and cortisol release. They saw that acute MDMA increased cortisol 100%–200% in laboratory conditions and up to 800% in a dance environment. MDMA also increases dehydroepiandrosterone (DHEA) plasma levels (Dunlap et al., 2018).

Oxytocin, Vasopressin, and Prolactin. MDMA increases plasma levels of oxytocin, vasopressin, and prolactin (Dunlap et al., 2018; Kirkpatrick, Lee, et al., 2014; Kuypers et al., 2018). These increases likely occur due to the increases in serotonergic activity that MDMA induces (Dunlap et al., 2018). The release of oxytocin by MDMA in humans appears to be dose-dependent, with 52.5 mg/70 kg not elevating oxytocin, while

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105 mg/70 kg elevated oxytocin to a level almost twice what 40 IU intranasal oxytocin achieved (Kirkpatrick, Francis, et al., 2014).

Oxytocin plays a significant role in the interoceptive effects of MDMA, as drug discrimination from amphetamine in rats was impaired when pre-treated with an oxytocin antagonist (Broadbear et al., 2010). There is evidence suggesting that oxytocin and vasopressin signaling is related to the prosocial effects of MDMA (Bershad et al., 2016; Dumont et al., 2009; Ramos et al., 2013; Thompson et al., 2007; Vizeli & Liechti, 2018). However, oxytocin administered on its own does not produce the same prosocial effects as MDMA (Kirkpatrick, Lee, et al., 2014; Kuypers et al., 2014).

TAARs. MDMA is a potent $TAAR_1$ agonist, strongly increasing cAMP production through this mechanism (Bunzow et al., 2001). This activation of $TAAR_1$ is likely to contribute to increased extracellular levels of serotonin, dopamine, and norepinephrine caused by MDMA (Dunlap et al., 2018).

Ketamine Pharmacology

Ketamine is a derivative of phencyclidine (PCP) that was discovered in 1956 (Hassan et al., 2017). Its chemical formula is $C_{13}H_{16}ClNO$ (National Center for Biotechnology Information, 2021b).

Dose and Pharmacokinetics

Ketamine is effective for analgesia and sedation with 0.5–1.0 mg/kg IV or anesthesia with 0.5–2.0 mg/kg IV (Amornyotin, 2014). For treating depression, a low dose of 0.1–0.5 mg/kg IV is typically used (Tyler et al., 2017; Zhu et al., 2016). Ketamine has an onset of approximately 5 minutes IN, with peak effects at 20.8 minutes and a total

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duration of 112 minutes on average (C. J. A. Morgan & Curran, 2011; Winstock et al., 2014). Ketamine's half-life is 2 to 3 hours (Tyler et al., 2017).

Ketamine is quickly and thoroughly metabolized, with less than 4% of the unmetabolized drug excreted in urine (Tyler et al., 2017). Ketamine is initially demethylated to the active metabolite norketamine by the CYP2B6 and CYP3A4 enzymes (Jelen et al., 2021). Those with the *CYP2B6*6* gene variant metabolize ketamine more slowly (P.-F. Wang et al., 2018). This gene is common in African, African American, and some Asian populations (P.-F. Wang et al., 2018). Additionally, both ketamine and norketamine are hydroxylated to form several metabolites, including hydroxyketamine, (*2R,6R*)-hydroxynorketamine, (*2S,6S*)-hydroxynorketamine, and dehydronorketamine (Tyler et al., 2017). Ketamine is metabolized more slowly in female rats than in male rats (Livingston & Waterman, 1977; Saland & Kabbaj, 2018).

Impacts on Neurotransmission

Because (*R*)- and (*S*)-ketamine have different effects on neurotransmission, enantiomers will be differentiated throughout this section. (*R,S*)-ketamine indicates that a blend of (*R*)- and (*S*)-enantiomers were used in the study. When a study did not specify which enantiomer was used, it is assumed that a racemic blend was used as isolated enantiomers of ketamine are a newer development in the research.

Glutamate. Ketamine's primary mode of action is by antagonizing the *N*-methyl-D-aspartate (NMDA) receptor through allosteric binding at a site distinct from the glutamate binding site (Tyler et al., 2017; Zanos et al., 2018). This results in less excitatory action from glutamate across the central nervous system. (*S*)-ketamine has approximately five to eight times as much affinity for the NMDA receptor [0.3 μM] as

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(*R*)-ketamine [1.4 μM] (Tyler et al., 2017). In addition to antagonizing the NMDA receptors, the (*R*)-ketamine metabolite (*2R,6R*)-hydroxynorketamine activates the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Duan et al., 2013; Tyler et al., 2017). Cognitive impairment by ketamine is substantially reduced by pretreatment with the metabotropic glutamate receptor agonist LY354740 (Krystal et al., 2004). Ketamine has some affinity for the PCP receptors [(*R*)=3.2 μM, (*S*)=1.1 μM, (*R,S*)=2.9 μM] (Hirota et al., 1999). Ketamine increases glutamate levels in the anterior cingulate cortex (Stone et al., 2019).

Serotonin. (*S*)-ketamine has very weak affinity for the 5-HT_2 receptors [15 μM] (Kapur & Seeman, 2002). The behavioral effects of (*R,S*)-ketamine were blocked by a 5-HT_2 antagonist in rats, indicating that agonism of these receptors is critical to its effects (Yoshizawa et al., 2013). The behavioral effects of (*R,S*)-ketamine were also blocked by a 5-HT_{1A} antagonist in mice (Fukumoto et al., 2014). (*R,S*)-ketamine antagonizes the 5-HT_3 receptors with negligible affinity [420 μM] (Yamakura et al., 2000).

In most studies, SERT was shown to be inhibited by (*R,S*)-ketamine (Tso, 2004; Yamamoto et al., 2013; Y. Zhao & Sun, 2008). However, one study by Can et al. (2016) did not find any binding affinity or inhibitory effect of (*R,S*)-ketamine on SERT. Tso et al. (2004) found that SERT inhibition was similar for both ketamine enantiomers.

Tso et al. (2004) found that in rats, both ketamine enantiomers increased serotonin efflux in the dorsal raphe nucleus (DRN), but (*R*)-ketamine had approximately twice the effect as (*S*)-ketamine. Conversely, Pham et al. (2016) found that in rats, (*R,S*)-ketamine injection increased extracellular serotonin in the mPFC but not the DRN.

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Dopamine. Kapor and Seeman (Kapur & Seeman, 2002) saw D_2 receptor affinity from (*R,S*)-ketamine [2.3 ± 0.3 μM] and (*S*)-ketamine [0.7 ± 0.3 μM] as an agonist, with a strength similar their affinities for the NMDA receptors. Can et al. (2016), however, found that (*R,S*)-ketamine had no affinity for any of the dopamine receptors, yet also remarked that repeat ketamine administration was "…consistent with its agonist actions on D_2 autoreceptors" (p. 163). Duan et al. (2013), however, found that a D_1/D_5 antagonist blocked the behavioral effects of (*R,S*)-ketamine in rats, indicating some agonist effect on these receptors.

Tso et al. (2004) found DAT inhibition in the rat caudoputamen to be enantiomer-specific, with (*S*)-ketamine inhibiting DAT and (*R*)-ketamine having no effect on DAT. In line with this finding, the authors also saw that (*S*)-ketamine increased dopamine efflux in the caudoputamen while (*R*)-ketamine did not. However, other studies have found that the DAT transporter is not inhibited by (*R,S*)-ketamine (Can et al., 2016; Yamamoto et al., 2013). In one study not finding DAT transporter inhibition, (*R,S*)-ketamine also did not increase dopamine release in the NA (Can et al., 2016). Lindefors et al. (1997), on the other hand, found that (*R,S*)-ketamine induced a five-fold increase in dopamine release in the mPFC of rats.

Norepinephrine. Y. Zhao and Sun (2008) found that (*R,S*)-ketamine inhibited NET, while Can et al. (2016) found that neither (*R*)- or (*S*)-ketamine had any effect on NET. Tso et al. (2004) found that both (*R*)- or (*S*)-ketamine increased norepinephrine by a small but significant amount in the ventral bed nucleus of the stria terminalis of rats.

Adrenal Steroids. In humans, (*R,S*)-ketamine increased cortisol in a dose-dependent manner compared to placebo (Hergovich et al., 2001; Krystal et al., 1994). In

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humans, saliva cortisol was found to be increased by (*R*)-ketamine compared to placebo (Khalili-Mahani et al., 2015).

GABA. (*R,S*)-ketamine inhibits GABA uptake through its moderate affinity for the GABA transporter (GAT) [6.2 ± 1.1 μM] (Zanos et al., 2018). While (*R,S*)-ketamine does not induce GABA release in the mPFC or subcortical regions (Lindefors et al., 1997; Stone et al., 2019), increased GABA is observed under ketamine anesthesia (Zanos et al., 2018). (*R,S*)-ketamine's mode of action does not depend on the $GABA_A$ receptor (Antkowiak, 1999).

Acetylcholine. (*S*)- and (*R*)-ketamine antagonize the nicotinic acetylcholine receptors (nAChR) via its metabolites (*R,S*)-norketamine, (*R,S*)-dehydronorketamine, (*2S,6S*)-hydroxynorketamine, and (*2R,6R*)-hydroxynorketamine (Tyler et al., 2017). Regarding the muscarinic acetylcholine receptors (mAChR), (*R,S*)-ketamine antagonizes $mAChR_1$ with very weak affinity [45 μM] but has negligible affinity for $mAChR_2$ [294 μM] and $mAChR_3$ [246 μM] (Zanos et al., 2018). (*R*)-ketamine inhibits acetylcholine release in the (Lydic & Baghdoyan, 2002). This reduction in acetylcholine release may be mediated by the NMDA receptors (Kohrs & Durieux, 1998).

Opioid Receptors. Ketamine has affinity as an agonist to the mu opioid receptors [(*R*)=28 μM, (*S*)=11 μM, (*R,S*)=2.5 μM], the delta opioid receptors [(*R*)=130 μM, (*S*)=130 μM, (*R,S*)=2.0 μM], and the kappa opioid receptors [(*R*)=100 μM, (*S*)=24 μM, (*R,S*)=4.2 μM] (da Fonseca Pacheco et al., 2014; Hirota et al., 1999). While antagonism of the opioid receptors by naltrexone does not block its subjective effects (Krystal et al., 2006; Tyler et al., 2017), ketamine's pain modulating effects are attenuated with opioid receptor antagonism by naloxone, mu opioid antagonism by clocinnamox, and delta

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opioid antagonism by naltrindole (da Fonseca Pacheco et al., 2014). However, the kappa opioid antagonist norbinaltorphimine does attenuate pain modulation (da Fonseca Pacheco et al., 2014). While withdrawal from ketamine dependence does not typically include opioid-like withdrawal symptoms, naltrexone can help alleviate cravings for ketamine (Garg et al., 2014). This elucidates the role of opioid receptor agonism in ketamine's effects.

Sigma Receptors. Robson et al. (2012) found that (*R,S*)-ketamine had weak affinity for the sigma-2 receptor [26.30 ± 2.98 μM] and very weak affinity for the sigma-1 receptor [139.60 ± 6.13 μM]. The sigma antagonist NE-100 but not BD104 attenuated the facilitating effect of (*R,S*)-ketamine on neurite outgrowth stimulated by nerve growth factor (Robson et al., 2012). Neither sigma antagonist blocked (*R,S*)-ketamine's behavioral effects (Robson et al., 2012). Together this shows that the sigma receptors may be crucial to the plasticity effects of ketamine.

Prolactin. In humans, (*R,S*)-ketamine increases prolactin in a dose-dependent manner (Hergovich et al., 2001; Krystal et al., 1994).

TAARs. No studies were found regarding ketamine's effects on TAARs. (*R,S*)-ketamine had no effect on cAMP levels at clinical doses (Hirota et al., 1999).

Ibogaine Pharmacology

Ibogaine is an indole alkaloid from the shrub *Tabernathe iboga* found in West Africa (Popik et al., 1995). Ibogaine has the chemical formula $C_{20}H_{26}N_2O$ (National Center for Biotechnology Information, 2021g). The metabolite noribogaine is responsible for much of ibogaine's effects (Zubaran, 2000). In rats, noribogaine administration has similar anti-addictive properties (Glick, Pearl, et al., 1997).

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Dose and Pharmacokinetics

A typical therapeutic dose of ibogaine is 6–30 mg/kg oral (Alper, 2001). However, Schep et al. (2016) suggest, based on a review of the literature, that a physiologically safe dose of ibogaine in humans is much lower at 0.87 mg/kg oral. The physiological risks posed by ibogaine are further discussed in Chapter 5.

The half-life of ibogaine is approximately 7 hours in humans (Wasko et al., 2018). Its effects, however, are much longer as ibogaine is metabolized in the liver to noribogaine, which is also psychoactive with a half-life of 27.6–49.7 hours (Glue, Lockhart, et al., 2015). This leads to a duration of effects typically lasting more than 24 hours (Wasko et al., 2018). Ibogaine is lipophilic and tends to concentrate in fat within an hour of administration rather than remaining in blood plasma (Wasko et al., 2018).

Like MDMA, ibogaine is metabolized by the CYP2D6 enzyme, for which 7%–10% of Caucasians are genetically deficient (Mash et al., 2000; J. Yang et al., 2006). In poor metabolizers, noribogaine plasma concentration is approximately twice as high as in normal metabolizers given the same dose (Glue, Winter, et al., 2015). Thus, Glue, Winter, et al. suggest screening for *CYP2D6* poor metabolizers before ibogaine treatment and administering at least half the typical dose. There is also some evidence from animal models that ibogaine may be more bioavailable in females than males, therefore requiring a lower dose in females (Pearl et al., 1997).

Impacts on Neurotransmission

Ibogaine and noribogaine generally have weak affinities for the receptor targets commonly associated with psychoactive drug effects (Wasko et al., 2018). Because both ibogaine and noribogaine have psychopharmacological effects, receptor affinities are

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provided for both compounds. For brevity, the affinity of ibogaine is listed prior to the affinity of noribogaine in brackets.

Serotonin. Ibogaine and noribogaine have negligible affinity for the serotonin receptors, with affinities >100 μM for all but 5-HT_{2A} [16 μM, >100 μM] and 5-HT_3 [2.6 μM, >100 μM] (Wasko et al., 2018). Both ibogaine and noribogaine act as SERT inhibitors, but noribogaine has a much stronger affinity for SERT [4.1 μM, 0.57 μM] (Wasko et al., 2018). SERT inhibition by noribogaine leads to elevated extracellular serotonin (Mash et al., 1995).

Dopamine. Ibogaine and noribogaine have little affinity for the dopamine receptors [D_1 and D_2: >10 μM, >10 μM; D_3: 70 μM, >100 μM] (Wasko et al., 2018). Ibogaine and noribogaine act as DAT inhibitors with moderate affinity [2.0 μM, 2.0 μM] (Wasko et al., 2018). However, rather than increasing extracellular dopamine due to DAT inhibition, ibogaine decreases extracellular dopamine by 50% while increasing the presence of dopamine metabolites in rats (Baumann et al., 2000, 2006; Maisonneuve et al., 1992). Instead, this reduction in dopamine release in the striatum is due to NMDA antagonism by ibogaine (Glick, Maisonneuve, et al., 1997).

Norepinephrine. Ibogaine has negligible affinity for the alpha-1, alpha-2, and beta-1 adrenergic receptors [>100 μM] (Deecher et al., 1992).

Glutamate. Ibogaine and noribogaine are NMDA antagonists [3.1–9.8 μM, 15–38 μM], which explains ibogaine's dissociative effects that are purported to be similar to ketamine (Wasko et al., 2018). In combination with ibogaine's kappa opioid agonist properties, NMDA antagonism is essential to ibogaine's anti-addictive properties (Glick, Maisonneuve, et al., 1997). In the cortex, ibogaine has very strong affinity for PCP_2

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[0.01–0.05 μM] and moderate affinity for PCP_1 [2–4 μM] (Itzhak & Ali, 2006). However, in the cerebellum, ibogaine had no significant affinity for PCP_2 and moderate affinity for PCP_1 [2–4 μM].

GABA. Ibogaine has negligible affinity for the $GABA_A$ receptor [>100 μM] (Popik et al., 1995).

Acetylcholine. Ibogaine is a noncompetitive antagonist of the $nAChR_{\alpha1\beta1}$ and $nAChR_{\alpha3\beta4}$ receptors with strong affinity [0.460 μM] (Wasko et al., 2018). Because these receptors mediate acetylcholine release, ibogaine causes a 70% reduction in acetylcholine release (Mah et al., 1998; Schneider et al., 1996). While ibogaine also inhibits acetylcholinesterase (AChE), the enzyme that breaks down acetylcholine, this effect has been deemed so small as to be "physiologically negligible" (Alper, Reith, et al., 2012, p. 879). Ibogaine has moderate affinity for $mAChR_3$ [12.5 μM] and very low affinity for $mAChR_1$ [31.6 μM] and $mAChR_2$ [50.1 μM] (Popik et al., 1995). Pretreatment with the muscarinic acetylcholine receptor inhibiter atropine prevents the autonomic arousal triggered by ibogaine in animal models, indicating mAChR agonism by ibogaine (Popik et al., 1995).

Opioid Receptors. Ibogaine and noribogaine have strong affinity for the kappa opioid receptors [2.2 μM, 0.61 μM], acting as agonists (Wasko et al., 2018). This kappa opioid agonism, in combination with its NMDA antagonism, is essential to ibogaine's anti-addictive properties (Glick, Maisonneuve, et al., 1997). With the mu opioid receptors ibogaine acts as an antagonist with moderate affinity [2.0 μM], while noribogaine acts as a partial agonist with strong affinity [0.68 μM] (Wasko et al., 2018). For the delta opioid

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receptors, noribogaine has some affinity [5.2 μM], while ibogaine has very weak affinity [>10 μM] (Wasko et al., 2018).

Sigma Receptors. Ibogaine has strong affinity for the sigma-2 receptor [0.40–0.19 μM], while noribogaine has weak affinity [5.2–19 μM] (Wasko et al., 2018). Similarly, ibogaine has moderate affinity for the sigma-1 receptor [2.5–8.5 μM], while noribogaine has weak affinity [11–15 μM] (Wasko et al., 2018). Ibogaine was shown to inhibit the binding of the sigma-1 receptor ligand [^{3}H]pentazocine (Popik et al., 1995).

Prolactin. Finally, ibogaine increases circulating prolactin in rats (Baumann et al., 2000, 2006).

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Summary and Comparison

Summary Table 2 describes the effects of the eight psychedelics studied on neurotransmission. In each cell, the effects on different aspects of neurotransmission are described using symbols as follows:

$D_2\uparrow$	Receptor agonism (D_2).
$D_2\times$	Receptor antagonism (D_2) or transporter inhibition (e.g., NET ×).
α_1	Receptor affinity, but no known agonism or antagonism (α_1 in this case)
NET ↵	Reversal of transporter
NET ×	Inhibition of transporter
NET +	Facilitation of transporter
5-HT ↑	Increase in neurotransmitter concentration
5-HT ↓	Decrease in neurotransmitter concentration
-	No change.
*	Theoretical effect that is reasonably inferred but has not yet been validated by empirical research.

Receptor affinity or strength of effect on transporters and neurotransmitter concentration is indicated with the gradations below. For receptor affinities, there is approximately one order of magnitude difference between each of the following gradations:

$D_1\uparrow$	Strong affinity or strong effect (bolded).
$D_1\uparrow$	Moderate affinity or moderate effect (normal text weight).
$D_1\uparrow$	Weak affinity or small effect (italicized and greyed).
~~*SERT*~~	Negligible affinity or effect (italicized, greyed, and strikethrough).

Summary Table 2

Psychedelic Impacts on Neurotransmission

System	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	(*R*)-ket.	(*R,S*)-ket.	(*S*)-ket.	Ibogaine
MAO				MAO-A ×	**MAO ×**					
Serotonin	~~*SERT*~~ **5-HT$_{1A}$↑** **5-HT$_{2A}$↑** 5-HT$_{2C}$↑ 5-HT$_{2B}$↑	~~*SERT*~~ **5-HT$_{1A}$↑** **5-HT$_{2A}$↑** 5-HT$_{2C}$↑ *5-HT$_{2B}$*↑	*SERT* × 5-HT ↑/- **5-HT$_{2A}$↑** **5-HT$_{2C}$↑** 5-HT$_{1A}$↑ *5-HT$_{2B}$*↑	~~*SERT*~~ **5-HT$_{1A}$↑** 5-HT$_{2A}$↑ 5-HT$_{2C}$↑ *5-HT$_{2B}$*↑	*SERT* ×$^{\beta}$ 5-HT ↑ **5-HT$_{1A}$↑*** 5-HT$_{2A}$↑ 5-HT$_{2C}$↑* *5-HT$_{2B}$*↑*	**SERT ↲** **5-HT ↑** 5-HT$_{2B}$↑ *5-HT$_{2A}$* × *5-HT$_{x}$*	SERT × **5-HT ↑** 5-HT$_{1B}$↑^{a}	SERT × 5-HT ↑/- 5-HT$_{1A}$↑ *5-HT$_{2}$* ↑ *5-HT$_{3}$* ×	SERT × 5-HT ↑ *5-HT$_{2}$* ↑	**SERT ×^{N}** **5-HT ↑** 5-HT$_{3}$ *5-HT$_{2A}$*
Dopamine	~~*DAT*~~ D$_{2}$↑ D$_{1}$↑ D$_{3}$↑	~~*DAT*~~ D$_{2}$↑ *D$_{3}$*↑ *D$_{1}$*↑	~~*DAT*~~ DA ↑/↓/- *D$_{2}$*↑ *D$_{3}$*↑ *D$_{1}$*↑	~~*DAT*~~ DA ↑/- *D$_{2}$*↑ *D$_{1}$*↑ *D$_{3}$*↑	*DAT* × DA ↑/- *D$_{2}$*↑* *D$_{1}$*↑* *D$_{3}$*↑*	DAT ↲ DA ↑	*DAT* - *DA* -	DAT ×/- DA ↑/- D$_{2}$↑ *D$_{1}$*↑ *D$_{5}$*↑ *D$_{3}$* - *D$_{4}$* -	DAT × DA ↑ **D$_{2}$↑**	DAT × **DA ↓** *D$_{1}$* *D$_{2}$* *D$_{3}$*
Norepinephrine	~~*NET*~~ NE ↓/↑ **α$_{2A}$↑** α$_{1A}$↑	~~*NET*~~ *NE* - α$_{2A}$↑ *α$_{1A}$*↑ β$_{x}$↑	*NET* × NE ↑/↓ α$_{2A}$↑ *α$_{1A}$*↑	~~*NET*~~ *α$_{2A}$*↑ *α$_{1A}$*↑	NET × NE ↑/- *α$_{2A}$*↑* *α$_{1A}$*↑*	**NET ↲** **NE ↑**	~~*NET*~~ *NE* ↑	NET ×	~~*NET*~~ *NE* ↑	~~*α$_{1}$*~~ ~~*α$_{2}$*~~ ~~*β$_{1}$*~~
Glutamate	Glu ↑	Glu ↑*	Glu ↑/↓	Glu ↑*	Glu ↑*	**Glu ↑**	NMDA × AMPA ↑^{b} PCP$_{x}$	Glu ↑ **NMDA ×** AMPA ↑^{b} PCP$_{x}$	**NMDA ×** PCP$_{x}$	**NMDA ×** **PCP$_{2}$** PCP$_{1}$
GABA	*GABA* -	*GABA* -			GABA ↓/↑	GABA ↑		GAT × GABA -/↑ ~~*GABA$_{A}$*~~		~~*GABA$_{A}$*~~

Summary Table 2

Psychedelic Impacts on Neurotransmission, Continued

System	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	(*R*)-ket.	(*R,S*)-ket.	(*S*)-ket.	Ibogaine
Acetylcholine	ACh ↑/-	ACh -/↓		ACh ↓/-	ACh ↓/-*	ACh ↑	ACh ↓ nAChR$_x$ ×		nAChR$_x$ ×	**ACh ↓** *AChE* × **nAChR$_{α3β4}$** × **nAChR$_{α1β1}$** × *mAChR$_3$*↑ ~~*mAChR$_1$*~~ ~~*mAChR$_2$*~~
								mAChR$_1$↑ ~~*mAChR$_2$*~~ ~~*mAChR$_3$*~~		
Opioid system				β-endorphin ↑	β-endorphin ↑*	δ ↑ ≠	*μ* ↑ *κ* ↑ *δ* ↑	**μ ↑** **κ ↑** **δ ↑**	μ ↑ κ ↑ *δ* ↑	**μ ↑^{N}**/↓ **κ ↑^{N}** δ^c
Sigma receptors				*σ$_1$*↑	*σ$_1$*↑*	**σ$_1$↑** **σ$_2$↑**		σ$_2$ *σ$_1$*		**σ$_2$** σ$_1$
Histamine	*H$_1$*	*H$_1$*	*H$_1$*	H$_1$	H$_1$*	*H$_1$* ×				
Adrenal steroids	*Cort* -	*Cort* -/↑	Cort ↑*	Cort ↑	Cort ↑*	**Cort ↑** DHEA ↑	Cort ↑	Cort ↑		
Hormones	Oxt ↑*	Oxt ↑*	Oxt ↑*	Oxt ↑* Prolac ↑	Oxt ↑* Prolac ↑*	**Oxt ↑** Vaso ↑ Prolac ↑		Prolac ↑		Prolac ↑
TAARs	TAAR$_1$	*TAAR$_1$* **cAMP ↑**	*TAAR$_1$*↑	TAAR$_1$↑ **cAMP ↑**	TAAR$_1$↑* **cAMP ↑***	**TAAR$_1$↑** **cAMP ↑**		*cAMP* -		

Note. Symbol key on page 58. SERT = serotonin transporter; 5-HT = serotonin; 5-HT$_x$ = serotonin receptor *x*; DAT = dopamine transporter; DA = dopamine; D$_x$ = dopamine receptor *x*; NET = norepinephrine transporter; NE = norepinephrine; Cor = cortisol; DHEA = dehydroepiandrosterone; α$_x$ = alpha adrenergic receptor *x*; β$_x$ = beta adrenergic receptor *x*; GABA = gamma-aminobutyric acid; GABA$_x$ = GABA receptor *x*; GAT = glutamate transporter; Glu = Glutamate; NMDA = *N*-Methyl-*D*-aspartic acid receptor; PCP$_x$ = phencyclidine receptor *x*; ACh = acetylcholine; AChE = acetylcholinesterase enzyme; nAChR$_x$ = nicotinic

Summary Table 2

Psychedelic Impacts on Neurotransmission, Continued

acetylcholine receptor *x*; $mAChR_x$ = muscarinic acetylcholine receptor *x*; σ_x = sigma receptor *x*; δ = delta opioid receptor; κ = kappa opioid receptor; μ = mu opioid receptor; H_x = histamine receptor *x*; Oxt = oxytocin; Vaso = vasopressin; Prolac = prolactin; $TAAR_x$ = trace amine-associated receptor *x*; cAMP = cyclic adenosine monophosphate; MAO = monoamine oxidase; MAO-A = MAO subtype A.

[β] Due to beta-carbolines commonly used as MAO inhibitors in ayahuasca brews.

[N] Effect is due primarily to noribogaine, ibogaine's active metabolite.

[a] Agonism is due to increased serotonin binding rather than direct effects of ketamine.

[b] Due to ketamine metabolites

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Chapter 4: Neuroscience

This chapter is intended to be a brief introduction to the neuropsychology of psychedelics with an emphasis on large-scale processes. The fundamental neuroscience of psychedelics is presented by progressing from the neuron scale to the brain-network scale, then to the whole-body scale. Finally, the neuroscience of fear and anxiety changes from psychedelics is described, given the importance of these processes in clinical applications of psychedelics. A large set of post hoc exclusions were made to limit the scope of this chapter:

- **Non-Clinically Relevant Neuroscientific Findings:** In general, findings in neuroscience were judged for their relevance to clinical psychology applications and excluded when there was no generalizable translation to practice.
- **Most Animal Studies:** When animal studies were determined to contribute significant clinical insight that applies to humans, they were included in this section. Otherwise, animal studies are excluded.
- **Neuroimaging Studies:** Only neuroimaging studies related to the entropic brain or connectome harmonics were included.
- **EEG and MEG Studies:** EEG and MEG studies were excluded given the availability of studies using more advanced neuroimaging techniques such as fMRI that were deemed more clinically useful.
- **Event-Related Potential:** Event-related potential studies were excluded because they relate primarily to acute sensory changes and typically rely on EEG measurements. Most papers with the phrases ‘mismatch negativity,’ ‘oddball paradigm,’ or ‘evoked response’ were excluded for this reason.

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- **Prepulse Inhibition, Startle Response, and Latent Inhibition:** While prepulse inhibition is modified in schizophrenia, studies of this phenomenon with psychedelics are not particularly relevant to clinical applications and were therefore excluded.
- **Binocular Rivalry:** Studies of binocular rivalry with psychedelics were also deemed not clinically relevant.
- **Sleep and Dreaming (semi-excluded):** Studies examining the impact of psychedelics on sleep are excluded. Some studies on dreaming and psychedelics are included in other chapters.
- **Sensory Processing (semi-excluded):** While the impacts of psychedelics on visual, auditory, olfaction, sensorimotor, and interoceptive processing were searched, these topics were not covered in full. Sensory processing changes were included only when judged to have translational clinical relevance. In most cases, included sensory processing studies were integrated into Chapter 6 "Phenomenology," or Chapter 8 "Neuropsychology and Cognition," rather than neuroscience. Therefore, this section has no specific sections describing sensory processing changes.

With these exclusions, the chapter following represents a general introduction to psychedelic neuroscience rather than an exhaustive review. The excluded literature certainly contains translatable findings, representing fertile grounds for further research.

Neuroplasticity

Neuroplasticity refers to "the brain's ability to modify, change, and adapt both structure and function throughout life and in response to experience" (Voss et al., 2017, p.

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1). Neuroplasticity is important therapeutically because changes in personality and psychopathology are modulated by changes in brain structure (Barsaglini et al., 2014; Garland & Howard, 2009; Hebb, 1949; Krystal, 2007; Solomon & Siegel, 2017). Until recently, it was believed that neural structure formed mainly during childhood "critical periods" of development in response to sensory experiences. During these early developmental periods, GABAergic neural networks form and are locked in place by plasticity inhibitors and molecular brakes. The GABAergic networks themselves are inhibitory and constrain plasticity (Fagiolini & Hensch, 2000). Therefore, downregulating these GABAergic cortical inhibition systems can induce neuroplasticity.

Perineuronal nets (PNNs) also inhibit brain plasticity by surrounding the cell bodies of neurons and their dendrites during early adulthood as the brain matures (Difei & James, 2012). While most PNNs form surrounding reticular neurons, there are also PNNs in the amygdala that serve to preserve fear memories (Gogolla et al., 2009). Interestingly, individuals with schizophrenia show PNN deficits that may be mechanistically related to symptoms (Bitanihirwe & Woo, 2014).

While neuroplasticity benefits early development and adult adaptation, it can also have negative effects. After spinal cord injury, neuroplasticity helps the process of recovering locomotor function but also results in alterations to the autonomic nervous system that can produce pain and organ dysfunction (A. Brown & Weaver, 2012). In aging rats, the loss of cortical GABAergic inhibition results in increased plasticity in response to auditory tones, which leads to distorted auditory representations (Cisneros-Franco et al., 2018). However, rather than these plastic changes being persistent, these

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distorted auditory representations decayed rapidly. Thus, in older adults, neuroplastic changes may not persist and may be disorienting due to a lack of stability.

Mechanisms

Voss et al. (2017) describe how sensory experiences can result in neuroplasticity. Enriched sensory environments prolong critical period plasticity and stimulate dendritic growth. Conversely, sensory experience deficits and prolonged unstructured noise can delay the onset of critical periods and maturation of cortical neurons. In adults, prolonged exposure to noisy environments can also trigger plasticity, leading to degradation of the auditory systems.

Next, neuromodulator systems mediate brain plasticity during juvenile critical periods and adulthood (Kirkwood, 2007; Voss et al., 2017). Neuromodulation can induce plasticity by increasing neuronal excitability, improving the signal-to-noise ratio, and controlling the propagation of activity in the cortex (Kirkwood, 2007). Through these mechanisms, modulation of the norepinephrine, dopamine, and cholinergic systems can all increase plasticity (Voss et al., 2017).

Neurotrophic factors can also modulate neuroplasticity. Brain-derived neurotrophic factor (BDNF) is known to increase axon branching, synaptogenesis, spinogenesis, and dendric growth (Aguado et al., 2003; Alsina et al., 2001; Haraguchi et al., 2011; Sasahara et al., 2007). Exercise-induced neuroplasticity is modulated in part by BDNF (Knaepen et al., 2010; P. Müller et al., 2020). *BDNF* expression has both antidepressant effects and anxiogenic effects, the latter due to BDNF signaling stress-induced amygdala plasticity (Govindarajan et al., 2006; Levy et al., 2018). Glial cell line-derived neurotrophic factor (GDNF) is related to depression etiology and antidepressant

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efficacy, though the nature of this relationship is not yet clear (Levy et al., 2018). Finally, the activity-regulated cytoskeletal gene (*Arc*) encodes a critical protein for memory consolidation that regulates synaptic strength and plasticity (Korb & Finkbeiner, 2011). Increased expression of *Arc* results in increased neural spine density.

Neuroplasticity from Psychedelics

LSD, DMT, and Ketamine. Ly et al. (2018) found that LSD, DMT, and ketamine robustly increase neurogenesis and spinogenesis in vitro and in vivo. These changes were associated with an increased number of synapses and increased functional activity. The mechanism of these changes was found to be through stimulation of 5-HT_{2A}, mTOR, and TrkB pathways. These findings give a cell-level mechanism for psychedelics promoting large-scale network plasticity across the cortex.

LSD. Hutten et al. (2020) found that low doses of LSD (5 and 20 μg) significantly ($p<.05$) increased plasma BDNF levels in humans. This effect was seen with 5 μg LSD at 4 and 6 hours but not 2 hours following administration [$n=10$]. With 20 μg LSD, significance was reached only at 6 hours following administration [$n=8$]. No significant increase in plasma BDNF was seen with 10 μg LSD [$n=9$], though there was a trending increase at 4 and 6 hours (4 hr: $p=.05$, however, 95% CI ranged to less than zero, indicating non-significance).

Psilocybin. Catlow et al. (2013) found that low-dose psilocybin (0.1 mg/kg) increased hippocampal neurogenesis and enhanced fear extinction in mice. High-dose psilocybin (0.5 mg/kg), however, decreased hippocampal neurogenesis and did not result in enhanced fear extinction compared to placebo.

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Ayahuasca. Morales-García et al. (2017) found that the alkaloids contained in the *B. caapi* vine, the common MAO inhibitor source in ayahuasca, stimulate neurogenesis in mouse neurons in vitro. The findings regarding the effect of ayahuasca on BDNF levels were mixed in an RCT by de Almeida et al. (2019) involving healthy normals [n=45] and those with treatment-resistant depression [n=28]. At 48-hour follow-up, there were significantly higher BDNF levels in the ayahuasca group than placebo (p=.03, d=0.03). However, at baseline, there was also higher BDNF in the ayahuasca group than placebo in a result that approached significance (p=.058). When visually examining the data (p. 7, Figure 4), there appears to be a downward trend in BDNF levels between baseline and follow-up in both groups. However, no statistical analysis of this trend was performed. Together, this raises the possibility that ayahuasca could have decreased BDNF. Further study is needed with care to match baseline BDNF in control and treatment groups.

MDMA. In adolescent rats, repeat MDMA administration decreased neurogenesis in the dentate gyrus of the hippocampus (Catlow et al., 2010). In neonate rats, 4 days of MDMA exposure increases BDNF in the occipital cortex but not the hippocampus or striatum (Piper et al., 2009). Ádori et al. (2010) saw reduced BDNF in the parietal cortex 1 day following MDMA, then a "robust increase" 8 weeks later, followed by a return to baseline after 12 weeks. Angelucci et al. (2010) found that recreational MDMA users had increased BDNF serum levels. Accordingly, Abad et al. (2016) saw sustained *Arc* and *BDNF* overexpression following repeat MDMA administration in mice. They suggest that hippocampal injury from MDMA may be due to this overexpression of *BDNF*. In rats, Petschner et al. (2018) found that a single dose of MDMA increased the expression of genes related to "dendrite development," "regulation of synaptic plasticity," and "positive

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regulation of synapse assembly" 3 weeks later. They did not, however, find alterations in *BDNF* gene expression.

Ketamine. L. S. Garcia et al. (2008) found that 14 days of daily 5, 10, or 15 mg/kg ketamine did not affect hippocampal BDNF levels in rats. Fraga et al. (2013) saw decreased BDNF levels in rats' prefrontal cortex (PFC), amygdala, striatum, and hippocampus 6 hours following 25 mg/kg ketamine. BDNF levels were also decreased 1 hour following 25 mg/kg ketamine in the hippocampus but not the other brain regions. In both these studies, however, ketamine doses were much higher than typically used for depression treatment in humans. Henderson et al. (2016) note that higher anesthetic doses of ketamine do not activate mTOR in animals and thus do not activate the mTOR-associated positive feedback loop that otherwise increases BDNF with lower doses.

In BDNF knockout mice, ketamine's synaptogenic effects in the medial PFC were impaired, as were its antidepressant effects based on the forced swim test (R.-J. Liu et al., 2012). This indicates that BDNF signaling has a potentially crucial role in the neuroplastic and antidepressant effects of ketamine. Sigma receptor antagonism also blocks the facilitating effect of (*R,S*)-ketamine on neurite outgrowth stimulated by nerve growth factor in mice (Robson et al., 2012).

In humans, Duncan et al. (2012) saw increased plasma BDNF following a single 0.5 mg/kg ketamine infusion for treatment-resistant depression [*N*=30]. BDNF levels were proportional to early sleep slow-wave activity, a marker of plasticity, in those who responded to treatment but not those who did not. In addition, Gálvez et al. (2017) saw increased neuroplasticity following a course of eight 100 mg intranasal ketamine treatments for depression based on a non-invasive nerve stimulation paradigm [*N*=3].

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Ibogaine. D.-Y. He et al. (2005; 2006) found that ibogaine 40 mg/kg increased mRNA expression of GDNF in both mice and rats. They also found that injection of GDNF into the ventral tegmental area (VTA) of rats resulted in alcohol reduction similar to what is induced by ibogaine. Injection of GDNF-neutralizing antibodies into the VTA blocked the alcohol-reducing properties of ibogaine. This suggests that the GDNF pathway may mediate ibogaine's anti-addiction effects.

Confirming the results of D.-Y. He et al., Carnicella et al. (2010) found that noribogaine also results in increased mRNA *GDNF* expression in the VTA of rats. 18-MC, however, while having similar anti-addictive properties to ibogaine, did not increase *GDNF* expression. Marton et al. (2019) saw dose-dependent increases in *GDNF* and *BDNF* expression 24 hours but not 3 hours following ibogaine in rats. *GDNF* expression was increased in the VTA and the substantia nigra (SN), while *BDNF* expression increased significantly in the SN, nucleus accumbens, and prefrontal cortex. *BDNF* expression also increased significantly in the VTA, but only for the higher dose of ibogaine.

Metaplasticity and the Reopening of Critical Periods

In the field of psychedelics, findings of psychedelic-induced neuroplasticity are often over-extrapolated to imply that this plasticity is responsible for therapeutic effects (personal communication, Ted Sawyer, July 26, 2022). Stimulant drugs such as cocaine also readily induce neuroplasticity despite lacking the same therapeutic effects shown with psychedelics (Capilla-Gonzalez & Hernandez-Rabaza, 2011; Kalivas, 2007; Nyberg, 2014). However, there is emerging evidence that psychedelics may have metaplastic effects that are not shared with other psychoactive substances, though much of this

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research is yet to be published (personal communication, Ted Sawyer, July 26, 2022). Metaplasticity is a change in the ability of synaptic plasticity to occur following synaptic or cellular activity, such as the administration of a drug (W. C. Abraham & Bear, 1996).

Metaplasticity has been demonstrated with MDMA. Nardou et al. (2019) found that a single dose of MDMA produced a metaplastic change facilitating oxytocin-mediated synaptic plasticity. This oxytocin-mediated plasticity was linked to reopening the critical period for social reward learning in mice. The same research group has since found that LSD, psilocybin, ketamine, and ibogaine also reopen the critical period for social reward learning in mice (Dölen, 2021; publication in preparation by Nardou et al.). The duration of this critical period reopening in mice was proportional to the duration of acute drug effects, lasting 48 hours with ketamine, 2 weeks with psilocybin and MDMA, 3 weeks with LSD, and up to 4 weeks with ibogaine. This finding is important in the clinical application of psychedelics. It implies that enriching social experiences in the days and weeks following psychedelics may contribute to their therapeutic impact.

Neuroprotection

DMT. DMT has neuroprotective properties due to sigma-1 receptor agonism (Frecska et al., 2013). Sigma-1 activation is known to be protective in cases of hypoxia and neurotoxicity. In line with this, DMT reduces the size of ischemic lesions in rats (Nardai et al., 2020).

Ayahuasca. Ayahuasca is neuroprotective against the toxic agent 6-OHDA in vitro, improving cell vitality and preventing neuronal damage (Katchborian-Neto et al., 2020).

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Ketamine. A review, Bell (2017) found ketamine to be neuroprotective in stroke, neurotrauma, subarachnoid hemorrhage, and status epilepticus. Ketamine prevents excitotoxicity through NMDA antagonism and reduce neuroinflammation. Ketamine also reduces cell death and apoptosis by upregulating B-cell lymphoma 2 expression. Finally, ketamine exhibits antiplatelet effects, helping to disrupt the process of microthrombosis that occurs following traumatic brain injury (TBI) and subarachnoid hemorrhage. Microthrombosis is the aggregation of platelets, blocking cerebral microvessels and creating small pockets of local hypoxia.

Entropic Brain and Connectome Harmonics

Carhart-Harris et al. (2014) developed a novel theory of consciousness based on their neuroimaging of psychedelic states, beginning with a psilocybin fMRI study described by Muthukumaraswamy (2013) [*N*=15, male, age *M*=34.5, race N/R]. The model, called the entropic brain, examines the amount of disorder present in the brain. They argue that the primary states of consciousness, such as those induced by psychedelics, are associated with elevated entropy states in the brain. Transitioning from normal waking consciousness to the psychedelic state involves passing a point of criticality in brain states. Criticality, a term borrowed from complex systems theory, involves a major transition in brain system dynamics where the “repertoire of functional connectivity motifs” drastically changes. The authors further suggest that ordinary waking consciousness suppresses entropy, leading the brain to operate below this critical point. They posit that the entropy-suppression mechanism is the default mode network (DMN), and that psilocybin causes decoupling between the DMN and medial temporal lobes leading the brain to transition beyond criticality into the higher-entropy state. The

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authors propose that this theory can be tested by examining brain entropy during psychosis and rapid eye movement (REM) sleep.

Several years following the initial development of the entropic brain theory, Atasoy et al. (2016) developed a new method of brain MRI data analysis called connectome harmonics. In this method, the Fourier transform is used to derive the natural harmonic oscillations of the brain based on structural connectivity mapped by diffusion tensor imaging (DTI). They found this technique to be predictive of resting-state network activity as measured with fMRI, providing empirical validation for the model. Atasoy et al. (2017) then compared fMRI data from people given LSD to connectome harmonics predictions derived from DTI [N=12]. As expected, LSD led to an expanded repertoire of brain states, matching the predictions of the entropic brain model. When the fMRI data was examined using "connectome-harmonic-decomposition," they found that "LSD alters the energy and power of individual harmonic brain states in a frequency-selective manner" (p. 1). Further, they observed that "the frequency distribution of the active repertoire of brain states under LSD closely follows power-laws indicating a reorganization of the dynamics at the edge of criticality" (p. 1). In other words, LSD causes the brain to operate in a different harmonic state than normal waking consciousness, which allows for different patterns of thinking to emerge. This harmonic state is within the set of states predicted by the connectome-harmonic-decomposition of DTI data, thus supporting connectome harmonics theory. Finally, it appears that the theories of the entropic brain and connectome harmonics converge in their explanation of the brain states seen under psilocybin and LSD.

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In a further theoretical development, Carhart-Harris et al. (2019) propose a unified model of psychedelic brain action called relaxed beliefs under psychedelics (REBUS) and the anarchic brain. This model links the increase in brain entropy seen with psychedelics to "relax[ing] the precision of high-level priors or beliefs, thereby liberating bottom-up information flow" (p. 316; also see Pink-Hashkes et al., 2017). Here, "bottom-up" refers to information taken in directly through the senses, while "top-down" or "high-level priors" refer to the influence of prior experiences upon perception. Regarding the therapeutic effectiveness of psychedelics they write, "psychedelics work to relax the precision weighting of pathologically overweighted priors underpinning various expressions of mental illness." Thus, in the REBUS model, psychedelics provide therapeutic impact by reducing the influence of pathological information filtering (priors), allowing for novel experience through novel bottom-up experience. This novel experience allows alternate priors to develop that can support healthy top-down processing of experiences and emotions. The authors further link this process to the insights reputedly gained through psychedelics. They hypothesize that transitioning the brain beyond criticality into a new repertoire of states, with relaxed prior interpretations of internal and external phenomena, can lead to new ways of thinking or insight. This insight is linked to both therapeutic outcomes and the creative process. Finally, the authors support their theory by examining its applicability to phenomena seen with psychosis, hallucinogen-persisting perceptual disorder (HPPD), autism spectrum disorder, and meditation states.

Classical Psychedelics. As mentioned above, both LSD and psilocybin have been shown to increase entropy in the form of brain state repertoire, and these changes match

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predictions of connectome harmonics (Atasoy et al., 2017; Carhart-Harris et al., 2014). Lebedev et al. (2016) also found that increased brain entropy induced by LSD was predictive of increased Openness. Carhart-Harris (2018) reviewed studies of psychedelic effects on brain entropy and found further support for the entropic brain hypothesis with LSD (Atasoy et al., 2017; Lebedev et al., 2016; Schartner et al., 2017), psilocybin (Tagliazucchi et al., 2014), and ayahuasca (Viol et al., 2017). Notably, Carhart-Harris was an author on all these papers except one (Viol et al., 2017). Since then, four additional studies have been confirmatory of the entropic brain hypothesis with LSD (Barnett et al., 2020; Girn et al., 2020; Pallavicini et al., 2019) and psilocybin (Barnett et al., 2020; Lord et al., 2018; Pallavicini et al., 2019).

Atasoy et al. (2018) present evidence that LSD and psilocybin share common connectome harmonic signatures, supporting a shared neurophenomenology between the two substances. Lord et al. (2018) saw that while increasing brain entropy, psilocybin also biased brain activity toward global processing at the expense of local network activity. Varley et al. (2019) found that both LSD and psilocybin increased the fractal dimension of functional connectivity networks. *Fractal dimension* is a novel measure developed by Varley et al. that "provides insights into the criticality of the psychedelic state, as well as providing a measure of 'complexity' that is related to but distinct from, the entropic measures" (p. 6). The finding of increased fractal dimension with LSD and psilocybin implies that these drugs move brain function across the point of criticality into a more complex realm of neurophenomenology. Varley et al.'s finding is consistent with entropic and connectome harmonics theories. They also found that LSD significantly increased the fractal dimension of the BOLD time-series, while psilocybin showed a

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trend in the same direction. Finally, Girn et al. (2020) found evidence for a "functional hierarchy" of brain activity that is flattened under LSD, in line with the predictions of REBUS.

Ketamine. Schartner et al. (2017) found higher brain entropy and Lempel-Ziv complexity under ketamine (0.25 mg/kg bolus + 0.375 mg/hr) correlated with the strength of phenomenological effects. Consistent with this, Pavllavicini et al. (Pallavicini et al., 2019) and Barnett et al. (Barnett et al., 2020) saw changes in functional connectivity with low-dose ketamine that aligned with the brain entropy hypothesis. Both studies also found differences in alternations in patterns of functional connectivity between ketamine, LSD, and psilocybin.

Gut Microbiome Changes

Given the abundance of serotonergic neurons in the gut, it is unsurprising that classical psychedelics would impact gastrointestinal functioning (Kuypers, 2019). More surprising is the rapid gut microbiome composition changes induced by MDMA, ketamine, and ibogaine (Getachew et al., 2018; Qu et al., 2017; Ridge et al., 2019; C. Yang et al., 2017; Yordanov, 2005). With ketamine, gut microbiome changes have been correlated with a reduction of depressive symptoms (Getachew et al., 2018; Qu et al., 2017; C. Yang et al., 2017). While this research is early, it shows promise in identifying a link between psychedelic-induced gut microbiome changes and improved mental health.

Neuroscience of Fear and Anxiety

LSD. F. Mueller et al. (2017) found that when viewing fearful faces, 100 µg LSD reduced ($p<.05$) activation of the left amygdala and right medial prefrontal cortex [$N=20$, 45% male, age=25–58, race N/R].

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Psilocybin. During angry face discrimination, psilocybin (0.16 mg/kg) decreased connectivity between the amygdala and striatum [*N*=25, age *M*=24.2, university students, race N/R] (Grimm et al., 2018). Conversely, psilocybin decreased connectivity between the amygdala and the frontal pole during happy face discrimination. F. S. Barrett et al. (2020) found a large reduction in left ($p<.00005$; $d=0.83$) and right ($p=.00005$; $d=0.77$) amygdala BOLD response to facial stimuli 1 week following psilocybin administration in healthy volunteers [*N*=12, 58% female, age=18–45, White]. However, this returned to baseline at 1-month follow-up (left: $p=.365$, $d=0.17$; right: $p=.402$, $d=0.15$).

MDMA. In rats, MDMA disrupted the reconsolidation of fear memories (Hake et al., 2019). The research is mixed regarding the impact that acute MDMA has on fear memory extinction in animal models. Two studies found that MDMA enhanced fear memory extinction (Young et al., 2015, 2017). In contrast, one study found that MDMA impeded fear memory extinction (Hake et al., 2019).

In humans, acute MDMA (0.5 or 1.0 mg/kg) produced no significant changes in stress response during a public speaking task [*N*=39, age=18–35, 77% male, 44% Caucasian, 77% African American, 18% Asian, light to moderate past ecstasy use] (Bershad et al., 2017).

Ketamine. Silote et al. (2020) performed a systematic literature review of animal studies examining the effects of ketamine on fear and anxiety [*N*=51]. Results among studies were mixed. In rats, 33% showed an anxiolytic-like effect, 21% showed an anxiogenic-like effect, and 45% found no effect [*n*=42]. However, of the studies that found no effect in rats [*n*=19], 42% used very low doses (<10 mg/kg) that may have been sub-effective, and 32% evaluated anxiety behaviors more than 24 hours following

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administration. In mice, 50% of studies showed an anxiolytic-like effect, 8% showed an anxiogenic-like effect, and 42% found no effect [*n*=24]. The authors also performed an experiment administering (*R*)-ketamine (10, 30, and 80 mg/kg) to rats. They found an acute but not sustained anxiolytic-like effect and no effect on panic-related behaviors.

Prophylactic ketamine administered up to 1 week before an uncontrollable stressor suppresses the stress response in juvenile rats, preventing the typical reductions in social investigation (Amat et al., 2016). The authors found that ketamine pretreatment led to the activation of prelimbic projections to the dorsal raphe nucleus (DRN), preventing serotonergic signaling from the DRN to the basolateral amygdala.

Ketamine has also been shown to disrupt traumatic memory formation in mice when administered 24 hours after exposure to stressor (Ito et al., 2019). However, this finding is contrasted by Clifton et al. (2017), who found no such memory disruption in rats. Ketamine seems to alleviate fear generalization in mice (Asim et al., 2020). Finally, Ju et al. found that long-term ketamine treatment in mice with model PTSD facilitated the extinction of the fear memory and reversed the biological markers of PTSD.

Ibogaine. Ibogaine acutely increases anxiety-related behavior in mice (Popik & Wróbel, 2001).

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Chapter 5: Medical Risks

This chapter examines the medical risks presented by psychedelics and potential medical contraindications. This chapter includes only risks shown to be present in humans and excludes theoretical risks outside of toxicity studies performed with animals. Because the risk literature for LSD, MDMA, and ketamine is extensive, a subset of articles is included for these compounds, with reviews prioritized. This strategy likely resulted in adequate coverage of the potential risks for these compounds but not an extensive summary of cases of adverse outcomes, as was completed for other substances. For this reason, when listing numbers of cases, a '+' sign is used to indicate when a case count is not exhaustive. At the end of this chapter, Summary Table 3 provides an overview of psychedelic safety in different stages of life. Summary Table 4 synthesizes the medical risk factors and contraindications for each psychedelic, while Summary Table 5 describes their long-term risks.

Stage of Life

Pregnancy and Teratogenicity

Most of this section focuses on the teratogenicity of psychedelics. However, it should also be noted that mescaline, LSD, and ibogaine can induce uterine contractions in rats, indicating the potential induce premature birth in humans (E. Costa, 1956; Jaques, 1976; Oreščanin-Dušić et al., 2018). Given the pharmacological similarity of psilocybin to mescaline and LSD, it is likely that psilocybin also has the potential to induce labor.

Mescaline. There are at least two known references to peyote use in pregnancy among indigenous people (Gilmore, 2001; Labate, 2011). No human epidemiological data was found for mescaline teratogenicity. In mice, maternal mescaline injection results

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in two to four times the concentration in fetal brain tissues than in maternal brain tissue (N. S. Shah et al., 1973). Mescaline produced a significant number of congenital abnormalities when injected into pregnant hamsters at 0.45–3.25 mg/kg doses, which are comparable to those taken by humans (Geber, 1967). In pups born from hamster mothers injected with mescaline during pregnancy, birth weight was close to that of controls, but their growth did not keep pace (Geber & Schramm, 1974). However, the 240 mg/kg dose given to these hamsters was far beyond what is typically taken by humans. Litter size was reduced in pregnant hamsters given high doses of mescaline compared to human doses (Hirsch & Fritz, 1981). The average litter size was 6.5 pups with 32 mg/kg mescaline and 10.3 pups for 16 mg/kg mescaline, compared to 12.0 pups for controls.

LSD. A review of human and animal studies [*N*=68] by Dishotsky et al. (1971) found no evidence of teratogenic effects due to LSD. Long (1972) also found no evidence for teratogenicity from LSD. While half of the children identified who were exposed in utero to LSD did show increased chromosome breakage, this effect was transitory, and there were no long-term consequences.

In an updated review, Vritsios and Deltsidou (2005) examined the evidence for teratogenic effects of LSD and found no conclusive evidence for causative teratogenic effects. While they found several studies pointing to congenital anomalies and chromosomal defects, these studies were confounded by the simultaneous use of other substances by the pregnant women studied. The reported congenital anomalies included deformations of limbs, hydrocephaly, neuroblastoma, ocular anomalies, and Fallot tetralogy. Regarding chromosomal defects, Vritsios and Deltsidou described LSD as “at

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best, a weak mutagen, if mutagenic at all" (p. 102). Together this represents weak evidence for teratogenicity, though abstinence during pregnancy is warranted.

Psilocybin. In the indigenous tradition of Maria Sabina, pregnant women are excluded from sacred mushroom ceremonies (Winkelman, 2014). No evidence for teratogenicity of psilocybin was found in a review by White (2001).

DMT. Gardner et al. (2014) administered 60 mg/kg of oral DMT to pregnant rats. They found a much higher rate of skeletal deformity, scoliosis, and cleft palate among offspring of rats given DMT compared to controls. It should be noted that while oral administration of DMT is very inefficient due to fast breakdown by MAO, 60 mg/kg oral is still a very high dose. As discussed below, ayahuasca is unlikely to be a human teratogen at ritual doses. By extension, DMT, as a component of ayahuasca that is also endogenously present in the brain, is also unlikely to have teratogenic properties with a typical dose and low frequency.

Ayahuasca. In Brazilian Santo Daime and União do Vegetal (UDV) ayahuasca churches, pregnant women commonly consume ayahuasca (dos Santos, 2010; Labate, 2011). However, the frequency of ayahuasca ceremonies and the doses administered are typically reduced (dos Santos, 2010). Labate (2011) surveyed several experts in the field about evidence of teratogenicity due to ayahuasca. The consensus was that there were no studies proving that ayahuasca is harmful in pregnancy and no studies proving it is innocuous.

In an editorial letter, dos Santos (2010) briefly reviewed animal studies of harmine and harmaline teratogenicity and concluded that while high and repeat doses of these substances do have an impact on offspring, these findings are unlikely to translate

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to human ritual ayahuasca consumption during pregnancy. They support their argument with research from ayahuasca-using adolescents [*n*=40, 55% male, age *M*=16.52, 79% White, Brazilian], 67.5% of which had been exposed to ayahuasca during pregnancy, who showed no psychiatric or neuropsychological problems compared with matched controls (Doering-Silveira, Lopez, et al., 2005; dos Santos, 2010). In response to dos Santos (2010), C. D. R. Oliveira (2010) highlights that toxicology animal studies use higher doses than typically taken by humans to increase the incidence of negative outcomes and thereby elucidate the potential hazards to humans. They point out that when potential teratogenic effects are found with high doses in animals, the FDA restricts drug prescription to non-pregnant people until more research is performed.

Since the review by dos Santos (2010), C. D. R. Oliveira et al. (2011) found that daily ayahuasca given to rats during pregnancy and lactation resulted in adult offspring with reduced anxiety, social motivation, and seizure threshold. da Motta et al. (2018) also found that daily ayahuasca resulted in increased embryolethality and incidence of soft-tissue and skeletal anomalies in offspring. In both studies, the dose used was comparable to human ayahuasca doses, but it is noted that daily ceremonial ayahuasca use is far from typical. At most, among non-pregnant ceremonial users in Brazil, ayahuasca is used several times weekly, though twice per month is a more typical maximum frequency (dos Santos, 2010). Finally, Andrade et al. (2018) found that ayahuasca caused "significant developmental anomalies in zebrafish embryos," though this effect was mostly seen at the highest dose tested (p. 133).

Together, it appears that there is a teratogenic risk associated with ayahuasca, but it is unclear whether these effects are a concern with typical human doses and frequency.

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Given the long-standing traditional use of ayahuasca in pregnant women with no documented negative outcomes, cautious use of ayahuasca during pregnancy is likely to have reasonably low risk.

MDMA. A systematic literature review by Barenys et al. (2019) found strong evidence for MDMA teratogenicity based on human [*n*=3] and animal studies [*n*=34]. The three epidemiological studies identified, all reporting on one dataset, found that MDMA use during pregnancy impairs infant neuromotor function. This finding was supported by animal studies showing locomotor deficits and impaired special learning in infants born to MDMA-exposed mothers. Mechanistically, two in vitro studies showed that these effects might be due to cytotoxicity.

Ketamine. Administration of ketamine during pregnancy in rodent models can result in neuronal death by apoptosis in the fetal brain that is linked to atypical neuronal development and behaviors consistent with depression and anxiety (T. Zhao et al., 2016; Zhu et al., 2016). Ketamine 200 mg/kg in pregnant rats also results in impaired learning and memory in offspring (X. Li et al., 2017). Birth defects were also seen in the pups of pregnant mice given ketamine 20 mg/kg (Abdel-Rahman & Ismail, 2000). In zebrafish, an animal model commonly used for assessing teratogenicity, ketamine exposure in early developmental stages has been shown in several studies to be harmful to development (Félix et al., 2019). Finally, in *Xenopus* frog embryos, ketamine exposure results in heart enlargement and dysfunction (Guo et al., 2016). Together, there is an abundance of evidence for the teratogenicity of ketamine, though it should be noted that the ketamine doses used in animal teratogen studies are often much higher than what is used in human treatment.

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Ibogaine. In a modern-day iboga lineage in Gabon, pregnant women are regularly initiated into iboga with no reported natal consequences (Mokambo et al., 2021). However, no formal evaluations of ibogaine teratogenicity were found in the literature.

Infancy

Currently, there are no compelling reasons to administer psychedelics to infants, and there is far from sufficient evidence to demonstrate safety. For this reason, all the psychedelics studied are considered contraindicated for infants. The few specific studies found regarding psychedelics and infancy are described below.

MDMA. In a systematic review, Barenys et al. (2019) found multiple rodent studies indicating that postnatal MDMA exposure caused locomotor deficits, impaired spatial learning, and was cytotoxic at high concentrations.

Ketamine. Ketamine shows significant neurotoxicity in neonates based on animal studies (Bhutta, 2007; Dong & Anand, 2013; Cheng Wang et al., 2005). R.-R. Wang et al. (2014) found that synaptic plasticity in the anterior cingulated cortex was impaired in adult rats who were given ketamine as neonates.

Childhood and Adolescence

LSD. In the 1960s, a number of practitioners used LSD to treat children (L. Bender et al., 1962, 1963, 1966; Freedman et al., 1962; Simmons et al., 1966) and adolescents (K. Cameron, 1961). After reviewing studies of child LSD therapy, Abramson (1967) concluded that "Comparatively large doses of LSD-25…may be safely administered to autistic schizophrenic children for extended periods of time. Brain damage was not observed. Rather, improvement is reported" (p. 142). A review by Mogar and Aldrich (1969) mentions no safety issues among 91 child cases examined, and Rhead

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(1977) goes as far as to assert that the "relative safety" of LSD in treating "…severely disturbed children [is] well established" (p. 99). Together, these early studies suggest that LSD is physiologically safe in children when administered in a therapeutic context, though caution is certainly warranted with such a vulnerable population.

Accidental Ingestion. Several cases of accidental ingestion of LSD by children are of note. S. Cohen (1966) describes three cases of accidental LSD ingestion by children. In two cases, young children experienced hallucinatory effects that subsided with chlorpromazine and had no further complications. In the third case, a 3-year-old who accidentally ingested 250 μg LSD "sustained a dissociation state accompanied by anxiety and visual illusions that lasted for weeks" (p. 182).

Milman (1967) describes a case of a 5-year-old girl who accidentally ingested 100 μg LSD. She became panicked, agitated, disoriented, and depressed, with flattened affect, feelings of depersonalization, and distorted body image. In the months following, the physician described ongoing body image distortion, thinking disorder, and reduced intellectual abilities. Five months later, she continued to have abnormal EEG as well as disorganized visual-motor functions, which remained impaired 9 months later.

Samuelsson (1974) reports on a case of a 2-year-old male who accidentally consumed 2,000 μg of LSD. Upon arrival at the hospital, the patient was extremely excitable but 1 hour later was in a catatonic but conscious state, with tachycardia. He regained movement 4 hours following LSD consumption and fell asleep 2 hours later. After sleeping for 9 hours, he had a brief series of small convulsions in his extremities. Forty-eight hours following LSD ingestion, the boy had returned to normal, and there

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were no further behavioral complications reported by the parents or medical complications identified by doctors at follow-up appointments.

Maslanka and Scott (1992) describe a case of an 8-month-old male who allegedly ingested five blotters of LSD. The child was found crying and brought to the hospital, where he had tachycardia. There he was observed for 24 hours, but no further treatment was given. There were no ongoing complications following discharge.

These cases illustrate that LSD, especially when ingested accidentally at high doses, can result in substantial acute distress that may persist for some time following the experience. However, in each of these cases, there were no physiological consequences.

Ayahuasca. In Brazilian Santo Daime and UDV ayahuasca churches, children and adolescents commonly consume ayahuasca in conjunction with their parents (Labate, 2011). Labate (2011) surveyed several experts in the field about evidence of harm from children taking ayahuasca. The consensus was that there were no studies proving that ayahuasca is harmful in children and no studies proving it is innocuous.

Doering-Silveira, Lopez, et al. (2005) compared the neuropsychological performance of Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church [*n*=40, 55% male, 79% White] to a demographic-matched control group who had never taken ayahuasca [*n*=40, 55% male, 82% White]. They found no significant difference in measures of speeded attention, visual search, sequencing, psychomotor speed, verbal abilities, visuospatial abilities, visual memory, or mental flexibility. They did, however, find a reduction in list-learning performance on some parts of the WHO/UCLA Auditory-Verbal Learning Test. See the “Memory” section in Chapter 8 for more details.

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Doering-Silveira, Grob, et al. (2005) examined other drug use among adolescents who use ayahuasca in a religious setting, given that premature access to psychoactive substances can be associated with drug abuse. They found no significant differences in lifetime substance consumption as compared with matched controls who had never used ayahuasca. In addition, the ceremonial ayahuasca-using group had significantly lower past-year alcohol use than controls.

Ketamine. Ketamine is routinely used as a child anesthetic with a solid safety record (Gao et al., 2016; Lin & Durieux, 2005). However, there are concerns about ketamine's developmental neurotoxicity based on animal studies, particularly in neonates (Bhutta, 2007; Dong & Anand, 2013). In children treated with ongoing ketamine chronic pain, there were no cognitive changes detected after 2 weeks of daily treatment or at 14-week follow-up [*N*=11, age=11–19, sex and race N/R] (Bredlau et al., 2015). There are clinical concerns, however, with the ongoing use of ketamine in childhood or adolescence, such as subacute cognitive impairment (not durable) and addiction potential (Strong & Kabbaj, 2018).

MDMA. Following successful FDA trials of MDMA-assisted psychotherapy for adult PTSD, the next step will be adolescent trials, as is congruent with drug development standards (R. Matthews, personal communication, September 21, 2019). These trials will first seek to determine treatment safety in adolescents. There are no known contraindications at present to using MDMA in treating children and adolescents, though caution should be used regarding dose and frequency due to neurotoxic and other adverse effects. Ongoing use of MDMA can also result in weight loss that can impair adolescent

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growth (Piper, 2007). Adolescent males may be more sensitive to MDMA than females to fatal toxicity, hyperthermia, and hyperactivity (Piper, 2007).

Ibogaine. In a modern-day iboga lineage in Gabon, children and adolescents are regularly initiated into iboga, albeit with low doses (Mokambo et al., 2021).

Adulthood

In healthy adults, all the psychedelics in this study have a reasonable risk profile for use in healthy adults except for ibogaine. Due to its cardiovascular risks and an extremely low safety ratio (0.9–4.4), ibogaine appears to always be risky to administer. However, there are ibogaine analogs such as 18-MC that may present lower risk with equivalent benefits and thus warrant additional study (Maisonneuve & Glick, 2003; Szumlinski et al., 2001; Wasko et al., 2018).

Clinically, ibogaine itself may still be indicated when the mortality of the treated condition (typically addiction) exceeds the risk of the treatment. In such cases, all other options should be exhausted, and the risk of death in treatment must be clearly communicated to patients before obtaining consent.

Older Adulthood

LSD. LSD microdoses of 5–20 µg every fourth day appear to be well-tolerated in older adults [N=48, 56% male, age M=62.9, 88% White, 8% Black, 4% Asian], with adverse events no different than placebo (Family et al., 2020). The safety and tolerability of LSD in older adults were tested by Family et al. due to evidence that 5-HT_{2A} agonism may hold promise as a therapeutic target for Alzheimer's disease.

Psilocybin. Psilocybin has been used successfully in palliative care to treat anxiety associated with life-threatening diseases among 92 patients (Griffiths et al., 2016;

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Grob et al., 2011; Ross et al., 2016). In these studies, high-dose (21 mg/70 kg) psilocybin was administered to participants as old as 75 with no serious adverse outcomes (Ross et al., 2016). While research in this area is still early, these studies demonstrate that psilocybin is relatively safe in older adults.

Ketamine. George et al. (2017) performed a pilot study using subcutaneous ketamine to treat depression in older adults [*N*=16, 62.5% male, age *M*=65.6, race N/R]. There were occasional increases in blood pressure that peaked 4 hours following ketamine. Heart rate compared to baseline increased by 20% in four instances of a total of 80 ketamine sessions, with no increases exceeding 31.5%. Heart palpitations occurred in a participant during only one session (0.2 mg/kg). Liver function in all participants was normal at baseline, and at completion, there were slight liver enzyme elevations in two of the 14 patients who completed the study. Orientation and reaction time was intact for all participants 4 hours following each treatment. Some minor side effects did occur, including flushing, light-headedness/dizziness, paresthesia, nausea, dry mouth, and blurred vision.

There is some evidence from animal models that NMDA antagonists such as ketamine and nitrous oxide show increased toxicity to aging brains (Jevtovic-Todorovic & Carter, 2005; S. Savage & Ma, 2014). Further research is needed to determine whether ketamine may exacerbate neurocognitive degeneration in older adults.

While ketamine for mental health treatment uses lower doses than those used in anesthesia, it is still worth considering the adverse effects that can happen when ketamine anesthesia is used in older adults. Postoperative cognitive dysfunction (amnesia, dementia, etc.) is seen at 1 week following anesthetized surgery in 25.8% of elderly

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patients and in 9.9% at 3 months following (Moller et al., 1998). If these effects are attributable to ketamine, then cognitive dysfunction following ketamine-assisted therapies in elderly patients is a concern. Y. Wang et al. (2000) compared the effects of ketamine and propofol, another commonly used anesthetic, on ACh release in the hippocampus in young and old rats. They found that ketamine tended to facilitate hippocampal ACh release while propofol inhibited it. The cholinergic system, with ACh as its primary neurotransmitter, is highly involved in learning and memory (Muir, 1997; Quirion et al., 1995; Schliebs & Arendt, 2011; Utkin, 2019). Y. Wang et al. hypothesize that aging brains may struggle to recover from the inhibitory effects of ACh suppression caused by propofol, not ketamine. This finding bodes well for ameliorating this mechanistic risk related to ketamine-induced cognitive dysfunction in older adults.

Ibogaine. In an indigenous iboga lineage in Gabon, old men were historically the only people initiated into iboga (Mokambo et al., 2021). While present-day lineages initiate people of all ages and genders, the historical initiation of old men is evidence of relative safety among that age group.

Acute Medical Risks

This section details adverse medical events that can occur as acute sequelae to the eight psychedelics studied.

Fatal Toxicity

The risk of fatality with most psychedelics is relatively low, with safety ratios greater than 20 for all the classical psychedelics. The safety ratio is the ratio of the therapeutic dose to a lethal dose. However, of the psychedelics studied here, MDMA and ibogaine pose a higher risk which is described further below. Table 1 provides the safety

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ratios and lethal doses for the psychedelics studied, while Table 2 at the end of this section lists fatal incidents related to the psychedelics studied.

Mescaline. The safety ratio of mescaline in humans is estimated to be 24, with an extrapolated lethal dose of 8.4 g (Gable, 2004). The LD_{50} of mescaline is approximately 370 mg/kg in rats (Speck, 1957).

LSD. A lethal dose of LSD in humans is extrapolated from limited data to be 100 mg, giving a safety ratio of approximately 1,000 (Gable, 2004). LSD has an LD_{50} of 46 mg/kg IV in mice and 17 mg/kg IV in rats (Gable, 2004).

Table 1

Safety Ratios and Lethal Doses of Psychedelics

	Estimated Safety Ratio	Estimated Human Lethal Dose	Therapeutic Dose (typical per 70 kg)	Rodent LD_{50}
LSD	1,000	100 mg	100 µg	17–46 mg/kg
Psilocybin	1,000	6 g	20–30 mg	293 mg/kg
Ketamine (non-anesthetic)	152	2.7 g IN	7–35 mg IV	400 mg/kg
DMT	50	2 g	0.2 mg/kg IV	32 mg/kg IV
Mescaline	24	8.4 g	300 mg	370 mg/kg
Ayahuasca	>20	560 mg DMT	35–70 mg DMT	SR > 50
MDMA	10–16	2 g	75–125 mg	29 mg/kg
Ibogaine	0.9–4.4	1,842 mg	420–2,100 mg	263 mg/kg

Note. Data sources are cited in chapter sections below, except for therapeutic dose references, which are provided in Chapter 3. All doses are oral unless otherwise specified. IV = intravenous; IN = intranasal; SR = safety ratio.

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Psilocybin. Gable (2004) estimates the safety ratio of psilocybin in humans to be approximately 1,000, with an extrapolated lethal dose of 6 g. The LD_{50} of psilocybin in mice is approximately 293 mg/kg (Zhuk et al., 2015).

DMT. Gable (2004) estimates the safety ratio of DMT in humans to be approximately 50 based on an extrapolated lethal dose of 2 g. The LD_{50} of DMT in mice is approximately 32 mg/kg IV or 47 mg/kg IP (Gable, 2007).

Ayahuasca. The safety ratio of ceremonial ayahuasca in humans is likely greater than 20 based on an extrapolated lethal oral DMT dose of 560 mg (Gable, 2007). Gabel focused on the toxicity of DMT rather than the beta-carbolines because the toxicity of the beta-carbolines was found to be substantially less. In rats, the safety ratio of ceremonial ayahuasca has been measured to be greater than 50 (Pic-Taylor et al., 2015). However, it is important to note that some indigenous brews of ayahuasca may contain other ingredients in addition to DMT and *B. caapi* that can add to toxicity and have led to fatalities (Ray & Lassiter, 2016). Such fatal additives have included *Brugmansia sp., Brunfelsia sp*., *Nicotiana rustica*, and the nightshade family, *Solanaceae*.

MDMA. Gable (2004) estimates a lethal dose of MDMA in humans to be 2 g (29 mg/kg), giving a safety ratio of 16. As noted above, the poor metabolizer *CYP2D6* phenotype present in 7%–10% of Caucasians leads to approximately 36% higher MDMA peak plasma concentration (J. Yang et al., 2006). Thus, for slow MDMA metabolizers, a lethal dose may be as low as 18.6 mg/kg giving a safety ratio of only 10.

Ketamine. Gable (2004) estimates the safety ratio of ketamine in humans to be approximately 38 based on an extrapolated lethal dose of 2.7 g. However, this margin of safety may be even larger given that there are very few incidents of fatal adverse

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reactions reported in the clinical literature (C. J. A. Morgan & Curran, 2011). Further, the doses used in treating mental health conditions are 4–20 times lower than those used for anesthesia, giving a safety ratio of 152 in this context. However, people with the *CYP2B6**6 gene variant will metabolize ketamine more slowly and, therefore, may need a lower dose (P.-F. Wang et al., 2018). This gene variant is common in African and some Asian populations. Ketamine has an LD_{50} of 400 mg/kg IP in mice (Gable, 2004).

In one case, nine children were accidentally given 100 times the intended anesthetic dose with no adverse outcome (Green et al., 1999).

Ibogaine. The LD_{50} of ibogaine in rodents is estimated to be 263 mg/kg oral (Schep et al., 2016). Based on an adjustment factor of 20, as was used by Gabel (2007) to estimate the human lethal dose of DMT, a lethal human dose of ibogaine would be approximately 13.2 mg/kg or 921 mg/70 kg. However, therapeutic doses of ibogaine are typically 420–2,100 mg/70 kg (Alper, 2001), making this lethal dose estimate too high given that ibogaine therapy is commonly survived. Still, ibogaine poses a higher risk of fatality due to its cardiovascular effects, which are described below in the "Cardiovascular Incidents" section of this chapter. As a lethal dose estimate, 26.4 mg/kg or 1,842 mg/70 kg is used based on an adjustment factor of 10. This gives an estimated safety ratio of 0.9–4.4.

As a further complication, ibogaine, like MDMA, is also metabolized by the CYP2D6 enzyme (J. Yang et al., 2006). The presence of the poor metabolizer *CYP2D6* phenotype can result in twice the plasma concentration of noribogaine, leading Glue, Winter et al. (2015) to suggest halving the dose for those with the phenotype. There is

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also evidence that ibogaine may be more bioavailable in females than males and thus may pose more risk at the same dose in females (Pearl et al., 1997).

Given the risks posed by ibogaine, it is desirable to find alternatives with similar therapeutic effects and less toxicity. The primary active metabolite of ibogaine, noribogaine, has been found to have half the toxicity of ibogaine (Kubilienė et al., 2008). In addition, an ibogaine analog, 18-methoxycoronaridine (18-MC), has similar antiaddictive properties as ibogaine but far fewer adverse effects (Maisonneuve & Glick, 2003; Szumlinski et al., 2001; Wasko et al., 2018).

Table 2

Fatalities Associated with Psychedelics

Mescaline	2	Death by esophageal lacerations attributed to forceful vomiting from peyote (Nolte & Zumwalt, 1999). White male, 22, fatality following mescaline mixed with alcohol and methadone (Chaikin, 1980).
LSD	7+	Five deaths among the 3,554 U.S. poison control center calls related to LSD from 2000–2016 (Leonard et al., 2018). One death reported by Registrar General of Scotland (A. J. M. Forsyth, 2001). One sudden and inexplicable death during 200 μg LSD session among 4,300 patients (Malleson, 1971).
Psilocybin	5	Three deaths among the 5,883 U.S. poison control center calls related to psilocybin from 2000–2016 (Leonard et al., 2018). Ingestion of psilocybin-containing mushrooms (Brandenburg & Ward, 2018). One death from psilocybin in the U.K. between 1993 and 2000 (Levitt et al., 2006). One fatality due to psilocybin mushrooms (McCawley et al., 1962). 6-year-old died following psilocybin mushroom ingestion (van Amsterdam et al., 2011).
Ayahuasca	3	Three fatalities among American Poison Control Centers' calls regarding ayahuasca ingestion 2005–2015 [*N*=538] (Heise & Brooks, 2017).
MDMA	Many	MDMA toxicity is sufficient to be fatal at a high enough dose (Gable, 2004).
Ketamine	Many	Ketamine toxicity is sufficient to be fatal at high enough dose (Gable, 2004).
Ibogaine	2	Male, 48, found dead in home following ibogaine ingestion (Kontrimaviciute et al., 2006). Male, 27, died of asphyxiation due to vomiting 12 hours after ibogaine ingestion in clinical setting for addiction treatment, 30 mg daily methadone, 50 mg daily diazepam (Mazoyer et al., 2013).

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Drug Interactions

Many psychedelics interact with other drugs in ways that can be dangerous. An exhaustive review of drug interactions was not performed in order to limit the scope of this study. A physician should be consulted before giving psychedelics in combination with any other drugs.

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening condition that typically occurs in patients taking multiple serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs) (Rodnitzky, 2005). Since many psychedelics are serotonergic, it can be risky to combine psychedelics with other serotonergic medications. Diagnosis of serotonin syndrome requires that at least three of the following symptoms are present: “agitation, mental status changes, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhoea, incoordination and fever” (p. 93). In addition, other causes must be ruled out, and an antipsychotic cannot have been started, or the dosage increased before symptom onset.

Mescaline, LSD, and Psilocybin. K. C. Mills (1997) listed LSD as having “medium” serotonergic potential in inducing serotonin syndrome. Psilocybin and LSD were also noted to be serotonin agonists and therefore have the potential to induce serotonin syndrome (Ener et al., 2003; K. C. Mills, 1997). However, no cases of serotonin syndrome involving mescaline, LSD, or psilocybin were found in the literature, indicating that there is likely very little risk of serotonin syndrome from any of these compounds.

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MDMA. Combining MDMA with SSRIs, MAOIs, stimulants, serotonin precursors, or other drugs increasing activity on the 5-HT_{1A} receptors is known to increase the risk of serotonin syndrome (Akasaki & Ohishi, 2019; Silins et al., 2016). Silins et al. (2016) examined the drugs most likely to interact with MDMA and lead to serotonin syndrome. Stimulants such as amphetamine, methamphetamine, and cocaine in high or repeat doses increase the risk of serotonin syndrome when combined with MDMA. In contrast, they found that SSRIs combined with MDMA have a lower risk of leading to life-threatening serotonin syndrome. Of all drug classes, MAOIs combined with MDMA had the highest risk of inducing serotonin syndrome. Because MAO breaks down serotonin, inhibition of MAO means that the flood of serotonin caused by MDMA cannot be efficiently broken down, leading to serotonin syndrome.

Due to the risk of serotonin syndrome, SSRI medications are typically tapered prior to MDMA treatment for PTSD. However, Feduccia et al. (2021) found that outcomes of MDMA-assisted psychotherapy for PTSD were poorer among those who tapered off SSRIs than those who did not have to taper off an SSRI (p=.009; d_c=-0.81). Based on this data, SSRI medication may interfere with the efficacy of PTSD treatment with MDMA.

Cardiovascular Incidents

Mescaline, LSD, and Psilocybin. Classical psychedelics are known to induce hypertension and tachycardia (Akasaki & Ohishi, 2019). However, these effects are relatively mild and do not typically require treatment with typical doses (Akasaki & Ohishi, 2019). Rarely, vasospasms can occur, which can cause peripheral ischemia or strokes (Akasaki & Ohishi, 2019).

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Psilocybin. Beck et al. (1998) report on three cases where the presence of high concentrations of phenylethylamine in magic mushrooms may have been responsible for adverse reactions involving tachycardia, anxiety, and nausea that led to hospitalization. Phenylethylamine occurs naturally in magic mushrooms, but its concentration can vary widely between different mushroom cultures.

DMT and Ayahuasca. No cases of cardiovascular incidents due to DMT alone were found in the literature. Four cases of cardiac arrest following ayahuasca ingestion were reported to American Poison Control Centers between 2005 and 2015 (Heise & Brooks, 2017). DMT elevates blood pressure and heart rate (Strassman & Qualls, 1994).

MDMA. MDMA is known to induce hypertension and tachycardia, and therefore caution should be exercised in administering MDMA to patients with cardiovascular problems (Vollenweider, Gamma, et al., 1998). There have several cases of negative cardiovascular incidents resulting from MDMA ingestion (Akasaki & Ohishi, 2019). These include intracranial hemorrhage (Kahn et al., 2012), subarachnoid hemorrhage (Gledhill et al., 1993; J. Johnson et al., 2014), aortic dissection (Duflou & Mark, 2000), atrial fibrillation (Madhok et al., 2003), and acute myocardial infarction (Lai et al., 2003). Larger cardiovascular responses to MDMA occur in men than women (Bedi & de Wit, 2011). Pretreatment with a beta-blocker may mitigate the cardiovascular risks of MDMA. The beta-blocker pindolol prevents MDMA-induced increases in heart rate with minimal impact on the subjective effects (Hysek et al., 2010).

Ketamine. Ketamine increases heart rate and blood pressure, therefore, presenting a risk of acute cardiac failure among those with pre-existing cardiac or stroke risk (C. J. A. Morgan & Curran, 2011). For this reason, caution should be used in

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administering ketamine to patients with pre-existing cardiovascular disease (Zhu et al., 2016).

Ibogaine. Ibogaine can induce life-threatening cardiac arrhythmia by disrupting potassium channel gating (Grogan et al., 2019; Hildyard et al., 2015; Koenig et al., 2012, 2013; Kovar et al., 2011; Litjens & Brunt, 2016; Rubi et al., 2017). Twenty-four cases of fatal cardiac arrest were found in the literature, with many of these fatalities occurring in people under 40 (Alper, Stajić, et al., 2012; Koenig & Hilber, 2015; Meisner et al., 2016). Maas and Strubelt (2006) suggest that the risk of cardiac arrhythmia following ibogaine ingestion may increase with: 1) sympathetic stimulation or 2) left-hemisphere sympathetic stimulation concurrent with high parasympathetic tone. They comment that healers in Gabon prevent cardiac arrhythmias from ibogaine by preparing their patients for several days in isolation from normal life and inducing a trance-state with right-hemispheric and vagal dominance.

Hyponatremia

Hyponatremia is an abnormally low concentration of sodium in the body, which can be life-threatening due to electrolyte imbalance (Upadhyay et al., 2006). Hyponatremia can be caused by over-hydration alongside other causes (Baggott et al., 2016). There is a significant association between age and occurrence of hyponatremia in a hospital setting (age 51–60: OR=4.1; 61–70: OR=6.0; 71–80: OR=9.7; >80: OR=12.8) (Upadhyay et al., 2006). Among those in nursing homes, the past-year occurrence of hyponatremia is 18%–53% (Upadhyay et al., 2006). The risk of hyponatremia is higher when taking diuretics and during the first 2 weeks of taking a new psychotropic drug (Madhusoodanan et al., 2002). Hyponatremia occurs postoperatively in 4.4% of patients

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(Upadhyay et al., 2006). Those with congestive heart failure, cirrhosis, pneumonia, and acquired immunodeficiency syndrome (AIDS) are at increased risk of hyponatremia (Upadhyay et al., 2006). Finally, hyponatremia commonly occurs acutely in marathon runners (Upadhyay et al., 2006).

MDMA. MDMA impairs the physiological response to water intake, causing people to continue consuming water beyond what is needed and therefore leading to hyponatremia (Baggott et al., 2016). One hundred three cases of MDMA-induced hyponatremia were found in the literature, some of which were fatal (Ajaelo et al., 1998; Brvar et al., 2004; Budisavljevic et al., 2003; Ghatol & Kazory, 2012; Hartung et al., 2002; Kalantar-Zadeh et al., 2006; Rella et al., 2000; Rosenson et al., 2007; Rukskul, 2005; Sue et al., 2002; Traub et al., 2002). Women have a higher risk of hyponatremia with MDMA ingestion, possibly due to more plasma arginine vasopressin secretion from MDMA in women than men (Allott & Redman, 2007; Simmler et al., 2011).

Pulmonary Edema

MDMA. One case of pulmonary edema is described following MDMA ingestion (Haaland et al., 2017).

Liver Failure

MDMA. MDMA can induce acute hepatitis with an onset ranging from several hours to several weeks following ingestion (Cajanding, 2019). Slow metabolizers of MDMA due to *CYP2D6* gene polymorphism may be more susceptible to MDMA hepatotoxicity (Cajanding, 2019).

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Respiratory Depression

Mescaline. Mescaline promotes slowing of the breath and an increase in respiratory depth in cats (Dallemagne & Heymans, 1955). There were no reports found of life-threatening respiratory depression from mescaline.

LSD. Forrer and Goldner (1951) measured respiration following LSD ingestion in six schizophrenic patients and found LSD no evidence of respiratory depression, with inconclusive data suggesting respiratory stimulation.

Ketamine. Unlike other anesthetics, ketamine's mode of action largely does not induce respiratory depression; rather, it is classified as a respiratory stimulant (Eikermann et al., 2012; Strayer & Nelson, 2008; Tyler et al., 2017). However, documented in the literature was one case of respiratory depression in a "debilitated" adult (Sears, 1971) and four cases of brief respiratory depression among nine children who received 5 to 100 times the intended anesthetic dose of ketamine (Green et al., 1999).

Temperature Dysregulation and Hyperthermia

Clark and Clark (1981) reviewed human and animal studies on temperature regulation in response to mescaline, LSD, and psilocybin.

Mescaline. In a review, Clark and Clark (1981) found one study indicating that mescaline tended to increase body temperature in humans. Results were mixed in animal studies, with body temperature decreasing, increasing, or staying the same in mice [n=3], decreasing in non-human primates [n=1], increasing in rabbits [n=2], and increasing or decreasing in rats [n=2].

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LSD. Clark and Clark (1981) found a consistent trend that LSD increased body temperature based on reviewed studies in humans [*n*=11], rabbits [*n*=44], mice [*n*=5], rats [*n*=14], pigeons [*n*=3], dogs [*n*=3], and cats [*n*=1].

Psilocybin. Clark and Clark's (1981) review found that psilocybin tended to increase body temperature in humans [*n*=2] and in rabbits [*n*=3], while in rats, psilocybin tended to decrease body temperature [*n*=1].

MDMA. MDMA has been found in many studies to increase body temperature in a dose-dependent and activity-dependent manner (Parrott, 2012b). Parrott surmised from eight studies that low doses (<1.0 mg/kg) of MDMA produce a or negligible change in body temperature, moderate doses (1.1–1.9 mg/kg) increase body temperature by approximately +0.4 °C, and high doses (2.0 mg/kg) increase body temperature by approximately +0.7 °C. In dance clubs, these temperature increases have been measured to be +1.0 °C or greater. While these typical increases represent moderate hyperthermia, there are case reports of hyperpyrexia, severe life-threatening hyperthermia (Connolly & O'Callaghan, 1999; Dar & McBrien, 1996; Davies et al., 2014; Eede et al., 2012; Lang et al., 2016; Rella et al., 2000; T. Russell et al., 2012; Sue et al., 2002). In rats, hyperthermia from MDMA is far more pronounced among males than females (Fonsart et al., 2008; Wyeth et al., 2009). However, among the seven cases of hyperpyrexia reported by Henry et al. (1992), three were female and four were male, indicating that, in humans, hyperthermia is a concern regardless of sex.

There is some evidence that MDMA-induced hyperthermia is mediated by the gut microbiome, with antibiotic pretreatment reducing hyperthermia in rats (Ridge et al., 2019). Hyperthermic conditions also appear to modulate MDMA-induced

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vasoconstriction, with approximately four times the magnitude of vasoconstriction occurring at 40 °C than at 37 °C (Fonseca et al., 2017). Further, prolonged hyperthermia can result in the breakdown of muscle tissue through rhabdomyolysis, which has been observed as an adverse outcome of MDMA use (E. M. Mills et al., 2003). Finally, extremely high 'neurotoxic' doses (12 mg/kg) have been shown to have a persistent negative impact on temperature regulation in rats (Mechan et al., 2001).

There is evidence that ambient temperature has a strong effect on MDMA-induced hyperthermia, with hotter ambient temperature increasing body temperature (P. L. Brown & Kiyatkin, 2004; Dafters, 1994; Malberg & Seiden, 1998). For this reason, MDMA sessions should be performed in a temperature-regulated environment.

MDMA-induced hyperthermia can be treated pharmacologically using the beta-blocker carvedilol or the antipsychotic clozapine (Hysek et al., 2012; Kiyatkin et al., 2016). In addition to attenuating temperature increases, carvedilol also attenuates the increase in blood pressure and heart rate brought on by MDMA without altering its subjective effects (Hysek et al., 2012). Thus, pretreatment with carvedilol may represent an effective harm-reduction technique in the clinical administration of MDMA. Clozapine provides relief of MDMA-induced hypothermia within 6 minutes via vasodilation (Kiyatkin et al., 2016). For that reason, clozapine and/or carvedilol should be available for emergency use in case of MDMA-induced hyperpyrexia, which can be life-threatening.

Ketamine. In a review, Clark and Clark (1981) found that in humans, ketamine tended to increase body temperature [n=3]. Results were mixed in animal studies, with body temperature decreasing in cats [n=1 study], not changing in mice [n=1], decreasing

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or not changing in non-human primates [*n*=3], decreasing or not changing in rats [*n*=4], and increasing in sheep [*n*=1].

Seizure

Mescaline. No reports of seizures due to mescaline were found. Boggan (1973) found that mescaline and LSD decreased susceptibility to audiogenic seizures in mice.

LSD. Baker (1964) describes epilepsy as a "partial" contraindication to LSD therapy. S. Cohen (1966) mentions five cases of grand mal seizures that were reported in a presentation by Baker (1965). Experiments with mice show that LSD reduces susceptibility to audiogenic seizures (Anlezark et al., 1978; Boggan, 1973; Rouse & Frank, 1974).

Psilocybin. One case of seizures followed by non-fatal cardiac arrest was described in an 18-year-old male following psilocybin mushrooms (Borowiak et al., 1998).

MDMA. MDMA reduces seizure threshold, possibly due to monoamine toxicity (Giorgi et al., 2006). Huff et al. (2016) argue, however, that increased seizure susceptibility is due to increased extracellular glutamate in the hippocampus. Examining cases in a London hospital, 58% of patients with MDMA-induced hyponatremia also had seizures (Giorgi et al., 2006).

Ketamine. No seizure-inducing effects have been found with ketamine in patients with or without epilepsy (Corssen et al., 1974). Still, Corssen et al. recommend caution when administering ketamine to epileptic patients. Kayama (1982) did find ketamine increased seizure waves in cats. However, they also found that these seizure waves were

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attenuated by the anti-epileptic trimethadione without affecting ketamine's anesthetic effect.

Ibogaine. In monkeys, ibogaine 160 and 320 mg/kg oral was not found to induce EEG patterns consistent with seizures (Authier et al., 2016).

Priapism

MDMA. Priapism is a male erection that persists long enough to present physiological risk. One case of MDMA-induced priapism was found in the literature (Dubin & Razack, 2000).

Ketamine. Ketamine has been used successfully in medical contexts to prevent and resolve erections in patients undergoing surgeries (Buffum, 1982). As such, it is unlikely that ketamine carries a risk of priapism.

Table 3

Serious Non-Fatal Medical Incidents due to Psychedelics

Coma		
LSD	54	Forty-nine incidences of coma among the 3,554 U.S. poison control center calls related to LSD from 2000–2016 (Leonard et al., 2018). After snorting lines of 80%–90% pure LSD (approximately 3x4x30 mm), five of eight people entered a coma (Klock et al., 1974).
Psilocybin	24	Twelve incidences of coma among the 5,883 U.S. poison control center calls related to psilocybin mushrooms from 2000–2016 (Leonard et al., 2018).
MDMA	1	Female, 19, coma, self-limited tonic seizure, hyponatremia rhabdomyolysis following 5–10 mg/kg MDMA along with 5 L of water (Sue et al., 2002).
Cardiovascular Events		
Psilocybin	1	Male, 18, seizures followed by non-fatal cardiac arrest following psilocybin mushroom ingestion (Borowiak et al., 1998).
Ayahuasca	4	Four cases of cardiac arrest among American Poison Control Centers' calls regarding ayahuasca ingestion 2005–2015 [*N*=538] (Heise & Brooks, 2017)
MDMA	12	Tachycardia, arrhythmia, hypertension, or hypotension were present in six of seven fatal MDMA-ingestion cases reported by Henry et al. (1992), with three of five cases having severe complications. Male, 29, aortic dissection (Duflou & Mark, 2000). Male, 27, acute myocardial infarction (Lai et al., 2003).

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		Adolescent atrial fibrillation (Madhok et al., 2003). Four cases of 'sudden cardiac death' (Suarez & Riemersma, 1988, full text not found)
Ketamine	5	Five incidents of severe hypertension in patients being treated for depression (X. Wang et al., 2012).
Ibogaine	28+	Twenty-five fatalities due to cardiac arrest (Alper, Stajić, et al., 2012; Koenig & Hilber, 2015; Meisner et al., 2016). Male, 26, non-fatal cardiac arrest resulting in neurological disability (Vlaanderen et al., 2013). Male, 61, non-fatal cardiac arrest (Steinberg & Deyell, 2018). Male, 33, non-fatal cardiac arrest (Pleskovic et al., 2012).
Cerebrovascular Accident		
LSD	2	Female, 20, carotid artery occlusion following vasoconstriction induced by LSD, which caused left hemiplegia (Lieberman et al., 1974). Female, 19, White, lower extremity vasospasm requiring angioplasty (Raval et al., 2008).
MDMA	11	Three cases of intracranial hemorrhage (Kahn et al., 2012). Subarachnoid hemorrhage due to an aneurysm (J. Johnson et al., 2014). Female, 25, subarachnoid hemorrhage (Gledhill et al., 1993). Female, 25, subarachnoid hemorrhage after 2–5 MDMA tablets (Henry et al., 1992). Male, 35, right hemiparesis and dysphasia following MDMA due to cerebral infarction, partial recovery (Manchanda & Connolly, 1993). Female, 21, incontinence, Broca's aphasia, and right hemiparesis following MDMA due to intracerebral hemorrhage (Hughes et al., 1993). Male, 28, right hemiparesis, hyperreflexia, and positive Babinski sign 10 days after taking MDMA due to a left striatocapsular infarct (Hanyu et al., 1995). Female, 22, cerebral venous sinus thrombosis following MDMA (Rothwell & Grant, 1993).
Paralysis		
MDMA	2	Male, 14, acute right-side hemiplegia due to spinal cord lesion due to acute vascular damage following MDMA and amphetamine use, complete recovery after 6 months (Goldstein et al., 2008).White male, 21, thyrotoxic periodic paralysis following recreational ecstasy use (Forrest & Platts, 2009).
Hyponatremia		
MDMA	104+	MDMA can induce hyponatremia due to unintentional excess fluid consumption as well as increased ADH release (Devlin & Henry, 2008). 104 specific cases were found in the literature (Ajaelo et al., 1998; Brvar et al., 2004; Budisavljevic et al., 2003; Ghatol & Kazory, 2012; Hartung et al., 2002; Kalantar-Zadeh et al., 2006; Maxwell et al., 1993; Rella et al., 2000; Rosenson et al., 2007; Rukskul, 2005; Sue et al., 2002; Traub et al., 2002).
Rhabdomyolysis		
Mescaline	1	White male, 22, ay following mescaline, methadone, and alcohol (Chaikin, 1980).
LSD	40+	Thirty-nine cases of rhabdomyolysis among the 3,554 U.S. poison control center calls related to LSD from 2000–2016 (Leonard et al., 2018). Hispanic male, 25, following 3 doses of LSD (Berrens et al., 2011).
Psilocybin	17	Sixteen cases of rhabdomyolysis among the 5,883 U.S. poison control center calls related to psilocybin mushrooms from 2000–2016 (Leonard et al., 2018).

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		Russian male, 25, with hepatitis C, after psilocybin mushrooms (Bickel et al., 2005)
DMT	1	White male, 42, recent repeated DMT use, psychotic symptoms as well (Paterson et al., 2015).
Ayahuasca	1	Male, 22, DMT, Syrian rue seeds and amphetamine led to hospitalization with rhabdomyolysis; full recovery (C.-H. Liu et al., 2019).
MDMA	26+	MDMA can induce rhabdomyolysis by diffuse tissue disruption (Devlin & Henry, 2008). Twenty-six cases were found in the literature (Davies et al., 2014; Eede et al., 2012; Haaland et al., 2017; Halachanova et al., 2001; Henry et al., 1992; Lang et al., 2016; Lehmann et al., 1995; T. Russell et al., 2012; Rusyniak et al., 2005; Sprague et al., 2004; Sue et al., 2002).
Ketamine	2	Among 20 patients presenting to the emergency room for ketamine-related issues, 2 developed mild rhabdomyolysis (Weiner et al., 2000).
Seizures		
Mescaline	1	Male, 22, seizure (Carstairs & Cantrell, 2010).
LSD	146+	One-hundred and forty-four cases involving seizures among the 3,554 U.S. poison control center calls related to LSD from 2000–2016 (Leonard et al., 2018). Caucasian male, 32, grand mal seizure 50 min following LSD ingestion (Fisher & Ungerleider, 1967). Female, 15, bipolar I disorder, likely seizure following 1,100-1,200 µg LSD (Haden & Woods, 2020).
Psilocybin	45	Forty-four cases involving seizures among the 5,883 U.S. poison control center calls related to psilocybin mushrooms from 2000–2016 (Leonard et al., 2018). One fatal case of seizures in a 6-year-old after psilocybin mushroom ingestion, leading to hyperthermia and status epilepticus (van Amsterdam et al., 2011).
Ayahuasca	12	Twelve cases of seizure among American Poison Control Centers' calls regarding ayahuasca ingestion 2005–2015 [*N*=538] (Heise & Brooks, 2017).
MDMA	12+	MDMA reduces seizure threshold (Giorgi et al., 2006). One specific case was found in the literature: Female, 19, coma, self-limited tonic seizure, hyponatremia rhabdomyolysis, following 5–10 mg/kg MDMA along with 5 L of water (Sue et al., 2002). Female, 17, 1.5 tablets of MDMA followed by three epileptiform seizures, full recovery (Maxwell et al., 1993). Male, 13 months, accidental ingestion of 1 capsule of ecstasy, convulsion, hypertension, tachyarrhythmia, and fever within an hour, full recovery (A. R. B. Russell et al., 1992). Five of seven MDMA-implicated deaths reported by Henry et al. (1992) involved seizures, along with seizures in two more MDMA cases that had serious complications. Two toddlers (19 and 20 months) intoxicated with MDMA had convulsions and hyperthermia as a result but recovered fully (Pauwels et al., 2013).
Ibogaine	2	Female, 34, 4–5 seizure-like episodes, each lasting 2–4 minutes after 2 g self-administered ibogaine for heroin detoxification (Grogan et al., 2019). Male, 39, 3 seizures after 7 g ibogaine (Hildyard et al., 2015). White male, 22, generalized tonic-clonic seizure with grand mal seizures (L. Breuer et al., 2015).
Extreme Temperature dysregulation		
LSD	140+	One-hundred and thirty-six cases of fever among the 3,554 U.S. poison control center calls related to LSD from 2000–2016 (Leonard et al., 2018). 100–107 °F

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		temperatures in 4 of 8 people after snorting lines of 80%–90% pure LSD (approximately 3x4x30 mm) (Klock et al., 1974).
Psilocybin	117	116 cases of fever among the 5,883 U.S. poison control center calls related to psilocybin from 2000–2016 (Leonard et al., 2018). One fatal case in a 6-year-old following psilocybin mushroom ingestion that led to seizures, hyperthermia, and status epilepticus (van Amsterdam et al., 2011).
MDMA	Many	MDMA can induce hyperthermia due to increased exertion, arousal, and changes in muscle excitation-contraction coupling (Devlin & Henry, 2008). Many cases of hyperthermia have occurred. All seven MDMA-implicated deaths reported by Henry et al. (1992) involved body temperatures at or above 40 °C.
Severe Respiratory Depression		
LSD	36+	Thirty-three cases of respiratory depression among the 3,554 U.S. poison control center calls related to LSD from 2000–2016 (Leonard et al., 2018). Respiratory arrest in 3 of 8 people after snorting ~3x4x30 mm lines of 80%–90% pure LSD (Klock et al., 1974).
Psilocybin	9	Nine cases of respiratory depression among the 5,883 U.S. poison control center calls related to psilocybin mushrooms from 2000–2016 (Leonard et al., 2018).
Ayahuasca	7	Seven cases of respiratory arrest among American Poison Control Centers' calls regarding ayahuasca ingestion 2005–2015 [*N*=538] (Heise & Brooks, 2017).
Ketamine	6+	Four cases of brief respiratory depression among nine children who received 5–100x the intended anesthetic dose (Green et al., 1999). Respiratory arrest in neonates under anesthesia (Sears, 1971).
Pulmonary Edema		
MDMA	1	Male, 19, pulmonary edema requiring intubation (Haaland et al., 2017).
Pneumomediastinum and Epidural Pneumatosis		
MDMA	2	Male, 21, history of alcohol abuse and prescribed benzodiazepines (Mutlu et al., 2005). Male, 17, inhalation of ecstasy (Bernaerts et al., 2003).
Acute Renal Failure		
MDMA	5	Five cases of acute renal failure from MDMA, three of which were fatal (Henry et al., 1992).
Gastrointestinal Hemorrhage		
MDMA	1	Male, 18, gastrointestinal hemorrhage following 5 ecstasy tablets (MDMA confirmed), died after 15.5 hours (Henry et al., 1992).
Priapism		
MDMA	1	One case of MDMA-induced priapism (Dubin & Razack, 2000).

Note. Headings are bolded for clarity.

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Long-Term Risks

With all the psychedelics studied, a single administration is very unlikely to have a lasting physiological impact. However, ongoing, frequent, and/or high-dose administration of some psychedelics can have a lasting physiological impact. At the end of this chapter, Summary Table 5 provides an overview of the long-term risks associated with the chronic use of each psychedelic.

Neurotoxicity

The specific neurotoxic effects of the eight psychedelics studied are described below. The impacts of psychedelic neurotoxicity on neuropsychological functions are further elaborated in Chapter 8.

Mescaline. Mescaline shows some neurotoxicity to cerebellum neurons in vitro (Roubein et al., 1973). This toxicity is less than that of chlorpromazine, and it is unclear if toxicity exists with therapeutic doses.

LSD, Psilocybin, and DMT. No studies were found indicating neurotoxicity by LSD, psilocybin, or DMT. Given that there is substantial neuroscience research on each of these substances and that none of it has turned up neurotoxic effects, these psychedelics are unlikely to have neurotoxic effects.

Ayahuasca. O'hearn and Molliver (1993) found harmaline, a common component of ayahuasca was toxic to cerebellum Purkinje cells in rats. With doses 30 and 50 times those taken during ayahuasca rituals, Pic-Taylor et al. (2015) saw some transient brain injury in rats but no permanent damage. da Rocha Simão (2019) found that the harmine metabolite harmaline was toxic to dopaminergic neurons in vivo but only at very high concentrations. They also exposed dopaminergic neurons to five ayahuasca brews in vivo

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and saw toxic effects. However, this methodology is suspect in its applicability to human toxicity as ayahuasca brews are consumed orally, and thus only a small subset of compounds would arrive at dopaminergic cells.

MDMA. Chronic use of MDMA results in persistent brain changes, some of which are partially reversible with abstinence. Ongoing MDMA use results in increased brain resource utilization to perform cognitive tasks based on functional neuroimaging studies (C. A. Roberts et al., 2018). Further, mild recreational MDMA use (mean 6.0 tablets) in young adults [n=59] was found to impact brain microvasculature and white matter maturation and possibly cause axon damage based on a prospective longitudinal study [N=188] (de Win et al., 2008). Finally, reduced grey matter density was found in the cerebellum and some areas of the cortex and brainstem of MDMA polydrug users compared to non-MDMA using controls (Cowan et al., 2003). However, while controls were also substance users, there was significantly more use of all other substance classes except for alcohol and heroin among MDMA users, confounding these results.

Serotonergic Neurotoxicity. While there is conflict in the literature about the serotonergic neurotoxicity of MDMA, the combined evidence suggests altered serotonergic transmission in recreational MDMA users (Gouzoulis-Mayfrank & Daumann, 2006b; F. Müller et al., 2019). Chronic MDMA exposure leads to reduced SERT density in humans due to serotonergic neurotoxicity (Aguilar et al., 2020; Erritzoe et al., 2011; F. Müller et al., 2019; Parrott, 2012a; Quinton & Yamamoto, 2006). However, with mild MDMA use (M=6.0 tablets), MDMA was not found to be causative in reducing SERT density (de Win et al., 2008). These alterations in serotonergic function may be partially resolved after sustained abstinence (Gouzoulis-Mayfrank & Daumann,

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2006b; F. Müller et al., 2019). This serotonergic neurotoxicity can lead to neuronal injury at recreational doses in humans (McCann et al., 2000). Further, MDMA can cause neuronal apoptosis in cortical neurons (Capela et al., 2007). Repeat administration of MDMA at typical human doses desensitizes 5-HT_{1A} autoreceptors, leading to increased serotonin release up to a month after administration (Lanteri et al., 2014). This is consistent with the finding of increased serotonin plasma concentration among MDMA users, correlating positively to cumulative dose and consumption during the past 30 days and 1 year (Stuerenburg et al., 2002).

Dopaminergic Neurotoxicity. MDMA is toxic to dopaminergic neurons, reducing DAT concentration with an effect that persists for at least 3 months (G. Costa et al., 2013, 2017; Quinton & Yamamoto, 2006). Tai et al. (2011) found a long-term impact on nigrostriatal dopaminergic functions in past recreational MDMA users who had been abstinent for an average of 3.22 years. Dopamine plasma concentration is found to be higher among MDMA users, correlating positively to cumulative dose and consumption during the past 30 days and 1 year (2002).

Adrenergic Neurotoxicity. MDMA is not toxic to noradrenergic neurons (G. Costa et al., 2017). Repeat administration of MDMA at therapeutic/recreational doses does desensitize alpha-2A adrenergic autoreceptors, leading to increased norepinephrine release up to a month after MDMA administration (Lanteri et al., 2014). This is consistent with the finding of increased norepinephrine and epinephrine plasma concentration among MDMA users, correlating positively to cumulative dose and consumption during the past 30 days and 1 year (2002).

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GABAergic Neurotoxicity. MDMA is neurotoxic to GABAergic neurons, reducing their concentration for at least 3 months (G. Costa et al., 2013, 2017; Huff et al., 2016). This is likely due to glutamate toxicity (Huff et al., 2016).

Techniques for Preventing MDMA-Associated Neurotoxicity. In recreational contexts, many MDMA users reduce the risk of MDMA neurotoxicity by 'preloading' and 'postloading' supplements that are known to prevent neurotoxic damage from MDMA (Kelly, 2009). For instance, pretreatment with the antioxidant plant *Melissa officinalis L.* reduced neuronal death due to MDMA by 15%–20% in rats (Hassanzadeh et al., 2011). Given the evidence of neuroprotection by multiple different substances, similar harm-mitigation strategies may be beneficial in the clinical use of MDMA.

The neurotoxic and astroglial effects of MDMA on the serotonin system can also be reduced by preventing hyperthermia (Parrott, 2016), as can be done with cannabinoids, the beta-blocker carvedilol, the sedatives clomethiazole and pentobarbital, and the adrenergic-2A receptor agonist CGS[2] (Colado, Esteban, et al., 1999; Colado, O'Shea, et al., 1999; Hewitt, 1994; Hysek et al., 2012; Kermanian et al., 2012; Morley et al., 2004). Pretreatment with carvedilol prior to MDMA may be an excellent harm reduction strategy, as carvedilol pretreatment is known to be safe and preserve the subjective effects of MDMA (Hysek et al., 2012). Alternatively, concurrent treatment with cannabinoids can prevent acute hyperthermia and also reduce serotonin depletion following MDMA (Morley et al., 2004). There is also evidence that *S*(+)-MDMA and racemic MDMA increase body temperature while *R*(–)-MDMA does not (Frau et al., 2012). Thus, *R*(–)-MDMA may present less neurotoxicity than other enantiomers.

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[2] 2-[p-(2-carboxyethyl) phenethylamino]-5'-*N*-ethylcarboxamido adenosine

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Finally, SSRIs can also be effective in preventing the neurotoxic effects of MDMA by inhibiting the serotonin transporter, but this is also the main mechanism of MDMA's effect (I.-H. Li et al., 2010; Piper et al., 2007; Sanchez et al., 2001). However, concurrent use of SSRIs and MDMA substantially increases the risk of serotonin syndrome. The antibiotic minocycline has also been found to be neuroprotective against MDMA toxicity in animals (Orio et al., 2009). However, the use of antibiotics should be avoided when other options are available in order to reduce evolutionary pressures toward antibiotic resistance (Read & Woods, 2014).

Ketamine. A review by Bell (2017) found that, in adults, ketamine reduced cell death and apoptosis by upregulating B-cell lymphoma 2 expression, an effect that can be neuroprotective in stroke, neurotrauma, subarachnoid hemorrhage, and status epilepticus. Still, there are neurotoxic effects that occur with frequent, high-dose, and/or prolonged ketamine administration that are linked to cognitive deficits (C. J. A. Morgan et al., 2009; Zhu et al., 2016). Chronic recreational ketamine users show reduced dopamine receptor density in the dorsolateral prefrontal cortex, which may be related to cognitive deficits (Narendran et al., 2005). Further, people who chronically use ketamine show frontal, parietal, and occipital atrophy along with lesions in multiple brain regions after 2–4 years of abuse (Liao et al., 2011; Chunmei Wang et al., 2013). Finally, ketamine users show disrupted white matter pathways and microstructure compared to poly-substance using controls (R. E. Roberts et al., 2014). Given that ketamine therapies for depression sometimes involve prolonged administration, these neurotoxic effects must be considered. Still, findings regarding recreational use may not apply due to drug impurities and different patterns of use.

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While the neurotoxicity of ketamine is of concern in adults only with chronic use, ketamine shows far more acute toxicity in neonates. This neurotoxic vulnerability primarily occurs during the period of synaptogenesis (Cheng Wang et al., 2005). In neonate rodents, ketamine can induce apoptosis or programmed cell death (C. P. Turner et al., 2012; Zhu et al., 2016).

Ibogaine. Ibogaine has been shown to cause neurodegeneration of Purkinje cells in the cerebellum of rats, likely due to glutamate excitotoxicity (Litjens & Brunt, 2016; O'Hearn & Molliver, 1993, 2004; Z. Xu et al., 2000). Neurotoxicity was not observed with doses lower than 25 mg/kg IP (Litjens & Brunt, 2016).

Astrogliosis and Associated Neuroplasticity Inhibition

Astrogliosis is a neurological defense response to minimize CNS damage and support repair (Kartavya et al., 2015). However, it eventually causes long-term harm by suppressing neuronal elongation and erecting barriers to axon regeneration and thereby reducing neuroplasticity.

MDMA. In animal models, MDMA is known to induce astrogliosis in response to its neurotoxic effects (O'Callaghan et al., 1995). However at 3- and 7-days post MDMA treatment, rats no longer showed astroglial activation, with dopaminergic lesions in the striatum present at 3 days but resolved at 7 days (Pubill et al., 2003). There is evidence that astrogliosis in response to MDMA is temperature-dependent, developing in rats treated at an ambient temperature of 22 °C but not at 10 °C (Ádori et al., 2011). There is also evidence that astrogliosis is dependent on the combination of MDMA enantiomers administered, with S(+)-MDMA increasing body temperature while R(–)-MDMA does

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not (Frau et al., 2012). Astrogliosis is increased when MDMA is combined with caffeine (Khairnar et al., 2014).

Ketamine. No studies were found linking ketamine to astrogliosis. Conversely, ketamine can prevent astrogliosis in response to neural stressors (Miyamoto et al., 2004).

Ibogaine. Ibogaine induces acute astrogliosis in the cerebellum of rats (O'Hearn et al., 1993). In female rats, astrogliosis also occurred in the striatum, while in male rats, astrogliosis also occurred in the hippocampus, cortex, striatum, and olfactory bulbs (O'Callaghan et al., 1996).

Chromosome and Genetic Damage

LSD. In a thorough review of human and animal studies [*N*=68], Dishotsky et al. (1971) found that LSD in its pure form, with concentrations used by humans, does not cause chromosome or genetic damage. Instead, Dishotsky et al. found that when chromosome damage is found in LSD users, it can be attributed to the effects of other drug abuse. In a second review, Long (1972) also found that while LSD may cause some chromosome breakage in humans, this effect is transitory.

Mescaline. Despite the concerns raised about chromosome and genetic damage in response to LSD, little research has been done to study these effects in mescaline. One study found that chromosome abnormalities were not significantly more prevalent among indigenous Huichol people residing in Mexico who frequently ingested peyote (Dorrance et al., 1975).

Ayahuasca. Boeira et al. (2001) found that harmine was cytotoxic and caused DNA damage and chromosome aberration in hamster lung cells in vitro. While the authors conclude that ayahuasca may pose a genotoxic risk in humans, more research is

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needed to validate this finding. As is seen with LSD and ketamine (see below), the DNA and chromosome abnormalities observed by Boeira et al. could be transient.

MDMA. Alvarenga et al. (2010) found that MDMA combined with 72 hours of sleep deprivation caused genetic damage in mice. A non-sleep-deprived condition was not tested. More research is needed to determine if this effect is present with therapeutic doses in humans.

Ketamine. In *Drosophila* flies, ketamine also showed genotoxic effects (Koksal & Gürbüzel, 2015). In mice, ketamine showed genotoxic effects in blood and brain cells with a dose of 140 mg/kg but not with the 80 or 100 mg/kg IP doses tested (Leffa et al., 2016). DNA damage was seen at all doses 1- and 12-hours following administration, but this damage was reversed at 24 hours for 80 and 100 mg/kg doses but not 140 mg/kg. Since even the lowest dose tested was orders of magnitude higher than doses used in ketamine therapies and that genotoxic effects were reversed after 24 hours, it is unlikely that therapeutic ketamine has lasting genotoxic effects in humans.

Carcinogenic Effects

LSD. A review by Dishotsky et al. (1971) found no evidence of carcinogenic effects of LSD [*N*=68].

Cardiovascular Disease

Classical Psychedelics and Carcinoid Heart Disease. Carcinoid heart valve disease results from neuroendocrine tumor growth on the heart valve (Hutcheson et al., 2011). Carcinoid heart valve disease pathogenesis has been linked to 5-HT_{2B} agonist medications (Hutcheson et al., 2011). Since mescaline, LSD, psilocybin, DMT, and MDMA all have 5-HT_{2B} agonist properties, there is some associated risk of developing

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heart valve disease. While most psychedelic use is infrequent and therefore presents less risk of carcinoid development, this is a particular concern with ongoing microdosing of classical psychedelics (K. Thomas, 2019).

MDMA. Altered regulation of the 5-HT_2 receptors in MDMA users can result in altered blood vessel volumes in different parts of the brain (some constricted, some dilated) that may increase the risk of cerebrovascular accidents (Ferrington et al., 2006; Reneman et al., 2000).

Oxidative Stress

MDMA. MDMA use may cause oxidative stress due to changes in brain energy regulation and can cause free radical damage (Downey & Loftis, 2014; Zhou et al., 2009). Oxidative stress contributes to the serotonergic toxicity of MDMA (Darvesh & Gudelsky, 2005)

Autonomic Dysfunction

MDMA. Heart rate variability and autonomic responsiveness markers were reduced among MDMA polydrug users compared to controls, with three of 12 MDMA users meeting the criteria for autonomic dysfunction (Brody et al., 1998). However, this study is not sufficient to demonstrate a causative effect for MDMA, especially given the associations between autonomic function, trauma, and substance use.

Parrott, Montgomery, et al. (2014) infer that MDMA increases long-term cortisol levels and stress response based on a finding by Parrott, Sands, et al. (2014) that cortisol levels were 400% higher in regular MDMA users than in controls. However, this study relied on a comparison between chronic MDMA users and a non-user control sample, which is not sufficient to determine causation. As a confound to the study, chronic stress

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has a medium to large effect on elevated cortisol levels, while the level of psychopathology has a small to medium effect based on a systematic review (Staufenbiel et al., 2013).

Hepatoxicity

Ayahuasca. Mello et al. (2018) found no evidence of hepatic damage among 22 people who took ayahuasca at least twice a month for a year or more.

MDMA. MDMA has hepatotoxic effects, particularly with chronic use (Cajanding, 2019). Corn silk was shown to be hepatoprotective against MDMA liver toxicity in rats (Karami et al., 2013).

Ketamine. There are reports of ketamine-induced liver toxicity both with recreational use and abuse and in clinical settings (R. F. Bell, 2012; Sassano-Higgins et al., 2016). However, this risk does not appear consistently across the literature.

Cystitis

MDMA. A case study describes a 25-year-old male with neurogenic bladder dysfunction following chronic MDMA use of 4 tablets/day for 3 months (Beuerle & Barrueto, 2008).

Ketamine. Ketamine can induce ulcerative cystitis, a severe bladder disorder (C. J. A. Morgan & Curran, 2011; Sassano-Higgins et al., 2016). In a web survey of 462 Spanish people who had used ketamine recreationally in the past year, 32% reported cystitis due to ketamine use (Giné et al., 2016). Cystitis was more likely among those who used ketamine once or more per week (OR=1.499). Middela and Pearce (2010) identified 110 individual cases of lower urinary tract symptoms related to ketamine abuse

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among 22 studies. Kidney dysfunction can also occur with heavy ketamine use as a secondary consequence of cystitis (C. J. A. Morgan & Curran, 2011).

Abdominal Pain

Ketamine. Frequent users of ketamine often report intense abdominal pain, sometimes called 'K-cramps' (Giné et al., 2016; C. J. A. Morgan & Curran, 2011; Sassano-Higgins et al., 2016; Tackett-Gibson, 2009). Additional ketamine is sometimes taken by recreational users to alleviate these cramps, despite perpetuating the problem (C. J. A. Morgan & Curran, 2011). Though the etiology of K-cramps is not fully known, it seems to be related to dilation of the bile duct that occurs in conjunction with ongoing ketamine use (C. J. A. Morgan & Curran, 2011).

Weight Loss

MDMA. Chronic use of MDMA can result in weight loss due to reduced food and water intake, increased urination and defecation, and other molecular mechanisms (Piper, 2007).

Sexual Dysfunction

Classical Psychedelics. McWaine and Procci (1988) reviewed sexual dysfunction associated with different drugs. They did not find any evidence for long-term sexual dysfunction associated with classical psychedelic use.

MDMA. In a study of MDMA mono-users [n=62, male, age=19–40, Taiwanese], 1.6% had severe erectile dysfunction (ED), 1.6% had moderate ED, 4.8% had mild to moderate ED, 11.3% had mild ED, and 80.6% had no ED (Bang-Ping, 2009). In a group of 17 males with MDMA use disorder, 64.7% had severe ED, 23.5% had mild ED, and 11.8% had no ED [age M=33.4, Turkish] (Kumsar et al., 2016). The MDMA use disorder

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group also showed significantly less sexual desire ($p<.005$) than controls. The higher prevalence of ED is likely due to frequent MDMA use.

Ketamine. An uncontrolled study showed that ongoing ketamine is associated with ED [n=804, age M=27.76, Taiwanese] (S. S.-D. Yang et al., 2018). A mechanism exists for long-term ketamine to induce ED, as was demonstrated in rats (Shang et al., 2016). Acutely, ketamine has been used in medical contexts to prevent and resolve erections in patients undergoing surgeries (Buffum, 1982). Women with ketamine cystitis had significantly lower measures of sexual function in all domains except for sexual desire compared to controls [N=56, age≥18, Taiwanese] (Jang et al., 2011).

Female Fertility

LSD. B. A. Mueller et al. (1990) did not find any association between ovulary dysfunction [n=221] or tubal infertility [n=150] and the use of LSD when compared to occurrence in women who had recently given birth [n=1,108].

Ketamine. Lee et al. (2000) found that progesterone serum concentration was lowered 1, 4, and 5 days after ketamine administration in female rats. Progesterone is important in preparing the uterus for pregnancy. For this reason, ketamine may be contraindicated for women trying to become pregnant.

Male Fertility

Ayahuasca. Chronic ayahuasca administration to male rats decreased spermatic reserves and transit time in a group exposed to four but not eight times the dose used in ritual settings (de Fátima Andrade Santos et al., 2017). There was no impact on sperm count, motility, morphology, or production with any ayahuasca dose.

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Ketamine. Anesthetic ketamine (30 mg/kg) reduced sperm motility in mice (Tan et al., 2011). Absalan et al. (2014) found that adding ketamine to human sperm samples reduced sperm motility, increased normospermia, and produced DNA fragmentation.

Vulnerability to Alzheimer's Disease

MDMA. Abad et al. (2019) found that MDMA contributes to the amyloid cascade that can lead to Alzheimer's disease in mice.

Ketamine. Chronic ketamine administration was found to result in hyperphosphorylation of tau in mice and monkeys after 6 months (Yeung et al., 2010). Hyperphosphorylated tau is an early marker of Alzheimer's disease.

Vulnerability to Parkinson's Disease

MDMA. There is some evidence that MDMA can cause abnormalities in the substantia nigra that are a risk factor for Parkinson's disease (Mursaleen & Stamford, 2016). Further, oxidative stress from MDMA can be neurotoxic to striatal neurons that are lost to Parkinson's disease (Mursaleen & Stamford, 2016). In one case, a 19-year-old male was diagnosed with Parkinson's disease following twice-monthly use of MDMA for the preceding 6 months (Kuniyoshi & Jankovic, 2003). He had a paternal family history of Parkinson's disease, and the authors propose that MDMA use may have accelerated the course of the illness. However, there is no human epidemiological evidence to support MDMA as a causative factor in developing Parkinson's disease (Doblin et al., 2004; Kish, 2003).

Vulnerability to Epilepsy

MDMA. MDMA increases susceptibility to seizures in rats for 30 days following administration (Huff et al., 2016). This appears to be due to the reduced concentration of

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GABAnergic neurons in the hippocampus because of glutamate toxicity triggered by increased dopamine from MDMA (Huff et al., 2016). This reduction in GABAnergic neurons has been shown to persist for at least 3-months, indicating that the reduction in seizure threshold may be chronic (G. Costa et al., 2013, 2017).

Minor Side Effects

Nausea and Gastrointestinal

Mescaline. Mescaline often produces nausea (S. Cohen, 1960). Two cases of abdominal pain, nausea, and diarrhea related to mescaline ingestion are described by Teitelbaum and Wingeleth (1977).

Ayahuasca. Ayahuasca commonly produces nausea (Heise & Brooks, 2017). Fotiou and Gearin (2019) argue that "ayahuasca purging should not be dismissed as a drug side effect or irrational belief" and instead advocate for the potential therapeutic effects of purging (p. 1). Through a series of case examples, they associate purging with emotional healing and describe ethnographic beliefs that support this notion.

Headaches

Psilocybin. M. W. Johnson et al. (2012) found that headaches were induced following psilocybin sessions in up to 89% of participants, depending on the dose administered in an RCT [*N*=18, 44% male, age=29–62, 89% White, 11% African American]. These headaches had a delayed onset, lasted no more than a day, and had only mild to moderate intensity. Incidence of headache ranged from 47% of participants at 5 mg/70 kg to 89% at 30 mg/kg.

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In a pooled analysis of multiple studies [*N*=110 subjects], Studerus et al. (2011) found that psilocybin increased the incidence of "headaches, head pressure or face pain" in a dose-dependent fashion ($p<.001$).

Nystagmus

Hebbard and R. Fischer (1966) found that acute intoxication with mescaline, LSD, and psilocybin increased eye saccade frequency, indicating increased nystagmus [*N*=4, male, age=22–24, race N/R]. The authors emphasize that nystagmus is essential for vision and that their study shows a drug-related change in biological response rather than a harmful side effect. No incidences of persistent nystagmus were reported.

Radant et al. (1998) examined the physiological effects of ketamine among 10 healthy men [age=21–25, race N/R]. They found that ketamine did induce nystagmus but did not report any persistent effects. Weiner et al. (2000) examined 20 cases of people presenting to the emergency room for issues related to ketamine abuse [55% male, age=15–40, "almost all" White]. In three of these cases, rotary nystagmus was observed, and no persistent nystagmus was reported.

Together, no cases of harmful or persistent nystagmus were identified for any of the psychedelics studied. Though nystagmus occurs under mescaline, LSD, psilocybin, and ketamine, it is a benign condition and should not be seen as a concern.

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Summary and Comparison

Summary Table 3 gives an overview of the medical safety of psychedelics throughout different life stages, while Summary Table 4 shows psychedelic-related risk factors and contraindications. In both tables, the following symbols are used:

- ↓ Lower dose indicated due to medical risk
- × Contraindication due to acute risk.
- ×× Strongly contraindicated due to acute risk.
- ××× Fatal contraindication.
- ⊗ Possible acute contraindication based on theory or case studies.
- ⊖ Caution is warranted due to a possible negative outcome.
- ⊖⊖ Extreme caution and medical supervision are warranted.
- ○ Demonstrated medical safety.
- ◌ No known contraindication but also no research indicating safety.
- ⦵ No known or theoretical contraindication, but caution is warranted.

Summary Table 5 synthesizes the long-term medical risks associated with the frequent use of each psychedelic. The following symbols are used:

- *** Strong risk association backed by numerous studies.
- ** Moderate risk association backed by several studies.
- * Mild risk that may be backed by only one or two studies or have a very low association with negative outcomes.
- ∅ Research indicates no associated risk.
- ? Research is ambiguous regarding risk.
- - Blank indicates no research found.

Summary Table 3

Life Stage and Psychedelic Safety

Stage of Life	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Infancy	⊗	⊗	⊗	⊗	⊗	×[NT]	×[NT]	⊗[Ht, b]
Childhood	⊖	⊖	⊖	⊖	○	⊖	⊖	⊖[Ht, b]
Adolescence	◌	○	◌	◌	○	⊖	○	⊖[Ht, b]
Adulthood	○	○	○	○	○	○	○	⊖[Ht, b]
Older Adulthood	⊖	⊖ / ○[μ]	○	⊖	◌	⊖[HypN, Ht, Stk]	⊖	⊖[Ht, b]
Pregnancy	⊗	×	⊗	⊖	⊖	×	×	⊗[Ht, b]
Indigenous use during pregnancy	Some	N/A	Not Typical[a]	N/A	Common	N/A	N/A	Yes
Evidence of teratogenicity	Possible	Weak	Not Studied	Unlikely	Weak or None	Yes	Yes	Not Studied
Potential to induce labor	Yes	Yes	Theoretically	Unknown	Unknown	Unknown	Unknown	Yes

Note. Symbol key on page 122. N/A = not applicable; [NT] = neurotoxic; [Ht] = cardiovascular risk; [Stk] = stroke risk.

[a] Sacred mushrooms were not given to pregnant women in Maria Sabina's lineage, though other indigenous traditions may differ.

[b] Based on the reviewed evidence, ibogaine is always risky due to its cardiovascular risks and extremely low safety ratio (0.9–4.4).

[μ] Safety demonstrated for LSD microdosing (≤ 20 μg)

Summary Table 4

Medical Risk Factors and Contraindications

Risk Factor	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Medical Conditions (This list is NOT EXHAUSTIVE, and a physician should be consulted regarding the impact of a psychedelic on any medical condition.)								
Epilepsy	⊖	⊖	⊖	-	-	××	⊖	-
Heart disease	⊖	⊖	⊖	-	-	⊖⊖[Ht]	⊖[Ht]	×××[Ht]
Heart failure	-	-	-	-	-	⊖⊖[HypN]	-	××× [Ht]
High blood pressure	-	-	-	-	-	⊖[Ht, Stk]	-	×××[Ht, Stk]
High stroke risk	⊖	⊖	⊖	-	-	×××[Stk]	⊖	×××[Stk]
Cystitis	-	-	-	-	-	-	⊖⊖	-
HIV/AIDS	-	-	-	-	-	⊖[HypN]	-	-
Pneumonia	-	-	-	-	-	⊖[HypN]	-	-
Cirrhosis	-	-	-	-	-	×[Lv, HypN]	-	-
Postoperative	-	-	-	-	-	×[HypN]	-	-
Underweight	-	-	-	-	-	⊖	-	-
Common Drug Interactions (This list is NOT EXHAUSTIVE, and medication interactions should be checked against other references.)								
SSRIs	⊖[SS]	⊖[SS]	⊖[SS]	-	-	×××[SS]	-	-
MAOIs	⊖[SS]	⊖[SS]	⊖[SS]	⊖[a]	-	×××[SS]	-	-
Psychotropic initiation (within 2 weeks)	-	-	-	-	-	×[HypN]	-	-
Diuretics	-	-	-	-	-	⊖[HypN]	-	-

Summary Table 4

Medical Risk Factors and Contraindications, Continued

Risk Factor	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Genetic Factors (see Chapter 3: Pharmacology)								
CYP2D6 poor metabolizer gene	-	-	-	-	-	Dose ↓	-	Dose ↓
*CYP2B6*6* (Common in African, African American, and some Asian populations)	-	-	-	-	-	-	Dose ↓	-
Neurological Disease Vulnerability (family history)								
Alzheimer's disease	-	-	-	-	-	-	⊖	-
Parkinson's disease	-	-	-	-	-	⊖	-	-
Epilepsy	-	-	-	-	-	×	-	-
Environmental Conditions								
High ambient temperature	-	-	-	-	-	×	-	-

Note. Symbol key on page 122. [Ht] = cardiovascular risk; [Stk] = stroke risk; [HypN] = hyponatremia risk; [Lv] = liver failure risk, [SS] = serotonin syndrome risk.

[a] The effects of DMT will be substantially prolonged and more similar to ayahuasca.

Summary Table 5

Long-Term Medical Risks Associated with Psychedelics

Effect	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Neurotoxicity and cognitive dysfunction[a]	?	∅	∅	∅	*	***[b]	**	*
Neuroplasticity inhibition (astrogliosis)	-	-	-	-	-	*	∅	*
Chromosome and genetic damage	∅	∅	-	-	?	?	∅	-
Carcinogenic effects	-	∅	-	-	-	-	-	-
Carcinoid heart disease	*C, μ	*C, μ	*C, μ	*C, μ	*C, μ	*C, μ	-	-
Cerebrovascular risk (stroke)	-	-	-	-	-	*	-	-
Oxidative stress	-	-	-	-	-	**	-	-
Autonomic dysfunction	-	-	-	-	-	**	-	-
Hepatotoxicity	-	-	-	-	∅	*	?	-
Cystitis	-	-	-	-	-	*	***C	-
Abdominal pain	-	-	-	-	-	-	***C	-
Weight loss	-	-	-	-	-	***C	-	-
Female sexual dysfunction	∅	∅	∅	∅	∅	-	**C	-
Male erectile dysfunction	∅	∅	∅	∅	∅	**C	***C	-
Reduced female fertility	-	∅	-	-	-	-	**C	-
Reduced male fertility	-	-	-	-	?	-	**C	-

Summary Table 5

Long-Term Medical Risks Associated with Psychedelics, Continued

Effect	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Increased risk of…								
Alzheimer's dementia	-	-	-	-	-	*	*^{C}	-
Parkinson's disease	-	-	-	-	-	**	-	-
Epilepsy	-	-	-	-	-	**	-	-

Note. Symbol key on page 122. ^{C} = risk only with chronic use; $^{\mu}$ = risk with microdosing.

[a] The impact of neurotoxicity on neurocognitive functioning is elaborated in Chapter 8.

[b] Can occur after only a few uses with high doses, impure substance, or under non-ideal circumstances (high temperature).

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Chapter 6: Phenomenology

William James defined psychology as "the Science of Mental Life, both of its phenomena and of their conditions" (James, 1890, p. 1). Originally, the phenomenology of psychedelics was excluded from this review to limit the scope. However, it soon became clear that certain phenomenological experiences were linked with treatment outcomes, which necessitated that phenomenology be covered. The goal of this chapter is to give an overview of the phenomenology of different psychedelics through thematic analyses, a summary of specific experiences that are common with each psychedelic, and a deeper review of phenomenology that is specifically relevant to psychedelic treatment outcomes. Domains of literature specifically excluded are:

- **Animal Studies:** By definition, phenomenology excludes animal studies, given that animals are unable to communicate their internal experience directly to humans. Proxy behaviors in animals believed to align with human experiences are largely excluded from this review.
- **Psychedelics as Psychotomimetic:** Studies on whether psychedelics are psychotomimetic were excluded as the similarity of psychedelic states to psychosis or schizophrenia is not particularly relevant to psychedelic-assisted treatment. While psychosis-like phenomena are described, establishing psychedelic states as "model psychoses" is more useful to the study of psychosis than it is to the study of psychedelics.

For psychedelics with a larger body of phenomenological research, such as ketamine, MDMA, and ayahuasca, quantitative studies were only included if they provided incremental evidence of phenomena not otherwise documented in the review.

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Thematic Analyses of Psychedelic Phenomenology

Sixteen thematic analyses and five interpretive phenomenological analyses (IPA) were found examining psychedelic phenomenology. The themes identified prior to, during, and after psychedelic experiences are presented in Table 4, Table 5, and Table 6, respectively. Clusters of themes identified by the present author are listed in the left column of the tables, with quoted themes from each study categorized in the body of the tables. The text described below describes the studies referenced in the tables.

Mescaline and LSD. No thematic analyses or IPAs were found for mescaline or LSD experiences except for Neitzke-Spruill (2019), which was included under psilocybin for reasons detailed below.

Psilocybin. Turton et al. (2014) performed an IPA examining the experiences of healthy psychedelic-experienced volunteer subjects who were administered psilocybin within an MRI scanner [*N*=15, 66% male, age *M*=34.1, race N/R]. Nine phenomenological categories were uncovered that are summarized in the tables, with the exception of "aspects relating to the scanner and research environment," which was judged to be specific to the circumstances of the experiment rather than the general phenomenology of psilocybin.

Zamaria (2016) interviewed 8 adults about their experiences with psilocybin and performed within-case and cross-case analyses that produced 11 themes within the categories of Set, Experience of Psilocybin Effect, and Persisting Aftereffects [75% male, age=19–38, 75% White].

Belser et al. (2017) performed an IPA using semi-structured interviews with 13 adult participants ages 22–69 [54% male, 92% White]. All participants had clinically

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significant anxiety due to a cancer diagnosis and received psilocybin psychedelic therapy alongside psychotherapy with a focus on meaning-making. Transcribed interviews were analyzed by five researchers using an IPA methodology to uncover general themes.

Neitzke-Spruill (2019) examined 200 reports of psychedelic experiences from 100 people, sourced from the Timothy Leary Papers archival collection [approx. 86% male, age and race N/R]. Most of these sessions were with psilocybin, except for four mescaline-psilocybin combinations, 17 LSD experiences, six mescaline experiences, and four DMT experiences. As the analysis did not differentiate by substance, and the majority of the reports were with psilocybin, the data was taken to represent the phenomenology of psilocybin experience.

DMT. Cott and Rock (2008) performed a thematic analysis of 19 reports of DMT experiences procured through an online survey in response to the question "Please describe in as much detail as possible your subjective experience of the DMT-induced state" [95% male, age=16–41, race N/R] Nine themes were identified using a phenomenological methodology.

Ayahuasca. Kjellgren et al. (2009) collected narratives of group ayahuasca experiences from 25 Northern Europeans [56% female, age=22–63]. The narratives were analyzed using The Empirical Phenomenological Psychological Method (Karlsson, 1995) to reveal 33 categories that were organized into six themes.

Osborn (2012) looked at the effect of ayahuasca experience on anxiety and mental health among six Americans who traveled to Peru for the experience [50% male, age>18, race N/R]. Twenty-nine themes were identified through a narrative phenomenological method. Many of these identified themes were related to the specific circumstances of

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participants engaging in ayahuasca for the purpose of treating anxiety. These themes were excluded from the tables.

Ryan (2015) performed an IPA examining the experience of three British ayahuasca users [2/3 female, age=35–41, race N/R]. Semi-structured interviews were performed, and analysis revealed three major themes.

Wolff et al. (2019) examined the ayahuasca experiences of nine tourist participants in a Peruvian ayahuasca retreat [6/9 male, age=27–71, race N/R]. Qualitative content analysis was used to extract themes and categories from interviews following the ayahuasca ceremonies.

Trichter et al. (2009) performed half-hour semi-structured interviews 24–72 hours prior, 12 hours following, within 1 week, 1 month, and 3 months following novice ayahuasca ceremonies in San Francisco and Canada [*N*=49, 47% male, age *M*=33, 100% White]. Interviews were transcribed, and themes were extracted.

Bresnick and Levin (2006) developed a structured interview based on the phenomenological descriptions by Strassman (2001) and Shanon (2002a, 2002b). This questionnaire was then given to 21 people participating in a 10-day ayahuasca seminar in Brazil [67% male, age *M*=44.2, nationalities: 48% U.S., 23% S. America, 15% W. Europe, 5% E. Europe, 5% Asia, 5% N. Africa).

MDMA. Herzberg (2012) examined reports of five participants in MDMA-assisted psychotherapy [4/5 female, age=30–46, White]. Thematic analysis using a qualitative, quasi-phenomenological framework revealed 30 themes. Some themes were excluded from the tables as they were specific to participants' motives for engaging in MDMA-assisted psychotherapy.

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Sola (2017) recorded narrative accounts of MDMA-assisted psychotherapy for PTSD among four combat veterans [male, age=29–36, White]. Thematic analysis was performed, yielding nine primary categories. One category, "direct statements about MDMA psychotherapy," was excluded from the tables.

Ruger (2018) performed an IPA examining the experience of seven people in the United States treated for PTSD with MDMA-assisted psychotherapy [demographics N/R]. Three superordinate themes emerged, along with eight subordinate themes that are summarized in the tables.

Ketamine. Muetzelfeldt et al. (2008) interviewed 90 ketamine users: 30 frequent users [63% male, age *M*=25.9, 87% White], 30 infrequent 'recreational' users [80% male, age *M*=27.4, 70% White], and 30 ex-users who had abstained for at least 3 months [67% male, age *M*=27.3, 70% White]. Interviews were coded for categories, and frequencies of codes were used to identify themes. These themes were very broad (i.e., "negative psychological aspects"), so sub-themes were reported instead. As these were recreational and frequent users, only themes identified regarding the phenomenological effects of ketamine during the experience were included, as therapeutic use is less likely to produce the same reported after-effects of frequent use, many of which were quite negative.

Ibogaine. Schenberg et al. (2017) performed semi-structured interviews examining the subjective effects of ibogaine in 22 patients being treated for substance use disorder [68% male, age=22–53, White, 95% Brazilian]. 26 themes were identified through thematic analysis of transcripts, which are reported in the tables.

Camlin et al. (2018) performed semi-structured interviews with ten U.S. citizens who underwent ibogaine treatment for opioid use disorder in Mexico [70% male,

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age=21–48, 7 Caucasian, 2 Hispanic, 1 African American]. Four categories of themes emerged.

Terpak (2019) interviewed seven American and Canadian patients undergoing ibogaine addiction treatment at a center in Mexico [5/7 male, age=27–56, race N/R]. Interviews were transcribed and coded to identify themes.

Kohek et al. (2020) performed a semi-structured interview with 20 individuals who had recently taken ibogaine [60% male, age=23–57, race N/R]. A grounded theory approach was used to analyze these interviews and generate categories and sub-categories of themes.

Table 4

Phenomenological Themes Prior to Psychedelic Experience

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Preparation	"Substantial preparation" (Zamaria, 2016).		"Motivation and aim" (Kjellgren et al., 2009). "Had positive expectations of ayahuasca experience" (Osborn, 2012). "Conscious mindset or pre-experienced" and "unprepared" (Wolff et al., 2019).	"Preparation" and "expectations" (Herzberg, 2012).		
Anxiety Prior to Experience	"Preliminary anxiety" (Zamaria, 2016).			"Trepidation" (Herzberg, 2012).		
Waiting for Effects	"The waiting game" (Neitzke-Spruill, 2019).					

Table 5

Phenomenological Themes During Psychedelic Experience

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Intensity & Onset	"Intensity and onset of effects" (Turton et al., 2014).	"Extreme intensity" (Cott, 2008).	"Intensification of imaginations and contemplative thoughts" and "intense visions" (Wolff et al., 2019).	"Slide into the medicine," referring to sudden onset, surprise, and letting go (Herzberg, 2012).	"Intensity/a loss of control" (Muetzelfeldt et al., 2008).	
Physical Side Effects			Vomiting, stomach pain, diarrhea, tremor, raised temperature, restlessness, exhaustion, and others (Wolff et al., 2019). "Found physical component important and part of the healing experience" (Osborn, 2012).	"Somatic experience," "fluctuation in temperature, heat, sweating" (Herzberg, 2012). Nausea, bruxism, headache, increased energy, and others (Baylen & Rosenberg, 2006).	"Nausea/vomiting" and "restlessness" (Muetzelfeldt et al., 2008).	"Malaise, nausea, colics, and dizziness," "changes in heart rate," "difficulty in body movement," and "purgative cleansing" (Schenberg et al., 2017). "Vomiting," "physically draining experience" (Camlin et al., 2018). "Physical effects," body temperature fluctuations, appetite suppression, and dizziness (Kohek et al., 2020).
Cognitive Changes	"Cognitive changes" (Turton et al., 2014). "Profound shift in attention" (Zamaria, 2016).		"Boosted thought process," "inordinate thought process," "absorbed by content and thoughts," and "no sense was recognized" (Wolff et al., 2019). "High		"Cognitive disorganization," "helps me focus," "memory impairments," and "different ways of thinking/enhanced creativity"	"Thought acceleration and/or clarity" (Schenberg et al., 2017). "Sped-up thoughts" (Terpak, 2019). Wakefulness for at least 24 hours and enhanced problem-solving capabilities (Kohek et al.,

Table 5

Phenomenological Themes During Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
			rate of thought" and "other states of consciousness" (Bresnick & Levin, 2006).		(Muetzelfeldt et al., 2008).	2020). "Impaired psychomotor coordination, dizziness" (Camlin et al., 2018).
Distortions to Sense of Self	"Alterations to identity" (Belser et al., 2017).	"Distortion in sense of time, space, self" (Cott, 2008).	"Supernatural experience" including "becoming invisible, traveling through space/time without the body" (Trichter et al., 2009). "Similar to dream self" (Bresnick & Levin, 2006).		"Body/sensory distortion" (Muetzelfeldt et al., 2008).	"Ego dissolution (death and rebirth)" (Kohek et al., 2020).
Visual Distortions	"Perceptual changes including visual…distortions" (Turton et al., 2014). "Sensory phenomena" (Neitzke-Spruill, 2019).	"Hallucinations" (Cott, 2008).	"Visual hallucinations" (Wolff et al., 2019). "Presence of light and geometric patterns" (Trichter et al., 2009). "Geometric patterns," "synesthesia," and "aesthetic experiences" (Bresnick & Levin, 2006).		"Psychedelic aspects (including audio/visual hallucinations)" (Muetzelfeldt et al., 2008).	"Open eye visuals" (Kohek et al., 2020). "Cyclical/organizational imagery in visions" (Camlin et al., 2018).
Visions and hallucinations		"Hallucinations" (Cott, 2008).	"Scenic visions," "abstract visions," "aesthetic, positive		"Psychedelic aspects (including audio/visual	"Animals, indigenous peoples, and landscapes," "dreamlike visions"

Table 5

Phenomenological Themes During Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
			visions," and "caressing affective visions" (Wolff et al., 2019). "Presence of light and geometric patterns" (Trichter et al., 2009).		hallucinations)" (Muetzelfeldt et al., 2008).	(Schenberg et al., 2017). "Seemingly meaningless visions…" or "limited visions, or no visions at all" (Terpak, 2019). "Closed eye visuals" that included "sceneries and landscapes" and "horrific scenarios" (Kohek et al., 2020).
Vividness of Experience		"Lucidity" (Cott, 2008).	"Feelings of clarity" (Bresnick & Levin, 2006).			
Auditory Effects	"Auditory… distortions" (Turton et al., 2014).				"Audio/visual hallucinations" (Muetzelfeldt et al., 2008).	"Auditory hallucination (buzz)," "heightened hearing," "verbal (pseudo-) hallucinations" (Schenberg et al., 2017). "Auditory effects" (Terpak, 2019). "Buzzing and/or vibration sounds at onset of experience" (Camlin et al., 2018).
Somatic Effects	"Somatosensory distortions" (Turton et al., 2014). "Sensory phenomena" (Neitzke-Spruill, 2019).		"Haptic hallucinations" (Wolff et al., 2019).	"Somatic experience" including dancing, touching, fluffing, and desire for physical touch…experience of structural healing" (Herzberg, 2012). "An	"Enhanced appreciation of music/dancing" and "dissociation" (Muetzelfeldt et al., 2008).	"Physical sensations" (Terpak, 2019). "Subjective experience of localized brain activation" (Camlin et al., 2018). "Feelings of 'brain resetting'" (Schenberg et al., 2017).

Table 5

Phenomenological Themes During Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
				intellectual understanding vs. an embodied knowing" and "basking in novel felt experiences" (Ruger, 2018). "Unexplained phenomena" including merging with objects (Sola, 2017).		
Olfactory Effects						"Olfactory hallucinations" (Schenberg et al., 2017).
Altered Time Sense and/or Distortion of Space	"Time sense" (Neitzke-Spruill, 2019).	"Distortion in sense of time, space, self" (Cott, 2008).	"Supernatural experience" including "traveling through space/time without the body" (Trichter et al., 2009). "Unusual experience of space…unusual experience of time" (Bresnick & Levin, 2006).		Distorted time perception, timelessness, or irrelevance of time (Kohek et al., 2020).	
Sense of Familiarity		"Sense of Familiarity" (Cott, 2008).				

Table 5

Phenomenological Themes During Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Positive Emotions	"Exalted feelings of joy, bliss, and love" (Belser et al., 2017). "Positive emotional state" (Zamaria, 2016).	"Affective distortions," "intense positive (e.g., euphoria)" (Cott, 2008).	"Sense of honor, respect, gratitude and/or awe," "sense of peace and/or calm" (Trichter et al., 2009). "Pleasure" and "positive aspects" (Bresnick & Levin, 2006).	"Intense emotion," including positive emotions (Herzberg, 2012). "Basking in novel felt experiences" (Ruger, 2018).	"Enhanced amusement" and "contentedness/helps me relax" (Muetzelfeldt et al., 2008).	"Mix of dark/scary and joyful/peaceful imagery" (Camlin et al., 2018).
Negative Emotions & Distress	"Experiences of transient psychological distress" (Belser et al., 2017). "Changes in mood" (Turton et al., 2014). "Emotional phenomena" (Neitzke-Spruill, 2019).	"Affective distortions," "negative (e.g., anxiety)" (Cott, 2008).	"Contractile frightening state," during first half of the experience (Kjellgren et al., 2009). "Scary, hard, or out of control" (Osborn, 2012). "Doubts, worrying thoughts," "obscure, negative visions" (Wolff et al., 2019). "Desolation," "overwhelming and unpleasant feelings" (Trichter et al., 2009). "Fear or anxiety" (Bresnick & Levin, 2006).	"Resistance" and "intense emotion," including challenging emotions (Herzberg, 2012). "Tension, conflict, overwhelm" (Sola, 2017).	"Paranoia," "depression," and "increased anxiety" (Muetzelfeldt et al., 2008).	"Fear and distress due to past wrongdoings," "mood lability," "unpleasant and challenging sensations," and "fear of dying caused by symptoms" (Schenberg et al., 2017). "Mix of dark/scary and joyful/peaceful imagery" (Camlin et al., 2018). "Strong emotional component," primarily negative emotions and "withdrawal" feelings (Terpak, 2019).
Trauma Processing & Re-experiencing	"Effects of memory," referring to recollecting old, distressing		"Desolation," including "reexperienced traumas from earlier	"Regression and trauma work" (Herzberg, 2012). "Protector and	"Reliving childhood experiences," "past lived experiences," "fear and distress due	"Intensified memory recollections," visions of "past lived experiences" (Schenberg et al., 2017).

Table 5

Phenomenological Themes During Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
	memories (Turton et al., 2014).		times in their lives" (Trichter et al., 2009).	protected parts" and "processing trauma" (Sola, 2017). "Reclaiming lost parts of the self" and "being there and not there," regarding trauma memories (Ruger, 2018).	to past wrongdoings," (Schenberg et al., 2017). "Catharsis" (Kohek et al., 2020).	
Sudden Release from Distress			"Sudden transformation of the experience" following frightening state (Kjellgren et al., 2009). "Experienced changes after having vomited" (Wolff et al., 2019).	"Tolerance of conflict, release" (Sola, 2017). "Released from fear's captivity" (Ruger, 2018).		"Experience of addiction leaving body" (Terpak, 2019)
Social Relatedness & Spontaneity	"Spontaneity" (Neitzke-Spruill, 2019)				"Increased sociability," "feelings of introversion," and "negative sociability" (Muetzelfeldt et al., 2008).	
Enhanced Empathy				"Empathy" (Herzberg, 2012). "Prosocial experiencing: interpersonal" (Sola, 2017).	"Enhanced empathy" (Muetzelfeldt et al., 2008).	"Empathy, love and prosocial behavior" (Kohek et al., 2020).

Table 5

Phenomenological Themes During Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Spiritual & Mystical Experience	"Spiritual or mystical type experiences" (Turton et al., 2014). "Transcendental experience" (Zamaria, 2016).	"Spirituality, learning or being taught about truths of the universe/self" (Cott, 2008)	"Limitless expansive states with transpersonal experiences" (Kjellgren et al., 2009). "Wisdom, mystical, spiritual, or religious content" (Wolff et al., 2019). "Contact with inner wisdom" (Osborn, 2012). "Spiritual experience" (Trichter et al., 2009). "Related to spiritual" (Bresnick & Levin, 2006).	"Unexplained phenomena" including mystical type, transpersonal, and transcendent experiences (Sola, 2017).		"Experience described as 'spiritual'" and "religious iconography" visions (Schenberg et al., 2017). "Spiritual states" (Kohek et al., 2020).
Interconnectedness & Unity	"Movement from feelings of separateness to interconnectedness" (Belser et al., 2017). "Unity Consciousness" (Zamaria, 2016). "Boundless or Unitive Experiences" (Neitzke-Spruill, 2019).		"Felt a part of something bigger or a larger reality" (Osborn, 2012). "Sense of connection" (Trichter et al., 2009). "Oneness" (Bresnick & Levin, 2006).	"Unexplained phenomena" including unitive experiences (Sola, 2017)		
Death & Rebirth Experiences			"Death/near-death experiences" (Trichter et al.,			"Ego dissolution (death and rebirth)" (Kohek et al., 2020)

Table 5

Phenomenological Themes During Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
			2009). "Thoughts of death or dying" (Bresnick & Levin, 2006). "Spiritual re-birth" (Ryan, 2015).			
Introspection & Self-Reflection	"Increased introspection" (Zamaria, 2016). "Experience of Self" (Neitzke-Spruill, 2019).		"Reflections" (Kjellgren et al., 2009). "Insights through own reflection" (Wolff et al., 2019). "Self reflection and/or insights on personal life" (Trichter et al., 2009). "Exceptional understanding," "Aha! experience" (Bresnick & Levin, 2006).	"Insight" and "acceptance and openness" (Herzberg, 2012). "Prosocial experiencing: intrapsychic" (Sola, 2017).		"Insights and healing related to potential root causes of one's addiction and other mental health issues" (Terpak, 2019). "Self-psychoanalysis enhancement" and "observer quality" (Kohek et al., 2020).
New Perspective on the World	"Epoché" (Neitzke-Spruill, 2019).		"Experienced expanded world view" (Osborn, 2012).	"Living authentically: truth vs. denial" (Ruger, 2018).		
Imagining Future Scenarios						"Hypothetical future situations" and "accidents" (Schenberg et al., 2017). "Entering into specific settings" (Camlin et al., 2018).
Experiencing Other Realities		"Entering other realities" (Cott, 2008).	"Placed into other realm" (Wolff et al., 2019). "Alternate			

Table 5

Phenomenological Themes During Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
			realities" (Bresnick & Levin, 2006).			
Personification of the Substance			"Received messages" from "ayahuasca" (Wolff et al., 2019). "Found that Ayahuasca as a medicine knows issues that need most immediate work" (Osborn, 2012).	"The 'maternal container': A personification of MDMA" (Ruger, 2018).		"Meeting with iboga entities" (Schenberg et al., 2017). "Communicating with ibogaine" (Terpak, 2019).
Encountering Other Sentient Beings		"Contact with other sentient beings, which were described as true or real experiences rather than hallucinations" (Cott, 2008).	"Weird beings," "visions of animals," and "received messages" from "unrecognized other" (Wolff et al., 2019). "Supernatural experience" including "interacting with spirit creatures, spirit guides, or spirit animals" (Trichter et al., 2009).			
Encounters with the Dead/ Ancestors/ Loved Ones	"Appearance of loved ones as guiding spirits" (Belser et al., 2017).		"Felt presence of others" and "received messages" from "ancestor, family member" (Wolff et al., 2019).			"Meeting with deceased relatives" (Schenberg et al., 2017). "Ancestors and entities" (Kohek et al., 2020).

Table 6

Phenomenological Themes After Psychedelic Experience

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Improvement in Psychological Functioning	"Short term reduction in anxiety," "assistance with psychological distress," and "inspired behavioral change" (Zamaria, 2016).		"Psychotherapeutic healing" (Ryan, 2015). "Reduced symptoms of anxiety, depression, drug and or alcohol abuse, and improved ability to cope with stress," "improved health overall," "addressed core or challenging issues," "learned not to take things personally," "learned not to judge others or self," "liked self better," (Osborn, 2012). "Healing" (Trichter et al., 2009).	"Clarity" and "peace" (Herzberg, 2012). "Released from fear's captivity,'" "making meaning in the tragedy," and "reclaiming lost parts of the self" (Ruger, 2018). "Processing trauma," "prosocial experiencing: interpersonal," and "prosocial experiencing: intrapsychic" (Sola, 2017).		"Nearly immediate and lasting attenuation of withdrawal symptoms," "minimal to no cravings during or after the experience," and "increased self-acceptance/decreased self-critical thought patterns" (Camlin et al., 2018). Feeling happy and joyful for days or months afterward (Kohek et al., 2020).
Persisting Insight	"Persisting insight" (Zamaria, 2016). "Embodied knowledge," "boundary shifts," and "moments of clarity" (Neitzke-Spruill, 2019).		"Changed worldview and new orientation to life" (Kjellgren et al., 2009). "Learned everything is interconnected," "experienced spiritual component positively," and			"More spiritual outlook" (Camlin et al., 2018). Increased self-awareness for days or months afterward (Kohek et al., 2020).

Table 6

Phenomenological Themes After Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
			"found truth, cut through layers of false belief" (Osborn, 2012). "Self reflection and/or insights on personal life" (Trichter et al., 2009).			
Integration of Experience	"Framing the experience" (Neitzke-Spruill, 2019). "Individual interpretation of the experience" (Turton et al., 2014).			"Integration" (Herzberg, 2012)		
Ineffability	"Ineffability" (Belser et al., 2017). "Individual interpretation of the experience" (Turton et al., 2014). "Mere words!" (Neitzke-Spruill, 2019).		"Ineffability" (Cott, 2008)			"The experience is difficult to describe" (Camlin et al., 2018)
Difficulty Recalling Experience						"Seemingly meaningless visions; difficulty remembering visions" (Terpak, 2019)
Comparisons with Other Experiences	"Comparisons with other experiences" (Turton et al., 2014)		"Appraisal of the process" (Wolff et al., 2019)			"Ibogaine is different from any other drug" (Schenberg et al., 2017)

Table 6

Phenomenological Themes After Psychedelic Experience, Continued

Theme	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Sharing the Experience	"Sharing the experience with loved ones posttreatment" (Belser et al., 2017)					"Ibogaine would be effective in helping others" (Camlin et al., 2018)
Change in Social Perspective			"Materialistic society anti-spiritual" (Ryan, 2015). "Learned not to judge others or self" (Osborn, 2012).			
Desire to Repeat the Experience			"Wanted to return for more healing and learning" and "wants to continue using ayahuasca as a medicine for foreseeable future" (Osborn, 2012)			
Distress & Negative Reflections				"Distress" and "disappointment" (Herzberg, 2012)		

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Changes in Mental Process and Organization

Psychotomimetic

Classical Psychedelics. Early psychedelic researchers often classified the effects of mescaline, LSD, and psilocybin as "psychotomimetic" or mimicking psychosis (Bercel, 1956; Guttmann, 1936; Hollister, 1964; Kleinman et al., 1977; Osmond & Smythies, 1951; Sloane & Doust, 1954; Stockings, 1940). As time has progressed, the phenomenology of classical psychedelics has been differentiated from that of psychosis. While classical psychedelics do induce an ego disturbance similar to schizophrenia, Hermle and Kraehenmann (2018) classify these disturbances as more severe in schizophrenia. They also note more dread of ego dissolution associated with schizophrenia. In terms of hallucinatory content, classical psychedelics and schizophrenia can both involve visual hallucinations, but delusions and auditory hallucinations are not typically experienced with classical psychedelics.

DMT. DMT tends to produce phenomena similar to the positive symptoms of schizophrenia, including disordered thoughts and inappropriate affect (Gouzoulis-Mayfrank et al., 2005). This was compared with ketamine, which tends to produce more of the negative symptoms of schizophrenia such as, attentional deficits, bodily perception disturbance, and catatonia.

MDMA. MDMA appears to produce only mild psychotomimetic symptoms compared to psilocybin and ketamine (Hermle & Kraehenmann, 2018; Vollenweider, 2001). These mild symptoms tend to include disordered thinking and attention along with depersonalization and derealization (Vollenweider, 2001).

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Ketamine. The acute effects of ketamine continue to be characterized as a model psychosis that is used to study psychosis and schizophrenia (Corlett et al., 2019; Frohlich & Van Horn, 2014). Ketamine has been found to stimulate the positive, negative, and cognitive symptoms of acute schizophrenia (Frohlich & Van Horn, 2014). It also induces similar dopaminergic and GABAergic dysfunction, functional dysconnectivity, and abnormal cortical EEG patterns (Frohlich & Van Horn, 2014).

Delusions and Paranoia

LSD. Barr et al. (1972) saw an increase in suspiciousness ($p<.05$) under 100 μg LSD compared to baseline and placebo [N=50, 100% male, age=21–43, race N/R, professional actors] (p. 41). Suspiciousness was measured using a 74-item questionnaire developed specifically for the study with the aim of capturing the subjective aspects of altered states of consciousness.

Psilocybin. Griffiths et al. (2011) found that delusions and paranoid thinking occurred in 44% of participants over the course of 4 psilocybin sessions at doses ranging from 0–30 mg/70 kg [N=18, 45% male, age=29–62, race N/R]. All of these experiences occurred during high-dose sessions, with 7 of 8 such experiences occurring at 30 mg/70 kg and 1 of 8 occurring at 20 mg/70 kg. Such experiences did not affect the frequency of complete mystical experiences, with 4 occurrences among the 8 who experienced delusions and paranoid thinking (50%).

Ayahuasca. Shannon (2002b) reveals an instance where enhanced meaningfulness and occurrence of synchronicities during ayahuasca ceremonies led to lasting thoughts that could be classified as paranoia and delusions. Shannon writes:

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> In one of my first Ayahuasca sessions, I found myself sensing that all that had happened to me during the day before the session had been orchestrated. The people I met, those I joined, and those I avoided were all part of a scheme. There was sense, I felt, and order to it all, nothing was by chance. (p. 245)

Enhanced meaningfulness and synchronistic phenomena occur with other psychedelics, including LSD and psilocybin, and could lead to paranoia and delusions through a similar mechanism. Regarding this phenomenon, Sola comments that "Paranoid thinking and mystical thinking are not to be fully separated. They are overlapping and intricately related, in a sense one phenomena in the shift from duality to non-duality." (E. Sola, personal communication, October 12, 2020). Thus, with all the psychedelics, experiences of paranoia and delusions must be contextualized by their potential alignment with spiritual and mystical development and the confusion that can come from having such novel and numinous experiences.

Ketamine. Micallef et al. (2002) saw increased self-reported delusions under 0.5 mg/kg IV ketamine (p=.002) compared to placebo [N=8, 50% male, age=22–33, race N/R]. G. D. Honey et al. (2005) and R. A. E. Honey et al. (2003) saw delusions of reference in three of 13 participants under 100 ng/ml plasma ketamine as measured by the Present State Examination, ninth edition [46% male, age=18–64, race N/R]. Delusions of reference were not seen with placebo or 50 ng/ml plasma ketamine.

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Visual Effects

Visual Distortions and Illusions

Mescaline. Hartman and Hollister (Hartman & Hollister, 1963) found no significant impact of mescaline (5 mg/kg) on objective color perception [n=18, age, sex, and race N/R].

LSD. Brengelmann (1958) found a significant increase (p=.005; d_c=0.60) in after-image persistence of a square viewed continuously for 20 seconds in a lighted tube among healthy normal volunteers under 60 μg IV LSD in a double-blind placebo-controlled design [N=8, age=25–31, sex and race N/R]. Liebert (1958) found that under 25–40 μg LSD, subjects estimated the size of their head and external objects to be larger than without LSD (p<.05) [n=18, 61% male, age=21–38, race N/R]. Weckowicz (1959) saw no difference in size constancy with 35 μg LSD compared to placebo but did see an increased scatter of size estimates [N=18, 50% male, age=17–33, university students].

Hartman and Hollister (Hartman & Hollister, 1963) found that while subjects reported enhanced color perception and vividness, LSD (1 μg/kg) decreased (p<.05) objective perception of the color of red-yellow and yellow-orange hues [n=18, age, sex, and race N/R].

Barr et al. (1972) saw a highly significant increase in self-reported visual distortions (p<.001) under 100 μg LSD compared to baseline and placebo [N=50, 100% male, age=21–43, race N/R, professional actors] (p. 41). Visual distortions were measured using a 74-item questionnaire developed specifically for the study with the aim of capturing the subjective aspects of altered states of consciousness.

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Psilocybin. Keeler (1965) found that psilocybin (200 μg/kg) significantly increased (p<.01) after-image perception with a positive correlation to altered visual experience [N=10, young adults, race and sex N/R]. Hartman and Hollister (Hartman & Hollister, 1963) found that psilocybin (150 μg/kg) decreased (p<.05) objective perception of color across all hue ranges [n=18, age, sex, and race N/R].

MDMA. MDMA is associated with visual illusions such as "objects in room 'breathing,' grass stains on shoes 'glowing,' or things looking 'dreamy' or magnified" (D. S. Harris et al., 2002, p. 399). Davidson and Parrott (1997) found that distorted vision occurred in 65% of recreational MDMA users, while hallucinations occurred in 60% [N=20, 55% male, age=18–31, race N/R].

Ketamine. Coull et al. (2011) found no significant effect of ketamine (100 ng/ml plasma) on color discrimination [N=13, 46% male, age M=23.1, race N/R].

Synesthesia

R. J. Stevenson and Tomiczek (2007) suggest that the experiences of synesthesia occasioned by psychedelics may be due to thalamic down-regulation. Petri et al. (2014), on the other hand, suggest that synesthesia may arise with psychedelics due to greater functional communication across the brain.

Mescaline. Simpson and McKellar (1955) documented various synesthesias that occurred during a series of mescaline (0.3–0.5 g) sessions [N=4; gender, age, and race N/R; two synesthetes].

LSD. Terhune et al. (2016) found that LSD synesthesia does not show stimulus-specificity or consistency between color-grapheme or color-sound associations as is present in "genuine synesthesia."

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Dream-Like Experience

Sanz et al. (2018) compared accounts of psychedelic experiences obtained from www.erowid.org [*n*>20,000] with dream reports from www.dreamjournal.net [*n*>200,000] using latent semantic analysis [sample demographics not available]. The analysis found descriptions of dissociative drugs (including ketamine) to be most similar to dreams, followed by deliriant drugs, serotonergic psychedelics (including mescaline, LSD, psilocybin, DMT, ayahuasca, and ibogaine), entactogens (including MDMA), depressants/sedatives, antipsychotics/antidepressants, and stimulants. The study demonstrates that psychedelic experiences do have strong similarities to dream experiences but that dissociative and deliriant drug experiences tend to be most dream-like. In comparison to high-lucidity dreams, LSD, psilocybin, and mescaline experiences were ranked first, fourth, and ninth, respectively, out of 165 substances. This lends support to the notion that classical psychedelics preserve the capacity for meta-cognition within a dream-like state.

Kraehenmann (2017) also remarks on the similarities between classical psychedelics and dreaming but highlights the differences with psychedelic experience, including more input from the environment, clarity of consciousness, and meta-cognitive abilities. Kraehenmann goes on to characterize classical psychedelic experiences as closer to lucid dreaming, "characterized by a mixed state of dreaming and waking consciousness" (p. 1032).

Carhart-Harris and Nutt (2014) noted the similarity between psilocybin experience and a "transient dreamlike state with vivid visual imagery" that was induced in a patient through electrical stimulation of the PCC (Herbet et al., 2014). Jacobs (1978)

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suggests that the phenomenological similarity observed between classical psychedelics and dreaming is due to suppressed serotonergic neuron firing during both phenomena. Paralleling this, LSD increases the electrical spiking rate in the lateral geniculate nucleolus of cats to levels similar to what occurs during REM sleep (W. C. Stern et al., 1972). Carhart-Harris (2007) noted that high-voltage bursts of theta and slow-wave activity in the medial temporal lobes occur with dreaming, psychedelic experience, acute psychosis, and temporal lobe epilepsy. Finally, Kraehenmann, Pokorny, Aicher, et al. (2017) found that LSD increased primary process thinking compared to placebo ($p<.001$) and was measured by the Primary Index. Primary process thinking is an "early, implicit, associative, and automatic mode of thinking which is typically occurring during altered states of consciousness such as dreaming" (p. 1).

Auditory Effects

LSD. LSD increased the emotional response to music, with participants especially reporting increased emotions of "wonder," "transcendence," "power," and "tenderness" [*N*=10, 90% male, age=26–47, race N/R, psychedelic experienced] (Kaelen et al., 2015).

Ayahuasca. Shannon (2002b) describes that under ayahuasca, "Overall, one's audition becomes subtler and more acute, and auditory stimuli sound fuller and stronger" (p. 182). Further, they describe experiences of sound dislocation, buzzing sounds, and "the sound of running water." Shannon also chronicles several experiences of musical hallucinations with significant affective responses (p. 184).

MDMA. Kuypers et al. (2018) found that 75 mg MDMA made people indifferent to negative sounds, rating their response arousal as equal to positive sounds [*N*=20, 60% male, age *M*=21.2, race N/R, polydrug users].

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Ketamine. Powers et al. (2015) describe the experiences of three participants who experienced auditory-verbal and musical hallucinations with ketamine (0.23 mg/kg bolus + 0.58 mg/kg/hr) while in an fMRI scanner. The authors note that auditory hallucinations are not typically reported with such a low ketamine dose.

Somatic and Dissociative Effects

Dissociation is commonly measured using the Clinician-Administered Dissociative States Scale (CADSS; Bremner et al., 1998). The CADSS has three factors: amnesia, depersonalization, and derealization. While early writers often referred to LSD and mescaline as causing "depersonalization" (de Groot, 1961; Guttmann & Maclay, 1936; Sedman & Kenna, 1964; Stockings, 1947; Waltzer, 1972), these effects are better classified the ego-dissolution (Nour et al., 2016).

LSD. Barr et al. (1972) saw a highly significant increase in bodily preoccupation ($p<.001$) under 100 μg LSD compared to baseline and placebo [N=50, 100% male, age=21–43, race N/R, professional actors] (p. 41). Bodily preoccupation was measured using a 74-item questionnaire developed specifically for the study with the aim of capturing the subjective aspects of altered states of consciousness.

Ayahuasca. Shannon (2002b) notes that "Tactile effects that are not directly related to stimuli in the external world are rare," but does describe some instances as well as significant distortions to the tactile experience of the world (p. 187). Further, Shannon reports "heightened sensibilities of their bodies," such as detailed musculoskeletal sensations, feelings in organs that typically do not have proprioception, and sensing/seeing individual body cells (p. 188). Sanches et al. (2016) saw significant increases in dissociation ($p<.01$) from ayahuasca, with mean CADSS scores close to zero

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at baseline and increasing to approximately twenty 80 minutes following ingestion [*N*=17, 82% women, age *M*=42.71, Brazilian].

MDMA. der Kloet et al. (2015) found significantly increased dissociation with 100 mg MDMA compared to placebo ($p<.001$) [*N*=16, 50% male, age *M*=22, race N/R, MDMA experienced]. Dissociation was measured using the CADSS, and the derealization factor showed a significant increase ($p<.05$), while the amnesia and depersonalization factors did not. This effect was not significant for 25 mg and 50 mg doses ($p=.22–0.72$). The magnitude of dissociation was approximately three times less than ketamine ($p<.001$).

Ketamine. C. J. A. Morgan, Mofeez, et al. (2004b) saw a significant increase in dissociative symptoms with 0.4 mg/kg ($p_t<.001$; $d_c=1.77$) and 0.8 mg/kg ($p_t<.001$; $d_c=2.29$) ketamine infusion compared to baseline [*N*=54, 50% male, age *M*=22.53, race N/R]. Dissociative symptoms were measured using the CADSS. H. L. Morgan et al. (2011) found that ketamine (200 ng/mL plasma) perturbed sense of body ownership based on the rubber hand illusion [*N*=15, 44% female, age *M*=22.4, race N/R].

Ibogaine. There are reports of ibogaine having dissociative effects like ketamine (Wasko et al., 2018).

Olfactory Effects

Ayahuasca. Shannon (2002b) writes that olfactory sensitivity under ayahuasca is common and describes some instances of olfactory hallucinations (p. 187).

MDMA. Sumnall et al. (2006) identified “If I try to smell something I can do so more vividly then [sic] when off ecstasy” as a factor in an analysis of MDMA

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phenomenology based on a survey of recreational users [*N*=268, 63.1% male, age=18–72, race N/R] (p. 677).

Distortions to Space, Time, and Physics

Many reports of classical psychedelic experience involve marked alterations in the experience of time, including the feeling of times speeding or slowing and feelings of timelessness (Preller & Vollenweider, 2018).

Mescaline and LSD. Mitrani et al. (1977) found no significant difference in identification of short time intervals (up to 2 s) under mescaline [*n*=2] or LSD [*n*=4]. The extremely small sample size of this study, however, calls into question its findings.

LSD. Sloane and Doust (1954) found that three of 28 subjects reported experiencing time as slowed under LSD (40–120 μg) [70% male, age=20–40, race N/R, 42% healthy normal, 36% depressive, 21% schizophrenic].

Boardman et al. (1957) found increased variance ($p<.005$) in estimates of a 1 s time interval under LSD (20–56 μg) compared to placebo [*N*=4, 100% male, age=30–35, race N/R]. For time periods ranging from 15 to 240 minutes, Aronson et al. (1959) found a consistent overestimation of the amount of time that had passed ($p<.01$) compared to controls [*N*=24, 100% male, age and race N/R].

Kenna and Sedman (1964) interviewed 29 LSD-experienced psychiatric patients about their experience of time under LSD [52% male, age=21–50, race N/R]. They found that with a moderate dose (40–200 μg), 28% of patients experienced time distortion. In a second test, the 12 patients who did not experience time distortion took a higher dose of LSD (70–400 μg). Time distortion was experienced by 42% of these patients and was described as a sense of eternity, losing all sense of time, or time passing very slowly.

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When compared to other reported phenomena, they found no correlations with types of time distortion.

Psilocybin. Wittman et al. (2007) found that acute psilocybin (8.05 or 17.5 mg/70 kg) impaired the ability to reproduce time intervals longer than 2.5 seconds and the ability to synchronize to beat intervals longer than 2 seconds compared to placebo [*N*=12, 50% male, age *M*=26.8, Swiss students]. Reproduced time intervals tended to be shorter than the original interval under all conditions but with a stronger effect under psilocybin. In a subsequent study, Wackermann et al. (2008) confirmed the results of their prior study using an alternate statistical analysis. They also found that a very low dose of psilocybin (0.84 mg/70 kg) resulted in a greater underestimation of time intervals compared to placebo [*N*=9, 56% male, age *M*=48.2]. Escobar and Roazzi (2011a) timed participants' mental counts of 15 seconds at different times following psilocybin mushroom administration [*N*=28, 71% male, age=18–28, race N/R]. Compared to baseline, participants took longer to count 15 seconds under psilocybin (24.5 mg/70 kg).

Ayahuasca. Shannon (2002b) notes that experiences of synchronicity are common with ayahuasca. Shannon describes Jung's concept of synchronicity as "the co-occurrence of two events that cannot be explained in the normal causal fashion; typically, this co-occurrence is highly improbable and it is associated with special meaningfulness" (p. 245).

MDMA. Sumnall et al. (2006) identified "Ecstasy makes me feel beyond or outside of time" as a factor in an analysis of MDMA phenomenology based on a survey of recreational users [*N*=268, 63.1% male, age=18–72, race N/R].

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Ketamine. Harborne et al. (1996) saw no significant difference in time estimation (p>.1) with 10 mg (d_c=0.00 to -0.48) or 25 mg (d_c=-0.02 to 0.44) IM ketamine [N=12, 75% male, age=25–43, race N/R]. Lofwall et al. (2006) also saw no significant effect of ketamine (0.2 or 0.4 mg/kg) on time interval estimation compared to placebo [N=18, 44% male, age=18–47, race N/R]. However, Coull et al. (2011) found that ketamine (100 ng/ml plasma) significantly reduced (p<.01) the accuracy of time interval reproduction [N=13, 46% male, age M=23.1, race N/R]. Interval under- and over-estimate errors occurred at equal frequency. They also found that subjective experience of time was significantly distorted as measured by the CADSS.

Emotional Effects

Mood and Anxiety

LSD. Barr et al. (1972) saw a significant increase in anxiety (p<.05) under 100 μg LSD compared to baseline and placebo [N=50, 100% male, age=21–43, race N/R, professional actors] (p. 41). They also saw a highly significant increase in silliness (p<.001). There was no significant change in a scale measuring depression versus elation. Anxiety and depression/elation were measured using a 74-item questionnaire developed specifically for the study with the aim of capturing the subjective aspects of altered states of consciousness.

Psilocybin. In a pooled analysis of multiple studies, Studerus et al. (2011) found that subjects retrospectively rated psilocybin experience as “very pleasant” in 49% of cases, “medium pleasant” in 43% of cases, and “no pleasant [sic]” in 8% of cases [n=90 subjects]. Five percent of participants rated the experience as “very frightening” and 28%

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as “medium frightening.” Finally, 10% of participants rated the experience as “very unpleasant” and 24% as “medium unpleasant.”

MDMA. R. S. Cohen (1995) surveyed 500 MDMA users about their experiences. Of the participants, 97% reported euphoria, 91% reported increased energy, 20% reported paranoia, 16% reported anxiety, and 12% reported depression. Kuypers et al. (2018) also found that MDMA decreased fatigue while increasing vigor, elation, arousal, positive mood, friendliness, anxiety, and confusion [N=20, 60% male, age M=21.2, race N/R, polydrug users]. Females [n=14] seem to be more vulnerable (p<.05) than males [n=21] to having acute negative mood effects of MDMA (Bedi & de Wit, 2011).

Ketamine. Stirling et al. (2012) found that 51% of participants reported feeling fearful, and 47% reported feeling anxious when retroactively describing recreational ketamine experiences [N=87, 52% male, age M=22.2, race N/R]. They also found that 82% reported feeling happy and relaxed.

Curran and Morgan (2000) found increased measures of depression (p<.001; d_c=1.46) during recreational ketamine intoxication compared to controls [N=39, 59% male, age=18–29, race N/R]. They found no significant difference in levels of anxiety (d_c=0.19). Anxiety and depression were measured using the 14-item Hospital Anxiety and Depression Scale (HADS).

Ibogaine. B. Forsyth et al. (2016) found no significant change in mood self-ratings (happy, sad, calm, tense, energetic, sleepy; 0–100 subjective rating) in men [N=21, age=20–40, race N/R] under a low, non-hallucinogenic ibogaine dose (20 mg) compared to baseline.

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Negative and Challenging Experiences

Challenging psychedelic experiences or ‘bad trips’ do occasionally occur. The incidence of negative and challenging experiences from psychedelics is described in Chapter 9 under “Negative and Challenging Experiences.”

Affect Tolerance

MDMA. Oehen et al. (2012) saw increased affect tolerance when performing psychotherapy to treat PTSD with 125 mg MDMA [N=12, 83% female, age M=41.4, race N/R].

Re-experiencing and Regression

Mescaline and LSD. Frederking (1955) observed that patients given LSD tended to experience scenes from their personal life, while this rarely happened with mescaline. In a survey study, Naditch (1974) found that mescaline or LSD use significantly correlated (p<.001; d_r=0.35) with a validated measure of psychological regression [N=483, male, age M=21.4, race N/R]. They found that cases of acute adverse reactions to mescaline or LSD were highly correlated (p<.001; d_r=0.87) with regressive experiences. Sola, however, notes that such regressive experiences may be important aspects of the treatment process (E. Sola, personal communication, June 12, 2022).

MDMA. Sumnall et al. (2006) identified “I play childish games with others when I have taken ecstasy” as a factor in an analysis of MDMA phenomenology based on a survey of recreational users [N=268, 63.1% male, age=18–72, race N/R].

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Interpersonal Effects

Introversion, Extraversion, Spontaneity, and Silliness

LSD. LSD 100 and 200 μg increased prosocial behavior and desire to be with others [*N*=40, 50% male, age=25–65, race N/R] (Dolder et al., 2016).

Psilocybin. In a pooled analysis of multiple studies [*N*=110 subjects], acute and subacute psilocybin was found to decrease Extraversion (p=.014) and increase introversion (p<.001) (Studerus et al., 2011).

MDMA. In a systematic review, Dumont and Verkes (2016) found that 70% of studies [*N*=29] showed increased Extraversion under MDMA. A systematic review by Kamilar-Britt and Bedi (2015) also found that MDMA consistently increased sociability, prosocial feelings, and social interactions while decreasing awareness of social rejection and recognition of negative emotional states in others [*N*=49 human and animal studies]. D. S. Harris et al. (2002) saw increased silliness and laughter in 75% of people given 1.5 mg/kg MDMA [*N*=8]. Bedi et al. (2009) saw increased sociability under 1.5 mg/kg MDMA (p<.05; $d_{\eta 2}$=1.25) compared to 0.75 mg/kg MDMA and placebo [*N*=9, age=18–29, 22% female, 67% Caucasian].

Increased Empathy

LSD. LSD (100 and 200 μg) increased emotional empathy and produced feelings of trust and closeness to others [*N*=40] (Dolder et al., 2016).

Psilocybin. Preller et al. (2015) found that 15.05 mg/70 kg psilocybin increased emotional empathy (p<.01) but did not significantly affect cognitive empathy (p>.27) compared to placebo [*N*=21]. Pokorny et al. (2017) confirmed this result in a second RCT with 15.05 mg/70 kg psilocybin. Mason et al. (2019) also found that psilocybin increased

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emotional empathy the morning following (p=.02; d=0.45; n=50) and increased emotional empathy to negatively valenced stimuli 7 days following (p=.05; d=0.41; n=22) compared to baseline.

MDMA. Through a meta-analysis of 6 studies [N=118 participants], Kuypers et al. (2017) found that MDMA increases emotional empathy (p=.004–.008; $d_{\eta 2}$=0.51–0.59) but has no significant effect on cognitive empathy. Explicit emotional empathy (expressed concern) increased more in females than in males (p=.01; $d_{\eta 2}$=0.51), though this trend was not seen for implicit emotional empathy (physiological arousal).

Huxster et al. (2006) saw no significant difference in empathy in the 6 days following recreational MDMA (p>.05; d_c=0.40) compared to MDMA users who did not take the drug during the study period [N=38, 60% male, age M=21.25, race N/R].

Increased Suggestibility

Mescaline, LSD, and Psilocybin. Sjoberg and Hollister (1965) measured behavioral and cognitive responsiveness to suggestion during drug and hypnotic experiences using the 17-item Stanford Suggestibility Scale [N=24, male, age=21–40, race N/R]. They found a significant increase in suggestibility for mescaline (p<.005; d_c=0.52) and LSD (p<.025; d_c=0.34) but not psilocybin (d_c=0.02) compared to baseline. The authors also measured trance induction using the Trance Indicator Score (TIS). TIS increased for all three drugs: mescaline (p<.005; d_c=1.40), LSD (p<.005; d_c=1.45), and psilocybin (p<.005; d_c=0.41). TIS was also significantly correlated to suggestibility during intoxication for all three drugs (p<.05–.0005; *rho*=.35–.70). The increase in suggestibility for mescaline and LSD was similar in magnitude to the increase during

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hypnosis ($p<.005$; $d_c=0.49$), though the magnitude of TIS effect was greater during hypnosis ($p<.005$; $d_c=1.99$).

LSD. Carhart-Harris et al. (2015) found that LSD significantly increased suggestibility ($p=.018$; $d=1$) as measured by the Creative Imagination Scale (CIS) [$N=10$, 10% female, age=26–47, race N/R]. The CIS asks subjects to rate the realism/vividness of their closed-eye subjective experience as they 'think along' to a 200- to 250-word descriptive suggestion read by the administrator. Carhart-Harris et al. did not, however, find a significant increase in self-rated vividness of experience when asked to imagine items with short descriptions ($p=.11$; $d=0.6$). However, the effect size of the increase in vividness scores while on LSD was relatively large, indicating that an experiment with more statistical power may yield a significant result.

Reduced Defensiveness

LSD. LSD resulted in significantly less use of some types of defensive language ($p<.05$) than *d*-amphetamine or placebo based on coded session transcripts [$N=7$, 43% male, age=22–44, race N/R] (Natale et al., 1979). LSD reduced the frequency of explanatory statements ($p<.05$) and value judgments such as liking or disliking ($p<.05$) as well as the frequency of personal statements or statements referencing a specific known person ($p<.01$). There was no significant change in frequency of negations, qualifiers, or retractions. While there was no significant increase in expressions of feelings, there did appear to be a trend. With placebo, expressions of feelings occurred in 0.8 per thousand words. With LSD, expressions of feelings increased to 2.3 per thousand words, while with *d*-amphetamine, it was 2.0.

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MDMA. Oehen et al. (2012) saw reduced defensiveness during 125 mg MDMA-assisted psychotherapy for treating PTSD. A review by Baylen and Rosenberg (2006) found reduced defensiveness as an acute effect of MDMA in 10%–80% (median=30%) of people [*n*=3 studies].

Sexual Effects

Sayin (2018) describes sexual experiences in psychedelic states, suggesting that LSD, psilocybin, and ibogaine are powerful aphrodisiacs. Generally, Sayin reports that sexual pleasure, arousal, and orgasm are enhanced, citing reports of male and female orgasms lasting from several minutes to hours.

Classical Psychedelics. McWaine and Procci (1988) note that higher doses of classical psychedelics appear to acutely reduce sexual desire, an effect corroborated by animal studies with LSD (Sietnieks, 1985) and ayahuasca (Alvarenga et al., 2014). McWaine and Procci also mention some subjective reports of enhanced sexual experience with classical psychedelics at lower doses.

Mescaline. Denber (1958) observed that sexual feelings and erotic transference were common in psychiatric patients given mescaline [*N*=124].

LSD. Sayin (2018) describes experiences of "cosmic orgasm" experienced under LSD and described in the psychedelic literature. The term "cosmic orgasm" is also used in the Tantric literature.

Psilocybin. Studerus et al. (2011) found no significant increase (p=1.00) in "sexually stimulating phantasies" under psilocybin (15.4–17.5 mg/70 kg) compared to placebo in a pooled analysis of multiple studies [*n*=72 subjects].

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MDMA. McWaine and Procci (1988) found acute enhancement of sexual desire and arousal due to MDMA. R. S. Cohen (1995) also found that 83% of people surveyed described sexual arousal due to MDMA [*N*=500]. These findings aligned with Zemishlany et al. (2001), who found that 90% of subjects reported increased sexual desire and satisfaction during MDMA experience [*N*=35, 57% male, age=21–48, race N/R]. Contrary to these findings, Schmid et al. (2015) found that methylphenidate but not MDMA increased ratings of sexual arousal in response to erotic pictures and also resulted in increased participant button-pushing to view images for longer [*N*=30]. Huxster et al. (2006) found that MDMA had little impact on interest in sexual activity over a 6-day period following MDMA [*N*=38, 60% male, age *M*=21.25, race N/R].

Sumnall et al. (2006) found reports of "Sexual orgasm has new qualities when on ecstasy" as a significant aspect of MDMA phenomenology based on a survey of recreational users [*N*=268, 63.1% male, age=18–72, race N/R].

Buffum and Moser (1986) surveyed 76 people on the effects of MDMA on sexual function [51% male, 49% female, age=20–63, race N/R]. Eighty-eight percent of women and 74% of men felt that the sensuality of sexual experience was enhanced by MDMA. However, 62% of men and 17% of women had trouble achieving orgasm while on MDMA, with an additional 25% of women and 8% of men unable to achieve orgasm. This was consistent with reports of MDMA as "a sensual drug, not a sexual drug" (p. 357). Still, 17% of females found it easier to achieve orgasm on MDMA compared to 0% of males. Forty-six percent of men reported decreased ability to attain erection, while most women (45%) felt MDMA had no effect on lubrication.

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Zemishlany et al. (2001) also surveyed MDMA users about sexual functioning during the experience [*N*=35]. Orgasm was reported to be delayed but more intense. Female lubrication was not reduced, but 40% of men had impaired erection under MDMA. Sumnall et al. (2006) also found reports of difficulty reaching orgasm while on MDMA. These impairments in sexual performance may be due to MDMA inducing a pharmacologically similar state to post-orgasm, with increased prolactin secretion (Passie, Hartmann, et al., 2005).

Ketamine. Ketamine has been used in medical contexts to prevent and resolve erections in patients undergoing surgeries (Buffum, 1982). Thus it is likely that ketamine interferes with male erection, at least in doses 0.5 mg/lb and greater.

Ibogaine. Ibogaine is rumored to have aphrodisiac properties (Ajao et al., 2019; Gawin, 2012; Sayin, 2018).

Mystical and Spiritual Experiences

The phenomenon of mystical experience was systematically enumerated by Pahnke (1963), who surveyed the available literature on the subject, much of which came from religious scholars. From this, he developed a "phenomenological typology of mystical states of consciousness" (pp. 46–81) that consists of nine experiential facets:

I. **'Unity':** These experiences are commonly described as "ego loss," wherein the sense of self dissolves completely to lead one to experience themselves as undifferentiated from the universe. Experiences of unity can occur either in one's inner world, which Pahnke called Inner Unity, or can occur with a focus on one's outer world, which Pahnke called Outer Unity.

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II. **'Transcendence of Time and Space':** In mystical states of consciousness, people tend to describe a loss of a sense of clock time and/or of a sense of past, present, and future. They often become disoriented to space as well and may experience the world in a way that is beyond typical three-dimensional perception.

III. **'Deeply Felt Positive Mood':** People often describe markedly positive moods arising from mystical experiences, using descriptors like "joy," "blessedness," "peace," "ecstasy," "rapture," and "bliss" (pp. 61–62). Further, Pahnke noted that the intensity of these feelings led people to highly value the experience afterward.

IV. **'Sense of Sacredness':** Pahnke defined the sacred as "…that which a person feels to be of special value and capable of being profaned" (p. 64). This sense of sacredness did not need to be associated with religious beliefs despite a sense of reverence.

V. **'Objectivity and Reality':** Here, Pahnke describes two additional elements of mystical experience "(1) insightful knowledge or illumination felt at an intuitive, non-rational level and gained by direct experience and (2) the authoritativeness of the experience or the certainty that such knowledge is truly real, in contrast to the feeling that the experience is a subjective delusion" (p. 67). This method of obtaining knowledge is also called gnosis.

VI. **'Paradoxicality':** Pahnke observed that rationality often breaks down when describing mystical experiences as statements are often found to be logically contradictory when analyzed.

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VII. **'Alleged Ineffability':** Possibly arising from the paradoxicality of mystical experience, those who have had mystical experiences tend to struggle to describe them adequately in words. Pahnke describes these experiences of ineffability as 'alleged' since "mystics have written descriptions of their remembered experiences while at the same time they have insisted that the actual experiences were indescribable" (p. 72).

VIII. **'Transiency':** The mystical experience is temporary, which has led to it being described as a "state of consciousness."

IX. **'Persisting Positive Changes in Attitude and/or Behavior':** Pahnke asserted that when a person goes through an experience characterized by Facets I–VIII, their orientation toward life and/or behavior changes. He observed that these experiences tended to have a "profound personal impact" (p. 77).

Pahnke asserts that mystical experiences are not necessarily contingent on religious beliefs, despite their association with religion. The phenomenon of mystical experience may indeed be the source of many religions, but one need not be religious to have a mystical experience.

Measures of Mystical Experience

The States of Consciousness Questionnaire (SOCQ; Griffiths et al., 2006) is a 100-item questionnaire with six-point Likert scale rankings where 0 = *none, not at all*; 1 = *so slight, cannot decide*; 2 = *slight*; 3 = *moderate*; 4 = *strong (equivalent in degree to any previous strong experience or expectation of this description)*; and 5 = *extreme (more than ever before in my life and stronger than 4)*. The SOCQ consists of 43 items from the

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Pahnke-Richards Mystical Experience Questionnaire (PRMEQ; Pahnke, 1969; W. A. Richards, 1975) combined with 57 distractor items.

The MEQ was the outcome measure used in the Good Friday Experiment (Doblin, 1991; Pahnke, 1963). The MEQ and SOCQ have seven subscales:

> "[1] internal unity (pure awareness; a merging with ultimate reality);
>
> [2] external unity (unity of all things; all things are alive; all is one);
>
> [3] transcendence of time and space;
>
> [4] ineffability and paradoxicality (claim of difficulty in describing the experience in words);
>
> [5] sense of sacredness (awe);
>
> [6] noetic quality (claim of intuitive knowledge of ultimate reality); and
>
> [7] deeply felt positive mood (joy, peace, and love)" (Griffiths et al., 2006, p. 272).

Pahnke (1969) defined criteria for "complete mystical experience" as consisting of scores of at least 0.6 (60%) on all scales, with the exception that one of internal or external unity may be below that threshold. Unless otherwise noted, "complete mystical experience" refers to Pahnke's definition.

Maclean et al. (2012) performed a factor analysis of the MEQ using the responses of 1,602 participants in reference to psilocybin experience. The authors uncovered and validated a four-factor structure:

[F1] "unity, noetic quality, sacredness"

[F2] "positive mood"

[F3] "transcendence of time/space"

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[F4] “ineffability” (p. 721)

Despite the stronger validity of this 4-factor model, Pahnke’s definition of complete mystical experience continues to dominate the literature.

The Mysticism Scale (MS; Hood, 1975; Hood et al., 2001) is another measure of primary mystical experience. The scale has three factors:

> “[1] interpretation (corresponding to noetic quality, sacredness, and deeply felt positive mood),
>
> [2] introvertive mysticism (corresponding to internal unity, transcendence of time and space, and ineffability), and
>
> [3] extrovertive mysticism (corresponding to unity of all things/all things are alive)” (Schmid & Liechti, 2018, p. 538).

Related to the MS is the Death Transcendence Scale (DTS; Hood & Morris, 1983). The DTS has five factors:

[1] “mystical” (experiences of unity and oneness),

[2] “religious” (views of life persisting after death),

[3] “nature” (views of nature as continuous, death as part of nature, and self as part of nature),

[4] “biosocial” (views of family lasting beyond death and valuing children for this purpose), and

[5] “creative” (finding meaningfulness and significance in work) (Vandecreek & Nye, 1993).

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Mystical and Spiritual Experiences Across Psychedelics

Psilocybin. In the famous "Good Friday Experiment," Pahnke (1963) administered 30 mg psilocybin or placebo to 20 seminary students prior to Good Friday services at Boston University's Marsh Chapel [male, White, Protestant]. The experiment was double-blinded and randomized. The psilocybin group showed significantly more ($p<.02$) mystical experience in all nine of Pahnke's facets except for sacredness ($p=.37$). These categories would later become the 9-factor MEQ. In a critique and follow-up to Pahnke's experiment, Doblin (1991) noted that this outcome measure had not been validated and had some design flaws, and that blinding was broken as all subjects correctly determined their group. Doblin was able to contact 19 of the original participants almost 30 years following Pahnke's original experiment. There was little change in participants' retrospective ratings of mystical experience, with only ineffability decreasing, perhaps as participants were able to find words to describe their experiences through integration over time.

Griffiths et al. (2006) found that high-dose (30 mg/70 kg) psilocybin sessions induced a complete mystical experience in 22 of 36 (61%) psychedelic-naïve participants compared to 4 of 36 (11%) with a methylphenidate control (40 mg/70 kg) [$N=36$, 39% male, age=24–64, race N/R]. At 2 months following, participants rated the experience as "having substantial personal meaning and spiritual significance and attributed to the experience sustained positive changes in attitudes and behavior consistent with changes rated by community observers" (p. 268). In a follow-up study 14 months later, 67% of participants rated the psilocybin experience as "among the five most spiritually significant experiences of their lives" (Griffiths et al., 2008, p. 626).

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In a subsequent study, Griffiths et al. (2011) replicated this result, with 72% of participants having a complete mystical experience during a series of psilocybin sessions at 1-month intervals with various doses (0, 5, 10, 20, 30 mg/70 kg) [*N*=18, 45% male, age=29–62, race N/R]. The frequency of complete mystical experience increased monotonically with dose (see Influence of Dose section in the current chapter). In contrast, Nicholas et al. (2018) did not find that frequency of complete mystical experiences increased with psilocybin dose (21, 31.5, and 42 mg/70 kg) [*N*=12]. They did find a significant linear relationship between escalating doses and higher total MEQ score and score on the transcendence of time and space subscale. Together, it appears that higher doses of psilocybin are associated with increased mystical experience but may not result in increased frequency of complete mystical experiences as defined by Pahnke.

In "recreational" use, outside of religious and clinical research settings, psilocybin also appears to occasion mystical experiences. In an online survey [*N*=504], 52% of participants met Pahnke's criteria for having a complete mystical experience in response to psilocybin (Bunch, 2009). In another online survey [*N*=337], Lyvers and Meester (2012) also found that increasing doses of psilocybin were correlated with a higher occurrence of mystical experiences (MQ and SOCQ; $p<.01$; $d_r=0.39$), according to retrospective self-report [68.5% male, age=16–79, race N/R]. Finally, Cummins and Lyke (2013) found that among a group of recreational psilocybin users, 47% felt that the peak experience of their life had occurred with psilocybin [*n*=34; undergraduates and music festival attendees].

LSD. In an online survey, Lyvers and Meester (2012) found that LSD was correlated with mystical experiences in a dose-dependent manner (MQ and SOCQ;

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$p<.01$; $d_r=0.47–0.54$), according to retrospective self-report [$N=337$, 68.5% male, age=16–79, race N/R]. In a placebo-controlled study, Liechti et al. (2016) found that 200 µg LSD induced mystical experiences (MEQ) [$n=16$, 50% male, age=25–51, race N/R]. Despite a mean MEQ30 score of 61%, comparable to a mean score of 77% found with people given 30 mg/70 kg psilocybin, only two (12.5%) of the LSD study participants experienced complete mystical experience compared to up to 67% with 30 mg/70 kg psilocybin. However, 200 µg LSD is still a moderate dose that may not be comparable to the effects of high-dose psilocybin (30 mg/70 kg).

DMT. No studies were found directly measuring mystical experience from DMT using validated measures. In an online survey of Australian recreational DMT users [$N=121$], 54.1% had had spiritual experiences related to smoking DMT (Cakic et al., 2010). However, it is not known if these spiritual experiences would qualify as mystical experiences by the above definition.

Ayahuasca. Trichter (2006) found no significant difference in Mysticism Scale scores 6 hours following an ayahuasca ceremony compared to baseline among novices taking part in ceremonies in Canada and San Francisco [$n=49$, 47% male, age $M=33$, 100% White]. They did find a significant increase in scores on the Spiritual Well-Being Scale 6 hours following ceremony among novices taking part in ceremonies in Canada, but not in similar ceremonies that took place in San Francisco. Pooled data from both ceremonies did still show a significant increase.

Shannon (2002b) describes specific mystical and spiritual phenomena occurring with ayahuasca, including those already described in this chapter, along with experiences of light and luminance (p. 274).

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MDMA. Lyvers and Meester (2012) found that MDMA use, unlike LSD and psilocybin, was not correlated (p>.05; d_r=0.14–0.16) with mystical experiences (MQ and SOCQ) in a dose-dependent manner according to retrospective self-report in an online survey [N=337]. Schmid et al. (2014) also found that 75 mg MDMA was not associated with mystical experience when compared to a 40 mg methylphenidate placebo [N=30] (findings reported by Liechti et al., 2016). Finally, Mitsunaga-Whitten (2017) examined mystical experience occurrence in a Phase 2 clinical study of MDMA-assisted psychotherapy for treating PTSD in first responders (Mithoefer et al., 2018). They found that mystical experiences (MEQ30) were not associated with MDMA therapy as they are with LSD, psilocybin, ayahuasca, and ketamine. Further, mystical experiences did not mediate treatment outcomes as measured by the Clinician-Administered PTSD Scale (CAPS; r=.036; p=.890).

Ketamine. Passie et al. (2005) performed a randomized controlled crossover study with low-dose (5 mg bolus + 0.003 mg/kg/min) and high-dose (5 mg bolus + 0.005 mg/kg/min) (*S*)-ketamine compared to placebo [N=12, 100% male, age M=26.8, race N/R, medical staff and students]. They found significantly increased oceanic boundlessness (p=.184) and dread of ego dissolution (p<.001) with the high-dose condition compared to placebo and measured using the German version of the Altered States of Consciousness Questionnaire. For the low-dose condition, these differences did not reach significance (p=.158–.184) but did trend in the same direction.

Dakwar et al. (2014) measured mystical experience in response to ketamine infusions in crack cocaine-dependent people using a modified version of the MS [N=8]. Ketamine resulted in significantly elevated mystical experience (p=.012; median MS

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0.41 mg/kg: 22, 0.71 mg/kg: 30) in comparison to a lorazepam control (median MS: 4). Change in motivation to quit using cocaine was positively correlated with mystical experience ($p<.005$; $\beta=0.678$).

Lofwall et al. (2006) administered the MS 85 minutes after a bolus injection of 0.2 mg/kg ketamine, 0.4 mg/kg ketamine, or placebo [N=18, 44% male, age=18–47, race N/R]. In contrast with Passie et al. and Dakwar et al., they saw a significant decrease ($p<.05$) in total mysticism (0.2 mg/kg: d_c=-0.66; 0.4 mg/kg: d_c=-1.28) as well as the introvertive mysticism (0.2 mg/kg: d_c=-0.99; 0.4 mg/kg: d_c=-2.07) and extrovertive mysticism (0.2 mg/kg: d_c=-0.47; 0.4 mg/kg: d_c=-0.50) with ketamine compared to placebo. The interpretation factor ("noetic quality, sacredness, and deeply felt positive mood;" Schmid & Liechti, 2018, p. 538) did not show a significant difference (0.2 mg/kg: d_c=-0.23; 0.4 mg/kg: d_c=-0.21).

Ibogaine. Heink et al. (2017) found that mean oceanic boundlessness in response to ibogaine was 49.7% greater than with 22.05 mg/70 kg psilocybin (Studerus, 2012) as measured by retrospective 5d-ASC ratings [N=27, 56% male, age M=35.11, 96% White]. Mean dread of ego dissolution was 86.2% higher than with psilocybin. No statistical comparisons were made.

Similarity to Meditation States

Millière et al. (2018) examined the neuroscientific similarities between classical psychedelic states and meditation. The authors found phenomenological and neurophenomenological similarities between the two states, inducing an experience of "self-loss." However, they stress that self-loss is not a uniform construct and that meditation and psychedelic states vary in what dimensions of self-consciousness are

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altered. They hypothesize that low-dose psychedelic experiences may increase bodily awareness in a similar way that breath-based meditation practices do. In contrast, a high-dose psychedelic experience results in substantially reduced bodily awareness, body ownership, and self-location in a way that is similar but not identical to a "selfless" state described by experienced meditators. The frequency of self-related thought is strongly reduced in both forms of meditation and with high-dose psychedelics, but this reduction is small for low-dose psychedelics. Finally, access to autobiographical semantic information is moderately reduced with both forms of meditation and with low-dose psychedelics but strongly reduced with high-dose psychedelics.

Paranormal Phenomena

Luke and Kittenis (2005) performed an online survey [N=139] inquiring about paranormal experiences associated with psychedelics. Table 7 shows the number of reports of paranormal phenomena they found related to different psychedelics.

DMT. Timmermann et al. (2018) compared the DMT state to near-death experiences (NDE) using the well-validated Near-Death Experience scale using a randomized placebo-controlled design [N=13, 54% male, age M=34.4, race N/R]. They found a significant increase (p=1.39e^{-7}; d=3.09) in NDE scores from DMT experiences compared to placebo.

Davis et al. (2020) performed an online study [N=2,561] asking about DMT users' single most memorable entity-encounter experiences. Common descriptive labels for the entities encountered were "being, guide, spirit, alien, and helper" (p. 1). Typically, these entities were believed to be intelligent and conscious and to reside in "…some real but

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different dimension of reality, and continued to exist after the encounter" (p. 1). These experiences were rated as highly meaningful and resulted in positive life changes.

Ayahuasca. Shannon (2002b) reports on many experiences of transforming into other people, animals, and plants (p. 210). They also describe instances of flying and traveling to other locations (pp. 215–218).

Heuser (2006) analyzed entity experiences of ayahuasca users based on the content of ayahuasca experiences posted to online forums. They identified 140 different categories of entities and their respective interactions that were organized around positive and negative affective antipodes. While the specific content of this study is too large to summarize here, the study demonstrates that entity experiences are commonly associated with ayahuasca.

MDMA. One subject of eight given 1.5 mg/kg MDMA by D. S. Harris et al. (2002) reported telepathy during the experience.

Ketamine. Wilkins et al. (2012) surveyed 128 ketamine users and 64 non-ketamine polydrug users online about out-of-body experiences [63% male, age M=22, race N/R]. They found that the typical progression to out-of-body experience among ketamine users fit a disintegration model where illusory movement led to an out-of-body feeling that then led to an experience of out-of-body remote viewing (autoscopy). Lifetime ketamine use was predictive of a higher frequency of illusory movement experiences.

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Table 7

Paranormal Phenomena in Psychedelic Experiences of 139 People

Experience	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine
Out-of-body Experiences	**4**	**26**	**15**	**17**	**3**	**5**	**15**
…on the material plane	2	14	8	3	1	2	6
…on another plane	2	12	7	14	2	3	9
Extrasensory Perception	**4**	**28**	**31**	**7**	**3**	**8**	**2**
Telepathy	1	14	9	1	-	6	-
Clairvoyance	2	8	10	2	-	2	2
Precognition	1	4	7	1	-	-	-
Communication w/ the dead		2	5	3	3	-	-
Influence “other” w/ my mind	2	5	5	-	-	1	2
Lost sense of causality	2	14	5	-	-	1	4
Death, rebirth, or past life	1	9	7	6	2	2	4
Entity encounters	**9**	**14**	**49**	**29**	**11**	**-**	**1**
Unspecified entity	2	3	12	13	3	1	-
Mythical being		4	7	2	2	-	-
Divine being	2	4	10	7	1	1	1
Plant/substance entity	5	3	20	7	5	-	-
Powerful religious awakening	3	13	14	7	1	4	2
Seeing an aura of light	6	21	13	-	-	8	-
Universal consciousness	5	21	17	6	2	5	4
Dissolving into pure energy	3	11	7	10	1	4	4

Note. Adapted from Luke and Kittenis (2005). Phenomenological categories are bolded, with bolded values equal to the sum of sub-categories. No data was provided regarding the relative frequency of psychedelic use in the sample. Thus, the number of experiences reported cannot be used to infer that those experiences occur more frequently with one psychedelic verse another.

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Subacute Phenomenology

Insight and Integration

MDMA. Greer and Tolbert (1986) found that 45% of participants reported lasting psychological insight following a clinical 75–150 mg MDMA session [N=29].

Ketamine. Stirling et al. (2012) found that 65% of participants reported "having transcendental insights that cannot be put into words" when retroactively describing recreational ketamine experiences [N=87, 52% male, age M=22.2, race N/R] (p. 167).

Meaningfulness of Experience

Psilocybin. Griffiths et al. (2006) found the experience of high-dose 30 mg/70 kg psilocybin to be significantly (p<.001) more personally (d_c=1.8) and spiritually (d_c=2.2) meaningful than a methylphenidate control (40 mg/70 kg) as measured by the Persisting Effects Questionnaire (PEQ) [N=36, 39% male, age=24–64, race N/R]. In a follow-up study 14 months later, 58% of participants rated the psilocybin experience "as being among the five most personally meaningful experiences of their lives" (Griffiths et al., 2008, p. 621). This finding was replicated by Griffiths et al. (2017), this time with a low-dose 1 mg/70 kg psilocybin active placebo control [N=75, 40% male, age M=43.3, 85% White, 9% Asian, 5% Black, 5% Hispanic]. Those given two doses of 20 and 30 mg/70 kg psilocybin with the typical 7 hours of preparation and aftercare [n=25] again rated the experience as significantly (p<.001) more personally meaningful (d_c=1.79) and spiritually significant (d_c=1.37). When given the same drug treatment, but instead with 35 hours of preparation and aftercare [n=25], spiritual significance was significantly enhanced (p<0.05; d_c=2.88), while personal meaning was increased but not enough to be statistically significant (d_c=2.55).

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Changes to Dream Content

Ketamine. In the days following ketamine infusion, significantly more (p=.008) unpleasant dreams were reported compared to placebo [N=30, 47% male, age=18–35, native English speakers, race N/R] (Blagrove et al., 2008).

Summary and Comparison

Summary Table 6 provides an overview of the acute phenomenology of psychedelic experiences, while subacute phenomena are synthesized in Summary Table 7. The following symbols are used in both tables:

+++	Phenomenon frequently associated with psychedelic with high intensity.
++	Phenomenon sometimes associated with psychedelic and/or of moderate relative intensity.
+	Phenomenon infrequently associated with psychedelic.
⊕⊕⊕	Phenomenon likely associated with psychedelic per the author's judgment based on unpublished reports or similarity to another psychedelic. However, no literature was found describing the occurrence of the phenomenon. The same frequency/intensity convention is used as with "+."
∅	Phenomenon found through research to not be associated with a psychedelic.
-	No literature was found indicating a phenomenon does or does not occur with a psychedelic, nor is this phenomenon expected to occur with the psychedelic based on the author's judgment.

Summary Table 6

Acute Psychedelic Phenomenology

Phenomenon	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Intense onset	⊕	⊕	+	+++	+	+	++	-
Physical side effects	⊕⊕	⊕	⊕⊕	⊕	+++	+++	+	+++
Cognitive changes (see Chapter 8)	⊕⊕⊕	+++	+++	⊕⊕⊕	+++	+++	+++	+++
Psychotomimetic Effects	+	+	+	++	⊕	∅	+++	-
Distortions to sense of self	⊕⊕	⊕⊕	++	+++	+++	∅	+++	+++
Delusions & paranoia	-	+++	+++	-	-	++	++	-
Visual Effects								
Perceptual distortions/illusions	+++	+++	+++	+++	+++	++	+++	++
Visions & hallucinations	+++	+++	+++	+++	+++	++	+++	+++
Synesthesia	++	++	⊕	-	++	-	-	-
Vividness & clarity	-	+	-	+++	+++	-	-	-
Dream-like experience	++	++	++	++	++	+	+++	++
Auditory Effects								
Auditory hallucinations/distortions	⊕⊕	⊕⊕	++	-	++	-	+++	++
Increased emotional response to music	⊕⊕	+++	⊕⊕	-	++	⊕⊕⊕	-	-
Indifference to negative sounds	-	-	-	-	-	+++	-	-

Summary Table 6

Acute Psychedelic Phenomenology, Continued

Phenomenon	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Somatic Effects and Dissociation								
Somatic hallucinations/distortions	-	-	++	-	++	+	++	++
Enhanced somatic experience	-	++	-	-	+++	+++	++	-
Dissociation	-	-	-	-	++	+	+++	++
Depersonalization	-	-	-	-	-	∅	+++	-
Derealization	-	-	-	-	-	++	⊕⊕⊕	-
Trance state	+++	+++	+	-	-	-	-	-
Olfactory Effects								
Olfactory hallucinations	-	-	-	-	++	-	-	++
Olfactory sensitivity	-	-	-	-	+++	++	-	-
Distortions to Space, Time, and Physics								
Distortion of time sense	-	++	+++	+++	+++	+	+	+++
Distortion of space	-	-	-	+++	+++	-	-	-
Sense of familiarity	-	-	-	+++	-	-	-	-
Lost sense of causality	+	+++	++	-	-	+	++	-
Synchronicity	-	-	-	-	+++	-	-	-
Emotional Effects								
Positive emotions	⊕⊕⊕	⊕⊕⊕	+++	+++	++	+++	+++	++
Negative emotions & distress	⊕⊕	⊕⊕	++	++	+++	++	++	+++

Summary Table 6

Acute Psychedelic Phenomenology, Continued

Phenomenon	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Challenging experiences or 'bad trips' (see Chapter 9)	+	++	++	++	++	+	⊕⊕	⊕⊕⊕
Increased anxiety	-	++	-	++	++	+	++	-
Depressed symptom report	-	∅	-	-	-	+	+++	-
Increased affect tolerance	-	-	-	-	-	+++	-	-
Trauma processing & re-experiencing	∅	+++	+++	-	+++	+++	-	+++
Regression	++	++	-	-	-	++	-	-
Sudden release from distress	-	-	-	-	+++	++	-	++
Interpersonal Effects								
Increased Extraversion	-	++	-	-	-	+++	+	-
Increased introversion	-	-	+++	⊕⊕⊕	-	-	+++	-
Increased spontaneity and silliness	-	+++	+++	-	-	+++	-	-
Increased emotional empathy	-	++	+++	-	-	+++	++	++
Increased cognitive empathy	-	-	∅	-	-	∅	-	-
Increased suggestibility	+++	++	∅	-	-	-	-	-
Reduced defensiveness	-	++	-	-	-	+++	-	-
Sexual Effects								
Enhancement of sexual experience	-	+++	+++	-	-	+++	-	+++
Increased sexual desire	$++^{LD}$	$++^{LD}$	$++^{LD}$	-	-	+++	-	-
Reduced sexual desire	$++^{HD}$	$++^{HD}$	$++^{HD}$	-	$++^{HD}$	-	-	-

Summary Table 6

Acute Psychedelic Phenomenology, Continued

Phenomenon	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Decreased sexual function	-	-	-	-	-	+++^{M} / ++^{F}	++^{M}	-
Mystical & Spiritual Effects								
Mystical experience (Pahnke criteria)	-	++	+++	-	∅	∅	++ / ∅^{a}	-
Spiritual experience	-	-	+++	+++	+++	++	-	+++
Religious awakening	+	+++	+++	++	+	++	+	+
Sense of unity & interconnectedness	-	-	+++	-	+++	++	++	++
Experiencing universal consciousness	++	+++	+++	++	+	++	++	-
Ego dissolution	+++	+++	+++	+++	+++	-	+++	+++
Similarity to meditation state	++	++	++	++	++	-	-	-
Death experiences	+	++	++	+++	+++	+	+	+++
Rebirth experiences	-	-	-	-	+++	-	-	+++
Dissolving into pure energy	+	++	++	++	+	++	++	-
Seeing an aura of light	++	+++	+++	-	+++	+++	-	-
Insight								
Introspection & self-reflection	⊕⊕⊕	⊕⊕⊕	+++	⊕⊕	+++	+++	⊕⊕	+++
New perspective on the world	-	-	+++	-	+++	+	-	-
Imagination of future scenarios	-	-	-	-	-	-	-	+++

Summary Table 6

Acute Psychedelic Phenomenology, Continued

Phenomenon	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Paranormal Phenomena								
Out-of-body experience (on material plane)	+	+++	++	+	+++	+	+++	-
Out-of-body experiences (on another plane)	+	+++	++	+++	+++	+	+++	-
Extrasensory perception	+	+++	+++	++	+	++	+	-
Influencing others through the mind	+	++	++	-	-	+	+	-
Experiencing other realities	-	-	-	+++	+++	-	-	-
Transforming into people, animals, or plants	-	-	-	-	+++	-	-	-
Merging with objects	-	-	-	-	-	++	-	-
Encounters with plant/substance entity	++	+	+++	++	+++	+	-	+++
Encounters with other sentient entities	+	++	+++	+++	+++	+	+	-
Encounters with the dead/ancestors/ loved ones	-	+	+++	+	+++	-	-	+++

Note. Symbol key on page 180. Phenomenological category headings are italicized for clarity. HD = high-dose; LD = low-dose; M = male; F = female.

[a] Mystical experiences were associated with ketamine in two studies but were found to be reduced in another.

Summary Table 7

Subacute Psychedelic Phenomenology

Phenomenon	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Improved psychological functioning	-	-	+++	-	+++	+++	-	+++
Persisting insight	⊕⊕⊕	⊕⊕⊕	+++	⊕⊕	+++	++	⊕⊕	++
Integration of experience into life	-	-	+++	-	-	++	-	-
Change in social perspective	-	-	-	-	+++	-	-	-
Increased empathy	-	-	++	-	-	∅	-	-
Meaningfulness of experience	-	-	+++	-	-	-	-	-
Distress and negative reflections	-	-	-	-	-	+	-	-
Ineffability	-	-	+++	+++	-	-	+++	+++
Difficulty recalling experience	-	-	-	-	-	-	-	+++
Increased frequency of unpleasant dreams	-	-	-	-	-	-	++	-

Note. Symbol key on page 180.

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Chapter 7: Psychological Change from Psychedelics

The goal of this chapter is to summarize in table form what is known about psychedelics' impact on long-term psychological constructs. Due to the breadth of studies on this topic, with most studies measuring multiple psychological traits, the bulk of this chapter consists of tables summarizing the research on each psychological trait. Findings are delineated between long-term (follow-up of 4 weeks or more) and subacute (follow-up of less than 4 weeks, italicized in table). At the end of the chapter, the subacute impacts of psychedelics on psychological traits are synthesized in Summary Table 8, while the long-term impacts are in Summary Table 9.

Excluded from this section are studies examining the characteristics of recreational psychedelic users, many of which were done with MDMA. Such studies do not provide information about the effects of a drug but rather information about the people who are drawn to use the drug. Thus, drug causality cannot be inferred. However, there were two exceptions to this rule:

1. Studies comparing MDMA users and non-MDMA polydrug-using controls were included, as these studies can infer causality. Recreational MDMA users also tend to use other drugs and are therefore considered polydrug users (Gouzoulis-Mayfrank & Daumann, 2006a). If recreational MDMA users were compared to a normative sample or non-substance users, the effects seen could be due to other substance use among the MDMA group. The effects seen could also be due to the pre-existing characteristics of people who choose to use MDMA (substance use prone). Using a non-MDMA polydrug control group eliminates these biases as both groups presumably have effects from non-MDMA substance use and have

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pre-existing characteristics that led them to use substances. This control group will simply be referred to as "polydrug" controls for brevity. While this methodology is found chiefly in MDMA studies, polydrug controls are used in a few studies with other psychedelics. For those studies, polydrug controls refer to people who use multiple substances except the psychedelic studied (e.g., non-ketamine polydrug-using controls).

2. Studies were included that compare psychological characteristics of religious groups who use psychedelics with culturally similar groups that do not use psychedelics. The population of people using psychedelics within a culturally acceptable religious framework is likely to have more diversity of psychological traits before psychedelic use than the population of people who self-select to use psychedelics in a prohibited context. For this reason, some causation can reasonably be inferred from this comparison.

Big Five Personality Traits

The Big Five model was developed from a series of progressive attempts to identify the independent factors of personality. In 1936 Allport and Odbert used a lexical approach to classify all the terms related to personality from a dictionary (John & Srivastava, 1999). In 1943, from a subset of 4,500 trait terms on this list, Cattell used semantic and empirical clustering to reduce those terms to 35 variables, which were then reduced via factor analyses to 12 personality factors (John & Srivastava, 1999). These factors would later become part of his 16 Personality Factors (16PF) questionnaire (Cattell et al., 1970). The personality factors identified by Cattell in 1943 were further analyzed by other researchers who looked at correlation matrices between the variables

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measured on different populations. These pioneering researchers included Fiske (1949) and Tupes and Christal (1992), whom both identified what would become the Big Five personality factors (Goldberg, 1981). The existence of the Big Five was replicated in several subsequent studies between 1963 and 1981, and it remains a preeminent model of personality (John & Srivastava, 1999). The Big Five factors are (reproduced from John & Srivastava, 1999):

I. Extraversion or Surgency (talkative, assertive, energetic)
II. Agreeableness (good-natured, cooperative, trustful)
III. Conscientiousness (orderly, responsible, dependable)
IV. Emotional Stability versus Neuroticism (calm, not neurotic, not easily upset), which is called Neuroticism in most measures.
V. Culture (intellectual, polished, independent-minded). In the current literature, this factor is referred to as Openness.

The fifth factor, Culture, eventually became known as “Openness” or “Openness to Experience” as measures of the Big Five were validated across languages, and the fifth factor was shown to be distinct from measures of intelligence (John & Srivastava, 1999). An alternate label, “Imagination,” has also been used to describe this factor, highlighting the influence of creativity, innovation, artistry, and introspection (Saucier, 2010).

Measures of the Big Five traits include the NEO Five-Factor Inventory (NEO-FFI), the NEO Personality Inventory (NEO-PI), and the Revised NEO Personality Inventory (NEO PI-R).

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I: Extraversion. Table 8 shows studies measuring changes in Extraversion following psychedelic administration. No studies reported a statistically significant change in Extraversion following psychedelic administration.

II: Agreeableness. Table 9 summarizes studies measuring changes in Agreeableness following psychedelic administration. No studies reported a statistically significant change in Agreeableness following psychedelic administration.

III: Conscientiousness. Table 10 summarizes studies measuring changes in Conscientiousness following psychedelic administration. Nour et al. (2017) found through survey data [N=893] that lifetime psychedelic use was not correlated with Conscientiousness (p=.414).

IV: Neuroticism. Table 11 summarizes studies measuring changes in Neuroticism following psychedelic administration. Wagner et al. (2017)[3] performed a randomized controlled trial using MDMA-assisted psychotherapy to treat PTSD [n=12] that was compared to psychotherapy with a placebo drug [n=8]. While decreases in Neuroticism at 2-month follow-up were not significant, there was a significant decrease at long-term follow-up (p=.003; d_n=-0.99) compared to baseline as measured by the NEO PI-R. An interaction was found between Neuroticism and PTSD symptom improvement, with PTSD symptoms improving alongside decreased Neuroticism (p<.001).

V: Openness. Table 12 summarizes studies measuring changes in Openness following psychedelic administration. Aday, Mitzkovitz, et al. (2020) performed a systematic review of the long-term effects of psychedelic drugs (follow-up longer than 2

[3] M. T. Wagner et al. (2017) did not measure Extraversion, Agreeableness, or Conscientiousness in their study.

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weeks). Four of seven studies they found assessing Openness to Experience found lasting changes following psilocybin or LSD administration. In one of the studies that did not report lasting changes in Openness (Griffiths et al., 2016), participants already had high levels of Openness prior to psychedelic administration, indicating a potential ceiling effect. MacLean et al. (2011) found that mystical-type experience (as measured by the Mysticism Scale) during a psilocybin experience was significantly correlated with greater changes in Openness as measured by the NEO-PI at 1-year follow-up. Lebedev et al. (2016) identified that greater changes in Openness 2 weeks following LSD were correlated with higher measures of neural entropy during the experience, as measured by fMRI. The group also found that high measures of brain entropy correlated with subjective experiences of "ego-dissolution," suggesting an overlap between the phenomena of ego-dissolution and mystical experience and change in Openness. Nour et al. (2017) found through survey data [N=893] that lifetime psychedelic use was positively correlated with Openness (r^2= .032; p<.0001).

M. T. Wagner et al. (2017) performed a randomized controlled trial comparing MDMA-assisted psychotherapy [n=12] with placebo and psychotherapy [n=8] for treating PTSD. While increases in Openness at 2-month follow-up were not significant, there was a significant increase at long-term follow-up (p=.032; d_n=0.33) compared to baseline as measured by the NEO PI-R. An interaction was found between Openness and the Clinician-Administered PTSD Scale (CAPS), where those with the largest increases in Openness improved the most on the CAPS (p=.029).

I. Extraversion

Table 8

Extraversion Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-					
			High severity patients:	MMPI^{E}: -*Si*^{a}	**0.8$_{n}$**	**Large**	**<.05**	17
			Moderate severity patients:		**0.9$_{n}$**	**Large**	**<.05**	18
			Healthy normals:		0.3$_{n}$	Moderate	NS	25
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: -*Si*^{a}	**0.78$_{n}$**	**Large**	**<.05**	30
				EPI: *E*$_{n}$	0.49$_{n}$	Moderate	NS	
	LSD 350 µg			MMPI: -*Si*^{a}	**1.05$_{n}$**	**V. Large**	**<.05**	29
				EPI: *E*$_{n}$	0.31$_{n}$	Moderate	NS	
Carhart-Harris et al. (2016)	LSD 75 µg IV	*2-week*	vs. placebo	NEO-PI-R	-	-	NS	20
Schmid & Liechti (2018)	LSD 200 µg	1-month	post- / pre-	NEO-FFI	0.04$_{n}$	Tiny	NS	15
		1-year	post- / pre-		-0.03$_{n}$	Tiny	NS	15
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: -*Si*^{a}	0.07$_{n}$	Small	NS	19
				CPI: Sociability (*Sy*)	**0.73$_{n}$**	**Large**	**<.01**	20

Table 8

Extraversion Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
MacLean et al. (2011); data from Griffiths et al. (2006, 2011)	Psilocybin 10–30 mg/70 kg, 2–5 sessions, + methylphenidate control	1- to 2-month	post- / pre-	NEO-PI	0.08	Small	.38	51
Erritzoe et al. (2018)	Psilocybin for depression, 10 mg and 25 mg	3-month	post- / pre-	NEO-PI-R	**0.716**	**Large**	**<.001**	19
Madsen et al. (2020)	Psilocybin 14–21 mg/kg	3-month	post- / pre-	NEO-PI-R	0.04$_g$	Tiny	.7	10
Ayahuasca								
Barbosa et al. (2016), unpublished data analysis	Ritual ayahuasca	N/A	vs. matched controls [*n*=27]	BFI	0.106	Small	.692	30
Quevedo (2009)	Neo-shamanic three-ceremony ayahuasca retreat	*Immediate*	post- / pre-	BFI	0.04	Tiny	.78	21
		4-week			0.14	Small	.38	18
		8-week			**0.24**	**Moderate**	**.03**	22
MDMA								
Mithoefer et al. (2018)	2x MDMA-assisted therapy for PTSD w/:							
	75 mg	1-month	vs. active placebo (30 mg MDMA therapy, *n*=7)	NEO-PI-R	1.04$_c$	V. Large	.17	7
	125 mg				0.50$_c$	Moderate	.22	12
	75 mg	12-month	vs. active placebo	NEO-PI-R	1.33$_c$	V. Large	N/R	7
	125 mg				0.89$_c$	Large	N/R	12
	30 mg	12-month	post- / pre-	NEO-PI-R	**0.51$_c$**	**Large**	**.0002**	7
	75 mg				**1.13$_c$**	**V. Large**	**.0002**	7
	125 mg				**1.14$_c$**	**V. Large**	**.0002**	12

Table 8

Extraversion Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	"after"	post- / pre-	MMPI[R]: -*Si*[a]	0.09_n	Small	NS	111

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*Si* = Social Introversion); EPI = Eysenck's Personality Inventory (*E* = Extraversion); NEO-FFI = NEO Five-Factor Inventory; NEO-PI = NEO Personality Inventory; NEO-PI-R = Revised NEO-PI; CPI = California Psychological Inventory; KPT = Ketamine Psychedelic Therapy (see Chapter 11); IM = intramuscular.

[a] Effect size represented by inverted Introversion to correspond with increased Extraversion.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

II. Agreeableness

Table 9

Agreeableness Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Carhart-Harris et al. (2016)	LSD 75 µg IV	*2-week*	vs. placebo	NEO-PI-R	0.21	Moderate	.15	20
Schmid & Liechti (2018)	LSD 200 µg	1-month	post- / pre-	NEO-FFI	-0.08_n	Small	NS	15
		1-year	post- / pre-	NEO-FFI	0.12_n	Small	NS	15
Psilocybin								
MacLean et al. (2011); data from Griffiths et al. (2006, 2011)	Psilocybin 10–30 mg/70 kg, 2–5 sessions, + methylphenidate control	1- to 2-month	post- / pre-	NEO-PI	0.17	Small	.16	51
Erritzoe et al. (2018)	Psilocybin for depression, 10 mg and 25 mg	3-month	post- / pre-	NEO-PI-R	-0.006	Tiny	.953	19
Madsen et al. (2020)	Psilocybin 14–21 mg/kg	3-month	post- / pre-	NEO-PI-R	0.013_g	Tiny	.9	10
Ayahuasca								
Barbosa et al. (2016), unpublished data analysis obtained through personal communication.	Ritual ayahuasca use	N/A	vs. matched controls [*n*=27]	BFI	**0.692**	**Large**	**.012**	30
Quevedo (2009)	Neo-shamanic three-ceremony ayahuasca retreat	*Immediate*	post- / pre-	BFI	0.02	Tiny	.97	21
		4-week			**0.47**	**Moderate**	**.04**	18
		8-week			**0.45**	**Moderate**	**.01**	22

Table 9

Agreeableness Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
MDMA								
Mithoefer et al. (2018)	2x MDMA-assisted therapy for PTSD w/:							
	75 mg	1-month	vs. active placebo (30 mg MDMA therapy, *n*=7)	NEO-PI-R	-0.61$_c$	Large	.13	7
	125 mg				**0.41$_c$**	**Moderate**	**.05**	12
	75 mg	12-month	vs. active placebo	NEO-PI-R	-0.48$_c$	Moderate	N/R	7
	125 mg				0.31$_c$	Moderate	N/R	12
	30 mg	12-month	post- / pre-	NEO-PI-R	**-0.10$_c$**	**Small**	**.007**	7
	75 mg				**0.41$_c$**	**Moderate**	**.007**	7
	125 mg				**0.58$_c$**	**Large**	**.007**	12

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). NEO-FFI = NEO Five-Factor Inventory; NEO-PI = NEO Personality Inventory; NEO-PI-R = Revised NEO-PI; BFI = Big Five Inventory.

III. Conscientiousness

Table 10

Conscientiousness Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Carhart-Harris et al. (2016)	LSD 75 µg IV	*2-week*	vs. placebo	NEO-PI-R	-	-	NS	20
Schmid & Liechti (2018)	LSD 200 µg	1-month	post- / pre-	NEO-FFI	**0.20$_n$**	**Small**	<.05	15
		1-year	post- / pre-		**0.54$_n$**	**Large**	<.05	15
Psilocybin								
MacLean et al. (2011); data from Griffiths et al. (2006, 2011)	Psilocybin 10–30 mg/70 kg, 2–5 sessions, + methylphenidate control	1- to 2-month	post- / pre-	NEO-PI	-0.09	Small	.28	51
Erritzoe et al. (2018)	Psilocybin for depression, 10 mg and 25 mg	3-month	post- / pre-	NEO-PI-R	*0.273*	*Moderate*	*.086*	19
Madsen et al. (2020)	Psilocybin 14–21 mg/kg	3-month	post- / pre-	NEO-PI-R	0.26$_g$	Moderate	.3	10
Ayahuasca								
Barbosa et al. (2016), unpublished data analysis obtained through personal communication.	Ritual ayahuasca use	N/A	vs. matched controls [*n*=27]	BFI	**0.572**	**Large**	**.036**	30
Quevedo (2009)	Neo-shamanic three-ceremony ayahuasca retreat	*Immediate*	post- / pre-	BFI	-0.02	Tiny	.95	21
		4-week			0.10	Small	.46	18
		8-week			-0.10	Small	.41	22

Table 10

Conscientiousness Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
MDMA								
Mithoefer et al. (2018)	2x MDMA-assisted therapy for PTSD w/:							
	75 mg	1-month	vs. active placebo (30 mg MDMA therapy, *n*=7)	NEO-PI-R	1.93$_c$	V. Large	.50	7
	125 mg				0.94$_c$	Large	.17	12
	75 mg	12-month	vs. active placebo	NEO-PI-R	1.06$_c$	V. Large	N/R	7
	125 mg				0.39$_c$	Moderate	N/R	12
	30 mg	12-month	post- / pre-	NEO-PI-R	0.27$_c$	Moderate	.36	7
	75 mg				-0.03$_c$	Tiny	.36	7
	125 mg				0.47$_c$	Moderate	.36	12

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). NEO-FFI = NEO Five-Factor Inventory; NEO-PI = NEO Personality Inventory; NEO-PI-R = Revised NEO-PI; BFI = Big Five Inventory.

IV. Neuroticism

Table 11

Neuroticism Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	EPI: *N*	**-0.61$_n$**	**Large**	**<.05**	30
	LSD 350 µg				**-1.29$_n$**	**V. Large**	**<.01**	29
Carhart-Harris et al. (2016)	LSD 75 µg IV	*2-week*	vs. placebo	NEO-PI-R	-	-	NS	20
Schmid & Liechti (2018)	LSD 200 µg	1-month	post- / pre-	NEO-FFI	0.03$_n$	Tiny	NS	15
		1-year			-0.16$_n$	Small	NS	15
Psilocybin								
MacLean et al. (2011); data from Griffiths et al. (2006, 2011)	Psilocybin 10–30 mg/70 kg, 2–5 sessions, + methylphenidate control	1- to 2-month	post- / pre-	NEO-PI	-0.05	Small	.62	51
Erritzoe et al. (2018)	Psilocybin for depression, 10 mg and 25 mg	3-month	post- / pre-	NEO-PI-R	**-0.571**	**Large**	**.002**	19
Madsen et al. (2020)	Psilocybin 14–21 mg/kg	3-month	post- / pre-	NEO-PI-R	**-0.29$_g$**	**Moderate**	**.02**	10
Ayahuasca								
Barbosa et al. (2016)	Ritual ayahuasca use	N/A	vs. matched controls [*n*=27]	BFI	-0.278	Moderate	.300	30

Table 11

Neuroticism Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Quevedo (2009)	Neo-shamanic three-ceremony ayahuasca retreat	*Immediate*	post- / pre-	BFI	**-0.47**	**Moderate**	**.02**	21
		4-week			**-0.57**	**Large**	**.01**	18
		8-week			**-0.56**	**Large**	**.01**	22
MDMA								
M. T. Wagner et al. (2017)	MDMA-assisted psychotherapy	2-month	post- / pre-	NEO-PI-R	-1.18$_n$	V. Large	NS	12
		2-month	vs. placebo		-0.48$_n$	Moderate	NS	12 / 8
		M=45.4 month	post- / pre-		**-0.99$_n$**	**Large**	**.003**	16
Mithoefer et al. (2018)	2x MDMA-assisted therapy for PTSD w/:							
	75 mg	1-month	vs. active placebo (30 mg MDMA therapy, *n*=7)	NEO-PI-R	-0.48$_c$	Moderate	.23	7
	125 mg				**-0.12$_c$**	**Small**	**.03**	12
	75 mg	12-month	vs. active placebo	NEO-PI-R	0.39$_c$	Moderate	N/R	7
	125 mg				0.02$_c$	Tiny	N/R	12
	30 mg	12-month	post- / pre-	NEO-PI-R	**-0.37$_c$**	**Moderate**	**<0.0001**	7
	75 mg				**-0.42$_c$**	**Moderate**	**<0.0001**	7
	125 mg				**-2.24$_c$**	**V. Large**	**<0.0001**	12

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). NEO-FFI = NEO Five-Factor Inventory; EPI = Eysenck's Personality Inventory (*N* = Neuroticism); NEO-PI = NEO Personality Inventory; NEO-PI-R = Revised NEO-PI; BFI = Big Five Inventory.

V. Openness

Table 12

Openness Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Carhart-Harris et al. (2016)	LSD 75 µg IV	*2-week*	post- / pre- (no effect in control)	NEO-PI-R	**0.16**	**Small**	**.03**	20
Schmid & Liechti (2018)	LSD 200 µg	1-month	post- / pre-	NEO-FFI	0.03_{n}	Small	NS	15
		1-year			-0.04_{n}	Small	NS	15
Psilocybin								
MacLean et al. (2011); data from Griffiths et al. (2006, 2011)	Psilocybin 10–30 mg/70 kg, 2–5 sessions, + methylphenidate control	1- to 2-month	post- / pre-	NEO-PI	$\mathbf{0.67_{\eta 2}}$	**Large**	**.023**	51
		M=16-month, w/ ME			$\mathbf{0.77_{\eta 2}}$	**Large**	**.050**	30
		M=16-month, w/o ME			NR	NR	.86	21
Erritzoe et al. (2018)	Psilocybin for depression, 10 and 25 mg	3-month	post- / pre-	NEO-PI-R	**0.437**	**Moderate**	**.012**	19
Madsen et al. (2020)	Psilocybin 14–21 mg/kg	3-month	post- / pre-	NEO PI-R	$\mathbf{0.23_{g}}$	**Moderate**	**.04**	10
Ayahuasca								
Barbosa et al. (2016), unpublished data analysis obtained through personal communication.	Ritual ayahuasca use	N/A	vs. matched controls [*n*=27]	BFI	**0.736**	**Large**	**.008**	30

Table 12

Openness Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Quevedo (2009)	Neo-shamanic three-ceremony ayahuasca retreat	*Immediate*	post- / pre-	BFI	-0.06	Small	.63	21
		4-week			0.10	Small	.42	18
		8-week			0.02	Tiny	.90	22
MDMA								
M. T. Wagner et al. (2017)	MDMA-assisted psychotherapy	2-month	post- / pre-	NEO PI-R	0.32_{n}	Moderate	NS	12
		2-month	vs. placebo		-0.23_{n}	Moderate	NS	12 / 8
		M=45.4 month	post- / pre-		**0.33_{n}**	**Moderate**	**.032**	16
Mithoefer et al. (2018)	2x MDMA-assisted therapy for PTSD w/:							
	75 mg	1-month	vs. active placebo (30 mg MDMA therapy, *n*=7)	NEO-PI-R	**1.85_{c}**	**V. Large**	**.02**	7
	125 mg				1.01_{c}	V. Large	.62	12
	75 mg	12-month	vs. active placebo	NEO-PI-R	1.44_{c}	V. Large	N/R	7
	125 mg				0.69_{c}	Large	N/R	12
	30 mg	12-month	post- / pre-	NEO-PI-R	**0.20_{c}**	**Small**	**.015**	7
	75 mg				**0.93_{c}**	**Large**	**.015**	7
	125 mg				**0.19_{c}**	**Small**	**.015**	12

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). NEO-PI = NEO Personality Inventory; NEO-PI-R = Revised NEO-PI; NEO-FFI = NEO Five-Factor Inventory; BFI = Big Five Inventory; ME = complete mystical experience.

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Self-Regulation

Psychedelic effects on non-pathological personality constructs other than the Big Five are described here. The constructs summarized are as follows:

- **Self-Concept:** Table 13
- **Ego Strength, Repression, and Regression:** Table 14
- **Emotional Regulation:** Table 15
- **Narcissism:** Described in paragraph form
- **Reward Dependence:** Table 16

Self-Concept

Table 13

Self-Concept Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Self-concept	**0.98$_c$**	**Large**	**<.01**	14
		2-month			**0.83$_c$**	**Large**	**<.05**	
	LSD + psychotherapy	*2-week*	post- / pre-		*0.82$_c$*	*Large*	*<.1*	14
		2-month			**1.22$_c$**	**V. Large**	**<.01**	
	LSD + hypnosis + psychotherapy	*2-week*	post- / pre-		**1.45$_c$**	**V. Large**	**<.01**	14
		2-month			**2.03$_c$**	**V. Large**	**<.01**	
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 wk group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	CPI: Self-acceptance (*Sa*)	-0.08$_n$	Small	NS	20

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Griffiths et al. (2011)	Psilocybin 20 or 30 mg/70 kg			PEQ – Attitudes about self:				
		1-month	Retrospective impact of psilocybin experience vs. placebo	Positive	**0.98$_c$**	**Large**	**<.05**	18
				Negative	0.58$_c$[a]	Large	NS	
		14-month		Positive	**1.19$_c$**	**V. Large**	**.002$_t$**	18
				Negative	**0.81$_c$**[a]	**Large**	**.026$_t$**	
Griffiths et al. (2017)	Psilocybin 20 and 30 mg/70 kg:	6-month	vs. active placebo (1 mg/70 kg psilocybin, 2x, *n*=25)	PEQ – Attitudes about self:				
	w/ 5 hr individual prep. + 2:20 hr individual follow-up			Positive	**1.15$_c$**	**V. Large**	**<.001**	25
				Negative	0.64$_c$[a]	Large	NS	
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up			Positive	**1.96$_c$**	**V. Large**	**<.001**	25
				Negative	**0.64$_c$**[a]	**Large**	**<.05**	
Smigielski et al. (2019)	22.05 mg/ 70 kg psilocybin	4-month	vs. placebo	LCI-R: Self-acceptance	+	**Increase**	**<.01**	39
F. S. Barrett et al. (2020)	Psilocybin 25 mg/70 kg	1-week	post- / pre-	DPES: Pride	**0.85**	**Large**	**.009**	12
		1-month			**0.76**	**Large**	**.007**	12
Ayahuasca								
Sampedro et al. (2017)	Ayahuasca	2-month	post- / pre-	Spanish Self-Compassion Questionnaire	-0.09$_c$	Small	.953	14

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). PEP = Psychiatric Evaluation Profile; CPI = California Psychological Inventory; PEQ = Persisting Effects Questionnaire; LCI-R = Life Changes Inventory, Revised; DPES = Dispositional Positive Emotion Scale.

[a] PEQ Negative Attitudes About Self showed a significant floor effect. For this reason, these increases in negative attitudes about self are unlikely to be clinically significant. They may instead be due to a more realistic appraisal of self, earned through treatment. For this reason, these values are not reported in the summary tables at the end of the chapter.

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Ego Strength, Repression, and Regression

Table 14

Ego Strength, Repression, and Regression Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-	MMPI[E]:				
			High severity patients:	*R*	-0.7$_n$	Large	NS	17
				Es	0.8$_n$	Large	NS	
			Moderate sev. patients:	*R*	**-0.5$_n$**	**Moderate**	**<.05**	**18**
				Es	**0.3$_n$**	**Moderate**	**<.05**	
			Healthy normals:	*R*	-0.3$_n$	Moderate	NS	25
				Es	-0.3$_n$	Moderate	NS	
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI:				30
				R	-0.26$_n$	Moderate	NS	
				Es	0.34$_n$	Moderate	NS	
	LSD 350 µg			*R*	-0.11$_n$	Large	NS	29
				Es	0.41$_n$	Moderate	NS	
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI[R]:				111
				S-R	**-0.78$_n$**	**Large**	**<.01**	
				Es	**0.38$_n$**	**Moderate**	**<.01**	
				Eo	0.04$_n$	Tiny	NS	
				LSI: Regression	**-0.96$_c$**	**Large**	**<.01**	37

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*R* = Repression; *Es* = Ego-Strength; *S-R* = Sensitivity-Repression; *Eo* = Ego Overcontrol); LSI = Plutchik's Life Style Index; KPT = Ketamine Psychedelic Therapy (see Chapter 11); IM = intramuscular.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

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Emotional Regulation

Table 15

Emotional Regulation Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Mescaline								
Halpern et al. (2005)	Ritual peyote	N/A	vs. controls	RMHI:				140
				Loss of behavioral/emotional control	-0.27c	Moderate	.18	
Ayahuasca								
G. Thomas et al. (2013)	4-day retreat w/ 2 ayahuasca ceremonies + group counseling	6-month	post- / pre-	DERS	–	Improved	.124	9
Domínguez-Clavé et al. (2019)	Ritual ayahuasca	*1-day*	post- / pre-	DERS (Spanish):				45
				Emotional non-acceptance	**-0.50c**	**Moderate**	**<.001**	
				Emotional interference	**-0.18c**	**Small**	**.007**	
				Emotional awareness	0.31c	Moderate	.19	
				Lack of clarity	*-0.09c*	*Small*	*.06*	
				Lack of control	**-0.27c**	**Moderate**	**<.001**	

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). RMHI = Rand Mental Health Inventory; DERS = Difficulties in Emotion Regulation Scale; YA = young adults.

Narcissism

van Mulukom et al. (2020) found through a retrospective online survey that recent classical psychedelic experiences were significantly associated with decreased "exploitative-entitled narcissism" as measured by the Narcissistic Personality Inventory 13 [N=414]. Two pathways mediated this effect. First, the experience of awe during the psychedelic experience was correlated with increased feelings of connectedness (p<.001; β=0.24), which correlated to less exploitative-entitled narcissism (p<.05; β=-0.13) with

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an overall statistically significant effect (p=.05). Second, awe was correlated with higher affective empathetic drive (p<.001; β=0.21), which correlated to less exploitative-entitled narcissism (p<.001; β=-0.21), again with an overall statistically significant effect (p=.01). Ego dissolution during the experience had no statistically significant association with exploitative-entitled narcissism when controlling for sensation-seeking personality features. It should be noted that this was a correlational study, and no causation can be inferred from this data.

Reward Dependence

Table 16

Reward Dependence Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Ayahuasca								
Grob et al. (1996)	Ritual ayahuasca	N/A	vs. matched controls [*n*=15]	TPQ: RD	0.27$_c$	Moderate	0.496	15
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	TCI: RD	**0.27$_c$**	**Moderate**	**0.009**	127

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). TPQ = Tridimensional Personality Questionnaire; TCI = Temperament and Character Inventory; RD = reward dependence.

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Coping and Adaptive Functioning

The impacts of psychedelics on measures of coping and adaptive functioning are summarized in Table 17.

Table 17

Coping and Adaptive Functioning Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Coping attitudes	**0.82**$_c$	**Large**	**<.05**	14
		2-month			**1.39**$_c$	**V. Large**	**<.01**	
	LSD + psychotherapy	*2-week*	post- / pre-		**1.04**$_c$	**V. Large**	**<.05**	14
		2-month			**1.29**$_c$	**V. Large**	**<.01**	
	LSD + hypnosis + psychotherapy	*2-week*	post- / pre-		**2.11**$_c$	**V. Large**	**<.01**	14
		2-month			**1.97**$_c$	**V. Large**	**<.01**	
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 wk group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	CPI:				20
				Responsibility (*Re*)	**0.97**$_n$	**Large**	**<.01**	
				Intellectual efficiency (*Ie*)	**0.90**$_n$	**Large**	**<.01**	
				Capacity for status (*Cs*)	**0.60**$_n$	**Large**	**<.01**	
				Achievement via independence (*Ai*)	**0.52**$_n$	**Large**	**<.02**	
Griffiths et al. (2011)	Psilocybin 20 or 30 mg/70 kg			PEQ – Behavior changes:				
		1-month	Retrospective psilocybin experience vs. placebo	Positive	**0.89**	**Large**	**<.05**	18
				Negative	-1.67	V. Large	NS	
		14-month		Positive	**1.11**	**V. Large**	**.004**	18
				Negative	**-1.67**	**V. Large**	**<.001**	
Griffiths et al. (2017)	Psilocybin 20 and 30 mg/70 kg:	6-month	vs. active placebo (1 mg/70 kg psilocybin, 2x, *n*=25)					
				PEQ – Behavior changes:				
	w/ 5 hr individual prep. + 2:20 hr individual follow-up			Positive	**1.16**	**V. Large**	**<.001**	25
				Negative	-0.28	Large	NS	
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up			Positive	**2.00**	**V. Large**	**<.001**	25
				Negative	-0.28	Large	NS	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Erritzoe et al. (2018)	Psilocybin for depression, 10 and 25 mg	3-month	post- / pre-	NEO-PI-R: Dutifulness	0.250	Moderate	.191	19
				Achievement striving	0.294	Moderate	.110	
				Self-discipline	**0.465**	**Moderate**	**.010**	
				Competence	**0.743**	**Large**	**.011**	
Ayahuasca								
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	TCI: Persistence	0.12[c]	Small	NS	127
				Self-directedness	**-0.50[c]**	**Moderate**	**<.002**	
G. Thomas et al. (2013)	4-day retreat w/ group counseling + 2 ayahuasca ceremonies	6-month	post- / pre-	Empowerment (ES)	+	**Increase**	**.002**	11
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	TCI-R: Self-directedness	**12.5%**	**Increase**	**<.01**	10
				Responsibility	**8.5%**	**Increase**	**<.05**	10

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). PEP = Psychiatric Evaluation Profile; CPI = California Psychological Inventory; TCI = Temperament and Character Inventory.

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Interpersonal Functioning

The impacts of psychedelics on various interpersonal traits are summarized in Table 18 while changes in empathy are described in Table 19. Finally, changes in social orientation such as altruistic and antisocial tendencies are described in Table 20.

Interpersonal Traits

Table 18

Interpersonal Trait Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Mescaline								
Halpern et al. (2005)	Ritual peyote	N/A	vs. controls	RMHI: Emotional ties	0.20$_c$	Small	.20	140
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 wk group therapy	*2 weeks after 2nd session*	post- / pre-	CPI:				20
				Dominance (*Do*)	0.33$_n$	Moderate	NS	
				Social presence (*Sp*)	**0.62$_n$**	**Large**	**<.01**	
				Socialization (*So*)	**0.88$_n$**	**Large**	**<.01**	
				Tolerance (*To*)	**0.86$_n$**	**Large**	**<.01**	
				Achievement via conformance (*Ac*)	**0.80$_n$**	**Large**	**<.01**	
				Flexibility (*Fx*; thinking, social behavior)	-0.14	Small	NS	
Studerus et al. (2011)	1–4 doses psilocybin 8.05–22.05 mg/70 kg	8–16 months following final session, retrospective rating		Change in relationships to other people:				90
				positive	25%			
				unchanged	68%			
				negative	7%			
				Change in professional relationships:				
				positive	6%			
				unchanged	89%			
				negative	5%			
				Change in awareness of personal problems:				
				positive	29%			
				unchanged	66%			
				negative	5%			

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Griffiths et al. (2017)	Psilocybin 20 and 30 mg/70 kg:	6-month	vs. active placebo (1 mg/70 kg psilocybin, 2x, *n*=25)					
	w/ 5 hr individual prep. + 2:20 hr individual follow-up			IOS: Interpersonal closeness	0.44$_c$	Moderate	NS	25
				TFS: Forgiveness	-0.08$_c$	Small	NS	
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up			IOS: Interpersonal closeness	**0.71$_c$**	**Large**	**<.05**	25
				TFS: Forgiveness	0.58$_c$	Large	NS	
Erritzoe et al. (2018)	Psilocybin for dep., 10 and 25 mg	3-month	post- / pre-	NEO-PI-R: Anger-hostility	-0.277	Moderate	.222	19
				Vulnerability	**-0.706**	**Large**	**.004**	
				Warmth	**0.604**	**Large**	**.001**	
				Gregariousness	**0.503**	**Large**	**.011**	
				Assertiveness	0.304	Moderate	.152	
				Compliance	-0.069	Tiny	.685	
				Trust	0.372	Moderate	.085	
				Straightforwardness	-0.120	Small	.478	
				Tendermindedness	0.215	Moderate	.274	
F. S. Barrett et al. (2020)	Psilocybin 25 mg/70 kg	*1-week*	post- / pre-	DPES: Compassion	**0.50**	**Moderate**	**.001**	12
		1-month	post- / pre-	Compassion	**0.24**	**Moderate**	**.003**	12
Ayahuasca								
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	SCL-90-R: *I-S*	**-0.63$_c$**	**Large**	**<.001**	127
				HOS	**-0.38$_c$**	**Large**	**<.04**	
				TCI: Cooperativeness	0.00$_c$	Tiny	NS	
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SCL-90-R: *I-S*	-32.1%	Decrease	NS	9
				HOS	-68.2%	Decrease	NS	
MDMA								
Huxster et al. (2006)	MDMA-using young adults [*n*=38]	9-day, prospect.	vs. MDMA-abstinent group [*n*=18]	SCL-90-R: *I-S*	0.32$_c$	Moderate	NS	20
				HOS	-0.02$_c$	Tiny	NS	

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Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). RMHI = Rand Mental Health Inventory; CPI = California Psychological Inventory; DERS = Difficulties in Emotion Regulation Scale; IOS = Inclusion of Others in the Self scale; TFS = Trait Forgiveness Scale; NEO-PI-R = Revised NEO Personality Inventory; SCL-90-R = Symptom Checklist-90-Revised (*I-S* = Interpersonal Sensitivity; *HOS* = Hostility); TCI = Temperament and Character Inventory; IVE = Impulsiveness, Venturesomeness, and Empathy questionnaire.

Empathy

Table 19

Empathy Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
General								
M. Lerner & Lyvers (2004, 2006)	Recreational high-dose psychedelic experience	N/A	vs. polydrug	EETS (emotional empathy)	+	Greater	NS	183
			vs. non-drug		**+**	**Greater**	**<.001**	
LSD								
Lyvers & Meester (2012)	Recreational LSD users	N/A	LSD frequency	BEES (emotional empathy)	0.02_r	Tiny	NS	280
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 wk group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	CPI: Psychological-mindedness (*Py*)	0.31_n	Moderate	NS	20
Lyvers & Meester (2012)	Recreational psilocybin users	N/A	Psilocybin frequency	BEES (emotional empathy)	-0.02_r	Tiny	NS	300
Edelson (2017)	Psilocybin experienced, in committed relationship	vs. no psilocybin experience		IRIC:				209
				Empathetic concern	-0.09_c	Small	>.05	
				Perspective taking	-0.16_c	Small	>.05	
Smigielski et al. (2019)	22.05 mg/ 70 kg psilocybin	4-month	vs. placebo	LCI-R: Concern for others	+	*Increase*	*<.07*	39

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Rucker et al. (2022)	Psilocybin 10 or 25 mg	*8-day*	vs. placebo	Emotional empathy		No change	NS	60
				Cognitive empathy		No change	NS	
		85-day	vs. placebo	Emotional empathy		No change	NS	59
				Cognitive empathy		No change	NS	
MDMA								
Huxster et al. (2006)	MDMA-using young adults [*n*=38]	*9-day, prospective*	vs. MDMA-abstinent group [*n*=18]	IVE: Empathy (emotional)	0.40_c	Moderate	NS	20
Lyvers & Meester (2012)	Recreational MDMA users	N/A	MDMA frequency	BEES (emotional empathy)	$\leq 0.01_r$	Tiny	NS	249
Carlyle et al. (2019)	Long-term recreational MDMA users	N/A	vs. polydrug controls	MET:				67
				Emotional	$0.29_{\eta 2}$	Moderate	.496	
				Cognitive	$\mathbf{0.87}_{\eta 2}$	**Large**	**.028**	
			vs. alcohol w/o drug use	Emotional	$0.29_{\eta 2}$	Moderate	.496	
				Cognitive	$0.41_{\eta 2}$	Moderate	.342	

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). EETS = Emotional Empathic Tendency Scale; BEES = Balanced Emotional Empathy Scale; CPI = California Psychological Inventory; IRIC = Interpersonal Reactivity Index for Couples; LCI-R = Life Changes Inventory, Revised; IVE = Impulsiveness, Venturesomeness, and Empathy questionnaire; MET = Multifaceted Empathy Test.

Table 20

Altruistic and Antisocial Trait Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-					
			High severity patients:	MMPI[E]: *Pd*	**-0.8$_n$**	**Large**	**<.05**	17
			Moderate severity patients:		-0.4$_n$	Moderate	NS	18
			Healthy normals:		**0.6$_n$**[a]	**Large**	**<.05**	25
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Sociopathy	*-0.61$_c$*	*Large*	*<.1*	14
		2-month			-0.62$_c$	Large	>.1	
	LSD + psychotherapy	*2-week*	post- / pre-		**-0.58$_c$**	**Large**	**<.05**	14
		2-month			**-0.78$_c$**	**Large**	**<.01**	
	LSD + hypnosis + psychotherapy	*2-week*	post- / pre-		**-0.95$_c$**	**Large**	**<.01**	14
		2-month			**-1.07$_c$**	**V. Large**	**<.01**	
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: *Pd*	0.34$_n$	Moderate	NS	30
	LSD 350 µg				-0.08$_n$	Small	NS	29

Table 20

Altruistic and Antisocial Trait Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *Pd*	-0.82$_{n}$	Large	"near" .05	19
Griffiths et al. (2011)	Psilocybin, 20 or 30 mg/70 kg	1-month	Impact of experience vs. placebo, retrospect.	PEG – Social effects:				
				Altruistic/positive	**1.00$_{c}$**	**Large**	**<.05**	18
				Antisocial/negative	0.29$_{c}$[b]	Moderate	NS	
		14-month		Altruistic/positive	**0.97$_{c}$**	**Large**	**.01$_{t}$**	18
				Antisocial/negative	**0.83$_{c}$**[b]	**Large**	**.023$_{t}$**	
Griffiths et al. (2017)	Psilocybin, 20 and 30 mg/70 kg:	6-month	vs. active placebo (1 mg/70 kg psilocybin, 2x, *n*=25)					
				PEG – Social effects:				
	w/ 5 hr individual prep. + 2:20 hr individual follow-up			Altruistic/positive	**1.23$_{c}$**	**V. Large**	**<.001**	25
				Antisocial/negative	-0.20$_{c}$	Small	NS	
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up			Altruistic/positive	**2.11$_{c}$**	**V. Large**	**<.001**	25
				Antisocial/negative	0.13$_{c}$	Small	NS	
Erritzoe et al. (2018)	Psilocybin for depression, 10 and 25 mg	3-month	post- / pre-	NEO-PI-R: Altruism	-0.177	Small	.318	19
Rucker et al. (2022)	Psilocybin, 10 or 25 mg	*8-day*	vs. placebo	Social responsibility (SSR)		No change	NS	60
				Prosocial values (SVO)		No change	NS	
		85-day	vs. placebo	Social responsibility (SSR)		No change	NS	59
				Prosocial values (SVO)		No change	NS	

Table 20

Altruistic and Antisocial Trait Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Ayahuasca								
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SOI: Altruism	0.4%	Increase	NS	9
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI[R]: *Pd*	-0.09$_n$	Small	NS	111

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*Pd* = Psychopathic Deviance); PEP = Psychiatric Evaluation Profile; PEQ = Persisting Effects Questionnaire; NEO-PI-R = Revised NEO Personality Inventory; SSR = Scale of Social Responsibility; SVO = Social Value Orientation; SOI = Spiritual Orientation Inventory; KPT = Ketamine Psychedelic Therapy (see Chapter 11); IM = intramuscular.

[a] This large increase in *Pd* among healthy normals may be due to altered perspectives on drug use following an LSD session, given that *Pd* loads heavily on substance use. For this reason, this finding is not reported in the summary tables at the end of the chapter.

[b] Antisocial/negative social effects showed a significant floor effect. For this reason, these values are not reported in the summary tables at the end of the chapter.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

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Well-Being and Positive Psychology

The impact of psychedelics on well-being and positive psychological constructs are described here. The constructs are summarized as follows:

- **Well-Being:** Table 21
- **Positive and Negative Affect:** Table 22
- **Disposition Toward Life:** Table 23
- **Nature Relatedness:** Table 24
- **Aesthetic Experience:** Described in paragraph form
- **Spontaneity:** Described in paragraph form

Well-Being

Table 21

Well-Being Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
General Psychedelics								
Haijen et al. (2018)	Non-clinical psychedelic[a], prospective	*2-week*	post- / pre-	WEMWBS	**+7.3%**	**Increase**	**<.05**	315
		4-week	post- / pre-	WEMWBS	**+5.7%**	**Increase**	**<.05**	212
Mescaline								
Halpern et al. (2005)	Ritual peyote	N/A	vs. controls	RMHI: Well-being	**0.48$_c$**	**Moderate**	**.015**	140
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 wk group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	CPI: Well-being (*Wb*)	**0.91$_n$**	**Large**	**<.01**	20
Griffiths et al. (2011)	Psilocybin 20 or 30 mg/70 kg	1-month	Retrospective impact of psilocybin experience vs. placebo	Did the experience change your sense of well-being or life satisfaction?	**1.41$_c$**	**V. Large**	**<.05**	18
		14-month			**1.34$_c$**	**V. Large**	**.001$_t$**	18

Table 21

Well-Being Change from Psychedelics, Continued

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Griffiths et al. (2017)	Psilocybin 20 and 30 mg/70 kg:	6-month	vs. active placebo (1 mg/70 kg psilocybin, 2x, *n*=25)					
	w/ 5 hr individual prep. + 2:20 hr individual follow-up			Did the experience change your sense of well-being or life satisfaction?	**0.97**$_c$	**Large**	**<.001**	25
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up				**1.63**$_c$	**V. Large**	**<.001**	25
Nicholas et al. (2018)	Psilocybin 21, 31.5, and 42 mg/70 kg	30-day	Positive vs. negative impact of experience	PEQ: All scales	+	**Positive**	**<.001**	**12**
Ayahuasca								
G. Thomas et al. (2013)	4-day retreat w/ 2 ayahuasca ceremonies + group counseling	6-month	post- / pre-	MQL: Overall	+	Increase	.105	11
				Psychological	+	*Increase*	*.055*	12
Ketamine								
Curran & C. J. A. Morgan (2000)	Recreational ketamine	*3-day, prospect.*	Ketamine-abstinent group	MRS: Contentedness	-0.41$_c$	Moderate	NS	39

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). WEMWBS = Warwick-Edinburgh Mental Wellbeing Scale; RMHI = Rand Mental Health Inventory; CPI = California Psychological Inventory; PEQ = Persisting Effects Questionnaire; MQL = McGill Quality of Life survey; MRS = Mood Rating Scale.

[a] "Psilocybin/magic mushrooms/truffles, LSD/1P-LSD, ayahuasca, DMT/5-MeO-DMT, *Salvia divinorum*, mescaline, or iboga/ibogaine."

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Positive and Negative Affect

Table 22

Positive and Negative Affect Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Mescaline								
Halpern et al. (2005)	Ritual peyote	N/A	vs. controls	RMHI:				140
				Positive affect	**0.52$_c$**	**Large**	**.008**	
				Psychological distress	-0.19$_c$	Small	.31	
Psilocybin								
Griffiths et al. (2011)	Psilocybin 20 or 30 mg/70 kg			PEQ – Mood changes:				
		1-month	Retrospective impact of psilocybin experience vs. placebo	Positive	**1.05$_c$**	**V. Large**	**<.05**	18
				Negative	0.18$_c$	Small	NS	
		14-month		Positive	**1.19$_c$**	**V. Large**	**.002$_t$**	18
				Negative	0.57$_c$	Large	.108$_t$	
Griffiths et al. (2017)	Psilocybin 20 and 30 mg/70 kg:	6-month	vs. active placebo (1 mg/70 kg psilocybin, 2x, *n*=25)	PEQ – Mood changes:				
	w/ 5 hr individual prep. + 2:20 hr individual follow-up			Positive	**1.15$_c$**	**V. Large**	**<.001**	25
				Negative	-0.15$_c$	Small	NS	
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up			Positive	**1.92$_c$**	**V. Large**	**<.001**	25
				Negative	0.12$_c$	Small	NS	
Erritzoe et al. (2018)	Psilocybin for dep., 10 and 25 mg	3-month	post- / pre-	NEO-PI-R: Positive emotions	**0.740**	**Large**	**<.001**	19
F. S. Barrett et al. (2020)	Psilocybin 25 mg/70 kg	*1-week*	post- / pre-	PANAS-X: Negative Affect	**-1.12**	**V. Large**	**.00006**	12
		1-month	post- / pre-		**-0.62**	**Large**	**.025**	12

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). RMHI = Rand Mental Health Inventory; PEQ = Persisting Effects Questionnaire; NEO-PI-R = Revised NEO Personality Inventory; PANAS-X = Positive and Negative Affect Schedule–Expanded Form.

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Disposition Toward Life

Table 23

Life Disposition Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Mescaline								
Halpern et al. (2005)	Ritual peyote	N/A	vs. controls	RMHI: Life satisfaction	0.11_c	Small	.77	140
LSD								
Carhart-Harris et al. (2016)	LSD 75 µg IV	*2-week*	vs. placebo	LOT-R: Optimism	**0.56**	**Large**	**.005**	20
Psilocybin								
Studerus et al. (2011)	1–4 doses psilocybin 8.05–22.05 mg/70 kg	8–16 months following final session, retrospective rating		Changes in world view:				90
				positive		18%		
				unchanged		81%		
				negative		1%		
				Changes in values:				
				positive		18%		
				unchanged		77%		
				negative		5%		
Griffiths et al. (2011)	Psilocybin 20 or 30 mg/70 kg	1-month	Retrospect. impact of psilocybin experience vs. placebo	PEQ - Attitudes about life:				
				Positive	**1.17_c**	**V. Large**	**<.05**	18
				Negative	0.06_c	Small	NS	
		14-month		Positive	**1.45_c**	**V. Large**	**$<.001_t$**	18
				Negative	*0.64_c*	*Large*	*$.073_t$*	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Griffiths et al. (2017)	Psilocybin 20 and 30 mg/70 kg:	6-month	vs. active placebo (1 mg/70 kg psilocybin, 2x, *n*=25)					
				PEQ – Attitudes about life:				
	w/ 5 hr individual prep. + 2:20 hr individual follow-up			Positive	**1.37**	**V. Large**	**<.001**	25
				Negative	0.26	Moderate	NS	
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up			Positive	**2.17**	**V. Large**	**<.001**	25
				Negative	0.47	Moderate	NS	
	w/ 5 hr individual prep. + 2:20 hr individual follow-up			GQ-6: Gratitude	0.47	Moderate	NS	25
				LAP-R: Life meaning	0.28	Moderate	NS	
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up			GQ-6: Gratitude	**0.60**	**Large**	**<.05**	25
				LAP-R: Life meaning	**0.88**	**Large**	**<.05**	
Smigielski et al. (2019)	22.05 mg/ 70 kg psilocybin	4-month	vs. placebo	LCI-R:				39
				Appreciation for life	+	**Increase**	**<.001**	
				Concern with worldly achievements	-	*Decrease*	*<.07*	
				Concern for social/planetary values	+	Increase	NS	
				Quest for meaning/sense of purpose	+	**Increase**	**<.01**	
F. S. Barrett et al. (2020)	Psilocybin 25 mg/70 kg	*1-week*	post- / pre-	DPES:				12
				Joy	**0.86**	**Large**	**.007**	
				Content	**0.92**	**Large**	**.009**	
				Amusement	**0.53**	**Large**	**.004**	
		1-month	post- / pre-	Joy	**0.65**	**Large**	**.007**	12
				Content	**0.63**	**Large**	**.026**	
				Amusement	**0.64**	**Large**	**.001**	
Ayahuasca								
G. Thomas et al. (2013)	4-day retreat w/ 2 ayahuasca ceremonies + group counseling	6-month	post- / pre-	MQL:				
				Meaning	+	**Increase**	**.005**	12
				Outlook	+	**Increase**	**.004**	12
				Hope (HS):	+	**Increase**	**.023**	12

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SOI:				
				Meaning/purpose in life	**15.3%**	**Increase**	**<.05**	9
				Mission in life	**28.5%**	**Increase**	**<.05**	9
				Material values	3.3%	Increase	NS	9
				Idealism	4.8%	Increase	NS	9
				TCI-R: Purposefulness	**15.4%**	**Increase**	**<.05**	10
				Purpose in Life Test:	**18.7%**	**Increase**	**<.05**	9
Uthaug et al. (2018)	Ayahuasca ceremony	*1-day*	post- / pre-	Life-satisfaction	+	**Increase**	**.027**	57
		4-week			-	-	NS	31
Ona et al. (2019)	Ritual ayahuasca	N/A	Number of times used	Valued living	**0.50**	**Moderate**	**.01**	380
				Engaged living	**0.44**	**Moderate**	**.02**	

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). RMHI = Rand Mental Health Inventory; PEQ = Persisting Effects Questionnaire; GQ-6 = Gratitude Questionnaire, Six Item Form; LAP-R = Life Attitude Profile–Revised; LCI-R = Life Changes Inventory, Revised; NEO-PI-R = Revised NEO Personality Inventory; DPES = Dispositional Positive Emotion Scale; MQL = McGill Quality of Life survey; HS = Hope Scale; TCI-R = Temperament and Character Inventory-Revised; SOI = Spiritual Orientation Inventory.

Nature Relatedness

Table 24

Nature Relatedness Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
General Psychedelics								
Forstmann & Sagioglou (2017)	Past experience with classical psychedelics			Nature-relatedness	***β*=0.30**		**<.001**	1,487
				Pro-environmental behavior	***β*=0.23**		**<.001**	
Nour et al. (2017)	Lifetime classical psychedelic use			Nature-relatedness	+	**Increase**	**<.001**	893

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Kettner et al. (2019)	Non-clinical psychedelic[a]	*2-week*	post- / pre-	NR-6	**0.14**$_c$	**Small**	**.027**	315
		4-week			**0.13**$_c$	**Small**	**.024**	212
		2-year			**0.49**$_c$	**Moderate**	**<.0001**	64
LSD								
Schmid & Liechti (2018)	200 µg LSD	1-month	post- / pre-	DTS: Nature-relatedness	0.31	Moderate	NS	16
		1-year	post- / pre-		0.43	Moderate	NS	14
Psilocybin								
Studerus et al. (2011)	1–4 doses psilocybin 8.05–22.05 mg/70 kg	8–16 months following final session, retrospective rating		Change in the relationship to the environment:				90
				positive		38%		
				unchanged		58%		
				negative		5%		
Lyons & Carhart-Harris (2018)	Psilocybin, 10 and 25 mg	*1-week*	post- / pre-	NR-6	**2.5**$_g$	**V. Large**	**.003**	7
		7–12-month			**1.2**$_g$	**V. Large**	**.021**	7

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). DTS = Death Transcendence Scale; NR-6 = Nature Relatedness Scale, Short Form.

[a] Psilocybin, magic mushrooms, truffles, LSD, 1P-LSD, ayahuasca, DMT, 5-MeO-DMT, *Salvia divinorum*, mescaline, or ibogaine

Aesthetic Experience

When asked about the impact of 1–4 doses of 8.05–22.05 mg/70 kg psilocybin 8–16 months following the final session, 37% of participants reported positive changes in aesthetic experiencing, 62% felt it was unchanged, and 1% felt it was negatively impacted [*n*=90, 54% male, age=20–47, 100% Caucasian] (Studerus et al., 2011).

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Spontaneity

McCabe et al. (1972) found increases in spontaneity 5–7 days following LSD therapy (50 µg: $p<.05$, Δ=17.8%; 350 µg: $p<.05$, Δ=31.2%) compared to a group therapy control as measured by the Personal Orientation Inventory (POI) [*N*=85, 65% female, age *M*=32.9, 95% White].

Mindfulness and Decentering

Psychedelic effects on mindfulness and decentering are shown in Table 25. Decentering is the capacity to shift perspective from being within a subjective experience to observing that experience (Bernstein et al., 2015).

Table 25

Mindfulness Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
McCabe et al. (1972)	LSD therapy:	*5–7-day*	vs. group therapy	POI:				
	350 µg			Present-moment awareness (*Tc*)	+	**Increase**	**<.05**	30
				Past/future preoccupation (*Ti*)	-	**Increase**	**<.05**	
	50 µg			Present-moment awareness (*Tc*)		None	NS	29
				Past/future preoccupation (*Ti*)		None	NS	
Psilocybin								
Smigielski et al. (2019)	22.05 mg/ 70 kg psilocybin	*6-day*	vs. placebo	FMI (mindfulness)	+	**Increase**	**<.001**	39
Madsen et al. (2020)	14 or 21 mg/70 kg psilocybin	3-month	post- / pre-	MAAS (mindfulness)	**0.66_g**	**Large**	**.02**	10

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Ayahuasca								
G. Thomas et al. (2013)	4-day retreat w/ group counseling + 2 ayahuasca ceremonies	6-month	post- / pre-	PHLMS (mindfulness)	+	**Increase**	**.041**	11
Soler et al. (2015)	Ayahuasca session	*24-hour*	post- / pre-	FFMQ^{S}:				25
				Non-Reacting	-0.23$_{c}$	Moderate	NS	
				Non-Judging	**0.44$_{c}$**	**Moderate**	**.02**	
				EQ^{S}: Decentering	**-0.14$_{c}$**	**Small**	**<.01**	
Sampedro et al. (2017)	Ayahuasca session	*24-hour*	post- / pre-	FFMQ^{S}:				16
				Non-Reacting	**0.54$_{c}$**	**Large**	**.032**	
				Non-Judging	**0.83$_{c}$**	**Large**	**.022**	
				EQ^{S}: Decentering	**0.78$_{c}$**	**Large**	**.003**	
		2-month	post- / pre-	Non-Reacting	-0.10$_{c}$	Small	.948	14
				Non-Judging	**0.54$_{c}$**	**Large**	**.045**	
				EQ^{S}: Decentering	0.07$_{c}$	Small	.401	
Uthaug et al. (2018)	Ayahuasca session	*1-day*	post- / pre-	FFMQ:				57
				Observing	+	**Increase**	**.018**	
				Describing		None	NS	
				Acting with Awareness	+	**Increase**	**.006**	
				Non-Reacting	+	**Increase**	**.038**	
				Non-Judging	+	**Increase**	**.016**	
		4-week		FFMQ: All scales		None	NS	31
Domínguez-Clavé et al. (2019)	Ayahuasca session	*24-hour*	post- / pre-	FFMQ-SF^{S}:				45
				Observing	**1.36$_{c}$**	**V. Large**	**<.001**	
				Describing	-0.04$_{c}$	Tiny	.21	
				Acting with Awareness	**0.51$_{c}$**	**Large**	**.001**	
				Non-Reacting	**0.35$_{c}$**	**Moderate**	**.002**	
				Non-Judging	**0.37$_{c}$**	**Moderate**	**<.001**	
				EQ^{S}: Decentering	**0.64$_{c}$**	**Large**	**.006**	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Murphy-Beiner and Soar (2020)	Ayahuasca session	*1-day*	post- / pre-	FFMQ-SF:				48
				Observing	**0.31**$_c$	**Moderate**	**<.001**	
				Describing	**0.26**$_c$	**Moderate**	**.03**	
				Acting with Awareness	**0.26**$_c$	**Moderate**	**.005**	
				Non-Reacting	**0.24**$_c$	**Moderate**	**.015**	
				Non-Judging	*0.12*$_c$	*Small*	*.06*	
				EQ: Decentering	**0.18**$_c$	**Small**	**.025**	

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). POI = Personal Orientation Inventory; FMI = Freiburg Mindfulness Inventory; NEO-PI-R = Revised NEO Personality Inventory; MAAS = Mindfulness Questionnaire Mindful Attention Awareness Scale; PHLMS = Philadelphia Mindfulness Scale; FFMQ = Five Facet Mindfulness Questionnaire; FFMQ-SF = FFMQ Short Form; EQ = Experiences Questionnaire (decentering).

[S] Spanish language version.

Spirituality and Mysticism

The lasting impacts of psychedelics on spirituality and mystical orientation are summarized in Table 26. Notably, psychedelic-induced mystical experience is linked to durable improvements in various psychological traits, including:

- Spirituality and mysticism (Griffiths et al., 2017)
- Openness (MacLean et al., 2011)
- Well-being and life satisfaction (Griffiths et al., 2016, 2017; Haijen et al., 2018; Schmid & Liechti, 2018)
- Gratitude and forgiveness (Griffiths et al., 2017)
- Interpersonal closeness (Griffiths et al., 2017)
- Creative problem solving (Sweat et al., 2016)

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- Anxiety and depression (Griffiths et al., 2016; Roseman et al., 2018; Ross et al., 2016)
- Suicidality (Hendricks & Grob, 2016)
- Smoking cessation (Garcia-Romeu et al., 2015)
- Alcohol reduction/cessation (Bogenschutz et al., 2015; Rothberg et al., 2020)
- Motivation to quit cocaine (Dakwar, Anerella, et al., 2014)
- Positive life changes (Smigielski et al., 2019)

Further, Moreton et al. (2020) propose that reduced death anxiety is a mediator of the therapeutic benefits seen with classical psychedelics. While further empirical validation of this hypothesis is necessary, the authors provide compelling theoretical evidence to support their hypothesis. Together, the mystical and existential effects of psychedelics are essential to treatment efficacy.

Table 26

Spirituality and Mysticism Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
McGlothlin and Arnold (1971)	LSD:	10-year	vs. hallucinogen-naïve matched controls [*n*=110]					
	…administered by a therapist			"Eastern philosophy toward life and death"	+	**Increase**	**<.01**	88
	…administered in a nonmedical context				+	**Increase**	**<.05**	53
Schmid and Liechti (2018)	200 µg LSD	1-month	post- / pre-	MS	**0.99**$_c$	**Large**	**<.01**	16
				DTS	**0.90**$_c$	**Large**	**<.001**	
		1-year	post- / pre-	MS	**1.1**$_c$	**V. Large**	**<.001**	14
				DTS	**1.33**$_c$	**V. Large**	**<.001**	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Psilocybin								
Griffiths et al. (2011)	Psilocybin 20 or 30 mg/70 kg	1-month	Retrospective impact of psilocybin experience vs. placebo	PEQ – Spirituality:				
				Increased	**3.20**	V. Large	**<.05**	18
				Decreased	-1.55	V. Large	NS	
		14-month		Increased	**3.76**	**V. Large**	**<.001**	18
				Decreased	**-1.03**	**V. Large**	**.007**	
Griffiths et al. (2017)	Psilocybin 20 and 30 mg/70 kg:	6-month	vs. active placebo (1 mg/70 kg psilocybin, 2x, *n*=25)					
	w/ 5 hr individual prep. + 2:20 hr individual follow-up							25
				MS	**0.76**$_c$	**Large**	**<.01**	
				DTS	**0.58**$_c$	**Large**	**<.05**	
				Increased spirituality	**1.33**$_c$	**V. Large**	**<.001**	
				Decreased spirituality	-0.15$_c$	Small	NS	
				Daily spiritual experience (DSES)	**0.56**$_c$	**Large**	**<.05**	
				Faith maturity (FMS)	**0.61**$_c$	**Large**	**<.05**	
				Positive religious coping (B-RCOPE)	**0.84**$_c$	**Large**	**<.01**	
				Observer-rated spiritual/religious sentiments (ASPIRES)	**0.94**$_c$	**Large**	**<.01**	
	w/ 10 hr individual prep. + 13 hr individual follow-up + 12 hr group follow-up							25
				MS	**1.97**$_c$	**V. Large**	**<.001**	
				DTS	**1.01**$_c$	**V. Large**	**<.05**	
				Increased spirituality	**2.35**$_c$	**V. Large**	**<.001**	
				Decreased spirituality	0.03$_c$	Tiny	NS	
				Daily spiritual experience (DSES)	**0.88**$_c$	**Large**	**<.01**	
				Faith maturity (FMS)	**1.29**$_c$	**V. Large**	**<.001**	
				Positive religious coping (B-RCOPE)	**0.83**$_c$	**Large**	**<.01**	
				Observer-rated spiritual/religious sentiments (ASPIRES)	**1.20**$_c$	**V. Large**	**<.01**	
Smigielski et al. (2019)	22.05 mg/ 70 kg psilocybin	4-month	vs. placebo	LCI-R:				39
				Spirituality	+	*Increase*	*<.07*	
				Religiousness		No change	>.07	
				Appreciation of death	+	**Increase**	**<.01**	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Ayahuasca								
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	TCI: Self-transcendence	**0.61**$_c$	**Large**	**<.008**	127
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SOI:				
				Transcendent dimension	**48.2%**	**Increase**	**<.01**	9
				Sacredness of life	**10.5%**	**Increase**	**<.05**	9
				Awareness of the tragic	6.5%	Increase	NS	9
				Fruits of spirituality	**39.2%**	**Increase**	**<.01**	9

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). PEQ = Persisting Effects Questionnaire; MS = Mysticism Scale; DTS = Death Transcendence Scale; DSES = Daily Spiritual Experience Scale; FMS = Faith Maturity Scale; B-RCOPE = Brief RCOPE; ASPIRES = Assessment of Spirituality and Religious Sentiments Scale; LCI-R = Life Changes Inventory, Revised; TCI = Temperament and Character Inventory; SOI = Spiritual Orientation Inventory.

Distortions in Self-Reporting

Favorable Self-Report

Changes in self-favorable response patterns following psychedelics are summarized in Table 27. In most cases, self-favorable responding was measured using the MMPI Lie (*L*) and Defensiveness (*K*) scales. In one study, the Marlowe-Crowne Social Desirability (M-C) was used, which is similar to the *L* scale from the MMPI (McGlothlin et al., 1967).

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Table 27

Change in Favorable Self-Report from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-	MMPI[E]:				
			High severity patients:	*L*	0.2_n	Small	NS	17
				K	0.2_n	Small	NS	
			Moderate sev. patients:	*L*	0.2_n	Small	NS	**18**
				K	**0.6_n**	**Moderate**	**<.05**	
			Healthy normals:	*L*	-0.2_n	Small	NS	25
				K	0.3_n	Moderate	NS	
McGlothlin et al. (1967)	LSD 200 µg	6-month	post- / pre- vs. control post- / pre-	M-C	**-0.46_t**	**Moderate**	**<.05**	24
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI:				30
				L	0.18_n	Small	NS	
				K	**0.57_n**	**Large**	**<.05**	
	LSD 350 µg			*L*	**0.31_n**	**Moderate**	**<.05**	29
				K	**0.91_n**	**Large**	**<.01**	
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks biweekly group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI:				19
				L	-0.31_n	Moderate	NS	
				K	-0.33_n	Moderate	NS	
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI[R]:				111
				L	**0.29_n**	**Moderate**	**<.05**	
				K	**-0.24_n**	**Moderate**	**<.05**	

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*L* = Lie Scale; *K* = Defensiveness); M-C = Marlowe-Crowne Social Desirability Scale; CPI = California Psychological Inventory; KPT = Ketamine Psychedelic Therapy (see Chapter 11); IM = intramuscular.

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[E] Values were estimated by measuring published graphs.

[R] Russian translation.

Unfavorable Self-Report or High Symptom Responding

Changes in self-unfavorable or high symptom response patterns following psychedelics are summarized in Table 28. Self-unfavorable or high symptom responding was measured using the MMPI *F* scale (infrequency) or the SCL-90-R Global Severity Index (*GSI*), Positive Symptom Distress Index (*PSDI*), or Positive Symptom Total (*PST*).

Table 28

Change in Unfavorable Self-Report from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure		*d*	Descriptor	*p*	*n*
LSD									
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-	MMPI[E]:					
				High severity patients:	*F*	**-0.7$_n$**	**Large**	**<.05**	17
				Moderate sev. patients:	*F*	**-0.5$_n$**	**Moderate**	**<.05**	18
				Healthy normals:	*F*	-0.1$_n$	Small	NS	25
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI:	*F*	-0.57$_n$	Large	NS	30
	LSD 350 µg				*F*	**-0.71$_n$**	**Large**	**<.01**	29
Psilocybin									
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *F*		**-1.04$_n$**	**V. Large**	**<.01**	19
Ayahuasca									
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	SCL-90-R:	*GSI*	**-0.61$_c$**	**Large**	**<.008**	127
					PSDI	-0.04$_c$	Tiny	<.726	
					PST	**-0.68$_c$**	**Large**	**<.005**	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
MDMA								
Huxster et al. (2006)	MDMA-using young adults [*n*=38]	*9-day; prospect.*	vs. MDMA-abstinent [*n*=18]	SCL-90-R: *GSI*	**0.73**$_c$	**Large**	**<.05**	20
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI[R]: *F*	-0.30$_n$	Moderate	NS	111
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SCL-90-R: *GSI*	-42.6%	Decrease	NS	9

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*F* = Infrequency Scale); SCL-90-R = Symptom Checklist-90-Revised (*GSI* = Global Severity Index; *PSDI* = Positive Symptom Distress Index; *PST* = Positive Symptom Total); KPT = Ketamine Psychedelic Therapy (see Chapter 11); IM = intramuscular.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

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Clinical Syndromes

Described here are the impacts of psychedelics on measures of clinical psychological traits. Studies aimed explicitly at measuring clinical outcomes for treating conditions using psychedelics are omitted and instead described in Chapter 12. The summarized traits are as follows:

- **Anxiety:** Table 29
- **Obsessive-Compulsive Symptoms:** Table 30
- **Depression:** Table 31
- **Mania and Hypomania:** Table 32
- **Psychotic Symptoms:** Table 33
- **Paranoia and Delusions:** Table 34
- **Posttraumatic and Dissociative Symptoms:** Table 35
- **Somatization and Conversion:** Table 36
- **Somatic Complaints:** Table 37
- **Eating Disorders and Body Image:** Table 38
- **Attention-Deficit/Hyperactivity Disorder Symptoms:** Table 39

Anxiety

Table 29

Anxiety Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Mescaline								
Halpern et al. (2005)	Ritual peyote	N/A	vs. controls	RMHI: Anxiety	-0.10[c]	Small	.55	140

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-	MMPI[E]:				
				High severity patients: *Pt*	**-1.1$_n$**	**V. Large**	**<.05**	17
				A	**-1.2$_n$**	**V. Large**	**<.05**	
				Moderate sev. patients: *Pt*	**-0.3$_n$**	**Large**	**<.05**	18
				A	**-0.7$_n$**	**Large**	**<.05**	
				Healthy normals: *Pt*	-0.2$_n$	Moderate	NS	25
				A	**-0.5$_n$**	**Large**	**<.05**	
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Anxiety	*-0.52$_c$*	*Large*	*<.1*	14
		2-month			-0.36$_c$	Moderate	>.1	
	LSD 2 µg/kg + psychotherapy	*2-week*	post- / pre-		**-0.89$_c$**	**Large**	**<.05**	14
		2-month			**-0.78$_c$**	**Large**	**<.01**	
	LSD 2 µg/kg + hypnosis + psychotherapy	*2-week*	post- / pre-		**-0.81$_c$**	**Large**	**<.05**	14
		2-month			**-1.16$_c$**	**V. Large**	**<.01**	
McGlothlin et al. (1967)	LSD 200 µg	6-month	post- / pre- minus control post- / pre-					24
				Holtzman Anxiety Scale	-0.29$_t$	Moderate	NS	
				Galvanic skin response during:				
				…traumatic word repetition	-0.22$_t$	Moderate	NS	
				…neutral word repetition	-0.29$_t$	Moderate	NS	
				…digit span	**-0.69$_t$**	**Large**	**<.05**	
				…proper names	**-0.60$_t$**	**Large**	**<.05**	
				…mental arithmetic	-0.47$_t$	Moderate	NS	
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: *Pt*	**-0.45$_n$**	**Moderate**	**<.05**	30
				A	**-0.69$_n$**	**Moderate**	**<.05**	
	LSD 350 µg			*Pt*	**-0.77$_n$**	**Large**	**<.05**	29
				A	**-1.27$_n$**	**V. Large**	**<.01**	
Gasser et al. (2015)	2 sessions, 200 µg LSD psychotherapy	*1-week*	post- / pre-	STAI: State Anx.	-	**Decrease**	**.0008**	9
				Trait Anx.	-	**Decrease**	**.006**	
		12-month	post- / pre-	STAI: State Anx.	-	**Decrease**	**.0005**	9
				Trait Anx.	-	**Decrease**	**.004**	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *Pt*	-0.32$_n$	Moderate	NS	19
Erritzoe et al. (2018)	Psilocybin for depression, 10 mg and 25 mg	3-month	post- / pre-	NEO-PI-R	**-0.403**	**Moderate**	**.037**	19
F. S. Barrett et al. (2020)	Psilocybin 25 mg/70 kg	*1-week*	post- / pre-	STAI: State Anx.	**-0.76**	**Large**	**.016**	12
				Trait Anx.	*-0.49*	*Moderate*	*.07*	
				POMS: Tension	**-0.96**	**Large**	**.0013**	
		1-month	post- / pre-	STAI: State Anx.	-0.27	Moderate	.309	12
				Trait Anx.	**-0.57**	**Large**	**.024**	
				POMS: Tension	-0.24	Moderate	.219	
Stauffer et al. (2021)	Psilocybin group therapy 21–25.2 mg/70 kg	3-month	post- / pre-	Attachment: Anxiety	**-0.45**	**Moderate**	**.045**	17
				Avoidance	-0.19	Small	.367	18
Ayahuasca								
Grob et al. (1996)	Ritual ayahuasca	N/A	vs. matched controls [*n*=15]	TPQ: Harm avoidance	**-1.09$_c$**	**V. Large**	**.01**	15
Da Silveira et al. (2005)	Ritual ayahuasca among adolescents	N/A	vs. matched controls [*n*=40]	Diagnostic cutoff rate from…				40
				STAI: State Anx.	-0.69$_{OR}$	Large	NS	
				Trait Anx.	*-0.16$_{OR}$*	*Small*	*.087*	
				Beck Anxiety Inventory	0.61	Large	NS	
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	SCL-90-R: *ANX*	**-0.57$_c$**	**Large**	**<.003**	127
				PHOB	**-0.63$_c$**	**Large**	**<.001**	
				TCI: Harm avoidance	**-0.52$_c$**	**Large**	**<.030**	
Uthaug et al. (2018)	Ayahuasca ceremony	*1-day*	post- / pre-	DASS-21: Anxiety	No Change		NS	57
		4-week			No Change		NS	31

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	TCI-R:				
				Anticipatory worry	**-10.1%**	**Decrease**	**<.05**	10
				Shyness with strangers	**-18.6%**	**Decrease**	**<.05**	10
				SCL-90-R:				
				ANX	**-58.7%**	**Decrease**	**<.05**	9
				PHOB	-59.6%	Decrease	NS	9
MDMA								
Lieb et al. (2002)	Recreational MDMA-using adolescents and young adults	4-year, prospect. long.	vs. other drug users [*n*=1,008]	Lifetime DSM-IV:				211
				GAD	**0.42$_{OR}$**	**Moderate**	**<.05**	
				Panic attack	**0.41$_{OR}$**	**Moderate**	**<.05**	
				Panic disorder	0.22$_{OR}$	Moderate	NS	
				Agoraphobia w/o Panic disorder	0.08$_{OR}$	Small	NS	
				Social phobia	-0.11$_{OR}$	Small	NS	
				Specific phobia	0.15$_{OR}$	Small	NS	
				Phobia NOS	0.31$_{OR}$	Moderate	NS	
				Any anxiety disorder	**0.31$_{OR}$**	**Moderate**	**<.05**	
Huxster et al. (2006)	Recreational MDMA-using young adults [*n*=38]	*9-day, prospect.*	vs. MDMA-abstinent [*n*=18]	SCL-90-R:				20
				ANX	**0.82$_{c}$**	**Large**	**<.05**	
				PHOB	0.57$_{c}$	Large	NS	
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI^{R}:				
				Pt	**-0.35$_{n}$**	**Moderate**	**<.05**	111
				A	**-0.52$_{n}$**	**Large**	**<.001**	
Curran & C. J. A. Morgan (2000)	Recreational ketamine	*3-day, prospect.*	Ketamine-abstinent group	HADS: Anxiety	0.17$_{c}$	Small	NS	39
				MRS: Calmness	-0.25$_{c}$	Moderate	NS	
C. J. A. Morgan et al. (2010)	Ketamine recreational use	Frequent K. / polydrug		STAI: Trait Anx.	0.31$_{c}$	Moderate	NS	60
		Infrequent K. / polydrug			0.01$_{c}$	Tiny	NS	60
		Ex-K. / polydrug			0.01$_{c}$	Tiny	NS	60

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). RMHI = Rand Mental Health Inventory; MMPI = Minnesota Multiphasic Personality

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Inventory (*Pt* = Psychasthenia; *A* = Anxiety); PEP = Psychiatric Evaluation Profile; NEO-PI-R = NEO Personality Inventory; STAI = Spielberger Trait Anxiety Inventory; POMS = Profile of Mood States; SCL-90-R = Symptom Checklist-90-Revised (*ANX* = Anxiety; *PHOB* = Phobic Anxiety); DASS-21 = Depression, Anxiety, and Stress Scale, 21-item version; TCI-R = Temperament and Character Inventory-Revised; KPT = Ketamine Psychedelic Therapy (see Chapter 11, Ketamine Therapies); IM = intramuscular; HADS = Hospital Anxiety and Depression Scale; MRS = Mood Rating Scale; K. = ketamine.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

Obsessive-Compulsive Symptoms

Table 30

Obsessive-Compulsive Symptom Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Obs.	*-0.33*$_c$	*Moderate*	*<.1*	14
		2-month			**-0.54**$_c$	**Large**	**<.05**	
	LSD 2 µg/kg + psychotherapy	*2-week*	post- / pre-		*-0.34*$_c$	*Moderate*	*<.1*	14
		2-month			-0.05$_c$	Small	>.1	
	LSD 2 µg/kg + hypnosis + psychotherapy	*2-week*	post- / pre-		0.12$_c$	Small	>.1	14
		2-month			-0.30$_c$	Moderate	>.1	
Ayahuasca								
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	SCL-90-R: *O-C*	**-0.59**$_c$	**Large**	**<.003**	127
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SCL-90-R: *O-C*	**-56.0%**	**Decrease**	**<.01**	9

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
MDMA								
Lieb et al. (2002)	Recreational MDMA-using adolescents and young adults	4-year, prospect. long.	vs. other drug users [*n*=1,008]	Lifetime DSM-IV: OCD	0.38_{OR}	Moderate	NS	211
Huxster et al. (2006)	MDMA-using young adults [*n*=38]	*9-day, prospect.*	vs. MDMA-abstinent [*n*=18]	SCL-90-R: *O-C*	0.33_{c}	Moderate	NS	20

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). PEP = Psychiatric Evaluation Profile (Obs. = Obsessive Compulsiveness); OCD = Obsessive-compulsive disorder; SCL-90-R = Symptom Checklist-90-Revised (*O-C* = Obsessive-Compulsive).

Depression

Table 31

Depression Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Mescaline								
Halpern et al. (2005)	Ritual peyote	N/A	vs. controls	RMHI: Depression	-0.08_{c}	Small	.60	140
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-					
			High severity patients:	MMPI^{E}: *D*	**-1.2_{n}**	**V. Large**	**<.05**	17
			Moderate sev. patients:		**-1.1_{n}**	**V. Large**	**<.05**	18
			Healthy normals:		-0.4_{n}	Moderate	NS	25
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Depression	**-0.81_{c}**	**Large**	**<.01**	14
		2-month			-0.64_{c}	Large	>.1	
	LSD 2 µg/kg + psychotherapy	*2-week*	post- / pre-		*-0.37_{c}*	*Moderate*	*<.1*	14
		2-month			**-0.68_{c}**	**Large**	**<.01**	
	LSD 2 µg/kg + hypnosis + psychotherapy	*2-week*	post- / pre-		**-1.15_{c}**	**V. Large**	**<.01**	14
		2-month			**-1.27_{c}**	**V. Large**	**<.01**	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: *D*	-0.45$_n$	Moderate	NS	30
	LSD 350 µg				**-1.19$_n$**	**V. Large**	**<.05**	29
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *D*	-0.82$_n$	Large	NS	19
Erritzoe et al. (2018)	Psilocybin for depression, 10 mg and 25 mg	3-month	post- / pre-	NEO-PI-R	**-0.661**	**Large**	**.006**	19
F. S. Barrett et al. (2020)	Psilocybin 25 mg/70 kg	*1-week*	post- / pre-	POMS: Depression	**-1.35$_c$**	**V. Large**	**.004**	12
		1-month			-0.22$_c$	Moderate	.385	
		1-week	post- / pre-	DASS: Stress	**-0.98**	**Large**	**.009**	12
		1-month			-0.43	Moderate	.141	
Ayahuasca								
Da Silveira et al. (2005)	Ritual ayahuasca among adolescents	N/A	vs. matched controls [*n*=40]	Diagnostic cutoff rate from: CES-D	0.05$_{OR}$	Small	NS	40
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	SCL-90-R: *DEP*	*-0.58$_c$*	*Large*	*<.096*	127
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SCL-90-R: *DEP*	-44.8%	Decrease	NS	9
Barbosa et al. (2016)	Ritual ayahuasca	N/A	vs. matched controls [*n*=27]	POMS: Depression	**-0.56**	**Large**	**.043**	30
Uthaug et al. (2018)	Ayahuasca ceremony	*1-day*	post- / pre-	DASS-21: Depression	–	**Decrease**	**<.001**	57
				Stress	–	**Decrease**	**.006**	
		4-week		Depression	–	**Decrease**	**.013**	31
				Stress	–	**Decrease**	**.002**	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
MDMA								
Lieb et al. (2002)	Recreational MDMA-using adolescents and young adults	4-year, prospect. long.	Other drug users [*n*=1,008]	Lifetime DSM-IV:				211
				MDD	**0.23$_{OR}$**	**Moderate**	**<.05**	
				Dysthymia	0.11$_{OR}$	Small	NS	
				Suicidal ideation	0.20$_{OR}$	Small	NS	
Huxster et al. (2006)	MDMA-using young adults [*n*=38]	*9-day, prospect.*	vs. MDMA-abstinent group [*n*=18]	SCL-90-R: *DEP*	0.46$_c$	Moderate	NS	20
Taurah et al. (2013)	MDMA polydrug users	N/A	vs. polydrug controls [*n*=169]	BDI:	**1.41**	**V. Large**	**<.001**	154
				Somatic	**0.47**	**Moderate**	**<.001**	
				Cognitive	**1.78**	**V. Large**	**<.001**	
	Ex-MDMA users			BDI:	**1.66**	**V. Large**	**<.001**	154
				Somatic	**0.53**	**Large**	**<.001**	
				Cognitive	**1.70**	**V. Large**	**<.001**	
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI^R: *D*	**-0.55$_n$**	**Large**	**<.01**	111
Curran & C. J. A. Morgan (2000)	Recreational ketamine	*3-day, prospect.*	Ketamine-abstinent group	HADS: Depression	**1.28$_c$**	**V. Large**	**<.001**	39
C. J. A. Morgan et al. (2010)	Ketamine recreational use	Frequent K. / polydrug		BDI	0.52$_c$	Large	NS	60
		Infrequent K. / polydrug			0.52$_c$	Large	NS	60
		Ex-K. / polydrug			0.19$_c$	Small	NS	60
		1-year follow-up post- / pre-:						
			Frequent K.	BDI	**0.53$_c$**	**Large**	**.041**	25
			Infrequent K.		-0.27$_c$	Moderate	NS	27
			Ex-Ketamine		**0.62$_c$**	**Large**	**.013**	23

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). RMHI = Rand Mental Health Inventory; MMPI = Minnesota Multiphasic Personality Inventory (*D* = Depression); PEP = Psychiatric Evaluation Profile; NEO-PI-R = NEO Personality Inventory; POMS = Profile of Mood States; DASS = Depression, Anxiety, and Stress Scale; DASS-21 =

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DASS, 21-item version; MDD = major depressive disorder; SCL-90-R = Symptom Checklist-90-Revised (*DEP* = Depression); BDI = Beck Depression Inventory; KPT = Ketamine Psychedelic Therapy (see Chapter 11, Ketamine Therapies); IM = intramuscular; HADS = Hospital Anxiety and Depression Scale; K. = ketamine.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

Mania and Hypomania

Table 32

Mania/Hypomania Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-					
			High severity patients:	MMPI[E]: *Ma*	0.4_n	Moderate	NS	17
			Moderate sev. patients:		0.4_n	Moderate	NS	18
			Healthy normals:		0.6_n	Large	NS	25
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Mania	-0.13_c	Small	NS	14
		2-month			-0.06_c	Small	NS	
	LSD 2 µg/kg + psychotherapy	*2-week*	post- / pre-		0.53_c	Large	NS	14
		2-month			*0.68_c*	*Large*	*<.1*	
	LSD 2 µg/kg + hypnosis + psychotherapy	*2-week*	post- / pre-		0.50_c	Moderate	NS	14
		2-month			**0.79_c**	**Large**	**<.05**	
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: *Ma*	0.22_n	Moderate	NS	30
	LSD 350 µg				-0.18_n	Small	NS	29
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *Ma*	-0.13_n	Small	NS	19

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
MDMA								
Lieb et al. (2002)	Recreational MDMA-using adolescents and young adults	4-year, prospect. long.	vs. other drug users [*n*=1,008]	Lifetime DSM-IV:				211
				Bipolar I	0.18_{OR}	Small	NS	
				Bipolar II	0.01_{OR}	Tiny	NS	
				Hypomania	-0.27_{OR}	Moderate	NS	
				Single episode mania	-0.72_{OR}	Large	NS	
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI[R]: *Ma*	-0.04_{n}	Tiny	NS	111

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*Ma* = Mania); PEP = Psychiatric Evaluation Profile; KPT = Ketamine Psychedelic Therapy (see Chapter 11, Ketamine Therapies); IM = intramuscular.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

Psychotic Symptoms

Table 33

Psychotic Symptom Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-					
			High severity patients:	MMPI[E]: *Sc*	**-1.2_{n}**	**V. Large**	**<.05**	17
			Moderate sev. patients:		-0.3_{n}	Moderate	NS	18
			Healthy normals:		0.2_{n}	Small	NS	25

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Psychotic Ideation	**-0.68$_c$**	**Large**	**<.05**	14
		2-month			-0.50$_c$	Moderate	>.1	
	LSD 2 µg/kg + psychotherapy	*2-week*	post- / pre-		-0.26$_c$	Moderate	>.1	14
		2-month			-0.35$_c$	Moderate	>.1	
	LSD 2 µg/kg + hypnosis + psychotherapy	*2-week*	post- / pre-		*-0.43$_c$*	*Moderate*	*<.1*	14
		2-month			*-0.80$_c$*	*Large*	*<.1*	
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: *Sc*	-0.28$_n$	Moderate	NS	30
	LSD 350 µg				-0.25$_n$	Moderate	NS	29
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *Sc*	-0.80$_n$	Large	NS	19
Ayahuasca								
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	SCL-90-R: *PSY*	**-0.43$_c$**	**Large**	**<.042**	127
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SCL-90-R: *PSY*	-48.8%	Decrease	NS	9
MDMA								
Huxster et al. (2006)	MDMA-using young adults [*n*=38]	*9-day, prospect.*	vs. MDMA-abstinent group [*n*=18]	SCL-90-R: *PSY*	0.53$_c$	Large	NS	20
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI^R: *Sc*	**-0.46$_n$**	**Moderate**	**<.01**	111
Curran & C. J. A. Morgan (2000)	Recreational ketamine	*3-day, prospect.*	Ketamine-abstinent group	SSQ	**1.56$_c$**	**V. Large**	**<.001**	39

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
C. J. A. Morgan, Monaghan, & Curran (2004)	Ketamine recreational use	Baseline: K. users / polydrug		SSQ	**1.66$_c$**	**V. Large**	**<.01**	28
		3- to 4-year follow-up (88.3% ketamine reduction among users):						
			K. users / polydrug	SSQ	**1.18$_c$**	**V. Large**	**<.01**	28
			K. users post- / pre-		**-1.70$_c$**	**V. Large**	**<.001$_c$**	28
C. J. A. Morgan et al. (2010)	Ketamine recreational use	Frequent K. / polydrug		O-LIFE	**0.47$_c$**	**Moderate**	**.038**	60
		Infrequent K. / polydrug			**0.40$_c$**	**Moderate**	**.038**	60
		Ex-K. / polydrug			**0.42$_c$**	**Moderate**	**.038**	60
		1-year follow-up post- / pre-:						
			Frequent K.	O-LIFE	-0.16$_c$	Small	NS	25
			Infrequent K.		**-0.93$_c$**	**Large**	**<.001**	27
			Ex-Ketamine		**-0.58$_c$**	**Large**	**<.001**	23

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*Sc* = Schizophrenia); PEP = Psychiatric Evaluation Profile; SCL-90-R = Symptom Checklist-90-Revised (*PSY* = Psychoticism); SSQ = Schizotypal Symptomatology Questionnaire; O-LIFE = Oxford-Liverpool Inventory of Feelings and Experiences; KPT = Ketamine Psychedelic Therapy (see Chapter 11); IM = intramuscular; K. = ketamine.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

Paranoia and Delusions

Table 34

Paranoia and Delusional Symptom Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-					
			High severity patients:	MMPI[E]: *Pa*	-0.2$_n$	Small	NS	17
			Moderate sev. patients:		**-0.4$_n$**	**Moderate**	**<.05**	18
			Healthy normals:		0.2$_n$	Small	NS	25

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Paranoid Ideation	**-0.72$_c$**	**Large**	**<.05**	14
		2-month			*-0.65$_c$*	*Large*	*<.1*	
	LSD 2 µg/kg + psychotherapy	*2-week*	post- / pre-		-0.33$_c$	Moderate	>.1	14
		2-month			**-0.57$_c$**	**Large**	**<.01**	
	LSD 2 µg/kg + hypnosis + psychotherapy	*2-week*	post- / pre-		**-0.81$_c$**	**Large**	**<.05**	14
		2-month			**-1.23$_c$**	**V. Large**	**<.01**	
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: *Pa*	0.03$_n$	Tiny	NS	30
	LSD 350 µg				0.17$_n$	Small	NS	29
Carhart-Harris et al. (2016)	LSD 75 µg IV	*2-week*	vs. placebo	PDI		No effect	>.05	20
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *Pa*	0.05$_n$	Small	NS	19
Ayahuasca								
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	SCL-90-R: *PAR*	**-0.48$_c$**	**Large**	**<.008**	127
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SCL-90-R: *PAR*	-50.8%	Decrease	NS	9
MDMA								
Huxster et al. (2006)	MDMA-using young adults [*n*=38]	*9-day, prospect.*	vs. MDMA-abstinent group [*n*=18]	SCL-90-R: *PAR*	-0.11$_c$	Small	NS	20

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI[R]: *Pa*	-0.22$_n$	Moderate	NS	111
C. J. A. Morgan et al. (2010)	Ketamine recreational use	Frequent K. / polydrug		PDI	**0.92$_c$**	**Large**	**.002**	60
		Infrequent K. / polydrug			0.54$_c$	Large	NS	60
		Ex-K. / polydrug			0.45$_c$	Moderate	NS	60
		1-year follow-up post- / pre-:						
			Frequent K.	PDI	-0.09$_c$	Small	NS	25
			Infrequent K.		-0.09$_c$	Small	NS	27
			Ex-Ketamine		-0.11$_c$	Small	NS	23

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*Pa* = Paranoia); PEP = Psychiatric Evaluation Profile; SCL-90-R = Symptom Checklist-90-Revised (*PAR* = Paranoid Ideation); PDI = Peter's Delusion Inventory; KPT = Ketamine Psychedelic Therapy (see Chapter 11, Ketamine Therapies); IM = intramuscular; K. = ketamine.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

Posttraumatic and Dissociative Symptoms

Table 35

Posttraumatic and Dissociative Symptom Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
MDMA								
Lieb et al. (2002)	Recreational MDMA-using adolescents and young adults	4-year, prospect. long.	vs. other drug users [*n*=1,008]	Lifetime DSM-IV: PTSD	0.40$_{OR}$	Moderate	NS	211
Ketamine								
Curran & C. J. A. Morgan (2000)	Recreational ketamine	*3-day, prospect.*	Ketamine-abstinent group	CADSS	**0.93$_c$**	**Large**	**<.001**	39

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
C. J. A. Morgan, Mofeez, et al. (2004b)	Ketamine: 0.4 mg/kg IV	*3-day*	post- / pre-	CADSS	-0.23c	Moderate	.499	54
	0.8 mg/kg IV				0.36c	Moderate	.294	
C. J. A. Morgan, Monaghan, & Curran (2004)	Ketamine recreational use	Baseline: K. users vs. polydrug		CADSS	0.40c	Moderate	NS	28
		3- to 4-year follow-up (88.3% ketamine reduction among users):						
			K. users / polydrug	CADSS	0.72c	Large	NS	28
			K. users post- / pre-		-0.61c	Large	NS	28
C. J. A. Morgan et al. (2010)	Ketamine recreational use	Frequent K. / polydrug		DES	**0.82c**	**Large**	**.015**	60
		Infrequent K. / polydrug			0.52c	Large	NS	60
		Ex-K. / polydrug			0.15c	Small	NS	60
		1-year follow-up post- / pre-:						
			Frequent K.	DES	-0.04c	Tiny	NS	25
			Infrequent K.		0.02c	Tiny	NS	27
			Ex-Ketamine		0.16c	Small	NS	23

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). PTSD = Posttraumatic stress disorder; CADSS = Clinician-Administered Dissociative States Scale; DES = Dissociative Experiences Scale; K. = ketamine.

Somatization and Conversion

Table 36

Somatization and Conversion Symptom Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-					
			High severity patients:	MMPI[E]: *Hy*	-0.4n	Moderate	NS	17
			Moderate sev. patients:		-0.2n	Small	NS	18
			Healthy normals:		0.4n	Moderate	NS	25
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: *Hy*	0.18n	Small	NS	30
	LSD 350 µg				0.31n	Moderate	NS	29

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *Hy*	0.02_{n}	Tiny	NS	19
Ayahuasca								
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	SCL-90-R: *SOM*	-0.36_{c}	Moderate	<.147	127
Fernández et al. (2014)	3–9-month program w/ 1–2x /wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	SCL-90-R: *SOM*	-15.4%	Decrease	NS	9
MDMA								
Lieb et al. (2002)	Recreational MDMA-using adolescents and young adults	4-year, prospect. long.	vs. other drug users [*n*=1,008]	Lifetime DSM-IV: Somatoform disorders/syndromes	0.14_{OR}	Small	NS	
Huxster et al. (2006)	MDMA-using young adults [*n*=38]	*9-day, prospect.*	vs. MDMA-abstinent [*n*=18]	SCL-90-R: *SOM*	**0.76_{c}**	**Large**	**<.05**	20
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI[R]: *Hy*	**-0.24_{n}**	**Moderate**	**<.05**	111

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*Hy* = Hysteria [somatization]); SCL-90-R = Symptom Checklist-90-Revised (*SOM* = Somatization); KPT = Ketamine Psychedelic Therapy (see Chapter 11, Ketamine Therapies); IM = intramuscular.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

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Somatic Complaints

Table 37

Somatic Complaint Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
LSD								
Mogar & Savage (1964)	LSD 200–400 µg + mescaline 200–400 mg + more LSD 100–300 µg "if indicated"	6-month	post- / pre-	MMPI[E]:				
				High severity patients: *Hs*	**-0.5$_n$**	**Moderate**	**<.05**	17
				Moderate sev. patients:	-0.1$_n$	Small	NS	18
				Healthy normals:	-0.2$_n$	Small	NS	25
Ludwig & Levine (1965)	LSD 2 µg/kg	*2-week*	post- / pre-	PEP: Som.	-0.47$_c$	Moderate	>.1	14
		2-month			-0.04$_c$	Tiny	>.1	
	LSD 2 µg/kg + psychotherapy	*2-week*	post- / pre-		-0.20$_c$	Small	>.1	14
		2-month			-0.10$_c$	Small	>.1	
	LSD 2 µg/kg + hypnosis + psychotherapy	*2-week*	post- / pre-		0.14$_c$	Small	>.1	14
		2-month			-0.25$_c$	Moderate	>.1	
McCabe et al. (1972)	LSD 50 µg	*5–7-day*	vs. group therapy [*n*=27]	MMPI: *Hs*	-0.11$_n$	Small	NS	30
	LSD 350 µg				-0.20$_n$	Small	NS	29
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 weeks group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	MMPI: *Hs*	-0.28$_n$	Moderate	NS	19
Ketamine								
Krupitsky & Grinenko (1997)	2.5 mg/kg IM KPT	*"after"*	post- / pre-	MMPI[R]: *Hs*	**-0.32$_n$**	**Moderate**	**<.05**	111

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). MMPI = Minnesota Multiphasic Personality Inventory (*Hs* = Hypochondriasis); PEP = Psychiatric Evaluation Profile (Som. = Psychosomatic Complaints); KPT = Ketamine Psychedelic Therapy (see Chapter 11, Ketamine Therapies); IM = intramuscular.

[E] Values were estimated by measuring published graphs.

[R] Russian translation.

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Eating Disorders and Body Image

Table 38

Eating Disorder and Body Relatedness Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Psilocybin								
Studerus et al. (2011)	1–4 doses psilocybin 8.05–22.05 mg/70 kg	8–16 months following final session, retrospective rating		Changes in the relationship to one's body:				90
				positive		30%		
				unchanged		67%		
				negative		3%		
Ayahuasca								
Da Silveira et al. (2005)	Ritual ayahuasca among adolescents	N/A	vs. matched controls [*n*=40]	Body shape questionnaire	*-0.56*$_{OR}$	*Large*	*.083*	40
MDMA								
Lieb et al. (2002)	Recreational MDMA-using adolescents and young adults	4-year, prospect. long.	vs. other drug users [*n*=1,008]	Lifetime DSM-IV:				211
				Eating disorders	0.24$_{OR}$	Moderate	NS	

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks).

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Attention-Deficit/Hyperactivity Disorder (ADHD)-Related Symptoms

Table 39

ADHD-Related Symptom Change from Psychedelics

Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Mescaline								
Halpern et al. (2005)	Ritual peyote	N/A	vs. controls	RMHI: Loss of behavioral/ emotional control	-0.27$_c$	Moderate	.18	140
Psilocybin								
Leary et al. (1965)	2x psilocybin 20–70 mg + 6 wk group therapy	*2 weeks after 2nd psilocybin session*	post- / pre-	CPI: Self-control (*Sc*)	**0.69$_n$**	**Large**	**<.01**	20
Erritzoe et al. (2018)	Psilocybin 10 and 25 mg	3-month	post- / pre-	NEO-PI-R: Deliberation	-0.080	Small	.662	19
Ayahuasca								
Grob et al. (1996)	Ritual ayahuasca	N/A	vs. matched controls [*n*=15]	TPQ: Novelty-seeking	**-1.19$_c$**	**V. Large**	**.0054**	15
				Impulsiveness vs. reflection (NS2)	*-0.67$_c$*	*Large*	*.1*	
				Disorderliness vs. regimentation (NS4)	**-1.01$_c$**	**V. Large**	**.016**	
				Persistence vs. irresoluteness (RD2)	-0.01$_c$	Tiny	.972	
Da Silveira et al. (2005)	Ritual ayahuasca among adolescents	N/A	vs. matched controls [*n*=40]	DSM-III ADD	*-1.08$_{OR}$*	*V. Large*	*.057*	40
Bouso et al. (2012)	Ritual ayahuasca	N/A	vs. matched controls [*n*=112]	TCI: Novelty-seeking	-0.10$_c$	Small	<.300	127
				Impulsiveness vs. reflection (NS2)	-0.05$_c$	Tiny	<.360	
				Disorderliness vs. regimentation (NS4)	-0.20$_c$	Small	<.609	
				Self-Forgetfulness vs. Self-Conscious Experience (ST1)	0.10$_c$	Small	<.475	
				FrSBe: Disinhibition/Emotional Dysregulation	**-0.74$_c$**	**Large**	**<.046**	

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Study	Treatment	Follow-up	Comparator	Measure	*d*	Descriptor	*p*	*n*
Fernández et al. (2014)	3–9 mth program w/ 1–2x/wk ayahuasca, daily yoga + meditation, and individual therapy		post- / pre-	TCI-R: Impulsiveness	**-15.4%**	**Decrease**	**<.05**	10
				Disorderliness	**-7.1%**	**Decrease**	**<.05**	10
				FrSBe: Disinhibition	**-17.1%**	**Decrease**	**<.05**	11
				Executive dysfunction	**-22.6%**	**Decrease**	**<.01**	11
				Apathy	**-21.5%**	**Decrease**	**<.01**	11
MDMA								
Huxster et al. (2006)	MDMA-using YA [*n*=38]	*9-day, prospect.*	vs. MDMA-abstinent group [*n*=18]	IVE: Impulsiveness	-0.12_c	Small	NS	20
				Venturesomeness	0.18_c	Small	NS	

Note. Headings and statistically significant findings are bolded. Subacute follow-up periods are italicized (<4 weeks). RMHI = Rand Mental Health Inventory; CPI = California Psychological Inventory; NEO-PI-R = Revised NEO Personality Inventory; TPQ = Tridimensional Personality Questionnaire; ADD = attention deficit disorder; TCI = Temperament and Character Inventory; TCI-R = TCI-Revised; IVE = Impulsiveness, Venturesomeness, and Empathy questionnaire.

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Summary and Comparison

Summary Table 8 provides an overview of the subacute effects of psychedelics on psychological traits, while Summary Table 9 provides the long-term effects. Both tables use the following symbols:

↑	Statistically significant increase
↓	Statistically significant decrease
∅	No significant change
$\varnothing^{\uparrow}$	No significant change, but a directional trend
[2]	The number of references that demonstrate a finding. If not shown, only one study is referenced.
-	No research found

Effect size is designated using the conventions below:

	Small or Tiny effect size [no asterisk] ($d \leq 0.2$)
*	Moderate effect size ($d = 0.21–0.5$)
**	Large effect size ($d > 0.5$)
***	Very Large effect size ($d > 1.0$)

Summary Table 8

Subacute Psychological Change from Psychedelics

Trait	General	LSD	Psilocybin	Ayahuasca	MDMA	Ketamine
Big Five Personality Traits						
I. Extraversion	-	↑** / ∅	↑**	-	-	-
II. Agreeableness	-	∅↑*	-	-	-	-
III. Conscientiousness	-	∅	-	-	-	-
IV. Neuroticism	-	↓** / ∅	-	-	-	-
V. Openness	-	↑	-	-	-	-
Self-Regulation						
Self-acceptance / pride	-	↑***	∅	-	-	-
Emotional regulation	-	-	-	↑*	-	-
Emotional acceptance	-	-	-	↑*	-	-
Coping and Adaptive Functioning						
Coping attitudes/responsibility	-	↑***	↑**	-	-	-
Achievement striving	-	-	↑**	-	-	-
Competence/efficacy	-	-	↑**	-	-	-
Interpersonal Functioning						
Warmth/gregariousness	-	-	↑**	-	-	-
Assertiveness/dominance	-	-	∅↑*	-	-	-

Summary Table 8

Subacute Psychological Change from Psychedelics, Continued

Trait	General	LSD	Psilocybin	Ayahuasca	MDMA	Ketamine
Compliance/cooperativeness	-	-	↑**	-	-	-
Tolerance	-	-	↑**	-	-	-
Flexibility	-	-	∅↓	-	-	-
Compassion	-	-	↑*	-	-	-
Hostility	-	-	-	-	∅	-
Interpersonal sensitivity	-	-	-	-	∅↓*	-
Emotional empathy	-	-	∅	-	∅↑*	-
Cognitive empathy	-	-	∅ / ∅↑*	-	-	-
Social responsibility/prosocial values	-	-	∅	-	-	-
Antisocial/sociopathic traits	-	↓** / ∅	∅↓**	-	-	-
Well-Being and Positive Psychology						
Well-being	↑	-	↑**	-	-	∅
Joy	-	-	↑**	-	-	
Optimism	-	↑**	-	-	-	-
Negative affect/distress	-	-	↓***	-	-	-
Life satisfaction/contentment	-	-	↑**	↑	-	-
Amusement	-	-	↑**	-	-	-
Nature Relatedness	↑	-	↑***	-	-	-
Spontaneity	-	↑	-	-	-	-

Summary Table 8

Subacute Psychological Change from Psychedelics, Continued

Trait	General	LSD	Psilocybin	Ayahuasca	MDMA	Ketamine
Mindfulness and Decentering						
General mindfulness	-	-	↑	-	-	-
Observing/present-moment awareness	-	↑	-	$\uparrow^{***}$ / $\uparrow^{*}$ / ↑	-	-
Describing	-	-	-	$\uparrow^{*}$ / ∅[2]	-	-
Acting with Awareness	-	-	-	$\uparrow^{**}$ / $\uparrow^{*}$ / ↑	-	-
Non-Reactivity	-	-	-	$\uparrow^{**}$ / $\uparrow^{*[2]}$ / ↑ / ∅	-	-
Non-Judgment	-	-	-	$\uparrow^{**}$ / $\uparrow^{*[2]}$ / ↑ / ∅	-	-
Decentering	-	-	-	$\uparrow^{**[2]}$ / ↑ / ↓	-	-
Distortions in Self-Reporting						
Socially desirable responding (MMPI: *L*)	-	$\uparrow^{*}$	$\varnothing^{\downarrow *}$	-	-	-
Defensiveness (MMPI: *K*)	-	$\uparrow^{**}$	$\varnothing^{\downarrow *}$	-	-	-
High symptom/infrequent (MMPI: *F*)	-	$\downarrow^{**}$	$\downarrow^{***}$	-	$\uparrow^{**}$	-
Clinical Syndromes						
Anxiety	-	$\downarrow^{**[2]}$ / ↓	$\downarrow^{**}$ / $\varnothing^{\downarrow *}$	∅	$\uparrow^{**}$	∅
OCD symptoms	-	$\varnothing^{\downarrow *}$	-	-	$\varnothing^{\uparrow *}$	-
Depression	-	$\downarrow^{**[2]}$	$\downarrow^{***}$ / $\varnothing^{\downarrow **}$	↓	$\varnothing^{\uparrow *}$	$\uparrow^{***}$
Mania/hypomania	-	∅ / $\varnothing^{\uparrow *}$	∅	-	-	-
Psychotic symptoms	-	$\downarrow^{**}$ / $\varnothing^{\downarrow *}$	$\varnothing^{\downarrow **}$	-	$\varnothing^{\uparrow **}$	$\uparrow^{***}$
Paranoia	-	$\downarrow^{**}$ / ∅	∅	-	∅	-

Summary Table 8

Subacute Psychological Change from Psychedelics, Continued

Trait	General	LSD	Psilocybin	Ayahuasca	MDMA	Ketamine
Delusions	-	∅	-	-	-	-
Dissociative symptoms	-	-	-	-	-	↑** / ∅
Somatization/conversion	-	∅↑*	∅	-	↑**	-
Somatic complaints	-	∅	∅↓*	-	-	-
ADHD-Related Symptoms						
Novelty-seeking/venturesomeness	-	-	-	-	∅	-
Self-control	-	-	↑**	-	-	-

Note. Symbol key on page 254. Subacute effects were measured less than 4 weeks following administration, typically less than one week. OCD = obsessive-compulsive disorder; ADHD = attention-deficit/hyperactivity disorder.

Summary Table 9

Long-Term Psychological Change from Psychedelics

Trait	General (Naturalistic)	Mescaline (Session)	LSD (Session)	Psilocybin (Session)	Ayahuasca (Session)	Ayahuasca (Ritual)	MDMA (Session)	MDMA (Chronic)	Ketamine (KPT)	Ketamine (Chronic)
Big Five Personality Traits										
I. Extraversion	-	-	↑** / ∅	∅[2] / ↑**	-	↑* / ∅	↑***	-	∅	-
II. Agreeableness	-	-	∅	∅[3]	-	↑**[2]	↑*	-	-	-
III. Conscientiousness	-	-	↑*	∅↑*[3]	-	↑** / ∅	∅↑**	-	-	-
IV. Neuroticism	-	-	∅	↓**[2] / ∅	-	↓**[2] / ∅↓*	↓**[2]	-	-	-
V. Openness	-	-	↑ / ∅	↑*[3]	-	↑** / ∅	↑** / ∅↑*	-	-	-
Self-Regulation										
Self-concept/pride	-	-	↑***	↑***[3]	-	-	-	-	-	-
Self-compassion/acceptance	-	-	-	↑	-	-	-	-	-	-
Ego strength	-	-	↑* / ∅↑*	-	-	-	-	-	↑*	-
Repression	-	-	↓* / ∅↓	-	-	-	-	-	↓**	-
Regression	-	-	-	-	-	-	-	-	↓**	-
Emotional regulation	-	∅↑	-	-	∅↑	-	-	-	-	-
Narcissism	-	↓	↓	↓	-	↓	-	-	-	-
Reward dependence	-	-	-	-	-	↑* / ∅↑*	-	-	-	-

Summary Table 9

Long-Term Psychological Change from Psychedelics, Continued

Trait	General (Naturalistic)	Mescaline (Session)	LSD (Session)	Psilocybin (Session)	Ayahuasca (Session)	Ayahuasca (Ritual)	MDMA (Session)	MDMA (Chronic)	Ketamine (KPT)	Ketamine (Chronic)
Coping and Adaptive Functioning										
Coping attitudes/ dutifulness/responsibility	-	-	↑***	∅↑*	-	↑	-	-	-	-
Persistence/self-discipline	-	-	-	↑*	-	∅	-	-	-	-
Achievement striving	-	-	-	∅↑*	-	-	-	-	-	-
Self-directedness	-	-	-	-	-	↑ / ↓*	-	-	-	-
Empowerment	-	-	-	-	↑	-	-	-	-	-
Positive behavior changes	-	-	-	↑***[2]	-	-	-	-	-	-
Competence	-	-	-	↑**	-	-	-	-	-	-
Interpersonal Functioning										
Emotional ties/ interpersonal closeness	-	∅	-	↑**	-	-	-	-	-	-
Compassion/ tendermindedness	-	-	-	↑* / ∅↑*	-	-	-	-	-	-
Forgiveness	-	-	-	∅↑*	-	-	-	-	-	-
Warmth/gregariousness	-	-	-	↑**	-	-	-	-	-	-
Hostility/anger	-	-	-	∅↓*	-	↓** / ∅	-	-	-	-
Interpersonal sensitivity/ vulnerability	-	-	-	↓**	-	↓** / ∅	-	-	-	-
Assertiveness	-	-	-	∅↑*	-	-	-	-	-	-
Compliance/cooperativeness	-	-	-	∅	-	∅	-	-	-	-

Summary Table 9

Long-Term Psychological Change from Psychedelics, Continued

Trait	General (Naturalistic)	Mescaline (Session)	LSD (Session)	Psilocybin (Session)	Ayahuasca (Session)	Ayahuasca (Ritual)	MDMA (Session)	MDMA (Chronic)	Ketamine (KPT)	Ketamine (Chronic)
Trust	-	-	-	∅↑*	-	-	-	-	-	-
Emotional empathy	↑	-	∅	∅[3] / ∅↑	-	-	-	∅[2]	-	-
Cognitive empathy	-	-	-	∅[2]	-	-	-	∅ / ↑**	-	-
Altruism	-	-	-	↑***[2] / ∅	-	∅	-	-	-	-
Social responsibility/ prosocial values	-	-	-	∅	-	-	-	-	-	-
Antisocial/sociopathic traits	-	-	↓**[2]	∅	-	-	-	-	-	-
Well-Being and Positive Psychology										
Well-being	↑	↑*	-	↑***[2] / ↑	∅↑	-	-	-	-	-
Joy	-	-	-	↑**	-	-	-	-	-	-
Positive affect	-	↑**	-	↑***[3]	-	-	-	-	-	-
Negative affect/distress	-	∅	-	↓** / ∅[2]	-	-	-	-	-	-
Life meaning	-		-	↑** / ↑	↑	↑	-	-	-	-
Life satisfaction/ contentment	-	∅	-	↑**	-	∅	-	-	-	-
Positive attitudes toward life	-	-	-	↑***[2] / ↑	↑	-	-	-	-	-
Negative attitudes toward life	-	-	-	∅↑*[2]	-	-	-	-	-	-
Gratitude	-	-	-	↑**	-	-	-	-	-	-
Amusement	-	-	-	↑**	-	-	-	-	-	-

Summary Table 9

Long-Term Psychological Change from Psychedelics, Continued

Trait	General (Naturalistic)	Mescaline (Session)	LSD (Session)	Psilocybin (Session)	Ayahuasca (Session)	Ayahuasca (Ritual)	MDMA (Session)	MDMA (Chronic)	Ketamine (KPT)	Ketamine (Chronic)
Values-based living	-	-	-	↑	-	↑*	-	-	-	-
Nature Relatedness	↑[2] / ↑*	-	∅↑*	↑*** / ↑	-	-	-	-	-	-
Aesthetic Experience	-	-	-	↑	-	-	-	-	-	-
Mindfulness and Decentering										
General Mindfulness	-	-	-	↑**	↑	-	-	-	-	-
Non-Reactivity	-	-	-	-	∅[2]	-	-	-	-	-
Non-Judgment	-	-	-	-	↑** / ∅	-	-	-	-	-
Decentering	-	-	-	-	∅	-	-	-	-	-
Spirituality and Mysticism										
Mysticism	-	-	↑***	↑***	-	-	-	-	-	-
Spirituality	-	-	-	↑***[2] / ∅↑	-	↑	-	-	-	-
Religiousness	-	-	-	∅	-	-	-	-	-	-
Self-transcendence	-	-	-	-	-	↑** / ↑	-	-	-	-
Death transcendence	-	-	↑***	↑**	-	-	-	-	-	-
Awareness of the tragic/ appreciation of death	-	-	-	↑	-	↑	-	-	-	-
Daily spiritual experience	-	-	-	↑**	-	-	-	-	-	-
Faith maturity	-	-	-	↑***	-	-	-	-	-	-
Positive religious coping	-	-	-	↑**	-	-	-	-	-	-

Summary Table 9

Long-Term Psychological Change from Psychedelics, Continued

Trait	Mescaline (Session)	LSD (Session)	Psilocybin (Session)	Ayahuasca (Session)	Ayahuasca (Ritual)	MDMA (Chronic)	Ketamine (KPT)	Ketamine (Chronic)
Distortions in Self-Reporting								
Socially desirable responding (MMPI: *L*)	-	$\downarrow^{*}$ / ∅	-	-	-	-	$\uparrow^{*}$	-
Defensiveness (MMPI: *K*)	-	$\uparrow^{*}$	-	-	-	-	$\downarrow^{*}$	-
High symptom/infrequent responding (e.g., MMPI: *F*)	-	$\downarrow^{**}$	-	-	$\downarrow^{**}$ / ∅	-	$\varnothing^{\downarrow *}$	-
Clinical Syndromes								
Anxiety	∅	$\downarrow^{**[2]}$ / $\downarrow$ / $\varnothing^{\downarrow *}$	$\downarrow^{**[2]}$ / $\downarrow^{*}$	∅	$\downarrow^{**[2]}$ / $\downarrow$ / $\varnothing^{\downarrow **}$	$\uparrow^{**}$	$\downarrow^{**}$	∅
OCD symptoms	-	$\varnothing^{\downarrow *}$	$\downarrow^{**}$		$\downarrow^{**}$ / $\downarrow$	$\varnothing^{\uparrow *}$	-	-
Depression	∅	$\downarrow^{***[2]}$	$\downarrow^{**}$ / $\varnothing^{\downarrow *}$	$\downarrow$	$\downarrow^{**}$ / $\varnothing^{\downarrow **}$ / $\varnothing^{[2]}$	$\uparrow^{*}$ / $\uparrow^{***}$	$\downarrow^{**}$	$\uparrow^{**}$
Mania/hypomania	-	$\uparrow^{**}$ / $\varnothing^{\uparrow **}$ / ∅	-	-	-	$\varnothing^{\downarrow *}$	∅	-
Psychotic symptoms	-	$\downarrow^{***a}$ / $\varnothing^{\downarrow *[2]}$	-	-	$\downarrow^{**}$ / ∅	-	$\downarrow^{*}$	$\uparrow^{***}$ / $\uparrow^{*}$
Paranoia	-	$\downarrow^{**}$ / $\downarrow^{*}$	-	-	$\downarrow^{**}$ / ∅	-	$\varnothing^{\downarrow *}$	-
Delusions	-	-	-	-	-	-	-	$\uparrow^{**}$
PTSD symptoms	-	-	-	-	-	$\varnothing^{\uparrow *}$	-	-
Dissociative symptoms	-	-	-	-	-		-	$\uparrow^{**}$ / $\varnothing^{\uparrow *}$
Somatization/conversion	-	$\varnothing^{\downarrow \uparrow *}$	-	-	$\varnothing^{\downarrow **}$ / ∅	∅	$\downarrow^{*}$	-
Somatic complaints	-	$\downarrow^{*a}$ / $\varnothing^{\downarrow *}$	-	-	-	-	$\downarrow^{*}$	-

Summary Table 9

Long-Term Psychological Change from Psychedelics, Continued

Trait	Mescaline (Session)	LSD (Session)	Psilocybin (Session)	Ayahuasca (Session)	Ayahuasca (Ritual)	MDMA (Chronic)	Ketamine (KPT)	Ketamine (Chronic)
Eating disorders/ body-image preoccupation	-	-	-	-	∅↓**	∅	-	-
ADHD-Related Symptoms								
ADD diagnosis	-	-	-	-	∅↓***	-	-	-
Impulsiveness/disinhibition	-	-	∅	-	↓** / ↓ / ∅↓** / ∅	-	-	-
Disorderliness	-	-	-	-	↓*** / ↓ / ∅↓	-	-	-
Persistence	-	-	-	-	∅	-	-	-
Executive dysfunction	-	-	-	-	↓	-	-	-
Apathy	-	-	-	-	↓	-	-	-
Novelty-seeking/ venturesomeness	-	-	-	-	↓*** / ∅	-	-	-

Note. Symbol key on page 254. Long-term effects were persistent for greater than or equal to 4 weeks. Naturalistic refers to recreational use of unknown intensity and duration. Session refers to clinical session(s). Ritual refers to ongoing, ritualistic use. Chronic refers to ongoing, long-term recreational use. KPT = change "after" Ketamine Psychedelic Therapy (see Chapter 11 "Ketamine Therapies"); OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; ADHD = attention-deficit/hyperactivity disorder.

[a] Large effect size among high-severity patients, but Small to Moderate effect size in healthy normals and moderate severity patients.

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Chapter 8: Neuropsychology and Cognition

In this chapter, studies of psychedelics' impact on neuropsychological performance are summarized across functional domains. In each functional domain, findings are presented according to three timescales relative to psychedelic administration:

1. **Acute:** Effects during the acute effects of a psychedelic.
2. **Subacute:** Effects between 1 day and 4 weeks following psychedelic administration but after the acute subjective effects of the drug have subsided. Typically, effects are measured less than 1 week following administration.
3. **Long-term:** Effects persisting from psychedelics longer than 4 weeks following administration.

Excluded from this section are studies examining the characteristics of recreational psychedelic users, many of which were done with MDMA. Such studies do not provide information about the effects of a drug but rather information about the people drawn to use the drug. Thus, drug causality cannot be inferred. However, there were two exceptions to this exclusion rule:

1. Studies comparing MDMA users and non-MDMA polydrug-using controls were included, as causality can be inferred from these studies. See the start of Chapter 7 for more details.
2. Studies were included that compare neuropsychological characteristics of religious groups who use psychedelics with culturally similar groups that do not use psychedelics. The population of people using psychedelics within a culturally acceptable religious framework is likely to have more diversity of psychological

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and neurological traits before psychedelic use than the population of people who self-select to use psychedelics in a prohibited context. For this reason, some causation can reasonably be inferred from this comparison. For example, see Halpern et al. (2005) and Doering-Silveira et al. (2005).

3. Studies on creativity and psychedelics were categorized under neuropsychology, given that the creative process draws on all the neurocognitive functions to produce novel works. However, these studies were excluded to limit the scope.

There were no studies found on DMT's impact on neuropsychological functioning. This is likely because the effects are too dramatic and short-lived to make neuropsychological testing feasible. Many studies examining the neuropsychological effects of MDMA and ketamine were found, and for this reason, review articles were chosen to represent the literature related to these compounds in most functional domains.

Overall Neuropsychological Functioning

Long-Term.

MDMA. Mithoefer et al. (2011) saw no significant difference in RBANS total score between MDMA- and placebo-assisted psychotherapy (p=.31) at 2-month follow-up [N=20, 85% female, age M=40.4, 100% Caucasian]. In a long-term follow-up study with 19 of those same patients 17 to 74 months later (M=45.4), Mithoefer et al. (2013) asked whether participants subjectively perceived changes in "cognition (thinking), memory, or concentration" (p. 32). None of the participants reported decreased cognitive functioning following the study, but 13 (68%) felt that their cognition had improved since. This may be due to a lessening of PTSD-related neurocognitive impacts associated, given that PTSD improvements seen in the original study remained durable at follow-up.

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Intellectual Functioning

General and Fluid Intelligence

Acute.

LSD. Levine et al. (1955) found a significant decrease ($p<.01$; $d_n=0.73$) in Full-Scale IQ (FSIQ) from baseline under LSD (50–200 μg) as measured by Wechsler-Bellevue Intelligence Scale [*N*=21, 43% male, age=22–43, race N/R, FSIQ *M*=122.9].

Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference ($p=.80$; $d_c=0.03$) in fluid intelligence as measured by Raven's Progressive Matrices between Navajos who regularly took peyote and Navajos reporting minimal substance use [*N*=176, 28% male, age=18–45].

MDMA. P. N. Murphy et al. (2012) found no difference in fluid intelligence between recreational ecstasy users and drug-using controls in any of the four studies they identified in a systematic review. The studies measured fluid intelligence using Raven's Progressive Matrices [*n*=1], the Test of Non-Verbal Intelligence (TONI-3) [*n*=1], or the matrix reasoning test from WAIS-III and WASI [*n*=2].

Verbal Intelligence

Acute.

LSD. Levine et al. (1955) found a significant decrease ($p<.01$; $d_n=0.68$) in Verbal Scale IQ from baseline under LSD (50–200 μg) as measured by Wechsler-Bellevue Intelligence Scale [*N*=21, 43% male, age=22–43, race N/R, FSIQ *M*=122.9]. Participants had an average Verbal Scale IQ reduction of 10.14 points. Isbell et al. (1956) also saw a

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reduction in Verbal IQ of 8.63 points (d_n=0.58) under 1–2 μg/kg LSD among opioid-dependent African American patients compared to control conditions [n=6].

MDMA. Kuypers and Ramaekers (2005) found no significant difference in verbal reasoning with 75 mg MDMA compared to placebo, as measured by the Syntactic Reasoning Task [N=18, 50% male, age=20–39, race N/R].

Subacute.

MDMA. Kuypers and Ramaekers (2005) found no significant difference in verbal reasoning 1 day following 75 mg MDMA compared to placebo, as measured by the Syntactic Reasoning Task [N=18, 50% male, age=20–39, race N/R].

Long-Term.

Ayahuasca. Barbosa et al. (2016) found no significant difference (p=.99; $|d_r|$=0.01) in verbal intelligence among adult members of the U.S. UDV church who regularly used ayahuasca [n=30, 53% male, age=22–67, race N/R] compared to demographic-matched church-attending controls [n=27, 52% male, age=20–64, race N/R]. Verbal intelligence was measured using the American version of the Nelson Adult Reading Test, which estimates verbal intelligence by asking for the pronunciation of 45 irregularly spelled words.

MDMA. Zakzanis et al. (2007) also found reduced verbal comprehension in MDMA users (p<.001; d=-0.36; p_Q=0.04 ∴ homogeneous) compared to non-MDMA using controls in a meta-analysis of nine studies. The results of this meta-analysis should be interpreted with caution, as MDMA users were self-selecting, obscuring the causal relationship. Still, the consistency of these results is compelling enough to infer that MDMA is likely a causal factor.

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Visuospatial Intelligence

Acute.

LSD. Levine et al. (1955) found a significant decrease ($p<.01$; $d_n=0.63$) in Performance Scale IQ from baseline under LSD (50–200 μg) as measured by Wechsler-Bellevue Intelligence Scale [*N*=21, 43% male, age=22–43, race N/R, FSIQ *M*=122.9]. Performance Scale IQ included picture arrangement, picture completion, block design, object assembly, and digit symbol coding tasks, all of which showed significant reduction except for object assembly. Participants had an average Performance IQ reduction of 9.43 points. Isbell et al. (1956) also saw a reduction in Performance Scale IQ of 6.07 points ($d_n=0.41$) under 1–2 μg/kg LSD among opioid-dependent African American patients compared to control conditions [*n*=6].

Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference in WAIS-R Block Design ($p=.16$; $d_c=-0.06$) between Navajos who regularly took peyote and Navajos reporting minimal substance use [*N*=176, 28% male, age=18–45].

Ayahuasca. Doering-Silveira et al. (2005) found no significant difference in WAIS-III Object Assembly performance ($p=.30$; $d_c=-0.23$) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls who had never taken ayahuasca [*N*=80, 55% male, age=15–19, 81% White].

MDMA. Zakzanis and Campbell (2006) found no significant change in WAIS-III Block Design performance ($d=-0.30$) compared to baseline among MDMA users who continued use over the course of a 1-year study period [*n*=7, age *M*=29.0, sex and age

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N/R]. Performance relative to baseline improved in MDMA users who discontinued use over that same study period (p<.05; d=0.32) [n=8, age M=19.9, sex and age N/R].

Processing Speed

Acute.

LSD. Kornetsky et al. (1957) observed slower processing speed in response to 100 µg LSD (p<.05) as measured by digit symbol coding, 3-digit addition speed, and 9-digit addition speed compared to placebo [N=10, 60% male, age=18–23, race N/R]. With 50 µg LSD, only 3-digit addition speed was significantly slowed.

Psilocybin. F. S. Barrett et al. (2018) found reduced processing speed as measured by the Digit Symbol Substitution Task under 10–30 mg/70 kg psilocybin (p<.0001) compared to placebo [N=20, 55% female, age=22–43, race N/R]. While psilocybin reduced the speed of coding, no significant difference was found in accuracy.

Ayahuasca. Bouso et al. (2013) found decreased Stroop word reading speed (p=.047; d_c=-0.38) with ayahuasca compared to baseline [N=24, 50% male, age M=46.2, race N/R].

MDMA. Kuypers and Ramaekers (2005) found no significant difference in processing speed with 75 mg MDMA compared to placebo, as measured by the WAIS digit symbol substitution task [N=18, 50% male, age=20–39, race N/R].

Dumont et al. (2008) found that information processing speed was diminished (p=.022) for participants with 100 mg MDMA versus a placebo control as measured by the Symbol Digit Substitution [N=14, 56% male, age=18–29, race N/R].

Ketamine. Harborne et al. (1996) saw reduced speed on Trail Making Test Part A (TMT-A) under 25 mg IM ketamine (p=0.02; d_c=-0.63) but not 10 mg (p>.05; d_c=-0.05)

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[*N*=12, 75% male, age=25–43, race N/R]. They also saw a reduction in Stroop color naming speed with 25 mg (p=.007; d_c=-0.56) but this finding did not reach significance with 10 mg (p=.10; d_c=-0.25). C. J. A. Morgan, Mofeez, et al. (2004a) also found slowed speed on TMT-A that approached significance (p=.08) under 0.4 mg/kg and 0.8 mg/kg ketamine infusion [*N*=54, 50% male, age *M*=22.53, race N/R].

Curran and Morgan (2000) found a decrease in performance on a cancellation task (p<.001; d_c=-0.97) during recreational ketamine intoxication [*n*=20] compared to controls [*n*=19] who had not used ketamine [59% male, age=18–29, race N/R]. There was also an increase in omission errors (p=.002; d_c=1.02).

Hetem et al. (2000) found slower Digit Symbol Substitution (p=.01; d_c=-1.06) under 0.5 mg/kg IV ketamine compared to placebo [*N*=26, 38% male, age *M*=21.9, race N/R].

Lofwall et al. (2006) saw decreased processing speed under 0.4 mg/kg ketamine (p<.05; d_c=-0.67) compared to placebo controls [*N*=18, 44% male, age=18–47, race N/R]. The decrease in processing speed did not reach significance with 0.2 mg/kg ketamine (d_c=-0.21). Processing speed was measured using a computerized digit symbol substitution task (McLeod et al., 1982). Accuracy on the task was not significantly affected by either dose of ketamine (0.2 mg/kg: d_c=-0.31, 0.4 mg/kg: d_c=-0.58). However, a trend toward poorer accuracy with a higher dose suggests that there may be an effect that was not captured by the statistical power of the study.

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Subacute.

MDMA. Kuypers and Ramaekers (2005) found no significant difference in processing speed 1 day following 75 mg MDMA compared to placebo, as measured by the WAIS digit symbol substitution task [*N*=18, 50% male, age=20–39, race N/R].

Ketamine. Curran and Morgan (2000) found no significant difference in performance on a cancellation task (d_c=-0.05) 3 days following ketamine use [*n*=20] compared to controls [*n*=19] who had not used ketamine [59% male, age=18–29, race N/R]. There was, however, an increase in omission errors among the ketamine group (*p*=.002; d_c=0.76).

Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference (*p*=.26[4]) in WAIS-R Digit-Symbol Coding between Navajos who regularly took peyote and Navajos reporting minimal substance use [*N*=176, 28% male, age=18–45]. They also found no significant difference in time on the TMT-A (*p*=.74; *d*=0.00).

Ayahuasca. Doering-Silveira et al. (2005) found no significant difference in processing speed as measured by the WAIS-III Symbol Search (*p*=.67; d_c=-0.10) and the TMT-A (*p*=.31, d_c=0.23) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls [*N*=80, 55% male, age=15–19, 81% White].

Fernández et al. (2014) saw no significant change in WAIS-III Letter-Number Sequencing following a 3–9-month program involving ayahuasca ceremonies 1–2 times

[4] Effect size not reported due to likely error in the published data.

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per week, daily yoga and meditation, and individual therapy compared to baseline [N=13, 62% male, age M=35, race N/R].

Barbosa et al. (2016) found no significant difference in TMT-A speed (p=.42, $|d_r|$=0.22) between U.S. UDV church members who regularly used ayahuasca and matched church-attending controls [N=57, 53% male, age=20–67, race N/R].

MDMA. Zakzanis et al. (2007) found slower processing speed in MDMA users (p<.01; d=-0.33; p_Q=0.001 ∴ heterogeneous, random-effects model) compared to non-MDMA using controls in a meta-analysis of 16 studies (no control matching criteria). The results of this meta-analysis should be interpreted with caution, as MDMA users were self-selecting, obscuring the causal relationship. Still, the consistency of these results is compelling enough to infer that MDMA is likely a causal factor.

D. Wagner et al. (2015) found no significant change in processing speed attributable to MDMA use (p=.256–.908) in a 2-year cohort study [N=96, 66% male, age M=23.0, race N/R]. Processing speed was measured using the TMT-A (p=.256; Moderate Users: d_c=0.12; Heavy Users: d_c=-0.20) and the Digit Symbol task (p=.761; Moderate Users: d_c=-0.04; Heavy Users: d_c=-0.82) [n=96, 66% male, age M=23.0, race N/R].

Ketamine. Curran and Monaghan (2001) saw no significant difference in Digit Cancellation (d_c=-0.34) among 3-day abstinent frequent recreational ketamine users compared to infrequent users [N=37, 76% male, age M=25.5, race N/R].

C. J. A. Morgan et al. (2014) saw reduced TMT-A speed (p<.05; d_c=-1.08) among long-term ketamine users compared to polydrug, demographic-matched controls [N=26, 69% male, age=20–44, race N/R].

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M. Kim et al. (2016) saw reduced processing speed among people treated for complex regional pain syndrome (CRPS) with long-term frequent ketamine (p<.05; d_c=-1.05) compared to CRPS controls with little ketamine treatment, as measured with Digit Symbol Coding [N=30, 66% male, age M=38.0, race N/R].

Verbal Working Memory

Acute.

LSD. Sloane and Doust (1954) saw no significant change in digit span following 40–120 μg LSD in healthy normals (Δ=8%), schizophrenics (Δ=-13%), or depressives (Δ=-8%), compared to baseline [N=33, 70% male, age=20–56, race N/R]. Digit span was measured using Wittenborn's remembered numbers test. Similarly, Silverstein and Clay (1958) found no difference in digit span under 72 μg LSD compared to controls [N=16, male, age=20–24, race N/R]. In accordance, Jarvik, Abramson, and Hirsch (1955b) found no significant difference in digit span capacity with 50 or 100 μg LSD compared to baseline [N=12, 50% male, age=21–33, race N/R]. Finally, Barr et al. (1972) saw a significant decrease in Digit Span under 100 μg LSD when compared to baseline and placebo [N=50, 100% male, age=21–43, race N/R, professional actors] (p. 203).

Ayahuasca. Bouso et al. (2013) found an increase (p=.008; d_c=0.58) in total errors on the Sternberg Working Memory Task ayahuasca compared to baseline [N=24, 50% male, age M=46.2, race N/R]. No significant difference was found in reaction time.

Ketamine. J. A. Harris et al. (1975) found a significant reduction in digit span forward (p<.01; Δ=-1.54) but not backward digit span (p>.01; Δ=-1.00) under 0.4 mg/kg ketamine compared to baseline [N=11, 100% male, age=27–32, race N/R].

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R. A. E. Honey et al. (2003) measured verbal working memory under ketamine (50 or 100 ng/ml plasma) using WAIS-III Digit Span and an alphabetical letter series recall task [*N*=11, 46% male, age=18–64, race N/R]. They found that performance on working memory tasks requiring mental manipulation (backward digit span and alphabet sequencing) was significantly impaired ($p<.05$) by the higher ketamine dose but not the lower dose. Forward digit span and alphabet recall as presented were not significantly affected by either ketamine dose. They also measured spatial working memory using a computerized version of Corsi's block-tapping test. No significant effect was seen in spatial working memory.

In a subsequent study, R. A. E. Honey et al. (2004) found no significant difference in accuracy or response time on a 3- or 5-letter working memory task under ketamine (50 or 100 ng/ml plasma) compared to placebo [*N*=12, 50% male, age=18–49].

Koychev et al. (2017) saw reduced working memory accuracy ($p=.04$; $d_{\eta}^{2}=-0.84$) under ketamine (100 ng/ml plasma) compared to placebo and measured by the Delayed Matching-to-Sample task [*N*=44, age *M*=23.6, sex and race N/R].

Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference ($p=.47$; $d_c=-0.09$) in Digit Span between Navajos who regularly took peyote and Navajos reporting minimal substance use [*N*=176, 28% male, age=18–45].

Ayahuasca. Doering-Silveira et al. (2005) found no significant difference in Digit Span ($p=.27–.53$; $d_c=0.15$) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls [*N*=80, 55% male, age=15–19, 81% White].

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Bouso et al. (2012) found significantly higher WAIS-III Letter Number Sequencing (p<.020; d_c=0.54) among long-term ritual ayahuasca users compared to matched controls [N=242, 48% male, age M=36.9, 52% White, 48% Mestizo].

MDMA. D. Wagner et al. (2015) found a decrease in backward digit span that approached significance compared to baseline, which was attributable to MDMA use (p=.073) in a 2-year cohort study [N=96, 66% male, age M=23.0, race N/R]. The study compared those who chose to use MDMA moderately (<50 pills; d_c=-0.33) or heavily (>50 pills; d_c=-0.50) during that period to those who did not use MDMA.

Ketamine. M. Kim et al. (2016) saw reduced digit span among people treated for CRPS with long-term frequent ketamine (p<.05; d_c=-0.74) compared to CRPS controls with little ketamine treatment [N=30, 66% male, age M=38.0, race N/R].

Spatial Working Memory

Acute.

LSD. Pokorny et al. (2019) found that errors on the more complex trials of the Spatial Working Memory task significantly increased (p<.01–.001) under 100 µg LSD in an RCT [N=25, 76% male, age=20–40, race N/R].

Psilocybin. Carter et al. (2005) found no difference (p=.64) in spatial working memory capacity as measured by Corsi's Block-Tapping Test with 15.05 mg/70 kg psilocybin compared to a placebo condition [N=8, 63% male, age=21–31, race N/R]. Wittman et al. (2007) also saw no significant effect of psilocybin (8.05 or 17.5 mg/70 kg) on the CANTAB spatial span task [N=12, 50% male, age M=26.8, Swiss students].

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Ketamine. Krystal et al. (2004) observed a significant decrease in non-verbal working memory performance under ketamine (0.26 mg/kg bolus + 0.65 mg/kg/hr) when compared to placebo [*N*=19, 42% male, age *M*=22.6, race N/R].

Ibogaine. B. Forsyth et al. (2016) found no significant difference in performance on Corsi's Block-Tapping Test memory with a low, non-hallucinogenic ibogaine dose (20 mg) compared to baseline [*N*=21, male, age=20–40, race N/R].

Subacute.

Psilocybin. Rucker et al. (2022) saw no significant difference in Spatial Working Memory 8 days following 10 or 25 mg psilocybin compared to placebo [*N*=89, 54% male, age *M*=36.1, 81% White, 7% Asian, 5% mixed, 1% Black, 7% other].

Long-Term.

Psilocybin. Rucker et al. (2022) found no significant difference in Spatial Working Memory 29 days following 10 or 25 mg psilocybin compared to placebo.

MDMA. Fox et al. (2002) saw significantly more spatial working memory errors among MDMA users (p=.02; 4-box: d_c=0.00–0.33; 6-box: d_c=0.13–0.42; 8-box: d_c=0.81–0.89) compared to polydrug controls [*N*=40, 45% male, age=18–48, race N/R].

Ketamine. C. J. A. Morgan et al. (2009) saw more spatial memory errors (p<.01) and poorer strategy (p<.05; d_c=-1.18) among frequent ketamine users compared to polydrug controls [*n*=120, 71% male, age *M*=27.5, race N/R]. However, infrequent and ex-ketamine users showed no difference in spatial memory performance compared to polydrug controls. C. J. A. Morgan et al. (2010) also saw significantly more errors (p<.05; d_c=0.48) in spatial working memory among frequent ketamine users (>4x per week) compared to polydrug controls [*n*=49, 65% male, age *M*=28.4, race N/R].

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Attention

Overall Attention

Long-Term.

MDMA. Kalechstein et al. (2007) found impaired attention and concentration performance (p=.001; d=-0.40, SD=0.27) among non-treatment-seeking abstinent MDMA users compared with matched controls in a meta-analysis that included 11 studies[5]. Zakzanis et al. (2007) also found impaired attention and concentration in MDMA users (p<.001; d=-0.27; p_Q=0.26 ∴ homogeneous, fixed-effects model) compared to non-MDMA using controls in a meta-analysis of 22 studies (no control matching criteria). The results of both these meta-analyses should be interpreted with caution, as MDMA users were self-selecting, obscuring the causal relationship. Still, these consistent results are compelling enough to infer MDMA as a likely causal factor.

Sustained Attention

Acute.

MDMA. Kuypers et al. (2007) found an improved ability to sustain attention (p=.013) with 75–125 mg MDMA compared to placebo under conditions of sleep deprivation in a randomized controlled trial [N=14, 50% male, age=19–33, race N/R]. Sustained attention was measured using the Mackworth Clock task, which measures sustained attention over the course of 45 minutes with analysis divided into three 15-minute blocks. Performance under MDMA was approximately equal to placebo during

[5] Kalechstein et al. actually performed two meta-analyses, one with more stringent inclusion criteria [n=11], which is included in this study. The less stringent criteria included studies without matching of demographics and premorbid functioning for the controls [n=23]. Both meta-analyses yielded the same significant changes with very similar effect sizes.

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the first (d_c=-0.09) and second (d_c=0.09) blocks. In the third block, however, MDMA outperformed placebo by a substantial margin (d_c=2.80).

Ketamine. Krystal et al. (1994) saw significantly more continuous performance test (CPT) omission errors (p=.001; d_c=1.1) with 0.5 mg/kg ketamine compared to placebo [N=19, 63% male, age M=24.5, race N/R]. This trend did not reach significance with 0.1 mg/kg ketamine (d_c=0.17). Harborne et al. (1996) on the other hand saw no significant change in continuous performance test errors under 10 mg (d_c=-0.13) or 25 mg (d_c=0.42) IM ketamine [N=12, 75% male, age=25–43, race N/R].

Krystal et al. (2000) found no significant difference in CPT vigilance (p<.1; d_c=0.26) but increased distractibility (p=.006; d_c=0.08) under 0.011 mg/min/kg ketamine compared to placebo [N=22, 59% male, age M=31.5, 86% White, 9% Black, 5% Hispanic]. However, the effect size for increased distractibility is small, indicating that that the effect on attention may be minimal. In a subsequent study with a higher dose, Krystal et al. (2004) found a significant reduction in CPT vigilance (p=.001) and an increase in distractibility (p=.0001) under ketamine (0.26 mg/kg bolus followed by 0.65 mg/kg/hr) compared to placebo [N=19, 42% male, age M=22.6, race N/R].

Ibogaine. B. Forsyth et al. (2016) found no significant differences in sustained attention measured by the Simon Task except an increase in response time to congruent stimuli (p<.0006) under a low, non-hallucinogenic ibogaine dose (20 mg) compared to baseline [N=21, 100% male, age=20–40, race N/R].

Subacute.

Psilocybin. Rucker et al. (2022) saw no significant difference in sustained attention 8 days following 10 or 25 mg psilocybin compared to placebo and measured by

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the Rapid Visual Information Processing task [*N*=89, 54% male, age *M*=36.1, 81% White, 7% Asian, 5% mixed, 1% Black, 7% other].

Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference (p=.95; d_c=0.00) in Auditory CPT inattention errors between Navajos who regularly took peyote and Navajos reporting minimal substance use [*N*=176, 28% male, age=18–45].

Psilocybin. Rucker et al. (2022) saw no significant difference in sustained attention 29 days following 10 or 25 mg psilocybin compared to placebo.

Ayahuasca. Doering-Silveira et al. (2005) also found no significant difference in CPT test performance (p=.24-1.0) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls [*N*=80, 55% male, age=15–19, 81% White].

Barbosa et al. (2016) found no significant difference in CPT (p=.096-0.98, $|d_r|$=0.01-0.28) between U.S. UDV church members who regularly used ayahuasca and matched church-attending controls [*N*=57, 53% male, age=20–67, race N/R].

Divided Attention

Acute.

Psilocybin. Carter et al. (2005) found impaired visual tracking of multiple stimuli (p<.05) with 15.05 mg/70 kg psilocybin compared to placebo [*N*=8, 63% male, age=21–31, race N/R].

MDMA. Kuypers et al. (2007) found impaired performance on a divided attention tracking task (p=.005; d_c=-4.77) and a simultaneous visual stimulus-response task

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(p=.008–.047; d_c=-1.59–1.78) with 75–125 mg MDMA compared to placebo under conditions of sleep deprivation [N=14, 50% male, age=19–33, race N/R].

Lamers et al. (2016) found no significant difference in performance on a divided attention task for subjects administered 75 mg MDMA in a double-blind, placebo-controlled trial [N=12, 67% male, age=21–30, Dutch, race N/R].

Ketamine. Passie et al. (2005) found no significant difference in omission errors on a divided attention task under low-dose, 0.003 mg/min/kg, (*S*)-ketamine (p=.309; d_c=0.58) compared to placebo [N=12, 100% male, age M=26.8, race N/R, medical students]. However, at a high dose of 0.005 mg/min/kg, there was a significant increase in omission errors (p=.003; d_c=1.25).

Focused Attention

Acute.

LSD. Sloane and Doust (1954) saw slowed performance on the Serial Sevens task with 40–120 µg LSD among healthy normals (p=.05; Δ=-16%) and schizophrenics (p=.02; Δ=-21%) but not depressives (Δ=-8%), compared to baseline [N=33, 70% male, age=20–56, race N/R]. There was a significant increase in errors on the task only among schizophrenics.

Barr et al. (1972) saw a significant decrease in Serial Sevens performance under 100 µg LSD compared to baseline and placebo [N=50, 100% male, age=21–43, race N/R, professional actors] (p. 203).

Psilocybin. F. S. Barrett et al. (2018) found reduced Letter 2-back performance with 20 mg/70 kg (p<.05–.001) and 30 mg/70 kg (p<.05–.0001) psilocybin compared to placebo, but not with 10 mg/70 kg (p>.05) [N=20, 55% female, age=22–43, race N/R].

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MDMA. Dumont et al. (2008) found no significant difference in visual attention under 100 mg MDMA versus a placebo using the Tangle Task [*N*=14, 56% male, age=18–29, race N/R]. The Tangle Task requires that subjects visually track a line that is "wandering" through several other distractor lines on a computer screen and correctly identify the line at the end of the test.

Ketamine. Adler et al. (1998) found that ketamine (0.12 mg/kg bolus + 0.65 mg/kg/hr) impaired *n*-back performance (p=.006–.008; d_c=-1.25 to -1.28) in comparison to placebo [*N*=10, 70% male, age *M*=35.2, race N/R].

Curran and Morgan (2000) found impaired performance on the serial sevens task (p<.002; d_c=-1.56) during recreational ketamine intoxication [*n*=20] compared to controls [*n*=19] who had not used ketamine [59% male, age=18–29, race N/R]. They did not find a significant difference in error rate.

C. J. A. Morgan, Mofeez, et al. (2004a) saw reduced *n*-back test performance (p<.01) under 0.4 mg/kg and 0.8 mg/kg ketamine infusion [*N*=54, 50% male, age *M*=22.53, race N/R]. Lofwall et al. (2006) also saw decreased *n*-back performance under 0.4 mg/kg ketamine (p<.05) compared to placebo controls [*N*=18, 44% male, age=18–47, race N/R]. This decrease did not reach significance with 0.2 mg/kg ketamine.

Subacute.

MDMA. Pirona and M. J. Morgan (2010) found no difference in Serial Sevens performance 1- and 4-days following street ecstasy consumption compared to a control group of ecstasy users who did not use ecstasy during the same period [*N*=32, 59% male, age=19–30, race N/R].

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Ketamine. Curran and Morgan (2000) found no significant difference in Serial Sevens performance 3 days following ketamine use [n=20] compared to controls [n=19] who had not used ketamine [59% male, age=18–29, race N/R].

Long-Term.

MDMA. Daumann et al. (2004) saw no significant change in n-back performance in MDMA users who were either abstinent from MDMA during an 18-month follow-up period or continued to use MDMA during that period in comparison to their baseline scores [N=17, 65% male, age M=25.5, race N/R].

In an RCT, Mithoefer et al. (2011) saw no significant difference in Paced Auditory Serial Addition Test (PASAT) performance 2 months following MDMA-assisted psychotherapy (Trial 1: p=.19; Trial 2: p=.69) compared to placebo [N=20, 85% female, age M=40.4, 100% Caucasian].

Ketamine. Curran and Monaghan (2001) saw no significant difference in Serial Sevens performance (d_c=-0.16) among 3-day abstinent frequent recreational ketamine users compared to infrequent users [N=37, 76% male, age M=25.5, race N/R].

C. J. A. Morgan, Monaghan, and Curran (2004) saw no significant difference in Serial Sevens subtraction speed (d_c=-0.12 to 0.44) or errors (d_c=-0.37 to 0.35) among recreational ketamine users [n=18, 22% female, age M=28.1, race N/R] compared to polydrug controls [n=10, 60% female, age M=26.5, race N/R]. Between baseline and follow-up, ketamine users as a group reduced use by 88.3%, but there was no significant change in Serial Sevens speed (d_c=0.32), though errors were reduced (p_t=.44; d_c=-0.73).

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C. J. A. Morgan et al. (2014) saw reduced performance on the spatial *n*-back task (p<.001; 1-back: d_c=-0.92, 2-back: d_c=-0.72) among long-term ketamine users compared to polydrug controls [N=26, 69% male, age=20–44, race N/R].

Visual Search

Acute.

LSD. Jarvik, Abramson, and Hirsch (1955a) found a dose-dependent trend of reduced performance in cancellation of a single letter, number, or form embedded in a matrix under 50 and 100 μg LSD compared to placebo [N=12, 50% male, age=21–33, race N/R]. However, this trend only reached significance with 100 μg LSD for the single letter (p<.02) and vowels (p=.05) condition, though the dose-dependent directionality of change reached significance for three of five conditions. For whole words embedded in a matrix of letters, Jarvik et al. found increased performance with 50 (p<.01) and 100 (p<.05) μg LSD. Increased performance in detecting odd numbers preceded by odd numbers was seen with 50 (p=.05) but not 100 μg LSD, with the latter condition resulting in performance similar to placebo. Finally, there was no significant difference seen in speeded detection of sets of numbers that add up to nine.

Silverstein and Clay (1958) found reduced mental control (p<.05) under 72 μg LSD compared to controls as measured using the WMS mental control task that includes counting backward, saying the alphabet, and serial addition [N=16, male, age=20–24, race N/R].

MDMA. Parrott and Lasky (1998) found reduced performance on a visual letter search task (p<.01–.1; 2.1–2.6x increase in search time) with recreational MDMA-intoxicated regular MDMA users compared to controls intoxicated with alcohol and other

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drugs [*N*=45, 58% female, age=19–30, race N/R]. Performance was also diminished among MDMA-intoxicated novice users compared to controls (1.5–1.7x increase in search time), but these results did not reach significance.

Ketamine. Harborne et al. (1996) saw significant change in visual search performance under 10 mg (d_c=-0.32 to 0.23) or 25 mg (d_c=-0.32 to -0.35) IM ketamine [*N*=12, 75% male, age=25–43, race N/R].

Subacute.

MDMA. Parrott and Lasky (1998) found no significant difference in 15 of 16 comparisons of performance on a visual letter search task 2- and 7-days following MDMA compared to controls who used alcohol, cannabis, and/or cocaine at the same timepoint [*N*=45, 58% female, age=19–30, race N/R]. Given that multiple comparisons were made, the one comparison that reached significance at $p<.05$ is assumed to be a false-positive.

Long-Term.

Ketamine. C. J. A. Morgan, Monaghan, and Curran (2004) found reduced controlled visual search performance (p=.013) among recreational ketamine users [*n*=18, 22% female, age *M*=28.1, race N/R] at baseline measurement (d_c=-1.00) and 3- to 4-year follow-up (d_c=-0.92) compared to polydrug controls [*n*=10, 60% female, age *M*=26.5, race N/R]. Visual search was measured using a digit cancellation task within a field of random numbers. There was no significant difference in digit cancellation omission errors between the two groups (d_c=0.28-1.10). Between baseline and follow-up, ketamine users as a group reduced use by 88.3%, but there was no significant change in digit cancellation performance ($|d_c|$=0.05-0.34).

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Self-Rated Attention

Acute.

MDMA. Marrone et al. (2009) found increased (p<.05) self-ratings of "can't concentrate" under 100 mg MDMA compared to placebo and methamphetamine [N=11, 18% female, age=23–39, 36% White, 27% Black, 27% Hispanic, and 9% Asian].

Subacute.

MDMA. Jones et al. (2008) found a decrease in self-reported concentration (p<.001; $d_{\eta 2}$=-1.95 to -2.75) 2 to 5 days following ecstasy use compared to alcohol-using controls [N=36, 56% male, age M=19.9, race N/R]. This reduction in concentration appeared to be converging to baseline 6 days following, though there remained a significant difference (p<.05; $d_{\eta 2}$=-0.77) between ecstasy users and controls.

Huxter et al. (2006) found a significant increase in self-reported cognitive impairment (p=.005) 1 and 2 days following MDMA use [n=20] compared to control MDMA users [n=18] who had not used MDMA in that same period [53% male, age=18–29, race N/R]. Cognitive impairment included one item on concentration and one on memory, and the composite measure appeared to return to baseline 3 to 5 days later.

Long-Term.

Ayahuasca. Barbosa et al. (2016) found a decrease approaching significance in self-reported attentional difficulties (p=.070; $|d_r|$=-0.49) between ayahuasca using U.S. UDV church members and matched church-attending controls, as measured by the Barrett Impulsiveness Scale (BIS-11) [N=57, 53% male, age=20–67, race N/R].

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MDMA. Parrott et al. (2002) found that 32% of novice ecstasy users (1–9 occasions [x]), 62% of moderate users (10–99x), and 70% of heavy users (≥100x) reported "poor concentration" that they attributed to ecstasy [*N*=282, demographics N/R].

Taurah et al. (2013) also found decreased self-reported attention in active MDMA users (p<.001*; d*=-1.25) or ex-MDMA users (p<.001; *d*=-1.27) compared to polydrug controls and measured by the BIS-II [*N*=997, 52% male, age *M*=25.1, 32% White, 27% Asian, 23% Black, 18% Other].

Memory and Learning

General Memory Function

Subacute.

MDMA. Jones et al. (2008) found a decrease in self-reported "ease of taking in new information" (p<.001; $d_{\eta 2}$=-1.40 to -4.67) 2 to 5 days following ecstasy use compared to alcohol-using controls [*N*=36, 56% male, age *M*=19.9, race N/R]. There was no significant difference 6 days following.

Long-Term.

MDMA. Kalechstein et al. (2007) found impaired verbal learning and memory performance (p=.001; *d*=-0.73, SD=0.69) among non-treatment-seeking abstinent MDMA users compared with matched controls in a meta-analysis that included 11 studies. They also found that nonverbal learning and memory were impaired (p=.001; *d*=-0.58, SD=0.64). Zakzanis et al. (2007) also found impaired learning and memory in MDMA users (p<.001; *d*=-0.55; p_Q=.001) compared to non-MDMA using controls in a meta-analysis of 21 studies. The results of these meta-analyses are interpreted with

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caution, as MDMA users were self-selecting, obscuring the causal relationship. Still, the consistency of the results is compelling enough to infer MDMA as a likely causal factor.

Parrott et al. (2002) found that 19% of novice ecstasy users (1-9 occasions [x]), 52% of moderate users (10–99x), and 73% of heavy users (≥100x) had "memory problems" that they attributed to ecstasy use [*N*=282, demographics N/R]. Rodgers et al. (2003) found a correlation approaching significance (p=.084) between the level of MDMA use and self-reported memory problems from the Everyday Memory Questionnaire (EMQ) in a web survey [*N*=763, 61% female, modal age group=21-25, 71% from Europe]. However, there was a stronger association (p=.0005) between with participants' frequency of cannabis use and higher EMQ scores. This suggests that the participants in Parrott et al. (2002) could have been attributing "memory problems" to ecstasy use when many of these memory problems could be attributable to cannabis use, especially given that "many" of the study participants were polydrug users.

Verbal Encoding/Recognition

Acute.

Psilocybin. F. S. Barrett et al. (2018) found no significant difference in word list recognition under psilocybin in healthy adults compared to placebo [*N*=20, 55% female, age=22–43, race N/R].

MDMA. Kuypers and Ramaekers (2005) saw improvements in RAVLT recognition that approached significance (p=.079; d_c=2.26) under 75 mg MDMA compared to placebo [*N*=18, 50% male, age=20–39, race N/R].

Ketamine. Hetem et al. (2000) found poorer verbal recognition approaching significance (p=.11; d_c=-0.65) under 0.5 mg/kg IV ketamine compared to placebo [*N*=26,

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38% male, age *M*=21.9, race N/R]. However, for items learned during the ketamine session, there was significantly poorer recognition (p=.03), while there was no significant difference for items learned before the session (p=.48).

C. J. A. Morgan, Mofeez, et al. (2004a) found significantly poorer recognition memory (p<.001) for items encoded and recalled under 0.4 mg/kg and 0.8 mg/kg ketamine infusion [*N*=54, 50% male, age *M*=22.53, race N/R]. In line with this, G. D. Honey et al. (2005) concluded that acute ketamine (50 ng/ml or 100 ng/ml plasma) impaired encoding of a new word list but not retrieval of a prior-learned word list in a double-blind placebo-controlled experiment [*N*=12, 46% male, age=18–64, race N/R]. The authors differentiated between recognition due to recollection of "contextual detail associated with the item" and recognition due to familiarity. They speculate that ketamine interferes with the recollection process rather than familiarity explaining that shallowly encoded items are recognized through familiarity, resulting in less vulnerability to encoding disruption from ketamine than more deeply encoded items. G. D. Honey et al. (2005) also found that recognition was impaired for words learned under acute ketamine (100 ng/ml) [*N*=12, 58% male, age *M*=28.1, race N/R].

Lofwall et al. (2006) had subjects learn a word list during acute ketamine intoxication and then recall that list 1 hour later after the ketamine effects had somewhat dissipated [*N*=18, 44% male, age=18–47, race N/R]. They saw a significant decrease in recognition for with 0.4 mg/kg (p<.05; d_c=-0.36) but not 0.2 mg/kg (p<.05; d_c=0.30) ketamine relative to placebo. In addition, they saw a significant reduction in recall with 0.4 mg/kg (p<.05; d_c=-0.83) but not 0.2 mg/kg (d_c=-0.35) ketamine. This implies that ketamine at the higher dose interferes with the encoding of new verbal information. For a

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list learned prior to ketamine, recognition was not significantly different under either 0.2 mg/kg (d_c=0.28) or 0.4 mg/kg (d_c=0.61) ketamine. Thus, retrieval of previously learned information does not appear to be impaired under ketamine.

Malhotra et al. (1996), however, had found reduced recognition of a prior-learned word list under ketamine (0.12 mg/kg bolus + 0.65 mg/kg infusion) 10 minutes (p=.01) and 55 minutes (p=.001) post-infusion [N=15, 80% male, age M=27.9, race N/R].

Subacute.

Psilocybin. Rucker et al. (2022) saw no significant difference in Paired-Associate Learning 8 days following 10 or 25 mg psilocybin compared to placebo [N=89, 54% male, age M=36.1, 81% White, 7% Asian, 5% mixed, 1% Black, 7% other].

Long-Term.

Psilocybin. Rucker et al. (2022) also saw no significant difference in Paired-Associate Learning 29 days following 10 or 25 mg psilocybin.

Ayahuasca. Grob et al. (1996) found no significant difference in AVLT recognition (p=.253–.602; d_c=-0.20 to -0.43) among ritual ayahuasca users compared to matched controls [N=15, Brazilian]. Doering-Silveira et al. (2005) also found no significant reduction in AVLT recognition (p=.17; d_c=-0.32) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls [N=80, 55% male, 81% White].

Verbal Learning and Immediate Recall

Acute.

LSD. Silverstein and Clay (1958) found a reduction in story learning performance (p<.01) under 72 µg LSD compared to controls as measured by the WMS logical

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memory task [*N*=16, male, age=20–24, race N/R]. They found no difference in verbal association learning.

Jarvik, Abramson, and Hirsch (1955b) found a significant reduction in auditory sentence recall ($p<.01$), auditory paired-associate recall ($p<.05$), visual word opposite recall ($p=.05$), and visual nonsense syllable recall ($p=.02$) performance under 100 μg but not 50 μg LSD compared to baseline [*N*=12, 50% male, age=21–33, race N/R]. They found no significant difference in auditory list learning and nonsense syllable recognition during drug conditions.

Psilocybin. F. S. Barrett et al. (2018) found a dose-dependent reduction in word list learning performance under psilocybin (10 mg/70 kg: $p<.05$; 20 mg/70 kg: $p<.01$; 30 mg/70 kg: $p<.001$) in healthy adults compared to placebo [*N*=20, 55% female, age=22–43, race N/R].

MDMA. Parrott and Lasky (1998) found a 34% reduction in auditory-verbal list learning ($p<.01$) during recreational MDMA intoxication compared to controls using alcohol and other drugs in a club [*N*=45, 58% female, age=19–30, race N/R].

Dumont et al. (2008) found no significant difference in immediate recall of an 18-word list learning task for participants with 100 mg MDMA versus placebo control [*N*=14, 56% male, age=18–29, race N/R].

Kuypers and Ramaekers (2005) found impaired RAVLT immediate recall ($p=.009$; $d_c=-2.08$) with 75 mg MDMA compared to placebo [*N*=18, 50% male, age=20–39, race N/R]. Kuypers et al. (2010) also found that 75 mg MDMA impaired immediate verbal word-list recall ($p=.041$; $d_c=-0.54$) compared to placebo [*N*=14, 79% male, age=19-29, race N/R].

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Ketamine. J. A. Harris et al. (1975) found a significant reduction in immediate word-association recall for non-semantically-related word pairings ($p<.01$) but not for semantically-related word pairings ($p>.01$) under 0.4 mg/kg ketamine compared to baseline [N=11, 100% male, age=27–32, race N/R]. Associative memory pairings were from the WMS.

Curran and Morgan (2000) found impaired immediate story recall ($p<.001$; d_c=-2.01) during recreational ketamine intoxication compared to controls [N=39, 59% male, age=18–29, race N/R].

Krystal et al. (2004) saw impaired immediate recall ($p<.0001$) on the Hopkins Verbal Learning Test [HVLT] under ketamine (0.26 mg/kg bolus followed by 0.65 mg/kg/hr) compared to placebo [N=19, 42% male, age M=22.6, race N/R]. Murrough et al. (2013), however, found that acute 0.5 mg/kg ketamine had no significant effect on HVLT learning ($p=.42$) compared to baseline [N=25, 40% female, age M=49.0, race N/R].

Subacute.

MDMA. Parrott and Lasky (1998) found a 14% reduction in auditory-verbal list learning ($p<.05$) among regular MDMA users 2 days following MDMA compared to controls who used alcohol, cannabis, and/or cocaine at the same timepoint [N=45, 58% female, age=19–30, race N/R]. List learning performance in novice users did not show a significant difference 2 days following (8% reduction). Seven days following, list learning performance was reduced by 13% for novice users ($p<.05$) and 15% for regular MDMA users ($p<.05$).

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Kuypers and Ramaekers (2005) found no significant difference in immediate verbal recall 1 day following 75 mg MDMA compared to placebo and measured by the RAVLT [*N*=18, 50% male, age=20–39, race N/R].

Pirona and M. J. Morgan (2010) found no difference in immediate story memory 1- and 4-days following street ecstasy consumption compared to a control group of ecstasy users who did not use ecstasy during the same period, with post hoc group assignment based on ecstasy use in the study period [*N*=32, 59% male, age=19–30, race N/R]. Story memory was measured using the Rivermead Behavioral Memory Test (RBMT).

Ketamine. Curran and Morgan (2000) found impaired immediate story recall ($p<.001$; d_c=-0.94) 3 days following ketamine use [*n*=20] compared to controls [*n*=19] who had not used ketamine [59% male, age=18–29, race N/R].

Long-Term.

Ayahuasca. Grob et al. (1996) found worse verbal list learning performance ($p=.038$; d_c=-0.85) among ritual ayahuasca users compared to matched controls [*N*=15, Brazilian]. List learning was measured using the WHO/UCLA Auditory-Verbal Learning Test (AVLT).

Doering-Silveira et al. (2005) found reduced AVLT list-learning performance ($p=.01$; d_c=-0.59) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls [*N*=80, 55% male, 81% White]. In addition, there was reduced performance approaching significance on recall following an interference list ($p=.09$; d_c=-0.39). Interestingly, performance was not significantly reduced in Trial I ($p=.34$; d_c=-0.21) or

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the Interference List Trial VI (p=.54; d_c=-0.14) for the ayahuasca using group, indicating that list-learning without repetition may not be impaired.

Barbosa et al. (2016) found no significant difference (p=.98; $|d_r|$=0.01) in immediate recall on the California Verbal Learning Test (CVLT) between U.S. UDV church members who regularly used ayahuasca and church-attending matched controls [N=57, 53% male, age=20–67, race N/R].

MDMA. Laws and Kokkalis (2007) found impaired verbal memory (d=-1.0; 95% CI=-1.45 to -0.59) in recreational MDMA users compared to controls based on a meta-analysis of 22 studies. While they did not discriminate these findings between immediate and delayed recall, the present author estimated the effect size of immediate verbal recall to be d=-0.9 based on least squares regression.

D. Wagner et al. (2015) found no significant change in RAVLT immediate recall among MDMA users (p=.136–.967) in a 2-year cohort study [N=96, 66% male, age M=23.0, race N/R]. The study compared those who chose to use MDMA moderately (<50 pills; $|d_c|$=0.04–0.38) or heavily (>50 pills; $|d_c|$=0.25–0.68) during the study period to those who did not use MDMA [N=96, 66% male, age M=23.0, race N/R].

Ketamine. Curran and Monaghan (2001) saw impaired immediate prose recall (p<.01; d_c=-1.50) among 3-day abstinent frequent recreational ketamine users compared to infrequent users [N=37, 76% male, age M=25.5, race N/R].

C. J. A. Morgan, Monaghan, and Curran (2004) found reduced immediate story recall performance (p=.047) among recreational ketamine users [n=18, 22% female, age M=28.1, race N/R] compared to polydrug controls at baseline and 3- to 4-year follow-up [n=10, 60% female, age M=26.5, race N/R]. There was no significant change in memory

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among ketamine users between baseline and follow-up. In this same period, however, ketamine users reduced their use by 88.3%, indicating that changes in immediate memory may persist beyond reduced or discontinued recreational ketamine use.

C. J. A. Morgan et al. (2009) saw no significant difference in immediate story recall between frequent (d_c=-0.05), infrequent (d_c=-0.08), and ex- (d_c=-0.05) ketamine users compared to polydrug controls [n=120, 71% male, age M=27.5, race N/R]. C. J. A. Morgan et al. (2010) also found no significant difference (p>.05) in immediate auditory story recall between frequent (<4 x/wk; d_c=-0.34), infrequent (d_c=0.08), or past (d_c=-0.12) ketamine users [n=90, 69% male, age M=27.9, race N/R]. Finally, C. J. A. Morgan et al. (2014) saw no significant difference in immediate prose recall (p=.2; d_c=-0.48) among long-term ketamine users compared to matched polydrug controls [N=26, 69% male, age=20–44, race N/R]. However, this difference may approach significance with a larger sample.

Verbal Delayed Recall

Acute.

MDMA. Kuypers and Ramaekers (2005) found impaired performance in RAVLT 30-minute delayed recall (p=.006; d_c=-2.05) under 75 mg MDMA compared to placebo [N=18, 50% male, age=20–39, race N/R].

Dumont et al. (2008) found impaired performance in 22-minute delayed recall of an 18-word list-learning task (p=.007) for participants under 100 mg MDMA compared to placebo [N=14, 56% male, age=18–29, race N/R].

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Kuypers et al. (2010) found no significant difference (d_c=-0.03) in 40-min delayed verbal word-list recall with 75 mg MDMA compared to placebo [*N*=14, 79% male, age=19-29, race N/R].

Ketamine. Malhotra et al. (1996) saw reduced free recall of a word list learned prior to ketamine (0.12 mg/kg bolus + 0.65 mg/kg infusion) at 55 minutes (p=.001) and 90 minutes (p=.026) post-infusion [*N*=15, 80% male, age *M*=27.9, race N/R].

Curran and Morgan (2000) found impaired 15-minute delayed story recall (p<.001; d_c=-1.70) during recreational ketamine intoxication compared to controls.

Hetem et al. (2000) found impaired list free recall (p=.03; d_c=-0.88) under 0.5 mg/kg IV ketamine compared to placebo [*N*=26, 38% male, age *M*=21.9, race N/R]. Free recall for items learned under ketamine was significantly worse (p=.003) compared to placebo. However, for items learned prior to the ketamine session, there was no significant difference in free recall (p=.47).

Krystal et al. (2004) saw impaired HVLT delayed recall (p=.002) under ketamine (0.26 mg/kg bolus followed by 0.65 mg/kg/hr) compared to placebo [*N*=19, 42% male, age *M*=22.6, race N/R]. Murrough et al. (2013) also found that acute 0.5 mg/kg ketamine resulted in significantly worse HVLT delayed recall (p=.01) compared to baseline [*N*=25, 40% female, age *M*=49.0, race N/R].

Parwani et al. (2005) found decreased recall of a list learned prior to ketamine (0.27 mg/kg bolus + 0.12 mg/kg infusion) at 30 minutes post-infusion (p<.001; d_c=-0.76) compared to placebo [*N*=13, 38% male, age *M*=31.9, 69% Caucasian, 31% African American]. There was no significant difference in list recall at 60 minutes (d_c=-0.23) or 90 minutes (d_c=-0.24) post-infusion.

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Lofwall et al. (2006) observed no significant difference in retrieval of a prior-learned word list following 0.2 mg/kg (d_c=-0.06) or 0.4 mg/kg (d_c=-0.05) ketamine injection compared to placebo [*N*=18, 44% male, age=18–47, race N/R]. This suggests that ketamine does not impair the retrieval of prior-learned verbal information.

Subacute.

MDMA. Pirona and M. J. Morgan (2010) found no difference in 30-minute delayed story memory 1- and 4-days following street ecstasy consumption. Kuypers and Ramaekers (2005) also found no significant difference in RAVLT delayed recall 1 day following 75 mg MDMA compared to placebo [*N*=18, 50% male, age=20–39, race N/R].

Ketamine. Curran and Morgan (2000) found impaired 15-minute delayed story recall (p<.001; d_c=-1.03) 3 days following ketamine use compared to controls.

Long-Term.

Ayahuasca. Grob et al. (1996) saw no significant difference in AVLT delayed list recall (p=.248; d_c=-0.51) among ritual ayahuasca users compared to matched controls [*N*=15, Brazilian].

Doering-Silveira et al. (2005) found no significant reduction in AVLT delayed recall (p=.18; d_c=-0.30) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls [*N*=80, 55% male, 81% White].

Barbosa et al. (2016) found no significant difference in CVLT delayed recall (p=.80; $|d_r|$=0.07) between U.S. UDV church members who regularly used ayahuasca and church-attending matched controls [*N*=57, 53% male, age=20–67, race N/R].

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MDMA. Laws and Kokkalis (2007) found impaired delayed recall in recreational MDMA users relative to controls (d=-0.87; 95% CI=-1.38 to -0.45) based on a meta-analysis of 19 studies. While Laws and Kokkalis did not discriminate between effects on delayed verbal and visual memory, the present author estimated the effect size of delayed verbal recall to be d=-1.2 using least-squares regression.

D. Wagner et al. (2015) found no significant change in RAVLT delayed auditory-verbal recognition attributable to MDMA use (p=.106) in a 2-year cohort study [N=96, 66% male, age M=23.0, race N/R]. The study compared those who chose to use MDMA moderately (<50 pills; d_c=-0.42) or heavily (>50 pills; d_c=-1.14) during the study period to those who did not use MDMA.

Ketamine. Curran and Monaghan (2001) saw reduced delayed prose recall (p<.01; d_c=-1.19) among 3-day abstinent frequent recreational ketamine users compared to infrequent users [N=37, 76% male, age M=25.5, race N/R].

C. J. A. Morgan, Monaghan, and Curran (2004) also found reduced delayed story recall performance (p=.045) among recreational ketamine users at baseline and 3- to 4-year follow-up compared to polydrug controls. Since no significant difference in performance was found in ketamine users between baseline and follow-up, and ketamine users reduced use by 88.3% during the follow-up period, it is likely that reduced delayed story recall is a persistent effect of ongoing recreational ketamine use.

C. J. A. Morgan et al. (2009) saw no significant difference in delayed story recall between frequent (d_c=0.18), infrequent (d_c=0.06), and ex- (d_c=0.16) ketamine users compared to polydrug controls [n=120, 71% male, age M=27.5, race N/R]. C. J. A. Morgan et al. (2010) also found no significant difference (p>.05) in delayed auditory

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story recall between frequent (<4x/wk; d_c=-0.46), infrequent (d_c=-0.12), or past (d_c=-0.06) ketamine users [n=90, 69% male, age M=27.9, race N/R].

C. J. A. Morgan et al. (2014) saw no significant difference in delayed prose recall (p=.2; d_c=-0.63) among long-term ketamine users compared to polydrug using matched controls [N=26, 69% male, age=20–44, race N/R]. However, this difference may approach significance with a larger sample.

Visual Encoding/Recognition

Acute.

LSD. Brengelmann (1958) tested the recognition accuracy of 10 patterns exposed for 1 second each and then mixed into 30 patterns, with subjects asked to rate on a 5-point Likert scale their level of certainty of whether they recognized the pattern. There was no significant difference in the recognition accuracy under LSD (p=.1; d_c=0.26), but there was a significant decrease in the certainty of responses (p=.01; d_c=0.62).

MDMA. Doss et al. (2017) found that MDMA impairs encoding of affectively laden images with both negative (p=.038; d=-0.681) and positive valance (p=.037; d=-0.684), but not significantly for neutral valance images (p=.287; d=-0.341) [N=60, 50% male, age M=23.7, 48% Caucasian, 15% Asian, 10% Black, 23% other/multiracial]. This was evidenced by lower image recognition accuracy when no longer intoxicated with MDMA compared to placebo controls. They also found no significant effect of MDMA on retrieval from a paired verbal cue of image memories formed while not intoxicated with MDMA or on recognition or familiarity memory for these images compared to placebo controls. They did, however, find that MDMA led to an increase in

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image recognition false positives (p=.077; d=0.075), indicating a possible increase in false memory generation.

Long-Term.

Ayahuasca. Barbosa et al. (2016) found no significant difference in CVLT recognition (p=.92; $|d_r|$=0.03) between U.S. UDV church members who regularly used ayahuasca and matched controls [N=57, 53% male, age=20–67, race N/R].

MDMA. P. N. Murphy et al. (2012) found impaired visuospatial recognition memory (p<.0005; d_g=-0.379) among recreational ecstasy users compared to drug-using controls based on a meta-analysis of 16 studies.

Ketamine. C. J. A. Morgan et al. (2010) saw a significant difference (p=.002) in the recognition of visual patterns between frequent (<4x/wk), infrequent, or past ketamine users [n=90, 69% male, age M=27.9, race N/R]. However, none of these groups differed significantly from polydrug controls (frequent: d_c=-0.35; infrequent: d_c=0.21; past: d_c=0.65).

Visual Learning and Immediate Recall

Acute.

LSD. Jarvik, Abramson, and Hirsch (1955b) saw a significant reduction in visual object recall under 50 μg (p=.05) and 100 μg (p<.05) LSD compared to baseline [N=12, 50% male, age=21–33, race N/R]. Silverstein and Clay (1958) also found a reduction in short-term visual memory (p<.01) under 72 μg LSD compared to controls as measured by the visual reproduction task on the WMS [N=16, male, age=20–24, race N/R].

Brengelmann (1958) also found a significant reduction in immediate recall performance on the Figure Reconstruction Task among healthy normal volunteers under

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60 µg IV LSD compared to placebo [*N*=8, age=25-31, sex and race N/R]. This reduction in performance included increased rotation errors (p=.005; d_c=0.56), distance errors (p=.005; d_c=0.74), and size variability (p=.02; d_c=0.37).

Psilocybin. Escobar and Roazzi (2011b) found a significant decrease in performance on a short-term visual memory task (p<.001 for 15 s memorization time; p<.02 for 5 s) under 350 µg/kg psilocybin [*N*=28, age=19-44, sex and race N/R].

MDMA. Kuypers and Ramaekers (2007) found that 75 mg MDMA increased (p=.004) localization error by 13% on the Spatial Memory Task compared to placebo [*N*=18, 50% male, age=20–39, race N/R].

Ketamine. Harborne et al. (1996) saw reduced performance in associating faces with names and occupations under 25 mg IM ketamine (p=0.007*;* d_c=-0.79) but not with 10 mg (p>.05; d_c=0.12) [*N*=12, 75% male, age=25–43, race N/R].

Passie et al. (2005) found no significant difference in visual memory immediate recall during 0.003 mg/min/kg (p=.629–.674; $|d_c|$=0.43–0.45) or 0.005 mg/min/kg (p=.424–.294; $|d_c|$=0.64–0.75) (*S*)-ketamine infusion compared to placebo [*N*=12, 100% male, age *M*=26.8, race N/R, medical students]. Short-term visual memory was measured using the Benton Visual Retention Test.

Subacute.

MDMA. Kuypers and Ramaekers (2007) found no significant difference in Spatial Memory Task immediate recall 1 day following 75 mg MDMA compared to placebo [*N*=18, 50% male, age=20–39, race N/R].

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Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference in Rey-Osterrieth Complex Figure Test (ROCFT) immediate recall (p=.22; d_c=0.23) and WMS figures immediate recall (p=.57; d_c=0.00) among Navajos who regularly took peyote compared to Navajos reporting minimal substance use [N=176, 28% male, age=18–45].

Ayahuasca. Doering-Silveira et al. (2005) found no significant difference in immediate recall of the ROCFT (p=.88; d_c=0.03) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls [N=80, 55% male, 81% White].

Barbosa et al. (2016) found no significant difference (p=.21; $|d_r|$=0.35) in ROCFT immediate recall between U.S. UDV church members who regularly used ayahuasca and church-attending matched controls [N=57, 53% male, age=20–67, race N/R].

MDMA. Laws and Kokkalis (2007) found impaired visual memory (d=-0.27; 95% CI=-0.55 to -0.03) in recreational MDMA users compared to controls based on a meta-analysis of 14 studies. While they did not discriminate these findings between immediate and delayed recall, the present author estimated the effect size of immediate visual memory to be d=-0.2 based on least squares regression.

P. N. Murphy et al. (2012) found impaired short-term visuospatial recall (p<.0005; d_g=-0.394) among recreational ecstasy users compared to drug-using controls based on a meta-analysis of 12 studies. They also found impairment in the reproduction of previously seen figures, typically with the ROCFT (p<.0005; d_g=-0.247) in a meta-analysis of 12 studies.

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D. Wagner et al. (2015) found reduced immediate recall of paired visual associations among MDMA users (p=.026; Moderate Users: d_c=-0.21; Heavy Users: d_c=-0.95) compared to controls in a 2-year cohort study [N=96, 66% male, age M=23.0, race N/R].

Ketamine. C. J. A. Morgan et al. (2014) saw reduced performance on a virtual reality spatial memory task (p=.04; d_c=-0.48) among long-term ketamine users compared to matched polydrug controls [N=26, 69% male, age=20–44, race N/R].

Visual Delayed Recall

Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference in visuospatial delayed recall between Navajos who regularly took peyote and Navajos reporting minimal substance use as measured by the ROCFT delayed recall (p=.19; d_c=0.25), and WMS Figures delayed recall (p=.30; d_c=0.18) [N=176, 28% male, age=18–45].

Ayahuasca. Barbosa et al. (2016) found no significant difference (p=.35; $|d_r|$=0.24) in ROCFT delayed recall between U.S. UDV church members who regularly used ayahuasca and matched controls [N=57, 53% male, age=20–67, race N/R].

MDMA. Laws and Kokkalis (2007) found impaired delayed recall in recreational MDMA users compared to controls based on a meta-analysis of 19 studies. While Laws and Kokkalis did not discriminate between the effect of MDMA on delayed verbal and visual memory, the present author estimated the effect size of delayed visual recall to be d=-0.4 using least-squares regression. D. Wagner et al. (2015) also saw poorer delayed recall of paired visual associations among MDMA users (p=.028; Moderate Users:

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d_c=-0.14; Heavy Users: d_c=-1.04) compared to controls in a 2-year cohort study [*N*=96, 66% male, age *M*=23.0, race N/R].

In an RCT, Mithoefer et al. (2011) saw no significant difference in RCFT delayed recall 2 months following MDMA-assisted psychotherapy (p=.35) compared to placebo [*N*=20, 85% female, age *M*=40.4, 100% Caucasian].

Source Memory

Acute.

Ketamine. C. J. A. Morgan, Riccelli, et al. (2004) saw reduced source memory during acute recreational ketamine intoxication (p<.001; approximately 50% reduction relative to chance) compared to polydrug controls [*N*=40, 60% male, age *M*=23.5, race N/R]. C. J. A. Morgan, Mofeez, et al. (2004a) also found poorer source memory discrimination (p<.05) under 0.4 mg/kg and 0.8 mg/kg ketamine infusion [*N*=54, 50% male, age *M*=22.53, race N/R].

Lofwall et al. (2006) found no significant difference in source memory accuracy for a prior-learned word list following 0.2 mg/kg (d_c=0.14) or 0.4 mg/kg (d_c=0.12) ketamine compared to placebo [*N*=18, 44% male, age=18–47, race N/R]. For a word list learned under ketamine, there was a non-significant trend toward worse source memory attribution 1 hour later (0.2 mg/kg: d_c=-0.36, 0.4 mg/kg: d_c=-0.40).

Subacute.

Ketamine. C. J. A. Morgan, Riccelli, et al. (2004) saw reduced source memory performance (p<.001; approximately 16% reduction relative to chance) 3 days following recreational ketamine use compared to polydrug controls [*N*=40, 60% male, age *M*=23.5, race N/R].

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Long-Term.

Ketamine. C. J. A. Morgan et al. (2009) saw impaired source memory attribution among frequent ketamine users (p<.05; d_c=-0.65) compared to polydrug controls [n=120, 71% male, age M=27.5, race N/R]. Infrequent (d_c=-0.15) and ex- (d_c=0.17) ketamine users showed no significant difference compared to polydrug controls.

Prospective Memory

Acute.

MDMA. Ramaekers et al. (2009) found that acute 75 mg MDMA increased prospective memory errors (p=.012; d_c=1.15) compared to placebo controls, as measured by a task requiring participants to provide a specific response to a future event while engaged in another activity [N=12, 75% male, age=19-29, race N/R].

Long-Term.

MDMA. Ward et al. (2007) found a significant correlation (p=.001) between the level of MDMA use and self-reported prospective memory problems as measured by the Prospective Memory Questionnaire–Long-term subscale [N=91, 53% female, age M=24.4, race N/R]. This correlation was not present with participants' frequency of cannabis use (p=.114). Zakzanis and Campbell (2006), on the other hand, found no significant change in prospective memory (d=-0.06) compared to baseline among MDMA users who continued use over the course of the 1-year study period, as measured by the RBMT belonging task [n=7, age M=29.0, sex and age N/R]. Prospective memory also did not change in MDMA users who discontinued use over that same study period (d=1.40) compared to baseline [n=8, age M=19.9, sex and age N/R].

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Parrott et al. (2006) saw a correlation (p=.010-.013) between elevated Prospective Memory Questionnaire (PMQ) scores and frequency of dancing while on MDMA (d_c=0.25, “dancing all the time” vs. “no/occasional dancing”) in a web survey [N=206, 60% male, modal age=16-24, race N/R]. The correlation between PMQ scores and 5-point Likert responses to the question “While on Ecstasy did you generally experience feeling hot/overheating?” was not significant (p=.107). This finding by Parrott et al. indicates that damage to prospective memory may be mediated by physical exertion and/or elevated body temperature while on MDMA.

Executive Functions

General Executive Functioning

Long-Term.

Ayahuasca. Bouso et al. (2012) found fewer executive function deficits (p<.007; d=-0.74) among long-term ritual ayahuasca users compared to matched controls as measured by the self-report Frontal Systems Behavior Scale (FrSBe) [N=242, 48% male, age M=36.9, 52% White, 48% Mestizo]. These improvements in functioning persisted across the three subscales: Apathy/Akinesia (p<.001; d_c=-1.85), Disinhibition/Emotional Dysregulation (p<.046; d_c=-0.74), and Executive Dysfunction (p<.009; d_c=-0.44).

MDMA. Kalechstein et al. (2007) found impaired executive function (p=.001; d=-0.52, SD=0.38) among non-treatment-seeking abstinent MDMA users compared with age, education, and premorbid intellectual functioning matched controls in a meta-analysis that included 11 studies. Zakzanis et al. (2007), on the other hand, found a much smaller impairment in executive functioning among MDMA users (p=.02; d=-0.25; p_Q<.001 ∴ heterogeneous, random-effects model) compared to non-MDMA using

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controls in a meta-analysis of 16 of studies (no control matching criteria). The results of these meta-analyses should be interpreted with caution, as MDMA users were self-selecting, obscuring the causal relationship. Still, the consistency of these results is compelling enough to infer that MDMA is likely a causal factor.

Controlled Verbal Fluency

Acute.

LSD. Barr et al. (1972) saw a significant decrease in controlled verbal fluency (p=.01) under 100 µg LSD compared to baseline and placebo [N=50, 100% male, age=21–43, race N/R, professional actors] (p. 203). The task used to measure verbal fluency was to name as many 3- or 4-letter words as possible in 3 minutes. They also saw no significant change in the number of rhyming words able to be generated in 3 minutes.

Ketamine. Krystal et al. (1994) found a dose-dependent decreases (p=.02) in controlled verbal fluency under 0.1 and 0.5 mg/kg ketamine [N=19, 63% male, age M=24.5, race N/R]. Compared to placebo 0.5 mg/kg ketamine significantly reduced verbal fluency (p=.007; d_c=-0.64) while 0.1 mg/kg ketamine resulted in a reduction that approached significance (p=.06; d_c=-0.21).

Adler et al. (1998) found that ketamine (0.12 mg/kg bolus + 0.65 mg/kg/hr) reduced verbal fluency (p=.017; d_c=-0.88) in comparison to placebo [N=10, 70% male, age M=35.2, race N/R].

Curran and Morgan (2000) found impaired controlled verbal fluency word production (p<.04; d_c=-1.06) during recreational ketamine intoxication [n=20] compared to controls [n=19] who had not used ketamine [59% male, age=18–29, race N/R]. There

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was no significant difference in perseverative error rate with errors close to the floor in both groups.

C. J. A. Morgan, Mofeez, et al. (2004b) saw no significant difference in verbal fluency production with 0.4 mg/kg (p_t=.848; d_c=0.06) or 0.8 mg/kg (p_t=.157; d_c=-0.49) ketamine infusion compared to baseline [*N*=54, 50% male, age *M*=22.53, race N/R]. There was also no significant difference in perseverative error rate with either dose (0.4 mg/kg: p_t=.182, d_c=0.46; 0.8 mg/kg: p_t=.166, d_c=0.48).

Fu et al. (2005) found no significant difference (p=.95) in controlled verbal fluency performance with ketamine (0.23 mg/kg bolus + 0.65 mg/kg/hr) compared to placebo [*N*=10, 100% male, age *M*=26.9, native English-speaking].

Nagels et al. (2011) found a significant decrease (p<.01) in verbal fluency under ketamine (8 mg bolus + 0.01 mg/kg/min) infusion (approx. 32 words produced) compared to placebo (approx. 38 words) [*N*=15, 100% male, age *M*=27, German-speaking, race N/R]. They found no significant difference in rhyming word generation under ketamine compared to placebo.

Subacute.

Ketamine. Curran and Morgan (2000) found some impairment in controlled verbal fluency word production (p<.04; d_c=-0.42) 3 days following ketamine use compared to controls [*N*=39, 59% male, age=18–29, race N/R]. There was no significant difference in perseverative error rate. In contrast, C. J. A. Morgan, Mofeez, et al. (2004b) saw no significant difference in verbal fluency production 3 days following 0.4 mg/kg (p_t=.286; d_c=0.37) and 0.8 mg/kg (p_t=.523; d_c=0.22) ketamine infusion compared to baseline [*N*=54, 50% male, age *M*=22.53, race N/R]. There was an increase in

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perseverative errors that approached significance with 0.4 mg/kg ketamine (p_t=.089; d_c=0.60) but not with 0.8 mg/kg (p_t=.501; d_c=0.23).

Long-Term.

MDMA. Fox et al. (2002) found significantly reduced verbal fluency among MDMA users (p=.03; Δ=-13%) compared to polydrug controls [N=40, 45% male, age=18–48, race N/R].

Ketamine. Curran and Monaghan (2001) saw reduced verbal fluency (p<.001; d_c=-1.40) among 3-day abstinent frequent recreational ketamine users compared to infrequent users [N=37, 76% male, age M=25.5, race N/R]. In a 3- to 4-year follow-up, C. J. A. Morgan, Monaghan, and Curran (2004) found no significant difference in controlled verbal fluency word production (p=.552; d_c=-0.20 to 0.12) or perseverative errors (p=.095; d_c=0.33 to 0.83) among recreational ketamine users [n=18, 22% female, age M=28.1, race N/R] at baseline and follow-up compared to polydrug controls [n=10, 60% female, age M=26.5, race N/R]. However, the original analysis of baseline data by Curran and Morgan (2000) included 11 additional participants that were not available at follow-up. Curran and Morgan's analysis indicated that there was a significant impairment in controlled verbal fluency word production (p<.04; d_c=-0.42) but not perseverative errors. Given that ketamine use at follow-up had reduced 88.3% among the ketamine group, it is likely that reduced controlled verbal fluency word production persists beyond reduction or discontinuation of use.

C. J. A. Morgan et al. (2009) saw no significant difference in verbal fluency between frequent (d_c=0.10), infrequent (d_c=-0.19), or ex- (d_c=0.25) ketamine users compared to polydrug controls [n=120, 71% male, age M=27.5, race N/R].

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C. J. A. Morgan et al. (2010) found that controlled verbal fluency decreased over a 1-year study period in frequent (>4x/wk; p=.046; d_c=-0.64) and ex-ketamine users (p=.023; d_c=-0.44), but not in infrequent ketamine users (p>.05; d_c=0.55) [n=75, 68% male, age M=26.8, race N/R]. There was no significant difference in verbal fluency between frequent (d_c=-0.29), infrequent (d_c=-0.01), or past ketamine users (d_c=-0.01) and polydrug controls at initial measurement [n=90, 69% male, age M=27.9, race N/R].

C. J. A. Morgan et al. (2014) saw no significant difference in verbal fluency (p=.39; d_c=-0.35) among long-term ketamine users compared to polydrug controls.

M. Kim et al. (2016) saw reduced verbal fluency among people treated for CRPS with long-term frequent ketamine (p<.05; d_c=-0.94) compared to CRPS controls with little ketamine treatment [N=30, 66% male, age M=38.0, race N/R].

Category Fluency

Acute.

Ketamine. Adler et al. (1998) found that ketamine (0.12 mg/kg bolus + 0.65 mg/kg/hr) reduced category fluency (p=.006; d_c=-0.81) in comparison to placebo [N=10, 70% male, age M=35.2, race N/R]. Curran and Morgan (2000) also found that category fluency was impaired during recreational ketamine intoxication (p<.001; d_c=-1.33) alongside significantly more perseverative errors occurring (p<.05; d_c=0.49) [N=39, 59% male, age=18–29, race N/R].

C. J. A. Morgan, Mofeez, et al. (2004b) saw a decrease in category fluency production with a 0.8 mg/kg (p_t=.046; d_c=-0.72) ketamine infusion compared to baseline [N=54, 50% male, age M=22.53, race N/R]. There was a significant reduction in

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perseverative error rate under 0.4 mg/kg (p_t=.044; d_c=-0.73) but not at 0.8 mg/kg (p_t=.261; d_c=0.39).

Nagels et al. (2011) found a significant decrease (p<.05) in category fluency under ketamine (approx. 46 words produced) compared to placebo (approx. 56 words) [N=15, 100% male, age M=27, German-speaking, race N/R].

Finally, Murrough et al. (2013) found that acute 0.5 mg/kg ketamine had no significant effect on category fluency (p=.88) compared to baseline [N=25, 40% female, age M=49.0, race N/R].

Subacute.

Ketamine. Curran and Morgan (2000) found that category fluency word production was impaired 3 days following ketamine use (p<.001; d_c=-1.24) with significantly more perseverative errors occurring (p<.05; d_c=0.89) [N=39, 59% male, age=18–29, race N/R]. C. J. A. Morgan, Mofeez, et al. (2004b), on the other hand, found no significant difference in category fluency production 3 days following infusion with 0.4 mg/kg (p_t=.745; d_c=0.11) and 0.8 mg/kg (p_t=.780; d_c=0.09) ketamine compared to baseline [N=54, 50% male, age M=22.53, race N/R]. There was no significant difference in perseverative errors at either dose (0.4 mg/kg: p_t=.309, d_c=-0.35; 0.8 mg/kg: p_t=.535, d_c=-0.21).

Long-Term.

MDMA. M. Morgan et al. (2002) found lower category fluency approaching significance (p=.053) among current and past ecstasy users compared to polydrug controls [N=64, 42% male, age M=23.1, race N/R]. Fox et al. (2002), however, found no

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significant difference in category fluency (p=.59; d_c=-0.16) between MDMA users and polydrug controls [N=40, 45% male, age=18–48, race N/R].

Ketamine. Curran and Monaghan (2001) saw reduced category fluency (p<.05; d_c=-1.18) among 3-day abstinent frequent recreational ketamine users compared to infrequent users [N=37, 76% male, age M=25.5, race N/R].

C. J. A. Morgan, Monaghan, and Curran (2004) found a significant difference in category fluency word production at baseline, but performance among ketamine users increased at follow-up compared to controls. Ketamine users did show increased perseverative errors on a category fluency task at both time points (d_c=0.53 to 0.83), with no significant difference between the time points (p_t=.413; d_c=-0.28). Given that ketamine use was reduced by 88.3% in the ketamine group during this period, it appears that the increase in category fluency perseverative errors may persist beyond the reduction or discontinuation of recreational use while word production may recover.

C. J. A. Morgan et al. (2009) saw no significant difference in category fluency between frequent (d_c=-0.12), infrequent (d_c=-0.58), or ex- (d_c=0.08) ketamine users compared to polydrug controls [n=120, 71% male, age M=27.5, race N/R].

C. J. A. Morgan et al. (2010) found that category fluency significantly increased over a 1-year study period in infrequent ketamine users (<4x/wk; p=.022; d_c=0.74) but not in frequent (p>.05; d_c=-0.34) or ex-ketamine users (p>.05; d_c=0.17) [n=75, 68% male, age M=26.8, race N/R]. There was no significant difference in category fluency between frequent (d_c=0.05), infrequent (d_c=0.26), or past ketamine users (d_c=0.33) and polydrug controls [n=90, 69% male, age M=27.9, race N/R].

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Finally, C. J. A. Morgan et al. (2014) saw no significant difference in category fluency (p=.86; d_c=0.09) among long-term ketamine users compared to polydrug controls.

Cognitive Inhibition

Acute.

Ayahuasca. Bouso et al. (2013) found no change in Stroop interference effect (p>.1; d_c=-0.31) under ayahuasca compared to baseline [N=24, 50% male, age M=46.2, race N/R].

MDMA. Ramaekers and Kuypers (2005) found no significant difference in cognitive inhibition under 75 or 100 mg MDMA compared to placebo [N=18, 50% male, age=20–37, race N/R]. Cognitive inhibition was measured using the Stop-Signal Task commission errors (75 mg: d_c=-0.03; 100 mg: d_c=0.12) and the Go/No-Go Task (75 mg: d_c=0.03; 100 mg: d_c=-0.07).

Kuypers et al. (2007) found no significant difference in cognitive inhibition under 75–125 mg MDMA compared to placebo under conditions of sleep deprivation [N=14, 50% male, age=19–33, race N/R]. Cognitive inhibition was measured using Go/No-Go task errors (d_c=-0.17) and a Discounting task (d_c<0.01).

Schmidt et al. (2017) found no significant change in motor response inhibition as measured by an event-related Go/No-Go fMRI paradigm in healthy subjects administered 125 mg MDMA using a double-blind, placebo-controlled design [N=21, demographics N/R]. This decrease in response inhibition performance contrasted with the increased performance shown with modafinil and methylphenidate.

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Ketamine. Krystal et al. (1994) saw increased CPT commission errors with 0.5 mg/kg ketamine (p=.03; d_c=0.60) compared to placebo [N=19, 63% male, age M=24.5, race N/R]. This trend did not reach significance with 0.1 mg/kg ketamine (d_c=0.17).

Harborne et al. (1996) saw no significant difference in Stroop interference with 10 mg (d_c=-0.27) or 25 mg (d_c=-0.13) IM ketamine [N=12, 75% male, age=25–43, race N/R]. Parwani et al. (2005) also saw no significant difference in Stroop interaction effect from ketamine (0.27 mg/kg bolus + 0.12 mg/kg infusion) compared to placebo [N=13, 38% male, age M=31.9, 69% Caucasian, 31% African American].

Passie et al. (2005) found no significant difference in cognitive inhibition as measured by Go/No-Go task errors during 0.003 mg/min/kg (p=.692; d_c=-0.30) or 0.005 mg/min/kg (p=.669; d_c=0.41), (*S*)-ketamine infusion compared to placebo [N=12, 100% male, age M=26.8, race N/R, medical students].

C. J. A. Morgan, Mofeez, et al. (2004b) saw impaired response inhibition (p<.02) with 0.4 and 0.8 mg/kg ketamine infusion [N=54, 50% male, age M=22.53, race N/R]. Response inhibition was measured using Part B of the Hayling task, which requires that subjects rapidly fill in the blank of a sentence with a word that *does not* fit. Impairment to response inhibition was dose-dependent (p<.01), with the 0.8 mg/kg group averaging approximately 5.8 errors of 15 possible, the 0.4 mg/kg group averaging approximately 2.7 errors, and the placebo group averaging approximately 2.4 errors.

Ibogaine. B. Forsyth et al. (2016) found no significant change in commission errors on a task requiring a response opposite to an arrow direction under a low, non-hallucinogenic ibogaine dose (20 mg) compared to baseline performance [N=21, 100%

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male, age=20–40, race N/R]. They also found no significant differences in response inhibition as measured by the Flanker Task.

Subacute.

MDMA. Pirona and M. J. Morgan (2010) found no significant difference in cognitive inhibition 1- or 4-days following street ecstasy consumption compared to a control group of ecstasy users who did not use ecstasy during the same period [*N*=32, 59% male, age=19–30, race N/R]. Cognitive inhibition was measured by the Matching Familiar Figures test (MFF20).

Taurah et al. (2013) found increased motor impulsivity (p=.001; d=0.41) in active MDMA users compared to polydrug controls, but not ex-MDMA users (p=1.00; d=0.12) [*N*=997, 52% male, age *M*=25.1, 32% White, 27% Asian, 23% Black, 18% Other]. They saw no difference in impulsivity due to non-planning in MDMA users (p=.27; d=-0.22) or ex-MDMA users (p=1.00; d=0.14). Both constructs were measured by the BIS-II.

Huxter et al. (2006) found no significant difference in self-reported impulsivity among people who had used MDMA in the 9 days prior to testing [*n*=20] and control MDMA users [*n*=18] who had not used MDMA in that same period [53% male, age=18–29, race N/R]. Impulsivity was measured using the Adult Impulsiveness, Venturesomeness, and Empathy scale (IVE).

Ketamine. C. J. A. Morgan, Mofeez, et al. (2004b) saw no significant difference in Hayling Task response inhibition 3 days following 0.4 mg/kg and 0.8 mg/kg ketamine infusion compared to placebo controls [*N*=54, 50% male, age *M*=22.53, race N/R].

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Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference (p=.21; d_c=0.25) in Auditory CPT commission errors between Navajos who regularly took peyote and Navajos reporting minimal substance use [N=176, 28% male, age=18–45].

Psilocybin. Erritzoe et al. (2018) saw no significant change (p=.446; d=-0.184) in NEO-PI-R Impulsiveness 3 months following two sessions of psilocybin treatment (10 and 25 mg) for depression [N=19, 68% male, age=27–64, race N/R].

Ayahuasca. Doering-Silveira et al. (2005) found no significant difference in Stroop interference (p=.95) or CPT commission errors (p=.77; d_c=-0.07) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls [N=80, 55% male, age=15–19, 81% White]. Bouso et al. (2012) also found no consistent difference in Stroop interference among long-term ritual ayahuasca users compared to matched controls [N=242, 48% male, age M=36.9, 52% White, 48% Mestizo].

Contrasting these findings, Fernández et al. (2014) saw improved Stroop interference (p=.026) following a 3–9-month program involving ayahuasca ceremonies 1–2 times per week, daily yoga and meditation, and individual therapy compared to baseline [N=13, 62% male, age M=35, race N/R].

Barbosa et al. (2016) found no significant difference in Stroop interference effect (p=.30; $|d_r|$=0.28) or CPT commission errors (p=.90; $|d_r|$=0.03) between U.S. UDV church members who regularly used ayahuasca and matched church-attending controls [N=57, 53% male, age=20–67, race N/R]. They did, however, find a difference approaching significance in impulsivity (p=.081; $|d_r|$=0.49), as measured by the BIS-II.

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MDMA. Parrott et al. (2002) found that 18% of novice ecstasy users (1–9 occasions [x]), 26% of moderate users (10–99x), and 32% of heavy users (≥100x) reported increased "impulsivity" that they attributed to ecstasy use [*N*=282, demographics N/R].

M. Morgan et al. (2002) found decreased cognitive inhibition ($p<.001$) among current and past ecstasy users compared to polydrug controls [*N*=64, 42% male, age *M*=23.1, race N/R]. Cognitive inhibition was measured using the Matching Familiar Figures 20 (MFF20) test. They saw no significant difference in Stroop interference between groups.

Fox et al. (2002) saw no significant difference in Go/No Go commission errors ($p=.45$) between MDMA users and polydrug controls [*N*=40, 45% male, age=18–48, race N/R].

Taurah et al. (2013) found no significant difference in motor impulsivity ($p=1.00$; $d=0.12$) or impulsivity due to non-planning ($p=1.00$; $d=0.14$) among ex-MDMA users compared to polydrug controls and measured by the BIS-II [*N*=997, 52% male, age *M*=25.1, 32% White, 27% Asian, 23% Black, 18% Other].

D. Wagner et al. (2015) found no significant difference in Stroop interference attributable to MDMA use ($p=.981$) in a 2-year cohort study [*N*=96, 66% male, age *M*=23.0, race N/R]. The study compared those who chose to use MDMA moderately (<50 pills; $d_c=0.12$) or heavily (>50 pills; $d_c=-0.42$) during that period to those who chose not to use MDMA [*N*=96, 66% male, age *M*=23.0, race N/R].

Ketamine. C. J. A. Morgan et al. (2009) saw no significant difference in response inhibition in frequent ($d_c=-0.24$), infrequent ($d_c=-0.26$), or ex- ($d_c=0.19$) ketamine users

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compared to polydrug controls and measured using the Hayling test [n=120, 71% male, age M=27.5, race N/R].

M. Kim et al. (2016) saw no significant difference in Stroop interference (p>.05; d_c=-0.52) between people treated for CRPS with long-term frequent ketamine compared to controls with little ketamine treatment [N=30, 66% male, age M=38.0, race N/R].

Cognitive Flexibility

Acute.

LSD. Pokorny et al. (2019) found impaired performance on the computerized Wisconsin Card Sorting Test (WCST) under 100 µg LSD compared to placebo [N=25, 76% male, age=20–40, race N/R]. Under LSD conditions, subjects made significantly more errors (p<.05), though they completed the same number of sets.

Ayahuasca. Dumont et al. (2008) found no difference in performance on the Switch Task under 100 mg MDMA versus placebo control [N=14, 56% male, age=18–29, race N/R]. The Switch Task measures speed in responding to changing instructions presented, thereby measuring cognitive flexibility.

Ketamine. Harborne et al. (1996) saw reduced Trail Making Test Part B (TMT-B) performance (p=.04) with 10 mg (d_c=-0.38) and 25 mg (d_c=-0.66) IM ketamine [N=12, 75% male, age=25–43, race N/R]. C. J. A. Morgan, Mofeez, et al. (2004a) also found slowed TMT-B speed (p<.01) under 0.4 mg/kg and 0.8 mg/kg ketamine infusion [N=54, 50% male, age M=22.53, race N/R].

Krystal et al. (1994) found a dose-dependent increase (p=.03) in perseverative errors on the WCST under 0.1 and 0.5 mg/kg ketamine [N=19, 63% male, age M=24.5, race N/R]. Compared to placebo, 0.5 mg/kg ketamine produced significantly more

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(p<.01; d_c=1.81) perseverative errors, though this trend did not reach significance with 0.1 mg/kg ketamine (p>.05; d_c=0.82).

Krystal et al. (2000) also saw significantly reduced performance (p=.003–.04) on the WCST under acute 0.011 mg/min/kg ketamine compared to when taking the test for a second time under placebo conditions [n=11, 59% male, age M=31.5, 86% White, 9% Black, 5% Hispanic]. However, for participants taking the WCST while on ketamine who had already taken the WCST while not intoxicated, performance did not change significantly. This indicates that acute ketamine does affect cognitive flexibility but does not affect retrieval and execution of previously learned rules.

Ibogaine. B. Forsyth et al. (2016) also found no significant change in performance on a task requiring subjects to respond according to changing rules under a low, non-hallucinogenic ibogaine dose (20 mg) compared to baseline performance [N=21, 100% male, age=20–40, race N/R].

Subacute.

Ayahuasca. Murphy-Beiner and Soar (2020) found a significant increase in self-reported cognitive flexibility (p=.006; d_c=0.26) 1 day following ayahuasca compared to baseline, as measured by the Cognitive Flexibility Scale [N=48, 54% female, age M=38.5, 67% White]. They also found a significant increase in percent correct responses on the WCST. However, the latter result should not be interpreted due to substantial practice effects on the WCST.

Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference in performance on the WCST number of categories completed (p=.77; d_c=0.04) or perseverative errors

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(p=.10; d_c=0.14) between Navajos who regularly took peyote and Navajos reporting minimal substance use [N=176, 28% male, age=18–45]. They also found no significant difference in time on the TMT-B (p=.76; d=0.11).

Psilocybin. In an RCT crossover study, Doss et al. (2021) found that cognitive flexibility was increased 1 and 4 weeks following 20 and 30 mg/70 kg psilocybin sessions (p<.001; $d_{\eta 2}$=1.47) compared to waitlist control [N=24, 33% male, age=24–59, 92% White]. Cognitive flexibility was measured by decreased perseverative errors on the Penn Conditional Exclusion Test (PCET), a test like the WCST but with multiple forms to eliminate practice effects.

Ayahuasca. Doering-Silveira et al. (2005) found no significant difference in TMT-B performance (p=.26, d_c=0.26) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church when compared to matched controls [N=80, 55% male, age=15–19, 81% White]. Barbosa et al. (2016) also found no significant difference in TMT-B (p=.37, $|d_r|$=0.24) between U.S. UDV church members who regularly used ayahuasca and matched church-attending controls [N=57, 53% male, age=20–67, race N/R].

Bouso et al. (2012) found improved performance on the WCST among long-term ritual ayahuasca users compared to matched controls [N=242, 48% male, age M=36.9, 52% White, 48% Mestizo]. Ayahuasca users and controls completed the same number of categories. Ayahuasca users, however, had lower Total Errors (p<.001; d_c=-0.85), Perseverative Errors (p<.001; d_c=-0.82), Non-Perseverative Errors (p=.001; d_c=-0.47), and Failures to Maintain Set (p=.037; d_c=-0.28). While the authors repeated the WCST at

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1-year follow-up, these results were not considered in this review because the WCST has high practice effects.

MDMA. D. Wagner et al. (2015) found no significant change in performance on the TMT-B attributable to MDMA use over a 12-month period (p=.855; Moderate Users: d_c=0.02; Heavy Users: d_c=-0.68) [N=96, 66% male, age M=23.0, race N/R]. M. Morgan et al. (2002), on the other hand, did find reduced performance on the TMT-B (p=.05) among current and past ecstasy users compared to polydrug controls [N=64, 42% male, age M=23.1, race N/R]. Given the large effect size found by Wagner et al. for heavy users, it is likely that TMT-B performance is impacted by MDMA use.

Ketamine. C. J. A. Morgan et al. (2014) saw no significant difference in speed on TMT-B (p=.27; d_c=-0.45) among long-term ketamine users compared to polydrug controls [N=26, 69% male, age=20–44, race N/R]. In addition, the difference between TMT-B and TMT-A, which represents cognitive flexibility adjusted for psychomotor speed, did not differ significantly between the groups (p=.64; d_c=0.20). M. Kim et al. (2016) did see reduced TMT-B speed relative to TMT-A among people treated for CRPS with long-term frequent ketamine (p<.01; d_c=-1.19) compared to CRPS controls with little ketamine treatment [N=30, 66% male, age M=38.0, race N/R].

Planning

Acute.

LSD. Pokorny et al. (2019) found a significant decrease (p<.01) in the use of an efficient search strategy on the Spatial Working Memory task's most complex trial (8 boxes) under 100 μg LSD in an RCT [N=25, 76% male, age=20–40, race N/R]. It should

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be noted that the significant difference between strategy scores is relatively small, approximately 17 for the placebo and 18 for the LSD condition, a likely small effect.

Ayahuasca. Bouso et al. (2013) found slower completion (p=.012) and more moves required (p=.034) on the Tower of London (TOL) among occasional ayahuasca users (8-60 sessions; time: d_c=1.02, moves: d_c=0.52) but not experienced ayahuasca users (>60 ayahuasca sessions; time: d_c=-0.21, moves: d_c=-0.29) under ayahuasca [N=24, 50% male, age M=46.2, race N/R].

MDMA. Lamers et al. (2016) found no change in planning abilities as measured by the TOL for subjects administered 75 mg MDMA in a double-blind, placebo-controlled trial [N=12, 67% male, age=21–30, Dutch, race N/R].

Long-Term.

MDMA. Fox et al. (2002) observed no significant difference in Tower of London performance (p=.14–.59) between MDMA users and polydrug controls [N=40, 45% male, age=18–48, race N/R].

Ketamine. C. J. A. Morgan et al. (2009) measured planning ability in ketamine users and controls on the Stockings of Cambridge task, a task similar to the TOL. They found that frequent ketamine users completed significantly fewer problems in the fewest number of moves (p<.01; d_c=-1.18) compared to polydrug controls [n=120, 71% male, age M=27.5, race N/R]. No significant difference was found between infrequent (d_c=-0.11) and ex- (d_c=-0.43) ketamine users and polydrug controls.

C. J. A. Morgan et al. (2010) saw a trend approaching significance (p=.064) in SOC performance when comparing frequent, infrequent, and past ketamine users to other polydrug users [n=120, 68% male, age M=27.4, race N/R]. In comparison to polydrug

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controls, frequent ketamine users (d_c=-0.61) and ex-ketamine users (d_c=-0.33) trended toward poorer performance, with infrequent ketamine users showing little difference (d_c=-0.09) [n=90, 69% male, age M=27.9, race N/R].

Risk-Based Decision Making

Acute.

LSD. Pokorny et al. (2019) found no significant change in performance on the Cambridge Gambling Task under 100 µg LSD (p<.01) compared to placebo, indicating intact risk-based decision making [N=25, 76% male, age=20–40, race N/R].

MDMA. Ramaekers and Kuypers (2005) found no significant difference in good minus bad decision performance on the Iowa Gambling Task between 75 mg (d_c=0.53) or 100 mg (d_c=0.44) MDMA compared to placebo [N=18, 50% male, age=20–37, race N/R]. However, these effect sizes are large enough to consider that performance may be improved under MDMA, but measurement may require more statistical power.

Visuospatial Organization

Long-Term.

Mescaline. Halpern et al. (2005) found no significant difference in ROCFT copy performance (p=.42; d_c=0.14) between Navajos who regularly took peyote and Navajos reporting minimal substance use [N=176, 28% male, age=18–45].

Ayahuasca. Doering-Silveira et al. (2005) found no significant difference in ROCFT copy performance (p=.23; d_c=0.27) among Brazilian adolescents 15–19 who participated in sanctioned ayahuasca ceremonies through the UDV church compared to demographic-matched controls who had never taken ayahuasca [N=80, 55% male, age=15–19, 81% White]. Barbosa et al. (2016) also found no significant difference

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(p=.75; $|d_r|$=0.08) in ROCFT copy performance between U.S. UDV church members who regularly used ayahuasca and matched church-attending controls [N=57, 53% male, age=20–67, race N/R].

MDMA. Zakzanis et al. (2007) also found no significant difference in perceptual organization among MDMA users (p=.06; d=-0.11; p_Q=0.13 ∴ homogeneous, fixed-effects model) compared to non-MDMA using controls in a meta-analysis of 12 studies (no control matching criteria).

Visual Change Detection

Acute.

LSD. Kornetsky et al. (1957) saw a significant (p<.05) increase in visual discrimination errors under 100 μg LSD but not 50 μg LSD compared to placebo [N=10, 60% male, age=18–23, race N/R].

MDMA. Kuypers and Ramaekers (2007) found no difference in performance on the Change Blindness Task under 75 mg MDMA compared to placebo [N=18, 50% male, age=20–39, race N/R].

Subacute.

MDMA. Kuypers and Ramaekers (2007) found no difference in performance on the Change Blindness Task 1 day following 75 mg MDMA compared to placebo [N=18, 50% male, age=20–39, race N/R].

Verbal Functioning

Semantic Priming

Semantic priming is an increase in target word recognition speed following exposure to a priming word in the same semantic category (Ferrand & New, 2004). The

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time between exposure to the priming word and the target word is a variable called stimulus onset asynchrony (SOA).

Acute.

LSD. Neiloufar et al. (2016) found an increase in semantic priming effects under 40–80 μg LSD compared to placebo as measured using a picture naming task [*N*=10, 90% male, age=26–47, race N/R]. Under LSD, there were significantly more substitution errors where subjects gave semantically similar but inaccurate responses (p=.038). The authors observed that subjects were slow to self-correct these types of errors and hypothesized that this might be due to a decrease in self-monitoring under LSD.

Psilocybin. Spitzer et al. (1996) found a significant increase in priming effects for indirectly related words (p=.026) under 0.2 mg/kg psilocybin [*N*=8, male, age *M*=39.4, physicians, race N/R]. For more closely related words, the priming effect approached but did not reach significance (p=.059). This indicates that there may be an increase in "spreading" semantic activation under psilocybin or an ability to connect semantically distant concepts more rapidly.

Ketamine. C. J. A. Morgan et al. (2006) found an "inverse priming" effect (p=.018) due to ketamine when using a long 750 ms SOA, where response time was faster to target words unrelated to the priming word [*N*=48, age=18–35, English-speakers, race N/R]. With a short 250 ms SOA, the ketamine condition performed similarly to placebo controls with an ordinary priming effect occurring. Ketamine was administered in a low-dose condition (*M*=113.4 ng/mL plasma) and high-dose condition (*M*=236.7 ng/mL).

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Long-Term.

Ketamine. C. J. A. Morgan et al. (2006) also saw inverse priming effects ($p<.008$) under the long 750 ms SOA condition for uncommon words among chronic non-intoxicated ketamine users [N=32, 53% male, age=19–45, race N/R]. This effect was not seen in polydrug user controls, with ketamine users showing significantly less priming than controls under the long SOA ($p<.015$). The authors suggest that chronic ketamine use impairs cognitive controls, resulting in the inverse priming effect while also degrading the semantic store, resulting in the effect being more pronounced for uncommon words.

Proverb Interpretation

Acute.

LSD. Silverstein and Clay (1958) found a significant reduction in proverb interpretation performance ($p<.01$) under 72 μg LSD, with scores decreasing from 19.5 for controls to 13.5 for the drug condition [N=16, male, age=20–24, race N/R]. B. D. Cohen et al. (1962) found no significant difference in proverb interpretation with 1 μg/kg LSD in comparison to baseline [n=10, male, college students, age and race N/R].

Speech Quality

Acute.

LSD. Amarel and Cheek (1965) found a significant reduction ($p<.01$) in the communicative value of speech under LSD (100 μg: d_c=-0.47; 200 μg: d_c=-0.57) compared to pre- and post-drug baseline and measured using the cloze procedure [N=10, male, age=29–63, alcoholic, race N/R]. The cloze procedure (W. L. Taylor, 1953) analyzes transcripts of spontaneous speech by deleting every fifth word and then asking

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independent raters to fill in the missing words that best fit the context. The ratio of correctly guessed words by raters then serves as a measure of verbal predictability or "communicative value." Honigfeld (1965) also found a significant reduction (p<.001) in cloze method communicative value under LSD relative to baseline and epinephrine placebo [N=10, male, age and race N/R].

MDMA. Marrone et al. (2009) found no significant difference in speech coherence under 100 mg MDMA compared to placebo [N=11, 18% female, age=23–39, 36% White, 27% Black, 27% Hispanic, and 9% Asian]. Coherence was rated by 40 native English speakers on a 7-point Likert scale.

Ketamine. C. He (2004) found through computer-aided speech analysis that ketamine decreased the percentage of verbs used in speech (p<.003) while increasing the percentage of nouns (p<.037) [N=10; gender, age, race N/R]. Ketamine also increased the use of filler words (p<.011) and irregularities in the articulation of vowels (p<.013).

Covington et al. (2007) saw an increase in repetitiousness (p=.04; d_c=0.80), a decrease in verb usage (p=.03; d_c=-1.00), and no significant difference in idea density (p=.33; d_c=-0.49) during under ketamine (0.40 mg/kg bolus + 0.21 mg/kg/hr) compared to placebo [N=9, 100% male, age M=29.7, race N/R].

Convergent and Divergent Thinking

Acute.

Ayahuasca. Kuypers et al. (2016) found a decrease in convergent thinking performance (p=.017; d_c=-0.47) and no significant change in divergent thinking during ayahuasca as compared with baseline [N=26, 65% female, age M=43.6, 100% White]. Convergent thinking was measured using the Picture Concept Task (PCT) stimuli from

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the WPPSI and WISC and asked to identify the correct association between one of the pictures in each row with one correct solution. Divergent thinking was measured first by asking participants to provide as many alternative associations as possible with PCT stimuli. In addition, divergent thinking was measured using the Pattern/Line Meanings Task, which requires subjects to make meaning of patterns and lines and generate as many explanations as possible for the visual stimuli.

Subacute.

Ayahuasca. Uthaug et al. (2018) found no significant change in convergent and divergent thinking 1 day following ayahuasca, as measured by the PCT [*n*=56, 37% male, 53% Dutch, 47% Colombian, age and race N/R].

Long-Term.

Ayahuasca. Uthaug et al. (2018) found a significant increase in convergent thinking performance 4 weeks following ayahuasca administration, as measured by the PCT [*n*=31, 37% male, 53% Dutch, 47% Colombian, age and race N/R]. This increase was from a mean of approximately 9 correct at baseline to 12 correct at 4-week follow-up, demonstrating that this is likely to be a small effect. They found no significant changes in divergent thinking both immediately following ayahuasca administration and at 4 weeks following.

Color Naming Speed

Acute.

LSD. Abramson et al. (1955b) saw a significant decrease in color naming speed with 100 μg (*p*=.02) but not 50 μg LSD, compared to baseline [*N*=12, 50% male, age=21–33, race N/R].

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Ketamine. Parwani et al. (2005) found that ketamine (0.27 mg/kg bolus + 0.12 mg/kg infusion) slowed Stroop color naming speed (p<.01; d_c=0.21–0.64) compared to placebo [N=13, 38% male, age M=31.9, 69% Caucasian, 31% African American].

Subacute.

LSD. Abramson et al. (1955b) saw faster color naming speed (p=.05) approximately a week following a series of 50 μg and 100 μg LSD sessions compared to baseline [n=8, 25%–75% male, age=21–33, race N/R].

Word Reading Speed

Acute.

LSD. Abramson et al. (1955b) saw a significant decrease in rapid word naming speed with 100 μg (p<.01) and 50 μg (p=.02) LSD compared to baseline [N=12, 50% male, age=21–33, race N/R].

Long-Term.

Ayahuasca. Bouso et al. (2012) found increased Stroop word reading speed (p<.004; d_c=0.57) among long-term ritual ayahuasca users compared to matched controls [N=242, 48% male, age M=36.9, 52% White, 48% Mestizo].

D. Wagner et al. (2015) found no significant change in Stroop word reading (p=.908; Moderate Users: d_c=-0.24; Heavy Users: d_c=-0.13) attributable to MDMA use (p=.256–.908) in a 2-year cohort study [N=96, 66% male, age M=23.0, race N/R].

Comprehension Speed

Acute.

Ketamine. Curran and Morgan (2000) found significantly slower comprehension speed (p<.001; d_c=-1.89) during recreational ketamine intoxication compared to controls

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[*N*=39, 59% male, age=18–29, race N/R]. There was also an increase in errors in the ketamine group compared to controls (p=.01; d_c=0.77).

C. J. A. Morgan, Mofeez, et al. (2004a) found slowed semantic processing speed (p<.001) based on a sentence completion task under 0.4 mg/kg and 0.8 mg/kg ketamine infusion [*N*=54, 50% male, age *M*=22.53, race N/R].

Subacute.

Ketamine. Curran and Morgan (2000) found significantly slower comprehension speed (p<.009; d_c=-0.87) during recreational ketamine intoxication compared to controls [*N*=39, 59% male, age=18–29, race N/R]. There was also an increase in errors in the ketamine group compared to controls (p=.01; d_c=0.45).

Long-Term.

Ketamine. Curran and Monaghan (2001) saw slowed comprehension speed that approached significance (p=.086; d_c=-0.51) among 3-day abstinent frequent recreational ketamine users compared to infrequent users [*N*=37, 76% male, age *M*=25.5, race N/R].

Psychomotor Functioning

Acute.

LSD. Abramson, Jarvik, and Hirsch (1955a) saw no significant change (p>.05) in Pursuit Rotor performance with 50 or 100 μg LSD compared to placebo [*N*=12, 50% male, age=21–33]. However, there was a trend toward increased performance with 100 μg LSD under the faster 78 rpm rotor condition but not 33 1/3 rpm. They also found no significant difference in hand steadiness (p>.05) with either dose compared to placebo, though there was a trend toward less steadiness with increasing dose.

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Abramson, Jarvik, and Hirsch (1955b) saw reaction time to auditory stimuli slow (p<.05) with 100 μg LSD but not 50 μg, compared to baseline [n=11, 45 or 55% male, age=21–33, race N/R]. There was no significant effect of either LSD dose on reaction time to visual stimuli.

Kornetsky et al. (1957) saw no significant change in digit copying speed under 50 or 100 μg LSD compared to placebo [N=10, 60% male, age=18–23, race N/R]. LSD also did not impact Pursuit Rotor performance.

Rosenbaum et al. (1959) found no significant change in auditory-motor reaction time or pain-motor reaction time under 1 μg/kg LSD [n=10, healthy, demographics N/R]. They did find a significant improvement (p<.01) in performance on the Pursuit Rotor task under LSD, along with a corresponding acceleration of motor learning.

Psilocybin. Two studies found that handwriting area increases under psilocybin with area proportional to the intensity of the drug experience (R. Fischer et al., 1969; Panton & Fischer, 1973).

Gouzoulis-Mayfrank et al. (2002) found that psychomotor reaction time to visual cues was longer under psilocybin versus placebo as measured by the covert orienting of attention task [n=16, 66% male, age=27–47, professionals, race N/R].

F. S. Barrett et al. (2018) found a significant reduction in motor speed and accuracy in healthy adults compared to placebo as measured by the Motor Praxis test (Gur et al., 2001) under 20 mg/70 kg and 30 mg/70 kg (p<.05) psilocybin, but not 10 mg/70 kg psilocybin [N=20, 55% female, age=22–43, race N/R]. This effect was seen both in the circular lights and balance tasks of the Motor Praxis test.

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MDMA. Kuypers et al. (2007) found impaired performance (p=.025; d_c=-1.40) on the Critical Tracking Task with 75–125 mg MDMA compared to placebo under conditions of sleep deprivation [N=14, 50% male, age=19–33, race N/R].

Lamers et al. (2016), on the other hand, saw a 5.6%–13.7% increase on the Critical Tracking Test (p=.03) for subjects administered 75 mg MDMA in a double-blind, placebo-controlled trial [N=12, 67% male, age=21–30, Dutch, race N/R]. They also found slowed psychomotor speed (p=.01) as measured by The Motor Choice Reaction Time test. Finally, they found a significant decrease (p=.02) in object movement estimation performance from a divided Attention task. They linked this decreased performance to impaired time estimation, as the OMEDA requires subjects to estimate the position of a moving target after it has been concealed behind another object.

Ketamine. Krystal et al. (1994) saw no significant difference in CPT reaction time with 0.1 or 0.5 mg/kg ketamine compared to placebo [N=19, 63% male, age M=24.5, race N/R].

Harborne et al. (1996) saw no significant change in 4-Choice Reaction Time ($p\geq$.15) under 10 mg (d_c=-0.24 to -0.28) or 25 mg (d_c=-0.31 to 0.22) IM ketamine [N=12, 75% male, age=25–43, race N/R]. They did see a reduction in tactile letter perception approaching significance (p=.08) with both the 10 mg (d_c=-0.81) and the 25 mg (d_c=-0.85) doses.

Guillermain et al. (2001) found that 0.5 mg/kg IV ketamine slowed two-choice visual reaction time by 8.6% (p=.006) compared to placebo [N=8, age=22–33, 50% male, race N/R].

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Passie et al. (2005) found significantly slowed response speed on a pattern recognition test with low-dose 0.003 mg/min/kg (p=.047; d_c=-0.57) and high-dose 0.005 mg/min/kg (p=.016; d_c=-0.98) (*S*)-ketamine infusions compared to placebo [N=12, 100% male, age M=26.8, race N/R, medical students].

Parwani et al. (2005) found that ketamine (0.27 mg/kg bolus + 0.12 mg/kg infusion) slowed reaction time at 3 minutes (p<.001; d_c=-0.53 to -1.09) and 35 minutes (p<.03; d_c=-1.15 to 0.22) post-infusion compared to placebo [N=13, 38% male, age M=31.9, 69% Caucasian, 31% African American]. No significant effect on reaction time was seen at 75 minutes post-infusion (d_c=-0.33 to 0.66).

Micallef et al. (2002) found slower psychomotor reaction time (p<.001) under 0.5 mg/kg ketamine compared to placebo [N=8, 50% male, age=22–33, race N/R]. Passie et al. (2005) found no significant difference in psychomotor reaction time during low-dose, 0.003 mg/min/kg (p=.508; d_c=-0.39[6]), or high-dose, 0.005 mg/min/kg (p=.697; d_c=0.23), IV (*S*)-ketamine compared to placebo [N=12, 100% male, age M=26.8, race N/R, medical students].

Ibogaine. B. Forsyth et al. (2016) found no significant effect on psychomotor response time under a low, non-hallucinogenic ibogaine dose (20 mg) compared to baseline [N=21, 100% male, age=20–40, race N/R].

Subacute.

LSD. Abramson et al. (1955b) saw faster reaction time to auditory and visual stimuli (p≤0.02) approximately a week following a series of 50 µg and 100 µg LSD

[6] Negative effect size indicates faster reaction time, i.e. better performance.

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sessions compared to baseline [*n*=8, 25%–75% male, age=21–33, race N/R]. The magnitude of this effect was approximately 15%– 25% based on estimation from the printed graph.

Long-Term.

LSD. Matefy et al. (1979) measured auditory-motor reaction time among demographic-matched [52% male, age and race N/R] sets of psychedelic users experiencing flashbacks [*n*=29], psychedelic users not experiencing flashbacks [*n*=25], and non-psychedelic-user controls [*n*=23]. The psychedelic used was most likely LSD, as this is the drug referenced in the article, but it was not specified in the methodology. Matefy et al. found that psychedelic-users with flashbacks did not differ in reaction times from non-psychedelic users. However, both groups of psychedelic-users had faster reaction times (*M*=191 ms) than non-psychedelic-user controls (*M*=218 ms). This difference was statistically significant to $p < .05$ for most trials, and while the data was not available to compute the statistical significance of overall means, it is likely that this difference holds the same or better significance.

Psilocybin. Stamets (2021) presented new research finding that in people over 55, microdosing psilocybin [*n*=90] is associated with significantly higher finger tapping speed (*p*=.041) compared to age-matched controls [*n*=28]. This was not seen in people under 55 microdosing psilocybin [*n*=712] compared to controls [*n*=134].

MDMA. Kalechstein et al. (2007) found diminished psychomotor speed (*p*=.001; *d*=-0.55) among non-treatment-seeking abstinent MDMA users compared with age-, education-, and premorbid intellectual functioning- matched controls in a meta-analysis that included 11 studies. Zakzanis et al. (2007) found no significant difference in motor

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skill among MDMA users (p=.23; d=0.16; p_Q=0.11 ∴ homogeneous, fixed-effects model) compared to non-MDMA using controls in a meta-analysis of 2 studies (no control matching criteria). The results of both these meta-analyses should be interpreted with caution, as MDMA users were self-selecting, obscuring the causal relationship.

Synthesis of Neurocognitive Effects

Classical Psychedelics. During acute intoxication, classical psychedelics tend to impair attention, working memory, and executive functions while slowing processing speed. This results in lowered intellectual functioning, likely due to difficulty expressing knowledge rather than actual decreases in ability. Memory is also impaired while semantic priming effects increase. Reaction speed and hand steadiness decrease, though there are differences in how motor coordination is affected. While motor coordination is impaired with psilocybin, it may be improved with LSD, though findings are mixed.

There was less research on the neurocognitive effects in the days following classical psychedelic use. In the studies found regarding psilocybin, no difference in working memory, sustained attention, or memory encoding was seen compared to baseline. Subacute increases in cognitive flexibility are seen with ayahuasca. With LSD, faster reaction time and color naming speed are seen.

Long-term, classical psychedelics tend to have minimal neurocognitive impacts, with some exceptions. Sustained improvements in cognitive flexibility have been shown with psilocybin. Reaction time is improved with LSD, and finger tapping speed is improved in people over 55 who microdose psilocybin. Ayahuasca may actually improve working memory, executive functions, and word reading speed, though it can worsen memory and learning performance.

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MDMA. Acutely, MDMA tends to impair memory and more complex attention, but sustained attention is increased, possibly due to its stimulant effects. It does not appear to significantly impact other executive functions. Some studies find decreased processing speed and reaction speed, and findings regarding motor coordination are mixed. Subacutely, MDMA impairs attention and possibly memory.

With chronic recreational use, MDMA can severely impact neurocognitive functioning, with reductions in verbal intelligence, processing speed, working memory, attention, memory, executive functions, and reaction speed. Only one study has examined the neurocognitive impact of clinical MDMA therapy. No significant impacts were seen on objective measures 2 months later. Subjectively, 17 to 74 months later (M=45.4), none of these participants felt their neurocognitive functioning had declined, while 68% felt it had improved. This shows that pharmaceutical-grade MDMA, with appropriate dosing and a limited number of sessions, may have a negligible neurocognitive impact. However, more research is needed in this area.

Ketamine. During ketamine intoxication, processing speed, working memory, attention, memory, executive functions, and psychomotor reaction speed are all impaired. In the days following, verbal learning and delayed recall are reduced, as is verbal fluency and comprehension speed.

With long-term ketamine use, processing speed, working memory, attention, and executive functions can be negatively impacted. This has been found with both recreational and clinical ketamine use. Chronic recreational ketamine use is also associated with impaired verbal and visual memory, but no clinical studies were found regarding this domain of functioning.

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Ibogaine. Only one study was found investigating the neurocognitive effects of ibogaine. The study found no acute effects in the domains measured. However, the dose tested was quite low compared to what is used therapeutically.

Summary and Comparison

Acute and subacute neuropsychological effects of psychedelics are compiled into Summary Table 10, while long-term effects are in Summary Table 11. The symbols used in both tables are as follows:

↑	Statistically significant increase
↓	Statistically significant decrease
∅	No significant change
$\varnothing^{\uparrow}$	No significant change, but a directional trend
[2]	The number of references that demonstrate a finding. If not shown, only one study is referenced.
-	No research found

Effect size is designated using the following conventions:

	Small or Tiny effect size [no asterisk] ($d \leq 0.2$)
*	Moderate effect size ($d = 0.21–0.5$)
**	Large effect size ($d > 0.5$)
***	Very Large effect size ($d > 1.0$)

Summary Table 10

Acute and Subacute Neuropsychological Effects of Psychedelics

Neuropsychological Domain	LSD Acute	LSD SA	Psilocybin Acute	Psil. SA	Ayahuasca Acute	Aya. SA	MDMA Acute	MDMA SA	Ketamine Acute	Ket. SA	Ibogaine Acute
Intellectual Functioning											
Fluid/General Intelligence	↓**	-	-	-	-	-	-	-	-	-	-
Verbal	↓**[2]	-	-	-	-	-	∅	∅	-	-	-
Visuospatial	↓** / ↓*	-	-	-	-	-	-	-	-	-	-
Processing Speed	↓	-	↓	-	↓*	-	∅ / ↓	∅	↓**[5]	∅	-
Verbal Working Memory	∅[3] / ↓	-	-	-	↓**	-	-	-	↓[3] / ∅	-	-
Visual Working Memory	↓	-	∅[2]	∅	-	-	-	-	↓	-	∅[a]
Attention											
Sustained Attention	-	-		∅	-	-	↑***	-	↓***[2] / ∅[2]	-	∅[a]
Divided Attention	-	-	↓	-	-	-	∅ / ↓***	-	↓***	-	-
Focused Attention	↓[2]	-	↓	-	-	-	∅	∅	↓***[4]	∅	-
Visual Search	↓[2] / ↑	-	-	-	-	-	↓***	↓	↓*	-	-
Self-rated Attention/ Concentration	-	-	-	-	-	-	↓	↓***[2]	-	-	-

Summary Table 10

Acute and Subacute Neuropsychological Effects of Psychedelics, Continued

Neuropsychological Domain	LSD Acute	LSD SA	Psilocybin Acute	Psil. SA	Ayahuasca Acute	Aya. SA	MDMA Acute	MDMA SA	Ketamine Acute	Ket. SA	Ibogaine Acute
Memory and Learning											
General	-	-	-	-	-	-	-	$\downarrow^{***SR}$	-	-	-
Verbal											
Encoding	-	-	∅	∅	-	-	$\varnothing^{\uparrow***}$	-	$\downarrow^{**[2]}$ / $\downarrow^{[3]}$	-	-
Learning & Recall	$\downarrow^{[2]}$	-	$\downarrow$	-	-	-	$\downarrow^{***}$ / $\downarrow^{**}$ / $\downarrow$ / ∅	$\varnothing^{[2]}$ / $\downarrow$	$\downarrow^{***}$ / $\downarrow^{[2]}$ / $\varnothing^{[2]}$	$\downarrow^{**}$	-
Delayed Recall	-	-	-	-	-	-	$\downarrow^{***}$ / $\downarrow$ / ∅	$\varnothing^{[2]}$	$\downarrow^{**[2]}$ / $\downarrow^{[4]}$ / ∅	$\downarrow^{***}$	-
Visual											
Encoding	∅	-	-	-	-	-	$\downarrow^{**}$	-	-	-	-
Immediate Recall	$\downarrow^{**}$ / $\downarrow^{[2]}$	-	$\downarrow$	-	-	-	$\downarrow$	∅	$\downarrow^{**}$ / ∅	-	-
Source Memory	-	-	-	-	-	-	-	-	$\downarrow^{[2]}$ / $\varnothing^{\downarrow*}$	$\downarrow$	-
Prospective Memory	-	-	-	-	-	-	$\downarrow^{***}$	-	-	-	-
Executive Functions											
Controlled VF	$\downarrow$	-	-	-	-	-	-	-	$\downarrow^{**[4]}$ / $\varnothing^{\downarrow*}$ / ∅	$\downarrow^{*}$ / ∅	-
Category Fluency	-	-	-	-	-	-	-	-	$\downarrow$ / $\downarrow^{**}$ / $\downarrow^{***}$ / ∅	$\downarrow^{***}$ / ∅	-
Cognitive Inhibition	-	-	-	-	∅	-	$\varnothing^{[3]}$	$\downarrow^{*}$ / $\varnothing^{[2]}$	$\downarrow^{**[2]}$ / $\varnothing^{\downarrow*[3]}$	∅	$\varnothing^{a}$
Cognitive Flexibility	$\downarrow$	-	-	-	∅	$\uparrow^{*}$	-	-	$\downarrow^{**[2]}$ / $\downarrow^{***}$ / $\downarrow$	-	$\varnothing^{a}$
Planning	$\downarrow$	-	-	-	$\downarrow^{**}$ / $\varnothing^{b}$	-	∅	∅	-	-	-
Risk-Based Decision-Making	∅	-	-	-	-	-	$\varnothing^{\uparrow**}$	-	-	-	-
Visual change detection	$\downarrow$	-	-	-	-	-	∅	∅	-	-	-

Summary Table 10

Acute and Subacute Neuropsychological Effects of Psychedelics, Continued

Neuropsychological Domain	LSD Acute	LSD SA	Psilocybin Acute	Psil. SA	Ayahuasca Acute	Aya. SA	MDMA Acute	MDMA SA	Ketamine Acute	Ket. SA	Ibogaine Acute
Verbal Functioning											
Semantic Priming	↑	-	↑	-	-	-	-	-	↵[c]	-	-
Proverb Interpretation	↓ / ∅	-	-	-	-	-	-	-	-	-	-
Speech Quality	↓** / ↓	-	-	-	-	-	∅	-	↓[2]	-	-
Convergent Thinking	-	-	-	-	↓*	∅	-	-	-	-	-
Divergent Thinking	-	-	-	-	∅	∅	-	-	-	-	-
Color Naming Speed	↓	↑	-	-	-	-	-	-	↓*	-	-
Word Reading Speed	↓	-	-	-	-	-	-	-	-	-	-
Comprehension Speed	-	-	-	-	-	-	-	-	↓*** / ↓	↓**	-
Psychomotor Functioning											
Reaction Speed	↓ / ∅	↑	↓	-	-	-	↓	-	↓**[2] / ↓[2] / ∅[3]	-	∅[a]
Motor Coordination/ Tracking	∅ / ∅↑ / ↑	-	↓	-	-	-	↓*** / ↑	-	-	-	-
Hand Steadiness	∅↓	-	↓	-	-	-	-	-	-	-	-

Note. Symbol key on page 337. SA = subacute, measured less than 4 weeks following administration, typically less than one week; VF = verbal fluency; [SR] = self-report.

[a] Non-hallucinogenic ibogaine dose (20 mg).

[b] No acute effect on planning was seen among experienced ayahuasca users (>60 sessions).

[c] Inverse priming effect observed.

Summary Table 11

Long-Term Neuropsychological Effects of Psychedelics

Neuropsychological Domain	Mescaline Tx	LSD Tx	Psilocybin Tx	Ayahuasca Tx	Ayahuasca Ritual	MDMA Tx	MDMA Chronic	Ketamine Tx	Ketamine Chronic
Overall Neuropsychological Functioning									
RBANS Total Score	-	-	-	-	-	∅	-	-	-
Intellectual Functioning									
Fluid/General Intelligence	∅	-	-	-	-	-	∅	-	-
Verbal	-	-	-	-	∅	-	↓*[9]	-	-
Visuospatial	∅	-	-	-	∅	-	∅↓	-	-
Processing speed	∅	-	-	-	∅[3]	-	↓*[16] / ∅	↓***	↓*** / ∅↓
Verbal Working Memory	∅	-	-	-	↑* / ∅	-	∅↓*	↓**	
Visual Working Memory	-	-	∅	-	-	-	↓*	-	↓**[2]
Attention									
Overall Attention	-	-	-	-	-	-	↓*[11]	-	-
Sustained Attention	∅	-	∅	-	∅[2]	-	-	-	-
Focused Attention	-	-	-	-	∅	∅	∅	∅[2] / ↓**	-
Visual Search	-	-	-	-	-	-	-	-	↓**
Self-Rated Attention/ Concentration	-	-	-	-	↓*	-	↓***[2]	-	-

Summary Table 11

Long-Term Neuropsychological Effects of Psychedelics, Continued

Neuropsychological Domain	Mescaline Tx	LSD Tx	Psilocybin Tx	Ayahuasca Tx	Ayahuasca Ritual	MDMA Tx	MDMA Chronic	Ketamine Tx	Ketamine Chronic
Memory and Learning									
General	-	-	-	-	-	-	$\downarrow^{**[11,21]}$ / $\downarrow^{SR}$ / $\varnothing^{SR}$	-	-
Verbal									
Encoding	-	-	$\varnothing$	-	$\varnothing^{[2]}$	-	-	-	-
Learning & Recall	-	-	-	-	$\downarrow^{**[2]}$ / $\varnothing$	-	$\downarrow^{**[22]}$ / $\varnothing$	-	$\downarrow^{[2]}$ / $\varnothing^{[2]}$ / $\varnothing^{\downarrow *}$
Delayed Recall	-	-	-	-	$\varnothing^{[3]}$	-	$\downarrow^{***[19]}$ / $\varnothing^{\downarrow **}$	-	$\downarrow^{***}$ / $\downarrow$ / $\varnothing^{\downarrow *[2]}$ / $\varnothing$
Visual									
Encoding	-	-	-	-	$\varnothing$	-	$\varnothing^{\downarrow *}$	-	-
Immediate recall	$\varnothing$	-	-	$\varnothing^{[2]}$	-	-	$\downarrow^{*[12]}$ / $\downarrow^{[14]}$ / $\downarrow^{***}$	-	$\downarrow^{*}$
Delayed recall	$\varnothing$	-	-	$\varnothing$	-	$\varnothing$	$\downarrow^{*[19]}$ / $\downarrow^{***}$	-	-
Source memory	-	-	-	-	-	-	$\downarrow^{**}$	-	-
Prospective memory	-	-	-	-	-	-	$\downarrow^{[2]}$ / $\varnothing$	-	-
Executive Functions									
General	-	-	-	-	$\uparrow^{**}$	-	$\downarrow^{*[16]}$ / $\downarrow^{**[11]}$	-	-
Controlled Verbal Fluency	-	-	-	-	-	-	$\downarrow$	$\downarrow^{**}$	$\downarrow^{*}$ / $\downarrow^{***}$ / $\varnothing^{\downarrow *}$ / $\varnothing$
Category Fluency	-	-	-	-	-	-	$\downarrow$ / $\varnothing$	-	$\varnothing^{[4]}$ / $\downarrow^{***}$
Cognitive Inhibition	$\varnothing$	-	$\varnothing$	-	$\varnothing^{[3]}$ / $\uparrow$	-	$\varnothing^{[4]}$ / $\downarrow^{[2]}$	$\varnothing^{\downarrow **}$	$\varnothing^{\downarrow *}$
Cognitive Flexibility	$\varnothing$	-	$\uparrow^{***}$	-	$\varnothing^{[2]}$ / $\uparrow^{**}$	-	$\varnothing$ / $\downarrow^{**}$	$\downarrow^{***}$	$\varnothing^{\downarrow *}$
Planning	-	-	-	-	-	-	$\varnothing$	-	$\downarrow^{***}$ / $\varnothing^{\downarrow **}$
Visuospatial Organization	$\varnothing$	-	-	-	$\varnothing^{[2]}$	-	$\varnothing^{[12]}$	-	-

Summary Table 11

Long-Term Neuropsychological Effects of Psychedelics, Continued

Neuropsychological Domain	Mescaline Tx	LSD Tx	Psilocybin Tx	Ayahuasca Tx	Ayahuasca Ritual	MDMA Tx	MDMA Chronic	Ketamine Tx	Ketamine Chronic
Verbal Functioning									
Semantic Priming	-	-	-	-	-	-	-	-	↵[b]
Convergent Thinking	-	-	-	↑	-	-	-	-	-
Divergent Thinking	-	-	-	∅	-	-	-	-	-
Word Reading Speed	-	-	-	-	↑** / ∅	-	-	-	-
Comprehension Speed	-	-	-	-	-	-	-	-	↓**
Psychomotor Functioning									
Reaction Speed	-	↑	-	-	-	-	↓**[11]	-	-
Motor Coordination/Skill	-	-	-	-	-	-	∅[2]	-	-
Finger Tapping	-	-	↑[a]	-	-	-	-	-	-

Note. Symbol key on page 337. Long-term effects are persistent for ≥ 4 weeks. No research was found for long-term DMT or ibogaine effects. Tx = effects of clinical session(s); Ritual = ongoing, ritualistic use; Chronic = ongoing, long-term recreational use.

[a] Increased finger tapping speed was found among people over 55 microdosing psilocybin, but not people under 55.

[b] Inverse priming effect observed.

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Chapter 9: Psychological Risks

This chapter outlines the acute and long-term psychological risks posed by psychedelics. First, a general overview of the psychological risks of using psychedelics is provided. Following this overview, specific risks posed by psychedelics are described. If no sub-section is provided for a psychedelic under a psychological risk (e.g., psilocybin and depression), then there was no research found indicating a risk association for that combination, and there may indeed be research demonstrating a lack of associated risk. Studies indicating lack of risk, however, are only reported in the "General" section or if there are mixed findings regarding a specific psychedelic-associated risk.

General

In general, psychedelics studied have a low risk of causing or exacerbating mental health conditions, with some notable exceptions. Two very large population studies [*N*=130,152 and *N*=135,095] found no association between lifetime use of any psychedelic [*n*=21,967 and *n*=19,299] and increased rate of negative mental health symptoms or outcomes (Johansen & Krebs, 2015; Krebs & Johansen, 2013). Lifetime mescaline, LSD, and psilocybin use, as well as past-year LSD use, were associated with equal or lower risk of negative mental health outcomes, with one exception (see mescaline and depression below).

Classical Psychedelics. Aday, Mitzkovitz, et al. (2020) performed a systematic review of the long-term effects of classical psychedelic drugs, including mescaline, LSD, psilocybin, DMT, and ayahuasca. Among these 34 modern studies with follow-up periods of more than 2 weeks, they found few reports of long-term adverse effects. Aday,

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Mitzkovitz, et al. did note that acute fear and anxiety reactions were common during the psychedelic experiences.

Psilocybin. Ross et al. (2016) report that no serious long-term adverse effects had occurred among the 2,000 people who had participated in modern psilocybin trials at the time of publication. While there were no cases of prolonged psychosis or hallucinogen-persisting perceptual disorder (HPPD), there were cases involving transient psychosis-like symptoms and anxiety. This is not to imply that psilocybin experience is psychologically easy (see "Negative and Challenging Experiences" below), but that lasting psychological harm is rare.

MDMA. Parrott (2014) cautions against using MDMA with "psychiatrically vulnerable individuals" based on cases reported by Greer and Tolbert (1986) and a statement by Doblin (2002) directing research away from "…patients whose psychiatric symptoms originated with biological imbalances with possible genetic components…" (p. 39). The specific cases that Parrott references from Greer and Tolbert are not completely clear, but two stand out as distinct possibilities. The first was a patient (No. 19) with pre-existing difficulties coping with work and crippling anxiety, which appeared to be exacerbated by MDMA sessions. The second was a 74-year-old who experienced severe physiological side effects during and in the days following MDMA. She had been given a high dose of MDMA (350 mg total) due to not responding to lower doses. More clarity is needed in understanding what conditions may be exacerbated by MDMA therapy.

In contrast to Parrott's perspective, Ann Shulgin (1995) comments on the period where MDMA was legal and used by many therapists, writing that:

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> MDMA became a favorite tool of psychotherapists, because it can be given safely to people who are too emotionally fragile to benefit from any of the psychedelics. There is no loss of control with MDMA, and it produces none of the dramatic visual changes associated with psychedelics, effects which can be disturbing and do not necessarily contribute to the quality of the inner experience. (p. 3)

In this statement, Shulgin describes the possibility of using MDMA therapeutically in patients that would respond poorly to other psychedelics. This aligns with MDMA's demonstrated safety and effectiveness in treating PTSD (see Chapter 12).

In terms of MDMA pathogenesis, Soar et al. (2001) reviewed the 38 cases of psychiatric disorders following recreational MDMA/ecstasy use over the past 10 years. They concluded that the literature "strongly suggest[s] a causal relationship between the drug and neuro-psychiatric manifestations" since only 24% of cases had a previous psychiatric history and only 34% had psychiatric illness among first-degree relatives (p. 641). However, given that the cases reviewed were from recreational use, it is difficult to extend these findings to clinical MDMA, where safe dose and drug purity are ensured.

Ketamine. In a review of clinical investigations into treating physiologically healthy non-psychotic subjects [N=450] using IV ketamine, the authors found ten "adverse mental status events" following ketamine infusion (Perry et al., 2007). Of these adverse events, all but one were resolved by the end of the ketamine session, with the nightmares, insomnia, and concentration deficits reported resolved after 4 days. The remaining adverse events involved sensory discomfort [n=5], verbal non-responsiveness [n=3], and tearfulness with no other symptoms [n=1]. All subjects were medically stable throughout.

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Negative and Challenging Experiences

Challenging psychedelic experiences or ‘bad trips’ do occasionally occur. There is evidence that the high incidence of bad trips reported in the mid-1960s through 1975 may be attributable to social suggestion from media sensationalism (Bunce, 1979). By the mid-1970s, the incidence of bad trips had declined precipitously, which Bruce attributes to the “shift of social conflict away from psychedelic issues” (p. 213).

The term ‘challenging experiences’ is preferred by the author as it does not negate the experience as ‘bad’ but instead frames it as difficult while leaving the potential value of the experience intact. A web survey by Carbonaro et al. (2016) supports this idea, as 84% of participants felt they had benefited from “their most psychologically difficult or challenging experience (worst ‘bad trip’)” following psilocybin mushrooms [*N*=1,993]. Further, the degree of difficulty of the experience was predictive of durable increases in well-being. However, this only held true when the duration of the challenging portion of the experience was short, with longer durations predictive of lower well-being. Table 40 summarizes studies of challenging experiences across psychedelics. Only studies showing the prevalence or incidence of challenging experiences in response to psychedelics were included to limit the scope. Case studies and observational studies were excluded as these studies do not allow for prevalence estimation.

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Table 40

Prevalence of Challenging Experiences or 'Bad Trips' from Psychedelics

Study	Subjects	Setting	Dose	Outcome Measure	Result	*N*
Mescaline						
Bergman (1971)	Native American Church of Navajoland, referrals to the Indian Health Service		Various	Extrapolated "bad reactions" based on those "we hear about."	0.0014%	5 "bad reactions"
Patterson (1974)	U.S. military inductees	Recreational/ naturalistic	Various	Self-reported unpleasant effects	2.6%	1,817
LSD						
Patterson (1974)	U.S. military inductees	Recreational/ naturalistic	Various	Self-reported unpleasant effects	10.8%	1,839
Psilocybin						
Patterson (1974)	U.S. military inductees	Recreational/ naturalistic	Various	Self-reported unpleasant effects	1.8%	547
Studerus et al. (2011)	Healthy subjects	Supportive clinical	Various	Retrospectively: "Very frightening"	5%	90
				"Very unpleasant"	10%	
Griffiths et al. (2011)	Hallucinogen naïve community sample	Supportive clinical	20 or 30 mg/kg	Extreme anxiety/fear	39%	18
Bienemann et al. (2020)	EROWID database text	Recreational/ naturalistic	Various	Categorized as "health problems," "bad trips," or "train wreck & trip disasters"	346 reports	
DMT						
Patterson (1974)	U.S. military inductees	Recreational/ naturalistic	Various	Self-reported unpleasant effects	<1%	418
Cakic et al. (2010)	Australian online survey	Recreational/ naturalistic	Various	Psychospiritual distress	23.5%	103
Ayahuasca						
Cakic et al. (2010)	Australian online survey	Recreational/ naturalistic	Various	Psychospiritual distress	16%	25

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Study	Subjects	Setting	Dose	Outcome Measure	Result	*N*
MDMA						
Baylen & Rosenberg (2006)	Meta-analysis of prevalence	Recreational/ naturalistic	Various	Anxiety, nervousness, panic attacks, etc.	11%[a]	13 studies
				Depression, feeling lonely or sad, etc.	9.5%[a]	10 studies
				Fear and/or paranoia	8%[a]	9 studies

Note. Headings are bolded for clarity.

[a] Median prevalence

Psychosis

Abruzzi (1977) delineated drug-induced psychosis (DIP) from naturally occurring psychosis (NOP) by the criteria shown in Table 41. In addition, H. D. Abraham and Aldridge (1993) describe the common features of prolonged LSD psychosis across 75 case reports from 16 clinicians that include "mood swings, visual hallucinations, mania, grandiosity, and religiosity" (p. 1329).

Bowers (1972) observed similar distinctions to Abruzzi between DIP and NOP from studying a group of 12 LSD/mescaline-induced DIP patients compared with 26 non-drug-induced acutely psychotic patients (assumed NOP). They found that those with DIP had more favorable prognostic scores and less affective blunting. Bowers also performed a follow-up study 1.9–5.8 years later (M=3.5) with eight of the original subjects who had LSD/mescaline-induced DIP and seven additional subjects with the same condition (Bowers, 1977). When assessed 1.9–5.8 years following their initial DIP diagnosis, approximately half were "reasonably well" while the other half had poor outcomes, including two suicides. The most reliable predictors of poor outcomes were "withdrawal, motor retardation, blunt affect, energy, and suicidal thoughts" at initial hospitalization (p.

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835). Prognostic scores at initial hospitalization, however, were not predictive of outcomes.

Table 41

Criteria Differentiating Natural and Drug-Induced Psychosis

Drug-induced psychosis [DIP]	Naturally occurring psychosis [NOP]
No withdrawal	Withdrawal from personal contact
Lack of autism [assumed to mean internal preoccupation]	Autism, day dreaming
Hallucinations, usually visual	Hallucinations, frequently auditory as well
Usually know hallucinations are not real ("I see snakes crawling, but I know they're not there"), Ego dystonic	Hallucinations very real ("Get those snakes away from me"), Ego syntonic
Speech not as incongruous or symbolic	Speech vague, ambiguous, difficult to follow, not concrete, with inability to communicate
Usually not delusional	Delusions. Bizarre mannerism, attitudes
Not as frequently disoriented	Disoriented
Usually, no paranoid ideation	Paranoid ideation
Thinking usually not disturbed	Disturbed thinking

Note. Adapted from Abruzzi (1977, p. 184).

LSD. Baker (1964) writes that paranoid personality or overt psychosis are "partial" contraindications use of LSD therapy. According to S. Cohen (1985), psychotic reactions to LSD in clinical research settings are "almost completely preventable" (p. 294). In a survey of 44 clinicians who had administered LSD or mescaline a total of 25,000 times to 5,000 people without schizophrenia, prolonged psychotic states occurred in 0.18% of patients, with only one case lasting longer than 2 days (S. Cohen, 1960). However, H. D. Abraham and Aldridge (1993) identified five additional studies between 1963 and 1971 that showed a higher incidence of prolonged psychosis following clinical LSD, with rates ranging from 0.9% to 4.6% (median=2.7%; *N*-weighted *M*=1.09%).

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Of the five studies cited by H. D. Abraham and Aldridge (1993) since S. Cohen (1985), only three were available as full texts in English. Fink et al. (1966) saw prolonged psychotic reactions following 40–73 μg LSD treatment in three of 65 patients (4.6%). In all three patients, psychotic symptoms remitted fully within 3–5 months. Baker (1967) reported that four of 150 patients treated (2.7%) experienced paranoid psychosis following 400–600 μg LSD that lasted 3 or 4 days before being terminated by electroconvulsive therapy (ECT). Malleson (1971) reported a 0.9% per-patient rate of prolonged psychosis (>48 hours) among 4,300 subjects treated with 49,500 LSD sessions. Two-thirds of these patients recovered fully.

In experimental settings with a non-clinical population, prolonged psychosis rates are lower; 0.08% according to Cohen (1960) and 0.36% according to McFarling (1980; as reported by H. D. Abraham & Aldridge, 1993). This discrepancy between rates of LSD-associated prolonged psychosis in clinical treatment and non-clinical experiments may be due to greater occurrence and predisposition to psychotic disorders in clinical populations. H. D. Abraham and Aldridge (1993) note that from three studies of patients hospitalized for psychosis following hallucinogen use, 23–50% had prior incidents of psychosis.

In the treatment of 1,420 cases of people hospitalized for LSD-induced psychosis from recreational use, Abruzzi (1977) observed that some experienced DIP symptoms while others presented with NOP symptoms, which sometimes became chronic. Having observed some of these latter patients prior to LSD ingestion, Abruzzi noted that some were “seemingly ‘normal’ individuals who can by fright, shock, drugs, illness, etc., be precipitated into psychotic postures” and that “many of these subjects before such an

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insult, were apparently enjoying fairly 'normal' lives; that is, they were productive at work or school, they were fairly comfortable and satisfied with themselves, and they were in good contact with reality" (p. 189). He concluded, "that many, perhaps most, are capable (exposed to the proper circumstances of sufficient disintegration of ego, character, and/or personality) of performing and perceiving in a psychotic manner" (p. 189). In other words, Abruzzi concluded that with a sufficient dose of LSD, most people, regardless of their prior functioning, could become psychotic following LSD administration. While this is concerning, it should be noted that Abruzzi is reporting on his clinical experience, which was loosely documented and quantified. He followed 416 cases of LSD-induced psychosis and found that 31 still had "psychiatric residua" 6 months later. However, this is a small sample to make generalizations about, given that Abruzzi does not report the proportion of those 31 that were observed prior to treatment.

What is clear from Abruzzi's research is that prolonged DIP is relatively rare among those presenting with psychotic symptoms following recreational LSD ingestion, occurring approximately 7.5% of the time. This figure can be compared to the general rate of schizophrenia in the clinical population to get a sense of whether LSD caused persistent psychosis[7]. A study of inner-city psychiatric hospital admissions [*N*=247], performed around the time of Abruzzi's research, found that about 6% of admissions qualified for a diagnosis of schizophrenia (M. A. Taylor & Abrams, 1978). Thus, the rate of persistent psychotic reactions to LSD found by Abruzzi is similar to the rate of

[7] The clinical population is a more appropriate comparator than the general population, given that those in Abruzzi's study presented in a clinical setting. There would have been many other individuals in the general population who took LSD and did not require psychiatric treatment.

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schizophrenia in a comparable population, indicating that most with long-term LSD-induced psychosis likely had prodromal schizophrenia. This finding is supported by Vardy and Kay (1983) followed 52 patients with persistent psychosis due to LSD and 29 patients with first-break schizophrenia over 3 to 5 years. Vardy and Kay saw a similar course of illness in both groups.

Finally, it should be noted that, in rats, D. A. Martin et al. (2014) found that chronic 160 μg/kg LSD every other day for 90 days altered gene expression in the medial prefrontal cortex in a way consistent with pathogenic markers of schizophrenia. These markers persisted for several months following cessation. This provides some support that ongoing administration of LSD may increase the risk of psychosis.

Mescaline and Psilocybin. Among 101 hospitalizations due to mescaline-induced psychosis, 5.0% had "psychiatric residua" at 6-month follow-up (Abruzzi, 1977). For 53 hospitalizations due to psilocybin-induced psychosis, 5.7% had "psychiatric residua" at 6-month follow-up (Abruzzi, 1977). For both drugs, the rate of psychosis is similar to that of a hospitalized population, indicating that psychedelic etiology is unlikely. I. Stevenson and Richards (1960) document two cases of prolonged reactions to mescaline (400 mg oral), one lasting 4 days and another 11 days.

DMT and Ayahuasca. dos Santos et al. (2017a) performed a systematic review of prolonged psychotic reactions following DMT use. They found three case studies, all of which were self-administered and occurred alongside other drug use, particularly cannabis. There were no reports of prolonged psychosis in experimental/controlled environments, which typically include psychiatric screening prior to administration. dos Santos et al. (2017a) also identified between 36 and 45 cases of psychosis following

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ayahuasca ingestion. They recommend that those with a personal or family history of psychotic illness or mania avoid ayahuasca or DMT.

MDMA. Soar et al. (2001) reviewed the 38 cases of psychiatric disorders following MDMA use documented in the past 10 years. Twenty were cases of psychotic disorders (psychosis, paranoia, delusions, or hallucinations). Of those cases of psychotic disorder in response to MDMA, 55% had no personal or family history of psychotic disorder, 20% had a personal but no family history, 10% had a family history, and 15% had unknown personal or family history. The substantial prevalence of psychotic reactions in response to MDMA with no family history (75% of cases) suggests that MDMA has a pathogenic role rather than simply activating an underlying vulnerability. This is unsurprising as MDMA is a substituted amphetamine, and other stimulants such as amphetamine and methamphetamine can lead to stimulant-induced psychosis, particularly when used heavily (Alharbi & el-Guebaly, 2016; Glasner-Edwards & Mooney, 2014; Yui et al., 1999). However, it should be remembered that stimulant medications are routinely used in medicine with relative safety, typically for treating ADHD.

Ketamine. Curran and Morgan (2000) found increased dissociative and schizotypal symptomology 3 days following recreational ketamine use (p<.001–.008) compared to controls who had not used ketamine [N=39, 59% male, age=18–29, race N/R]. The effect sizes for acute ketamine were d_c=3.61 for dissociation and d_c=2.82 for schizotypal symptoms, while 3 days following ketamine, the effect sizes were d_c=0.93 for dissociation and d_c=1.56 for schizotypal symptoms. This indicates that there is a subacute increase in psychosis-like symptomology following recreational ketamine use. Corlett et

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al. (2010) also report on a case of Capgras syndrome (the delusion that a familiar person has been replaced by an imposter) following ketamine administration.

Long-term, several studies indicate that recreational ketamine use can increase symptoms of psychosis, while one study indicates that ketamine psychotherapy can reduce psychotic symptoms (see Psychotic Symptoms in Chapter 7). In addition, Tang et al. (2014) found that chronic ketamine users [*n*=26, 8% female, age *M*=25.1, from Chinese drug rehabilitation centers] experience a more aberrant sense of body ownership based on the rubber hand illusion compared to healthy controls [*n*=20, 8% female, age *M*=24.4, Han Chinese] when having not taken the drug recently. Recreational ketamine users also scored higher on self-report measures of schizophrenia-like behaviors and dissociative symptoms. In a treatment context, however, Krupitsky and Grinenko (1997) saw decreases in psychotic symptoms following ketamine psychotherapy (see Chapter 7 for more details).

Ibogaine. Houenou et al. (2011) describe one case of a 26-year-old male who presented to the hospital with delusions and psychosis following ibogaine ingestion. Since the age of 22, the man had had "intermittent hallucinations and persecutory delusions" as well as negative symptoms of schizophrenia (p. 659).

Mania

LSD. One report was found of acute mania following LSD ingestion involving a 31-year-old soldier with no family history of mental illness (Lake et al., 1978). He had recently separated from his wife and had been drinking heavily (12 drinks per day for 1 year). He took one slip of blotter paper and then experienced visual distortions along with fear, anxiety, and panic. Upon awakening the next morning, he felt guilty about his

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drinking and having taken LSD. He resolved to change and began going to church three times daily. Two weeks later, his sleep decreased as his religious interests intensified. A week, later he had a manic episode with religious delusions that led him to break into a stranger's house and smash windows with his bare hands. He was subsequently hospitalized for 3 weeks before his mania was resolved with lithium treatment.

Long-term, two studies found some increase in mania/hypomania symptoms following LSD treatment. Mogar and Savage (1964) saw non-significant increases in mania in patient groups (d_n=0.4; n=35) and healthy normals (d_n=0.6; n=25) at 2-month follow-up as measured by the MMPI. However, mania was not elevated to clinical levels at follow-up except in the high-severity patient group, for which it was already clinically elevated at baseline (baseline: T=63; 2-month: T=67). Ludwig & Levine (1965) saw significantly increased hypomania symptoms at 2-month follow-up among a group treated with 2 μg/kg LSD combined with hypnosis and psychotherapy (d_c=0.79; n=14), as measured with PEP. There were also increased hypomanic symptoms at 2-week follow-up in this group, but this result did not reach significance (d_c=0.50). In the group treated with 2 μg/kg LSD combined with psychotherapy (n=14), there were also non-significant increases in hypomanic symptoms at 2-week (d_c=0.53) and 2-month (d_c=0.68) follow-up. In the group treated with 2 μg/kg LSD alone (n=14), however, there was no trend toward increased mania at 2-week (d_c=-0.13) or 2-month (d_c=-0.06) follow-up. Subacutely, McCabe et al. (1972) saw no significant change in MMPI mania symptoms 5 to 7 days following 50 (d_n=0.22) or 350 μg (d_n=-0.18) LSD.

Together, it appears that caution is warranted in administering LSD to those with clinically elevated mania or hypomania symptoms or a history of bipolar disorder.

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Psilocybin. No studies were found directly examining symptoms of mania following psilocybin, though it may have similar effects as LSD, given their pharmacological similarities.

Ayahuasca and DMT. In a review of ayahuasca-related psychosis, dos Santos et al. (2017a) identified four cases of mania with psychotic features related to ayahuasca use. One additional case was found in which a 30-year-old Argentinian man with bipolar disorder had a manic episode with psychotic features following an ayahuasca ritual (Szmulewicz et al., 2015). He was hospitalized and prescribed 2 mg/day of risperidone and 2 mg/day of clonazepam before being discharged 1 month later to return to Argentina to continue treatment. Two weeks prior to the ceremony, the man had had a hypomanic episode that lasted 10 days before resolving to normal sleep and energy levels. He had had several prior incidences of hypomania but had never been manic or depressed. dos Santos et al. (2017a) concluded that those with a personal or family history of mania avoid ayahuasca or DMT.

MDMA. Among recreational MDMA-using adolescents and young adults, Lieb et al. (2002) saw no significant association with bipolar I disorder (aOR=1.39), bipolar II disorder (aOR=1.02), hypomania (aOR=0.61), or single episode mania (aOR=0.27) compared to peers who did not go on to use MDMA in a 4-year prospective longitudinal study [*N*=2,462].

Ketamine. In mice and rats, relatively high-dose ketamine (~25 mg/kg) is commonly used to induce a model of mania (Ghedim et al., 2012; Mahajan & Pawar, 2013; Wendler et al., 2016; and others). However, therapeutic doses are typically much lower, and there is no consistent pattern of mania induction in humans with these doses.

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Niciu et al. (2013) examined data from three ketamine trials for depression and bipolar disorder that measured mania symptoms following infusion using the Young Mania Rating Scale (YMRS), with a cutoff score of greater than 12 indicating mild mania. In the combined studies, 10% of patients who received ketamine [*n*=52] had manic-like worsening compared to 7% of patients who received a placebo [*n*=44]. In all patients, manic symptoms were mild and transient, resolving within a day.

Cases of mania following ketamine treatment include a 52-year-old male with TRD and no history of mania (Banwari et al., 2015), a 44-year-old woman with bipolar I disorder (McInnes et al., 2016), and four cases following ketamine treatment for chronic pain, some including psychotic features (Mandyam & Ahuja, 2017; S. D. Nichols et al., 2016; Ricke et al., 2011; Valdez & Makhinson, 2019). For one of the cases involving chronic pain treatment (Ricke et al., 2011), Niciu et al. (2013) argue that there are other possible diagnoses other than mania that need to be considered, including possible delirium, the effects of concomitant illicit opioid use, and the effects of other medication changes. There was also a case of mania found in a 26-year-old male following 12 months of ketamine abuse (Y.-Y. Lu et al., 2016).

Ibogaine. Marta et al. (2015) identified three cases of mania following ibogaine ingestion [male, 36, Caucasian, substance abuse; female, 35, Caucasian, substance abuse; male, 40, Caucasian]. In all three cases, there was no mania present prior to ibogaine use and no family history of mania or psychosis.

Anxiety and Depression

Mescaline. Johansen and Krebs (2015) found that lifetime mescaline/peyote use was associated with a higher likelihood of past year symptoms of a major depressive

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episode (p=.02; aOR=1.2) but not a diagnosis of depression (p=.59; aOR=1.0). Halpern et al. (2005), however, found no significant trend in anxiety or depression symptoms among ritual peyote users compared to controls.

LSD and Psilocybin. LSD and psilocybin are associated with subacute reductions in anxiety and depression symptoms, as well as long-term reductions in anxiety, depression, and obsessive-compulsive symptoms (see Chapter 7).

Ayahuasca. Ayahuasca is associated with long-term reductions in anxiety and depression symptoms, as well as subacute reductions in depression symptoms with no significant subacute change in anxiety (see Chapter 7). One case describes a 25-year-old Brazilian female with GAD and chronic insomnia who took ayahuasca and experienced "intense anxiety, panic, and hopelessness" that persisted for 3 days (dos Santos, Osorio, et al., 2017, p. 35).

MDMA. Recreational MDMA users commonly report a "blue Monday" or "black Tuesday" following MDMA use the weekend before (Sessa, 2017). These periods are characterized by low mood, fatigue, and irritability several days following MDMA use. Sessa (2017) asserts that these symptoms are not due to MDMA itself but rather the consequences of sleep deprivation, elevated physical activity (dancing), use of other drugs, including alcohol, and food restriction. Supporting this claim are several clinical studies where medical-grade MDMA is given alone and without sleep deprivation or dancing. In most of these studies, low mood is seen only occasionally in the days following administration and does not have a robust causative association with MDMA use (Greer & Tolbert, 1986; Mithoefer et al., 2011; Sessa, 2017; Sessa et al., 2022). However, Vizeli and Liechti (2017) saw significantly increased symptom complaints

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(p<.001) in the subacute period following 125 mg but not 75 mg MDMA compared to placebo [N=166, 50% women, age=18–45, 100% Caucasian]. Complaints included "headache, lack of appetite, lack of energy, dry mouth, difficulty concentrating, and bruxism" (p. 580). Depressed mood occurred in 4% of participants in the 14 days following 125 mg MDMA, though this finding did not reach significance. Subacute symptoms were significantly greater in women than men (p<.001). Huxster et al. (2006) also saw subacute increases in anxiety 9 days following recreational MDMA use compared to other MDMA users who did not take MDMA during that period [N=38].

Recreational MDMA use is associated with long-term increases in anxiety symptoms (see Chapter 7). Regarding depression, Guillot (2007) reviewed studies of the association between recreational MDMA use and depression [n=22]. Eleven of those studies found significantly elevated measures of depression among Ecstasy users compared to controls. However, only three of these studies used cannabis or polydrug controls. Guillot concluded that the evidence for an association between ongoing recreational Ecstasy use and depression is weak but that there may be an association that is due to other concomitant drug use. Since Guillot's review, Taurah et al. (2013) compared depression symptoms among recreational MDMA users, ex-MDMA users, and polydrug controls [N=997, 52% male, age M=25.1, 32% White, 27% Asian, 23% Black, 18% Other]. They found that recreational MDMA use, past and present, was associated with much more depression symptoms (d=1.41 to 1.66; p<0.001).

Lieb et al. (2002) found that recreational MDMA/ecstasy using adolescents and young adults [n=211] had a moderately higher risk of major depression (aOR=1.53; p<0.05) compared to polydrug users [n=1,008]. However, the prospective longitudinal

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design of the study also showed that major depressive disorder was equally likely to be present prior to MDMA/ecstasy use as it was after. However, this was not true for dysthymia, which showed a significantly higher incidence after initiating recreational MDMA/ecstasy use than before (p<.05), indicating a potential causative link. Still, illegally obtained MDMA is far from pure, and recreational use is often accompanied by the use of other drugs, sleep deprivation, and increased physical activity that may increase body temperature (Sessa, 2017). These factors likely contribute to the psychiatric consequences of recreational MDMA/ecstasy but are not present with clinical MDMA.

Ketamine. C. J. A. Morgan et al. (2010) found significantly increased depressive symptoms among recreational ketamine users when compared to polydrug controls [N=150]. They saw no significant difference in trait anxiety. In a treatment context, Krupitsky and Grinenko (1997) saw decreases in anxiety and depression symptoms following ketamine psychotherapy (see Chapter 7 for more details). Curran and Morgan (2000) saw increased depressive symptoms (p<.001; d_c=1.28) 3 days following ketamine use [n=20] compared to controls [n=19] who had not used ketamine [59% male, age=18–29, race N/R]. However, these levels of depression remained below the clinical threshold. There was no significant change in anxiety.

Somatization/conversion

LSD, Ayahuasca, and Ketamine. No significant association was found between LSD or ketamine treatment or ritual ayahuasca use and long-term increases in somatization (see Chapter 7). In addition, McCabe et al. (1972) found no subacute differences in somatization 5 to 7 days following LSD.

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MDMA. Huxster et al. (2006) saw subacute increases in somatization 9 days following recreational MDMA use compared to other MDMA users who did not take MDMA during that period [*N*=38]. Long-term, Lieb et al. (2002) did not find any significant difference in somatization among recreational MDMA users (see Chapter 7 for more details).

Suicidality

Table 42 summarizes the cases of suicide and accidental death associated with each psychedelic that were found in the literature. Overall, there is little association between psychedelics and suicide. MDMA may be an exception, perhaps due to low mood in the days following use (see above under "Anxiety and Depression").

Classical Psychedelics. Johansen (2015) found no association between suicidality and classical psychedelic use [*n*=19,299] compared to non-psychedelic-using adults [*n*=115,796]. Data was collected from the United States National Survey on Drug Use and Health. Classical psychedelic use was defined as reported lifetime use of LSD, Psilocybin, mescaline, or peyote. Results approached significance for reduced suicidal plans (p=.09; aOR[8]=0.8) and attempts (p=.09; aOR=0.7) among classical psychedelic users, but not for suicidal thoughts (p=.19; aOR=0.9).

Hendricks, Thorne, et al. (2015) also analyzed data from the 2008–2012 National Survey on Drug Use and Health with controls for a "variety of covariates" [*N*=190,000]. They found that lifetime classical psychedelic use (mescaline, LSD, psilocybin) was negatively correlated with reduced past-month psychological distress (weighted odds

[8] Adjusted odds ratio of less than one indicates a lower likelihood.

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ratio [wOR]=0.81; 95% confidence interval [CI]=0.72–0.91), past-year suicidal thoughts (wOR=0.86; 95% CI=0.78–0.94), past-year suicidal planning (wOR=0.71; 95% CI=0.54–0.94), and past-year suicide attempts (wOR=0.64; 95% CI=0.46–0.89) [*n*=27,235, 63% male, age>18, 83% White]. In contrast, lifetime use of most other illicit drugs was correlated with increases in each of these variables. Lifetime MDMA use had wORs for each variable around 1.0, indicating little correlation with negative or positive outcomes.

Psilocybin. Hendricks, Johnson, and Griffiths (2015) analyzed data from the 2008–2012 National Survey on Drug Use and Health using similar methods to Hendricks, Thorne, et al. (2015) to look specifically at suicide risk associated with psilocybin. They found that those who had used only psilocybin [*n*=7,550] had less likelihood of psychological distress ($p<.0001$; wOR=0.70), suicidal thinking ($p<.01$; wOR=0.76), suicidal planning ($p<.01$; wOR=0.54), and suicide attempt ($p<.05$; wOR=0.58) compared to those who had not used any psychedelic [*n*=164,595].

Ayahuasca. The "hopelessness" combined with intense anxiety and panic experienced in the 3 days following ayahuasca in a 25-year-old Brazilian female suggests the possibility of suicidal ideation precipitated by ayahuasca (dos Santos, Osorio, et al., 2017).

MDMA. The MAPS *MDMA Investigator's Brochure* (Multidisciplinary Association for Psychedelic Studies [MAPS], 2021) describes a low incidence of increased SI following MDMA treatment for PTSD, with none of the instances attributed directly to MDMA. There were no instances of suicidal behavior in the days following sessions, though one participant was hospitalized 6 days following due to SI. There was one suicide attempt 28 days following an MDMA session. During MDMA treatment

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sessions, there were three serious instances of acute suicidality. However, there were also three serious instances of acute suicidality with placebo or before drug ingestion.

Among recreational MDMA-using adolescents and young adults, Lieb et al. (2002) saw no significant association with SI (aOR=1.44) compared polydrug using peers in a 4-year prospective longitudinal study [*N*=2,462]. However, when compared to non-drug-using peers, there was a significantly higher risk of SI (aOR=2.24). While the latter figure cannot be taken as evidence of causality (those with SI could be more likely to use drugs), the relatively high odds ratio compared to polydrug controls suggests that MDMA may be a causal factor in increased SI.

Ketamine. Niciu et al. (2013) described two cases of increased anxiety and suicidal thoughts in people with OCD and a history of major depression in the days following ketamine treatment. The subjects were part of a trial involving ten people being treated for refractory OCD. Grunebaum et al. (2017) found increased suicidal ideation following ketamine treatment for bipolar depression. See Chapter 12 section on Bipolar Disorder for more details.

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Table 42

Psychedelic-Associated Suicide Attempts and Accidental Deaths

Deaths by Suicide		
Mescaline	1	Jumped off cliff while intoxicated with mescaline (Reynolds & Jindrich, 1985).
LSD	11	One person jumped from a window while on LSD (Keeler & Reifler, 1967). Three suicides were temporally related to LSD therapy sessions among 4,300 patients (Malleson, 1971)[a]. S. Cohen (1960) describes three cases of successful suicide temporally related to LSD, all in patients with severe psychopathology prior to LSD. Chandler and Hartman (1960) had one patient kill themselves a week following LSD therapy; they also refer to two reports of suicides related to LSD treatment from W. Stoll and one by Denber and Rinkel (1957).
Psilocybin	8	Jumped from a balcony while on psilocybin (Honyiglo et al., 2019). Suicide by cutting and stabbing while on psilocybin, causation unclear (K. Müller et al., 2013). Six suicides following psilocybin consumption, including five involving jumping from buildings (van Amsterdam et al., 2011).
MDMA	20	Male, 17, shot self in head 2 days following first ecstasy ingestion (R. S. Cohen, 1996). Nineteen suicide autopsies in an Australian sample revealed MDMA in toxicology screening (Darke et al., 2009) [*n*=1,226].
Ketamine	1	Male, 29, suicide by hanging while intoxicated with ketamine and alcohol, history of alcoholism (Dinis-Oliveira et al., 2010).
Attempted Suicide		
LSD	13	Nine suicide attempts were temporally related to LSD therapy sessions among 4,300 patients (Malleson, 1971)[a]. Four suicide attempts related to LSD are described by S. Cohen (1960).
Psilocybin	3	In an online survey of challenging psilocybin experiences, one suicide attempt by overdose, one unsuccessful attempt by firearm, and one case of exacerbation of existing depression that later led to a suicide attempt (Carbonaro et al., 2016).
Accidental Death		
Psilocybin	3	One death following psilocybin and alcohol due to accidentally falling from a building, and one death due to attempting to fly from windows (van Amsterdam et al., 2011). French male, 27, accidental death due to cold exposure after taking psilocybin and being found in a canal (van Amsterdam et al., 2011).
Ketamine	3	Two fatal ketamine-related accidents among 150 frequent ketamine users during a 1-year cohort study (C. J. A. Morgan et al., 2010). One case of autoerotic asphyxiation while intoxicated with ketamine (Breitmeier et al., 2002).
Ibogaine	1	Drowning following iboga (Chèze et al., 2008).

Note. Headings are bolded for clarity.

[a] LSD cannot necessarily be implicated in these suicides as they simply occurred after LSD sessions, just as suicides sometimes occur after ordinary psychotherapy sessions.

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Abuse Potential of Psychedelics

Before considering using psychedelics for treating substance use disorders, it is essential that the abuse potential of these drugs be considered. Gable (1993) performed an extensive literature review [*N*=950] comparing the dependence potential of 20 different substances based on quantitative studies. Dependence potential was described qualitatively from 'Very low' to 'Very high,' with 'Low,' 'Moderate,' and 'High' as intermediary descriptors. Mescaline, LSD, and Psilocybin were all classified as having 'Very low' dependence potential. Gabel classified MDMA (oral) as having 'Moderate/low' dependence potential, while IM ketamine was 'Low.' For comparison, alcohol was rated as 'Moderate,' IN cocaine as 'High/moderate,' and IV heroin as 'Very high.' Additional considerations regarding the abuse potential for specific psychedelics are described below.

Psilocybin. M. W. Johnson, Griffiths, et al. (2018) found that if psilocybin were to be rescheduled according to the eight factors of the Controlled Substances Act, its abuse potential would align with Schedule IV designation considering recent medical research.

DMT. In a large survey of DMT users [*n*=1,980], Winstock et al. (2014) found that DMT had strong pleasurable effects, few negative effects, and short duration. Despite such traits being commonly associated with a higher risk of dependence, DMT users did not report a strong urge to use more.

Ayahuasca. While no studies were found directly examining the abuse liability of ayahuasca, there were also no case reports of ayahuasca addiction found. In addition,

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patterns of ayahuasca use in ritual contexts do not support an addictive quality. Based on these factors, the abuse potential of ayahuasca is judged to be low.

MDMA. Gabel (1993) characterized MDMA as having 'Moderate/low' dependence potential. Rare cases of MDMA dependence are found in the literature (Jansen, 1999). While Huxster et al. (2006) found no reports of cravings for ecstasy in the days following recreation ecstasy use [*N*=20], Tancer and Johanson (2003) did observe reinforcing effects in participants given MDMA [*N*=12] as measured by a money versus drug preference questionnaire. In rodents, MDMA use is reinforcing but to a far lesser degree than with other drugs of abuse (De La Garza et al., 2006). Together, the relatively low reinforcing effects of MDMA make it unlikely for clinical administration to lead to MDMA dependence. Indeed, in a follow-up study 17 to 74 months after (*M*=45.4) MDMA-assisted psychotherapy for PTSD, only one of 19 participants reported using "ecstasy" (Mithoefer et al., 2013). This participant attempted to create a therapeutic environment with a friend present during the experience but "found the arrangement unsatisfactory and so reported no interest in repeating the experience" (p. 32).

Ketamine. Despite Gable (1993) rating IM ketamine as having 'Low' dependence potential, there are enough reports of ketamine addiction that further discussion is warranted (R. F. Bell, 2012; Giné et al., 2016; Muetzelfeldt et al., 2008; Schak et al., 2016). Ketamine has rewarding properties due to it increasing extracellular dopamine and stimulating both the mu opioid and sigma receptors (C. J. A. Morgan & Curran, 2011). In addition, the rapid onset (5 min) and relatively short half-life may also make it more appealing than other psychedelics for repeat recreational use.

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Ketamine does have the potential for dependence, with 43%–60% of recreational ketamine users and ex-users expressing concerns about ketamine addiction when asked [*N*=90] (Muetzelfeldt et al., 2008). In a web survey of 462 people who had used ketamine in the past year, 1.5% reported psychological ketamine dependence, 40.5% reported ketamine tolerance, and 5.6% reported receiving treatment to quit (Giné et al., 2016). Among frequent users, cravings for ketamine were common, with cravings cited as the reason that 28 of 30 daily ketamine users had tried to stop but could not (C. J. A. Morgan et al., 2008). Ketamine also produces tolerance, with some frequent users reportedly using six times the dose that they first used (C. J. A. Morgan et al., 2008).

Female adults and adolescents may be more susceptible to ketamine's addictive properties, based on a robust series of animal studies that align with subjective human reports (Strong & Kabbaj, 2018). Women dependent on ketamine tend to experience more discontinuation symptoms than men, which can include anxiety, dysphoria, and tremors (W.-Y. Chen et al., 2014). Naltrexone can help alleviate cravings for ketamine (Garg et al., 2014).

Ibogaine. Ibogaine does not have significant potential for abuse, given that animals will not self-administer it (Alper, 2001). In addition, ibogaine is neither rewarding nor aversive in conditioned place preference, and it does not produce signs of physiological withdrawal after 6 days of consecutive administration to rats.

Other Substance Abuse

Ayahuasca. Barbosa et al. (2012) identified five studies on drug and alcohol use among regular ayahuasca users. There were no findings indicating elevated substance use among ayahuasca users, with some studies indicating reduced substance use (e.g.,

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Doering-Silveira, Grob, et al., 2005; Fábregas et al., 2010; Grob et al., 1996). However, there was a high incidence of former drug and alcohol abuse among ayahuasca users, with many individuals attributing their recovery to membership in an ayahuasca church (Halpern et al., 2008).

MDMA. Lieb et al. (2002) found that lifetime rates of DSM-IV substance abuse and dependence were much higher among MDMA-using adolescents and young adults than those who used other drugs in a 4-year prospective longitudinal study [*N*=2,462]. There were large differences in lifetime alcohol use disorder ($p<.05$; aOR=1.67), alcohol dependence ($p<.05$; aOR=2.58), nicotine dependence ($p<.05$; aOR=1.84), illicit drug abuse ($p<.05$; aOR=5.16), and illicit drug dependence ($p<.05$; aOR=8.99). While this was a correlational study, it is reasonable to infer some causation due to MDMA, given that the comparison group was other substance users.

Persistent Psychedelic Experiences

There is some terminology confusion in the literature between "flashbacks" and Hallucinogen Persisting Perception Disorder (HPPD). A. G. Lerner et al. (2002) define flashbacks as a "usually short-term, non-distressing, spontaneous, recurrent, reversible and benign condition accompanied by a pleasant affect" (p. 92). They contrast this with HPPD, which is "a generally long-term, distressing, spontaneous, recurrent, pervasive, either slowly reversible or irreversible, non-benign condition accompanied by an unpleasant dysphoric affect" (p. 92). While popular media has cast flashbacks as a negative phenomenon caused by psychedelics, flashbacks are typically benign and may be a positive experience (A. G. Lerner et al., 2002). In contrast, HPPD tends to be a troubling condition.

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Some psychedelic therapists further question the classification of flashbacks and HPPD as negative phenomena, especially when they are the consequence of psychedelic-assisted therapy (E. Sola, personal communication, December 7, 2020). Instead, Sola characterizes flashbacks and HPPD as "reconnecting to the experience, including terror." He goes on to say that "Psychedelics open the door to primal mind, and the crossing of this threshold becomes hopefully more flexible without becoming overly loose." In this way, re-experiencing psychedelic states can be a way of integrating experiences from psychedelic therapy. Cases of ongoing HPPD, however, are characterized by significant distress and should be considered a negative outcome.

Flashbacks

In a large population study [N=130,152], lifetime use of any psychedelic [n=21,967] nor past year use of LSD [n=1,220] were not associated with past year symptoms of "seeing something others could not," panic attacks, psychosis, or overall serious psychological distress (Krebs & Johansen, 2013). The authors argue that this finding does not support the concepts of flashbacks or HPPD associated with psychedelic use. In comparing MMPI data from LSD users who reported psychedelic flashbacks to those who did not, Matefy and Krall (1974) saw no significant differences on any scale except for increased paranoia (*Pa*) among the flashback group [N=44, college students] (p<.05; d_n=0.45).

LSD. Stanton et al. (1976) found a significant correlation (p<.01; r=.18; d_r=0.37) between Vietnam veterans who reported LSD flashbacks and amount of cannabis use [n=241]. Surprisingly, the correlation between LSD use and flashbacks was not significant (p>.05; r=.01; d_r=0.02). Given this data, cannabis use should be examined

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any time a patient is reporting unpleasant persistent hallucinogen effects. Hemsley and Ward (1985) found a positive correlation between Neuroticism and "frequency of 'flashbacks'" ($p<.01$; $r=.47$) following LSD experiences [$N=29$, hospitalized].

MDMA. Five cases of flashbacks attributed to street MDMA use were found in the literature (Creighton et al., 1991; McGuire & Fahy, 1992).

Ketamine. In a web survey of 462 people who had used ketamine in the past year, 27.5% reported flashbacks that they attributed to ketamine use (Giné et al., 2016).

Hallucinogen Persisting Perception Disorder (HPPD)

HPPD has two subtypes. Type I HPPD has a short duration and is reversible and therefore tends to have positive outcomes (Skryabin et al., 2019). In contrast, HPPD type II has a long duration and is either irreversible or slowly reversed. In an internet survey, Halpern et al. (2018) found that HPPD is commonly associated with dissociative symptoms [$N=20$]. HPPD can be treated using clonidine, perphenazine, and clonazepam (A. G. Lerner et al., 2002).

In a large web survey [$N=626$] on user perceptions of the harms and benefits of hallucinogen use, Carhart-Harris and Nutt (2010) found that 1% of subjects reported long-term vision or hearing changes that "drove them mad," while 10% reported changes they would "rather not have but could live with," though the nature of these changes was not specified [15% female, age $M=26$, 44% American, 30% British, 10% other European, 6% Canadian, 5% Australian, 5% other]. Of those reporting long-term vision or hearing changes, 39% attributed those changes to LSD, 11% to psilocybin, 9% to MDMA and cannabis, 4% to ketamine, 1% to alcohol, and 6% to another drug, while 22% chose not to specify a drug.

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Martinotti et al. (2018) performed a systematic review of HPPD observational studies, clinical trials, and case reports [*N*=25]. They identified 298 HPPD cases associated with LSD, eight with cannabis, one with MDMA, and none with mescaline, psilocybin, DMT, ayahuasca, ketamine, or ibogaine.

LSD. Based on data from Martinotti et al. (2018), HPPD appears to be primarily associated with LSD, making up 298 of 306 cases identified in their review. However, HPPD cases associated with other psychedelics have also been identified.

Two cases are described by Markel et al. (1994) of adolescents experiencing HPPD related to prior LSD experiences following the onset of SSRI treatment. In another case, with a 47-year-old male, SSRI treatment also resulted in distressing 'flashbacks' that resembled the patient's LSD experience 25 years prior (Goldman et al., 2007).

Psilocybin. While no cases of psilocybin-associated HPPD were found in the review by Martinotti et al. (2018), several cases were found in the present review. In a web survey of people with HPPD, five of 20 cases were associated with psilocybin (Halpern et al., 2018). Two additional case reports of psilocybin-associated HPPD were also found (Benjamin, 1979; Skryabin et al., 2019).

MDMA. Despite Martinotti et al. (2018) finding few cases of MDMA-associated HPPD in the literature, quite a few cases were identified in the present review. Litjens et al. (2014) present 31 cases of MDMA-associated HPPD. In a web survey of people with HPPD, MDMA was associated with five of 20 cases (Halpern et al., 2018). One additional MDMA-associated HPPD case report was found (Skryabin et al., 2019).

Ketamine. A 15-year-old male began experiencing "visual pseudohallucinations and hypersensitivity to light and sound" 6 months following ketamine treatment for

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chronic pain (Salzman & Abraham, 2017). No evidence of psychosis or depression was found, and these symptoms were characterized as HPPD. Treatment with trials of divalproex sodium, multiple SSRIs, gabapentin, pregabalin, lorazepam, diazepam, or topiramate did not achieve long-term remission, indicating a Type II case of HPPD.

Ibogaine. A 31-year-old male was treated with ibogaine for opioid use disorder (Knuijver et al., 2018). Two days later, he began re-experiencing disturbing images and perceptual alterations from his recent ibogaine treatment, which resulted in strong cravings for opioids. These symptoms persisted for 20 days until he received Eye Movement Desensitization and Reprocessing (EMDR) therapy to target the distressing memories he was re-experiencing. Substantial symptom relief was achieved after one session, with symptoms fading over the next 14 days. However, opioid cravings continued, and around this time, he relapsed into heroin use.

Violent Behavior

While hallucinogens have been rumored to be associated with violence, there is little evidence to support this idea except with MDMA and PCP (Hendricks et al., 2018; M. Murphy & Bird, 2019). In contrast, most psychedelics, including LSD, psilocybin, and ketamine, tend to reduce aggression (Tomlinson et al., 2016). However, Boles and Miotto (2003) note that hallucinogens such as LSD can aggravate pre-existing psychopathologies that may include violent propensities. In a large United States population study [N=480,000], lifetime classical psychedelic use is correlated with a lower incidence of past year assault (p=.009; aOR=0.88) and past year arrest for a violent crime (p=.023; aOR=0.82) (Hendricks et al., 2018). In addition, among a sample of inmates [N=302], hallucinogen use was associated with a lower frequency of arrests for

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intimate partner violence (Walsh et al., 2016). In a community sample [*N*=1,266], lifetime use of LSD or psilocybin correlated with a decreased likelihood of violence ($p<.05$; OR=0.42) against a current partner (Thiessen et al., 2018).

LSD. In a review of psychedelics and violence, Holoyda (2020) identified ten cases of violent incidents associated with LSD, all of which took place with recreational use. They concluded that overall, psychedelics tend to reduce the risk of violence. When treating violent offenders with 500 μg LSD, Baker and Buck (1977) initially used restraints. However, after having treated eight patients, they felt comfortable discontinuing the use of restraints as no serious difficulties had arisen.

Psilocybin. In a web survey asking participants to describe "their most psychologically difficult or challenging experience (worst 'bad trip')" following psilocybin mushrooms [*N*=1,993], 2.6% reported they "behaved in a physically aggressive or violent manner" (Carbonaro et al., 2016). In an approximately one-month span, there were 44 emergency department admissions across three Scottish hospitals due to psilocybin mushroom use (Peden et al., 1982). Of these admissions, seven were physically aggressive.

Ayahuasca. Bilhimer et al. (2018) describe an incident of a 25-year-old schizophrenic male who was discovered by police in front of his house fighting with a cat following ayahuasca ingestion.

MDMA. During acute intoxication, MDMA tends to decrease self-reported feelings of aggression and biased perception toward facial expressions being seen as less aggressive (Tomlinson et al., 2016). However, 4 days following recreational MDMA use, self-reported aggression increases compared to baseline, and perception becomes biased

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toward viewing facial expressions as more aggressive (Curran et al., 2004; Hoshi et al., 2016; Tomlinson et al., 2016). It should be noted that recreational MDMA use is often accompanied by sleep deprivation, dancing, food restriction, and use of other drugs, factors that have been shown to account for the low mood, fatigue, and irritability often reported several days following MDMA use (Sessa, 2017).

In a large United States population study [N=480,000], lifetime MDMA/ecstasy use is correlated with a higher incidence of past year assault (p<.0001; aOR=1.38) and past year arrest for a violent crime (p=.006; aOR=1.23) (Hendricks et al., 2018). Long-term and abstinent MDMA users self-report increased aggression, which may be due to a neurotoxic effect on the serotonin syndrome (Tomlinson et al., 2016). However, these studies also do not account for polysubstance use, and therefore it is unclear whether increased aggression is due to MDMA itself. Further, the bias toward perceiving facial expressions as more aggressive that is seen in the days following MDMA use does not persist long-term (Curran et al., 2004; Hoshi et al., 2007). Finally, clinical conditions for MDMA administration are likely to reduce the risk of damage to the serotonin system due to less risk of hyperthermia that is linked to MDMA-associated brain damage (Parrott, 2016) and increased drug purity.

Ketamine. Ketamine is commonly used as a sedative for violent and agitated patients in emergency medicine (Bragg & Miller, 1990; Cong et al., 2012; Hopper et al., 2015; Normandin et al., 2016; Riddell et al., 2017; J. R. Roberts & Geeting, 2001; Scheppke et al., 2014).

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Accidental Injury

MDMA. Studies examining the effect of MDMA on simulated driving performance have mixed results. In summarizing the research, Kuyper (2009) concluded that evidence from epidemiological studies and case studies demonstrate that MDMA impairs driving ability more so than simulated driving tests, though sleep deprivation and concomitant use of other substances may play a large role. One consistent finding from the literature is that MDMA impairs judgment of whether it is safe to drive and increases the propensity for risk-taking (Brookhuis et al., 2004; Ramaekers et al., 2006; Veldstra et al., 2011). Thus, it is important that driving ability be assessed following MDMA therapy sessions based on factors outside of self-report.

Ketamine. Accidental injury while intoxicated with ketamine has been identified as a major risk that can be potentially fatal (Giné et al., 2016; Jansen, 1993, 2011; Muetzelfeldt et al., 2008; Sassano-Higgins et al., 2016; Stewart, 2001; Tackett-Gibson, 2009). Due to the dissociative, analgesic, and coordination-impairing effects of ketamine, there is a high risk of accidental injury while intoxicated with ketamine if movement is attempted (Curran & Morgan, 2000; C. J. A. Morgan & Curran, 2011; Muetzelfeldt et al., 2008). At higher doses, the effects of ketamine can be immobilizing, resulting in a helpless state (Jansen, 1993). The risk of accidental injury can be mitigated by preventing patients from moving during acute intoxication and assisting and supervising any necessary movement.

Jansen (1993) also reports that ketamine can result in a state of apathy toward living or dying, not due to depression or suicidality but rather a breakdown of the concept of death. Jansen (p. 601) quotes Stevens (1989) in saying, “If you have a full-blown

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experience of K [ketamine], you can never believe there is death, or that death can possibly influence who you are." Thus, it is important that clinicians understand the profound change in relation to death that may occur under ketamine and take precautions to ensure a safe environment.

Trauma Due to Therapy Abuse

Recent articles and podcasts in popular media have highlighted the need for more awareness about sexual assaults occurring within the context of psychedelic treatments (Hall, 2021; New York Magazine, 2021; Weiss, 2020). Sexual feelings during psychedelic-assisted therapy are common among patients, and unscrupulous providers can take advantage of these feelings along with the rapid familiarity, suggestibility, and disinhibition that come with psychedelic states (Carhart-Harris et al., 2015; H. A. Garcia, 2005; Passie, 2018; Sjoberg & Hollister, 1965). Sex between a patient and therapist is harmful, unethical, and illegal. Sexual abuse within the context of a psychedelic session is particularly harmful due to heightened sensitivity, distorted perception, and impaired episodic memory, which can complicate recovery from abuse.

Unfortunately, sexual abuse within the psychedelic healing context does happen, and therefore it is important to take precautions at the individual and systems level to prevent sexual abuse of patients (McCarthy, 2015; Weiss, 2020). In trials run by MAPS, sexual assault is prevented through the presence of two therapy providers, video recording, monitoring therapy activities, and clinical supervision (MAPS, 2020). Ann Shulgin (1995) suggests establishing a patient contract prior to beginning the psychedelic session. The first of four rules she presents is: "All sexual feelings are allowable; they can and should be discussed, but will not be physically acted out here" (p. 2). The MDMA-

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assisted therapy manual prescribes a similar agreement between patient and therapist (Mithoefer, 2017, p. 23).

While strict rules prohibiting sexual contact with patients during psychedelic therapy are clearly warranted, there is more ambiguity around the use of touch during psychedelic therapy. Unlike traditional talk therapy, psychedelic therapies commonly include “nurturing touch” (Mithoefer, 2017, p. 7). The ethical use of touch in psychedelic therapy is under active debate as the field progresses (Devenot et al., 2022; McLane et al., 2021). Again, most of these debates are occurring within the journalistic sphere rather than in academic and medical journals.

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Summary and Comparison

Summary Table 12 provides an overview of the acute and subacute psychological risks of each psychedelic. Presented in Summary Table 13 are the long-term psychological risks associated with each psychedelic. The following symbols are used:

+++	Strong risk association backed by numerous studies.
++	Moderate risk association backed by several studies.
+	Mild risk that may be backed by a single case study.
⊕⊕	Theoretical risk is based on indirect research findings or similarities to another psychedelic. The same frequency/intensity conventions are used as with "+."
∅	Research indicates little to no associated risk.
-	No research was found.

Summary Table 14 gives an overview of psychological risk factors. The following symbols are used:

×	Strong risk of a negative outcome.
⊖	Caution is warranted due to a possible negative outcome.
⊖	Extreme caution is warranted due to a high risk of a negative outcome.
⊖	Caution is warranted due to a risk of a negative outcome supported by indirect research findings, similarity to another psychedelic, or theory.
○	Generally considered safe.

Summary Table 12

Acute and Subacute Psychological Risks of Psychedelics

Outcome	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Acute								
Challenging experiences or 'bad trips'	+	++	++	++	++	+	⊕⊕	⊕⊕⊕
Suicidality	-	++	+	-	-	++	⊕	-
Violent behavior	-	+	+	-	+	∅	∅	-
Accidental injury	-	-	-	-	-	+	+++	-
Therapy abuse	+	+	+	+	+	+	++	+
Subacute								
Psychosis	++	++	++	++	++	++	+++	++
Mania/hypomania	-	+	⊕	++	++	-	+++	+++
Anxiety and panic	-	∅	∅	-	+	+	∅	-
Depression/low mood	-	∅	∅	-	∅	+	+	-
Somatization/conversion	-	∅	-	-	-	+	-	-
Suicidality	-	-	-	-	⊕	+	++	-
Violence/aggression	-	-	-	-	-	+	-	-

Note. Symbol key on page 379.

Summary Table 13

Risk of Long-Term Psychopathogenesis from Psychedelics

Outcome	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA (Chronic)	Ketamine (Chronic)	Ketamine (Treatment)	Ibogaine
Persistent psychosis	∅	∅	∅	∅	∅	++	++	∅	-
Dissociative disorder	-	-	-	-	-	-	-	⊕⊕	-
Bipolar disorder	-	⊕	-	-	-	∅	∅	-	⊕⊕
Anxiety	∅	∅	∅	-	∅	++	∅	∅	-
Depression	∅	∅	∅	-	∅	++	++	∅	-
Somatization/conversion	-	∅	-	-	∅	∅	-	∅	-
Suicidality	∅	∅	∅	∅	∅	∅	-	-	-
Abuse of psychedelic	∅	∅	∅	∅	∅	+	++	+	∅
Other drug abuse	-	-	-	-	∅	++	-	-	-
Flashbacks (non-distressing)	-	∅	-	-	-	+	++	-	-
HPPD (distressing)	∅	++	+	∅	∅	+	∅	+	+
Violent behavior	∅	∅	∅	-	-	++	-	-	-

Note. Symbol key on page 379. Long-term effects are persistent for greater than or equal to four weeks. Chronic refers to ongoing, long-term recreational use.

Summary Table 14

Psychological Risk Factors

Risk factor	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
General psychological vulnerability	⊖⊖	⊖⊖	⊖⊖	⊖⊖	⊖⊖	⊖	⊜	⊖⊖
Personal or family history of…								
Psychosis and schizophrenia[a]	×	×	×	×	×	×	⊖	×
Paranoia	⊖	⊖⊖	⊖	⊖	⊖	⊖	⊖	⊖
Bipolar disorder	⊖	⊖⊖	⊖	×	×	⊖	⊖	×
Anxiety	○	⊖	⊖	⊖	⊖	⊖	○	⊜
Depression	⊖	⊖	⊖	⊜	⊜	⊖	○	⊜
Prior suicide attempts	⊜	⊖⊖	⊖	⊜	⊜	⊖⊖	⊖⊖	⊜
History of violence	○	⊖	⊖	○	⊖	⊖	○	⊜
History of substance abuse	○	○	○	○	○	⊖	⊖⊖	○

Note. Symbol key on page 379.

[a] See Chapter 12 section titled “Schizophrenia” for more nuance on possible psychedelic treatments for psychosis.

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Chapter 10: Factors Influencing Psychedelic Experience

This section examines the impact of therapeutic factors and personality traits on the subjective experience of psychedelics. While in other sections of this study, correlation coefficients are normalized to effect sizes, this chapter primarily reports on correlational data. For this reason, this normalization was not performed. The known impacts of demographic and personality factors on psychedelic experience and expected outcome are outlined in Summary Table 15.

Set, Setting, and Intentions

Leary et al. (1964) described and popularized the terms [mind]*set* and *setting* to describe the main influencers on the outcome of a psychedelic experience. However, these principles were referenced by earlier psychedelic pioneers, including traditional shamans (Hartogsohn, 2017). *Set* refers to the mindset of the participant going into the experience: what they know about psychedelics, what they have been primed to expect, their mood, and their intentions. *Setting* refers to the physical place where the experience takes place: the environment, the people one is with, and the intrusion of outside information and forces. Since the early 1960s, these variables have been widely known and applied by researchers and recreational psychedelic users alike. They have been subsequently validated as significant influencers upon psychedelic experience.

Haijen et al. (2018) studied people intending to take classical psychedelics on their own, outside of a laboratory context [N=654, 74% male, age M=28.9, race N/R]. Their analysis identified three factors that accounted for 55.14% of the outcome variance: “set,” “setting,” and “clear intentions.” While there was some overlap between the three factors, this study provides empirical validation for the set and setting model described by

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Leary et al. and extends it to include intentions. These factors are described in more detail below, as are their effect on psychedelic experience and outcome.

Set

The set factor involves one's comfort, openness, preparedness, anxiety, and mood in relation to the upcoming psychedelic experience (Haijen et al., 2018). It also includes a person's readiness to surrender to the experience and preoccupation with work/life duties.

Classical Psychedelics. Haijen et al. (2018) found that with classical psychedelics, set predicted a less challenging experience ($p<.001$) [$n=379$, 74% male, age $M=28.9$, race N/R]. Improved set showed a correlation approaching significance to greater well-being 2 weeks ($p=.099$) but not 4 weeks ($p=.534$) following the experience.

Psilocybin. Metzner et al. (1965) found that a larger group size during a 25–30 mg psilocybin experience was correlated with a "mood of concentration" ($p<.01$; $r=.30$) and "feelings of unity with the whole group" ($p<.05$; $r=.25$) [$N=82$; age $M=26.9$, $SD=7.1$; sex and race N/R]. Smaller group size, on the other hand, correlated with more experiences of "confronting the mystery of life" ($p<.01$; $r=-.34$), "active mood" ($p<.01$; $r=-.29$), "feeling no separation between self & the visions" ($p<.01$; $r=-.29$), "floors, walls, objects, etc., moving" ($p<.05$; $r=-.22$), "feeling beyond good and evil" ($p<.05$; $r=-.22$), and "hallucinations involving the whole person" ($p<.05$; $r=-.22$).

Carbonaro et al. (2016) determined through an online web survey that increased difficulty of psilocybin mushroom experience (DOE) was predictive of enduring improvements to well-being but that the duration of this difficult experience (DODE) was negatively correlated to improved well-being [$n=1,897$]. They found that having a

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positive emotional state before taking psilocybin was correlated with reduced DOE ($p<.05$; $r=-.052$) and DODE ($p<.001$; $r=-.087$).

Russ et al. (2019b) found that a state of surrender prior to psilocybin experience was associated with mystical experience ($p<.001$; $\beta=0.607$) based on a retrospective online survey [$N=143$, 57% male, age=18–62, race N/R]. They describe surrender as "a readiness to accept whatever was, whether good or bad, without resisting or fighting or struggling" (p. 6). This finding was replicated in a second online survey ($\beta=0.477$) where participants were asked to reflect on a psilocybin experience in the last 12 months [$N=183$, 53.0% male, age=18–70, race N/R] (Russ et al., 2019a). An updated model incorporating data from both studies yielded a combined effect of $\beta=0.453$ ($p<.001$) for the impact of surrender on mystical experience.

The updated model by Russ et al. (2019a) also showed a significant effect of deservingness ($p<.01$; $\beta=-0.162$), spiritual motivations ($p<.001$; $\beta=0.289$), and apprehension ($p<.05$; $\beta=-0.117$) on mystical experience. Deservingness was represented by a 5-item measure of "the extent to which individuals believe they are uniquely entitled to wealth and resources" (p. 3). Spiritual motivations measured intent toward spiritual gain through the psilocybin experience. Apprehension was a single-item measure of how apprehensive the participant felt immediately prior to taking psilocybin. Russ et al. also found that preoccupation or "a state of being mentally busy with one's mundane daily concerns" (p. 2) was also associated with increased anxiety and impaired control and cognition ($p<.001$; $\beta=0.159$), as was apprehension ($p<.05$; $\beta=0.159$). Finally, confusion or "a state of uncertainty about who one was or where one was going" (p. 3) was also associated with increased anxiety and impaired control and cognition ($p<.01$; $\beta=0.220$).

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Setting

Setting refers to one's feelings about the environment where the psychedelic session will take place (Haijen et al., 2018). Included in this are relationships and feelings toward those present for the experience.

Across Psychedelics. Ona (2018) found that more adverse psychedelic reactions were associated with recreational use and using drugs in "large, open outdoor spaces" [*N*=233, age=18–54, sex N/R, international sample]. Adverse reactions were also more common with drugs of unknown purity or dosage and when mixing drugs.

Classical Psychedelics. Haijen et al. (2018) found a correlation approaching significance (p=.070) between improved setting and less challenging classical psychedelic experience [n=379, 74% male, age M=28.9, race N/R]. Improvements in setting were also correlated with greater well-being 2 weeks following the experience (p=.037) and 4 weeks following this trend approached significance (p=.077).

Psilocybin. Carbonaro et al. (2016) found through an online web survey that increased DOE was predictive of enduring improvements in well-being but that DODE was negatively correlated to improved well-being [n=1,897]. In terms of setting, they found that a comfortable setting was negatively correlated with both DOE (p<.01; r=-.068) and DODE (p<.001; r=-.074). Social support during the session was negatively correlated with DOE (p<.001; r=-.085) and DODE (p<.001; r=-.146). The presence of a guide showed no significant correlation with the DOE but was negatively correlated with DODE (p<.001; r=-.092). Across these factors, there are smaller negative correlation magnitudes for DOE compared to DODE. Since high DOE with low DODE was predictive of long-term improved well-being, this suggests that better therapeutic

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outcomes will be achieved when patients are in a positive emotional state, provided with social support, accompanied by a guide, and in a comfortable setting, though the impact of comfortable setting may be negligible (r=-.068 vs. -.074).

Russ et al. (2019b) found that more exposure to language during psilocybin experience was associated with less mystical experience (p<.05; β=-0.130) based on a retrospective online survey [N=143, 57% male, age=18–62, race N/R]. This finding was replicated in a second online survey (β=-0.140) where participants were asked to reflect on a psilocybin experience in the last 12 months [N=183, 53.0% male, age=18–70, race N/R] (Russ et al., 2019a). However, when the data was separated by gender, exposure to language during the experience only remained a significant factor for males. The factor no longer remained in the best-fitting model for the combined data.

MDMA. Kirkpatrick, Baggott, et al. (2014) found that the physiological and phenomenological effects of MDMA were consistent across three different laboratory environments [N=220].

Intentions

The "clear intentions" factor uncovered by Haijen et al. (2018) regarding classical psychedelic experience refers to having strong expectations and having a clear intention for the upcoming experience. However, Sola notes that therapeutic wisdom differs regarding patient expectations (E. Sola, personal communication, October 12, 2020). The MAPS MDMA-assisted psychotherapy protocol states that "Therapists encourage the participant to set aside expectations and remain open to whatever emerges…" (Mithoefer, 2017, p. 35). Orienting patients to the experience in this way prevents them from attempting to steer their experience in one direction or another and provides the

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opportunity for unexpected insights to emerge (E. Sola, ibid.). This preparatory strategy aligns with the findings of Russ et al. (2019b, 2019a) that a state of surrender prior to psilocybin experience correlates with increased mystical experience (see "Set" above).

Classical Psychedelics. Haijen et al. (2018) found that having "clear intentions" regarding a psychedelic experience increased visual effects (p=.033) and increased mystical experience (p=.013) [n=379, 74% male, age M=28.9, race N/R]. This conflicts with the findings by Russ et al. (2019b, 2019a) regarding a state of surrender correlating with increased mystical experience (see paragraph above). It is notable that the "set" factor from Haijen et al. (2018), which also includes questions about openness to the experience, was not correlated with increased mystical experience (p=.835). Having clear intentions showed no associated difference in well-being 2 or 4 weeks following (p=.208–.545).

Haijen et al. (2018) also identified three clusters of intentions: "spiritual connection," "recreation," and "emotional." Having an intention of spiritual connection showed a correlation approaching significance with mystical experience (p=.054) and was associated with greater well-being at 2-week (p=.036) and 4-week (p=.035) follow-up. This included intentions of gaining spiritual or religious experience, connecting with nature, or growing personally or therapeutically. Having an intention of recreation was negatively correlated with challenging experiences (p<.007), meaning those taking a psychedelic for pleasure were less likely to have a challenging experience. There was no significant correlation between recreational intention and well-being 2 or 4 weeks following (p=.438–.865). Having an emotional intention, which involved either escaping difficult emotions, confronting difficult emotions, or medicinal intention, showed no

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significant correlation to mystical experience (p=.335), challenging experience (p=.814), or visual effects (p=.617). Having an emotional intention was not correlated with well-being change 2 weeks following the experience (p=.992) but showed a correlation approaching significance with decreased well-being 4 weeks following (p=.086).

Dose

Psychedelic dosing is a complex subject that depends on many factors. Because this review is aimed at supporting decisions between psychedelic treatments rather than being a manual for executing treatments, the specifics of dosing are not described here. Rather, this section will be focused on understanding the impacts of "low-dose" versus "high-dose" psychedelic doses with limited granularity. Empirical research on the effects of dose on psychological change and experiential variables known to influence psychological change is emphasized.

Classical Psychedelics. Nour et al. (2016) found that classical psychedelic dose was correlated with increased ego-dissolution (rho=.371) based on an online survey of recreational experiences [N=691, 34% female, age median=28, race N/R]. The same was not true of cocaine (rho=.115) or alcohol (rho=-.055). Haijen et al. (2018) found that increased classical psychedelic dose was predictive of mystical experience (p<.001), challenging experience (p<.020), and increased visual effects (p<.004) [n=379, 74% male, age M=28.9, race N/R]. Higher doses showed no correlation with the change in well-being 2 or 4 weeks following the experience (p=.362–.526). Drug doses were normalized to approximate LSD equivalent.

Psilocybin. In a pooled analysis of multiple studies [N=110 subjects], Studerus et al. (2011) found that psilocybin acutely increased all sub-scales of the Altered States of

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Consciousness scale (5D-ASC) in a dose-dependent fashion. There was also a dose-dependent increase in fatigue (p<.001), lack of energy (p=.002), "heavy or tired legs" (p=.008), and decreased vigilance with higher doses of psilocybin. This trend was, however, not significant for exhaustion (p=.09) or sleeplessness (p=.290). There were dose-dependent increases in difficulty concentrating (p=.015) and "gone feeling" (p=.005). A second pooled analysis [N=261 subjects] by Studerus et al. (2012) also found significant correlations (p<.001) between psilocybin dose and altered states of consciousness (d_r≈1.5), experiences of oceanic boundlessness (d_r>0.87), dread of ego dissolution (d_r>0.41), and visual experiences (d_r>0.87).

Griffiths et al. (2011) found that subjective effects of psilocybin increased as a function of dose (0–30 mg/70 kg) [N=18, 45% male, age=29–62, race N/R]. They also found that the frequency of complete mystical experiences increased with dose, from 0% of participants at 0 mg/70 kg, 5.6% at 5, 11.1% at 10, 44.4% at 20, and 55.6% at 30. Further, the researchers found that experiences of extreme fear, fear of insanity, and feeling trapped occurred more frequently in high-dose sessions, with 1 of 7 such experiences occurring at 20 mg/70 kg and 6 of 7 occurring at 30 mg/70 kg.

In accordance, Carbonaro et al. (2016) found through an online survey that psilocybin mushroom dose was positively correlated with DOE (p<.001; r=.181) and DODE (p<.01; r=.069) in a recreational context [N=1,993]. Carbonaro et al. also found that DOE was predictive of durable increases in well-being, while DODE was negatively correlated with improved well-being. The larger magnitude of positive correlation between dose and DOE (r=.181) compared to DODE (r=.069) suggests a link between increased dose and well-being improvements.

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Finally, Bienemann et al. (2020) found that taking a single high dose of psilocybin in a recreational context was associated with medical emergencies based on 346 reports from the EROWID database.

DMT. DMT shows hallucinogenic effects beginning at a dose of approximately 0.2 mg/kg IV, with 0.05 and 0.1 mg/kg doses not producing hallucinations but instead producing emotional and somatic effects [*N*=12] (Strassman et al., 1994). A dose of 0.4 mg/kg IV was overwhelming for almost all subjects due to the fast and intense onset. There tended to be a brief "anxiety-provoking 'rush'" that corresponded with a rapid transition from a normal mental state to a state where hallucinatory effects dominated. All subjects had vibrant visual effects at this dose, and approximately half had auditory hallucinations or distortions. A 0.2 mg/kg dose was less intense than 0.4 mg/kg, which resulted in less frightfulness, some visual hallucinations, and few auditory hallucinations. With a 0.1 mg/kg dose, there was a somatic effect that most subjects found to be an "uncomfortable physical tension" but no hallucinogenic effect. A 0.05 mg/kg dose was commonly mistaken for a placebo, but some found it to have "relaxing, comforting, and 'warm' physical effects."

MDMA. In a review of the subjective effects of MDMA and ecstasy, Baylen and Rosenberg (2006) note that higher recreational doses were associated with additional adverse effects, including nystagmus, muddled thought, jittery feelings, loss of control, unpredictable mood, erratic behavior, and memory loss. Larger doses were also associated with more hallucinatory effects and disorientation.

Mithoefer et al. (2018) performed a dose-response study with MDMA-assisted psychotherapy for PTSD. They found that improvements in PTSD symptoms were

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significantly greater with 75 mg (p=.0005; d=2.8) and 125 mg (p=.004; d=1.1) MDMA compared to 30 mg [N=26, 73% male, age M=37.2; 85% White, 8% Latino or Hispanic, 4% Native American, 4% Native American and White]. No significant difference in efficacy was seen between 75 and 125 mg doses (p=.185).

Ketamine. The effects of ketamine are dose-dependent, with psychotomimetic effects becoming greater with progressively higher doses before consciousness is lost with anesthetic doses (Kolp et al., 2014). Low doses have anxiolytic and analgesic effects.

Effect of Other Drugs

Psilocybin. Carbonaro et al. (2016) found through an online web survey that cannabis use prior to psilocybin mushrooms correlated with reduced DOE (p<.05; r=-.057) but showed no correlation with DODE [n=1,897]. A similar trend was seen for any drug use prior to the session (DOE: p<.01; r=-.072; DODE: p=NS). Given their finding that difficulty of experience is predictive of improved well-being, cannabis or other drug use prior to psilocybin may not support therapeutic efficacy.

Sex and Gender

Sex Differences in Acute Effects

Psilocybin. In a text extraction study from the EROWID database, 346 reports of negative outcomes related to psilocybin were identified (Bienemann et al., 2020). The authors found that “bad trips” were more frequent in females and were typically associated with thinking distortions.

MDMA. Liechti et al. (2001) saw increased subjective effects of 70–150 mg MDMA in women compared to men in an RCT [N=74, 73% male, age=20–49, race

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N/R]. These included perceptual changes, thought disturbances, fear of loss of body control, and acute adverse effects.

Ketamine. Across studies, female rats show higher sensitivity to ketamine than male rats (Lees et al., 2016; Saland et al., 2017). However, there is very little evidence in humans regarding sex differences in ketamine sensitivity, which Saland et al. (2017) attribute to a lack of studies. However, Jane et al. (2016) note several studies that found ketamine metabolism and sensitivity to be different in primates than in rats. Further, no notes were found in the extensive clinical literature on ketamine treatment suggesting dose adjustment based on gender.

Freeman et al. (2019) saw no significant difference in adverse effects between men and women ($p>.21$) in an RCT treating depression with 0.1–1.0 mg/kg ketamine infusion [$N=99$, age $M=46.2$, 51% male, 89% White, 5% Asian, 4% Black, 3% Hispanic, 2% other].

C. J. A. Morgan et al. (2006) found greater memory impairment ($p<.034$) and perceived amnesia ($p<.013$) under ketamine in men than in women in an analysis of data from 11 placebo-controlled studies [$N=295$ participants].

Sex Differences in Subacute Effects

MDMA. Vizeli and Liechti (2017) also saw significantly more symptom complaints in the subacute period following 125 mg MDMA in women than men ($p<.001$) in a pooled analysis of nine RCTs [$N=166$, 50% women, age=18–45, 100% Caucasian]. Symptoms included "…headache, lack of appetite, lack of energy, dry mouth, difficulty concentrating, and bruxism" (p. 580). Increases in depressed mood did not reach significance.

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Verheyden et al. (2002) saw significantly more depressive symptoms among women than men ($p<.05$) 4 days after taking recreational MDMA, with more than a third of women experiencing mild to moderate depression [n=80, 48% female, age=18–35, race N/R]. The severity of depressive symptoms was correlated to MDMA dose in women but not in men and was also significant compared to controls.

Ketamine. Ketamine-dependent women had a higher likelihood of experiencing discontinuation symptoms than men [N=1614, 84% male, age M=26.3, Taiwanese] (W.-Y. Chen et al., 2014). Symptoms included anxiety, dysphoria, and tremors.

Sex Differences in Treatment Response

Ketamine. Freeman et al. (2019) saw no significant difference (p=.80) between men and women in response to 0.1–1.0 mg/kg ketamine infusion for treatment-resistant depression in an RCT [N=99, age M=46.2, 51% male, 89% White, 5% Asian, 4% Black, 3% Hispanic, 2% other]. There was also no difference in treatment response between pre- and postmenopausal women (p=.55; n=3).

Age

LSD. Eggert and Shagass (1966) found among non-psychotic psychiatric inpatients, none of six patients under 22 had an insightful response to 2.5 μg/kg LSD, while eight of 14 over 22 did [N=20; 65% male; age=16–36, median=24; race N/R]. Two independent raters judged whether an insightful response was seen (see the section "Psychopathy, Poor Marital History, and Lack of Guilt Feelings" below for more details).

Psilocybin. Metzner et al. (1965) found that age was positively correlated with "witnessing historic events" ($p<.01$; r=.33), "visions of buildings or parts of buildings" ($p<.01$; r=.31), and "visions of fabulous animals, monsters, etc." ($p<.05$; r=.25) during

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25–30 mg psilocybin experience [*N*=82; age *M*=26.9, *SD*=7.1; sex and race N/R]. Age was negatively correlated with "lost time sense" ($p<.01$; $r=-.33$), "feeling of being at several different levels" ($p<.05$; $r=-.24$), "numbness" ($p<.05$; $r=-.22$), "self and other people changing size" ($p<.05$; $r=-.21$), "feeling of insight into self, without being able to state what it was" ($p<.05$; $r=-.21$), and "egotist mood" ($p<.05$; $r=-.21$).

A pooled analysis by Studerus et al. (2012) saw a negative correlation between age and impaired control and cognition ($p<.05$; $r=-.2$ to $-.4$) during psilocybin experience in healthy volunteers [*N*=261 subjects; 62% male; age *M*=27.8, *SD*=6.0; race N/R].

Carbonaro et al. (2016) found through an online web survey that age was negatively correlated with DOE ($p<.01$; $r=-.062$) but not correlated with DODE [*n*=1,897; 78% male; age at last psilocybin use=18–66, *M*=26.1; 89% White, 1.3% American Indian, 1.2% Asian, 0.3% Black or African American, 1.7% other].

Russ et al. (2019b) found that increasing age was negatively correlated with mystical experiences from psilocybin ($p<.05$; $\beta=-0.126$) based on a retrospective online survey of recreational users [*N*=143, 57% male; age=18–62, *M*=31.3, *SD*=9.66; race N/R]. This finding was not replicated in a second survey study where participants were asked to reflect on a psilocybin experience in the last 12 months [*N*=183; 53.0% male; age=18–70, *M*=31.9, *SD*=9.43; race N/R] (Russ et al., 2019a).

Ketamine. Murrough et al. (2013) found that younger age was predictive of a larger treatment response ($p=.051$; $\beta=-0.39$) to 0.5 mg/kg ketamine infusion for depression in a finding that approached significance [*N*=25; 40% female; age=21–70, *M*=49.0, *SD*=11.2; race N/R].

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Big Five Personality Traits

The Big Five personality traits are empirically derived personality factors that are strongly supported by research. A more thorough description of these personality traits can be found in the Chapter 7 section, "Big Five Personality Traits."

I. Extraversion and IV. Neuroticism

LSD. Hemsley and Ward (1985) administered the Eysenck Personality Questionnaire (EPQ) along with a survey on past psychedelic use and experiences to 29 patients in the drug dependence unit of a London hospital [demographics N/R]. They found that Extraversion correlated negatively with the "frequency of reported 'bad trips'" ($p<.05$; $r=-.38$) following LSD ingestion. Neuroticism was correlated positively with "unpleasant visual hallucinations on a trip" ($p<.01$; $r=.53$), "frequency of reported 'bad trips'" ($p<.01$; $r=.47$), and "frequency of 'flashbacks'" ($p<.01$; $r=.47$) associated with LSD experiences [$N=29$, hospitalized].

Lienert and Netter (1996) examined the responses of 1 μg/kg LSD among four groups differentiated by combinations of high/low Extraversion and high/low Neuroticism [$N=65$, demographics N/R]. Three types of responses were coded: non-responsiveness (at least one instance of not reacting to their first name), thinking disturbances (not finishing a sentence at least once), and affective reactions (spontaneous laughter or weeping for no obvious reason). Because no statistical analysis was provided in the original study, the present author performed a binomial analysis of the response frequencies between those with high and low Extraversion and those with high and low Neuroticism. The findings from this analysis are provided in Table 43.

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Psilocybin. F. S. Barrett et al. (2017) found through an online survey [*N*=2,974] that higher trait Neuroticism is associated ($p<.0001$; $\beta=0.259$) with more challenging experience in response to psilocybin mushrooms as measured by the CEQ.

Table 43

Effect of Extraversion and Neuroticism on LSD Response (analysis of data from Lienert & Netter, 1996)

MPI Trait	*n*	Non-Responsiveness	Thinking Disturbances	Affective Reactions
High Extraversion	32	63%	47%	88%
Low Extraversion	33	52%	57%	36%
p		.266	.274	**<.001**
d_{OR}		0.11	-0.11	**0.40**
High Neuroticism	32	60%	75%	72%
Low Neuroticism	33	55%	30%	50%
p		.369	**<.001**	.189
d_{OR}		0.05	**0.50**	0.12

Note. Statistically significant effects are bolded. MPI = Eysenck's Maudsley Personality Inventory.

II. Agreeableness

LSD. Carhart-Harris et al. (2016) saw an inverse correlation between baseline Agreeableness and increases in optimism 2 weeks following 75 µg IV LSD ($p=.014$; $r=-.56$)[*N*=20, 20% female, age=22–47, race N/R]. However, this result did not reach significance when correcting for multiple comparisons.

III. Conscientiousness

LSD. Carhart-Harris et al. (2015) found that Conscientiousness was significantly correlated to increased suggestibility ($p=.0005$; $r=.89$) under LSD [*N*=10, 10% female, age=26–47, race N/R].

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V. Openness

Classical Psychedelics. Haijen et al. (2018) found that baseline Openness was correlated with greater well-being at 2 weeks (p=.030; β=1.273) but not 4 weeks (p=.829; β=0.166) following classical psychedelic use [n=379, 74% male, age M=28.9, race N/R].

Psilocybin. Russ et al. (2019a) found that Openness was associated with less anxiety and impaired cognition during psilocybin experience (p<.05; β=-0.129) based on an online survey [N=183, 53.0% male, age=18–70, race N/R].

Other Personality Traits

Absorption

The trait absorption was derived from a factor analysis of questions believed to be related to hypnotizability (Tellegen & Atkinson, 1974). Tellegen and Atkinson found that in addition to the known factors of stability and introversion, there was a third factor that they labeled absorption. They described this dimension as "a disposition for having episodes of 'total' attention that fully engage one's representational (i.e., perceptual, enactive, imaginative, and ideational) resources" (p. 268). It is commonly measured using Tellegen Absorption Scale (TAS; Tellegen & Atkinson, 1974) or the Modified Tellegen Absorption Scale (MODTAS; Jamieson, 2005).

Classical Psychedelics. Ott et al. (2005) found that absorption is correlated to the T/T genotype of the *T102C* polymorphism (p=.002), which corresponds to a stronger binding potential of 5-HT_{2A} receptors [N=336, 72% female, race N/R]. This finding implies that those higher in the trait of absorption are likely more affected by the classical psychedelics (mescaline, LSD, psilocybin, DMT, ayahuasca) that bind to the 5-HT_{2A} receptor. In addition, Haijen et al. (2018) found that trait absorption was correlated with

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more mystical experience (p<.001; β=0.347), challenging experience (p<.020; β=0.215), and visual effects (p<.004; β=0.227) during a recreational classical psychedelic experience [n=379, 74% male, age M=28.9, race N/R]. This indicates that higher trait absorption is correlated with experiencing classical psychedelics more intensely.

LSD. In studying synesthesia experiences under 40–80 µg LSD, Terhune et al. (2016) saw an association approaching significance between higher trait absorption and decreased grapheme-color consistency (p=.069, r=-.67) [N=10, 90% male, age=26–47, race N/R].

Psilocybin. Russ et al. (2019b) found that higher trait absorption correlated with more mystical experience from psilocybin (p<.001; β=0.308) based on a retrospective online survey [N=143, 57% male, age=18–62, race N/R]. This finding was replicated in a second online survey (β=0.359) where participants were asked to reflect on a psilocybin experience in the last 12 months [N=183, 53.0% male, age=18–70, race N/R] (Russ et al., 2019a). An updated model incorporating data from both studies yielded a combined correlation of β=0.247 (p<.001).

Ayahuasca. Bresnick and Levin (2006) found that trait absorption was positively correlated (p<.05) to experiences of synesthesia during a 10-day ayahuasca retreat [N=21, 81% male, race N/R].

Psychoticism

LSD. Hemsley and Ward (1985) found no significant correlation between EPQ psychoticism and "visual hallucinations on 'trip'" (p=NS; r=.14), "frequency of 'bad trips'" (p=NS; r=.18), "unpleasant visual hallucinations on trip" (p=NS; r=-.02), "frequency of 'flashbacks'" (p=NS; r=.22), or "persistence of 'flashbacks'" (p=NS;

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r=.03) in a survey on past psychedelic experiences to given to 29 patients in the drug dependence unit of a London hospital [demographics N/R].

Obsessiveness

LSD. Baker (1964) states that highly obsessional personalities require higher doses of LSD for effective treatment based on their experience treating 150 patients with various presentations. Similarly, Grof (Grof, 1975) writes that LSD dose was typically "very high for obsessive-compulsive neurotics, whose excessive psychological resistances represent the opposite extreme [from hysterical patients]" (p. 21). Grof writes in the same paragraph that the typical dose he used across patients was 200 μg, but that doses occasionally reached 400–500 μg.

Anxiety and Depression

Classical Psychedelics. Haijen et al. (2018) found that baseline trait anxiety correlated with lower well-being at 4 weeks (p=.023; β=-2.368) but not 2 weeks (p=.158; β=-1.188) following classical psychedelic use [n=379, 74% male, age M=28.9, race N/R].

LSD. Carhart-Harris et al. (2016) saw a positive correlation between baseline depression (p=.024; r=.53) and baseline anxiety (p=.04; r=.49) and increased Openness 2 weeks following 75 μg IV LSD [N=20, 20% female, age=22–47, race N/R].

Use of Positive and Negative Speech

Psilocybin. Carrillo et al. (2018) analyzed transcripts autobiographical memories recounted by patients associating to standardized cue words (e.g., "newspaper") prior to 10 and 25 mg psilocybin for treatment-resistant depression [N=12, 50% male, age=30–64, 75% White, 17% Black, 8% Hispanic]. They found that less use of positively

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valenced language was predictive of treatment response with 85% accuracy (p<.05). Use of negatively valenced language, however, was not predictive of treatment outcome.

Dissociation

Ayahuasca. Bresnick and Levin (2006) found that baseline dissociation was positively correlated (p<.05) to experiences of synesthesia during a 10-day ayahuasca retreat [N=21, 81% male, race N/R].

Psychopathy, Poor Marital History, and Lack of Guilt Feelings

LSD. Eggert and Shagass (1966) examined the level of insight gained through a 2.5 μg/kg LSD session among non-psychotic psychiatric inpatients based on two independent ratings [N=20, 65% male, age=16–36, race N/R]. The ratings had good concordance, and the final analysis used a cutoff score to separate responders who gained insight from non-responders who did not. Those more likely to be responders had "psychopathic personality" (p<.01), "poor marital history" (p<.05), and "lack of guilt feelings" (p<.05).

Attachment Security

Psilocybin. Stauffer et al. (2021) found that baseline attachment anxiety was strongly correlated to mystical experience (p=.029; r=.53) during 21–25.2 mg/70 kg psilocybin group therapy, while baseline attachment avoidance was not (p=.693; r=-.10) [N=18, 100% male, age M=59.2, long-term AIDS survivors, race N/R]. Challenging experiences were strongly associated with baseline attachment avoidance (p=.006; r=.62) but not attachment anxiety (p=.489; r=.18).

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Barriers to Peak Experience

Maslow (1964) describes hypothesized mental barriers that can prevent transformative 'peak experiences.' Russ et al. (2019b) suggest that peak experiences are related to mystical experiences and summarize these barriers as "a tendency to reject information that is not easily explained through rational, logical, and scientific processes" (p. 4). These same factors were also described by William James in *The varieties of religious experience* (1902, p. 72), which is referenced by Maslow. Russ et al. (Russ et al., 2019a, 2019b) developed a new five-item measure called the Barriers Scale to measure barriers to mystical/religious/peak experience as described by James and Maslow. This new measure demonstrated good internal consistency (Cronbach's α=.87–.88) but is yet to be otherwise validated.

Psilocybin. Russ et al. (2019b) found that higher Barriers Scale scores correlated with less mystical experience from psilocybin (p<.01; β=-0.151) based on a retrospective online survey [N=143, 57% male, age=18–62, race N/R]. However, this finding was not replicated in a second online survey study where participants were asked to reflect on a psilocybin experience in the last 12 months [N=183, 53.0% male, age=18–70, race N/R] (Russ et al., 2019a).

Family or Personal History of Substance Abuse

Ketamine. Permoda-Osip et al. (2014) saw a stronger treatment response to a single 0.5 mg/kg ketamine infusion for bipolar depression among those with a personal or family history of alcoholism (p=.033) [N=42, 76% women, age=22–67, Polish]. Niciu et al. (2014) also found that 0.5 mg/kg ketamine infusion was more effective in treating depressive symptoms among those with a family history of alcohol use disorder 1 day

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(p=.001; β=-0.37) and 7 days (p<.001; β=-0.41) following treatment [N=108, 50% male, age M=47.2, 85% White]. At 230 minutes post-treatment, this effect approached significance (p=.080; β=-0.17).

Previous Suicide Attempt

Ketamine. Niciu et al. (2014) saw greater improvement in depressive symptoms in those with no history of prior suicide attempts 7 days following 0.5 mg/kg ketamine infusion (p=.01; β=-0.28) but not at 230 minutes (p=.916; β=-0.01) or 1 day (p=.196; β=-0.14) following.

Baseline Cognitive Functioning

Ketamine. Murrough et al. (2013) saw larger treatment response to 0.5 mg/kg ketamine infusion for depression in those with poorer baseline neurocognitive performance (p=.004) [N=25, 40% female, age M=21–70, race N/R]. Of the domains tested, lower processing speed (p=.008; β=0.42) and poorer working memory (p=.045) were predictive of better treatment response, while this finding did not reach significance for attention, verbal memory, or visual memory.

Body Mass Index

Psilocybin. Metzner et al. (1965) used patients' weight-to-height ratio as a proxy for what we now describe as body mass index (BMI). Those with a higher weight-to-height ratio (greater BMI) had more experiences of "eyes staring at you" (p<.05; r=.24) and "bodily pleasure" (p<.05; r=.21) under 25–30 mg psilocybin [N=82; age M=26.9, SD=7.1; sex and race N/R]. Those with a lower weight-to-height ratio (lower BMI) had more experiences "feeling of being at several different levels" (p<.05; r=-.28), "feeling of insight into self, without being able to state what it was" (p<.05; r=-.26), "self or other

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people changing size" (p<.05; r=-.21), "fighting the oncoming effects of the drug" (p<.05; r=-.22), "feeling beyond good and evil" (p<.05; r=-.22), and "unusual cognitive phenomena" (p<.05; r=-.20).

Ketamine. Niciu et al. (2014) found that higher BMI was correlated with greater improvement in depressive symptoms at 230 minutes (p=.004; β=-0.30) and 1 day (p=.001; β=-0.37) following 0.5 mg/kg ketamine infusion. This correlation was not significant at 7 days following infusion (p=.10; β=-0.18).

Genetic Differences

Ketamine. Laje et al. (2012) found that *rs6265* gene polymorphism influenced the efficacy of ketamine treatment for depression [N=62, 55% female, age M=46.3, 94% European ancestry, 6% African ancestry]. The *rs6265* gene affects BDNF function. Met carriers (Val/Met ~35% of the population; Met/Met >5%) were hypothesized to have a poorer response to ketamine treatment than homozygous Val/Val individuals (60% of the population) based on a prior animal study. Laje et al. confirmed this hypothesis (p=.0007; d_c=-0.71), with *rs6265* polymorphism accounting for 28% of the outcome variance at 210 to 230 minutes following ketamine infusion. On average, Val/Val individuals showed 41% symptom improvement, while Met carriers only showed 24% improvement.

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Summary and Comparison

Patient factors that influence psychedelic experience and outcomes are provided in Summary Table 15. The following symbols are used:

↑	Statistically significant increase
↓	Statistically significant decrease
-	No significant change
-$^{\uparrow}$	No significant change, but a directional trend
[2]	The number of references that demonstrate a finding. If not shown, only one study is referenced.

Effect size is shown using the conventions below. With multiple findings, an approximation of combined effect size was made. The symbols are as follows:

	Small or Tiny effect size [no asterisk] ($d \leq 0.2$; $r \leq .3$)
*	Moderate effect size ($d = 0.21–0.5$; $r = .3–.5$)
**	Large effect size ($d > 0.5$; $r > .5$)
***	Very Large effect size ($d > 1.0$; $r > .7$)

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Summary Table 15

Patient Factors Affecting Psychedelic Experience and Outcome

Psychedelic	Experiential Impact		Therapeutic Implication	Study
Female Sex				
Psilocybin, recreational	↑	'Bad trips'	Monitor	Bienemann et al. (2020)
MDMA, clinical	↑	Subjective effects	Lower dose	Liechti et al. (2001)
	↑	Acute adverse effects	Monitor	
	↑[9]	Subacute adverse effects	Monitor	Vizeli & Liechti (2017)
	-	Subacute depressive symptoms	None	
MDMA, recreational	↑	Subacute depressive symptoms	Monitor	Verheyden et al. (2002)
Ketamine, recreational	↑	Withdrawal symptoms following dependence	Monitor	W.-Y. Chen et al. (2014)
Male Sex				
Ketamine, clinical	↑[11]	Acute memory impairment	Intervention during experience less effective	C. J. A. Morgan et al. (2006)
Age Under 22				
LSD, clinical	↓	Insight from treatment (weak evidence)	Reduced efficacy	Eggert & Shagass (1966)
Increasing Age (Age *M*=27.2 across studies)				
Psilocybin, clinical	↓**	Impaired cognition and control	Monitor	Studerus et al. (2012)
Psilocybin, recreational	↓	Difficulty of experience	Possible reduced efficacy	Carbonaro et al. (2016)
	- / ↓	Mystical experience	Possible reduced efficacy	Russ et al. (2019b)
Ketamine infusion	↓*	Treatment response for depression	Reduced efficacy	Murrough et al. (2013)

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Psychedelic	Experiential Impact		Therapeutic Implication	Study
I. Extraversion				
LSD, recreational	↓*	Frequency of 'Bad trips'	None	Hemsley & Ward (1985)
LSD, clinical	↑*	Emotional reactions	None	Lienert & Netter (1996)
II. Agreeableness				
LSD, clinical	-↓**	Increases in optimism 2 weeks following	Decreased efficacy	Carhart-Harris et al. (2016)
III. Conscientiousness				
LSD, clinical	↑***	Suggestibility	Increased ability to use suggestion to enhance treatment.	Carhart-Harris et al. (2015)
IV. Neuroticism				
LSD, recreational	↑**	Frequency of 'Bad trips'	None	Hemsley & Ward (1985)
	↑**	Unpleasant visual hallucinations	None	
	↑**	Frequency of 'flashbacks'	None	
LSD, clinical	↑*	Thinking disturbances	None	Lienert & Netter (1996)
Psilocybin, recreational	↑*	Challenging experience	Increased efficacy	F. S. Barrett et al. (2017)
V. Openness				
Classical psychedelic, recreational	↑***	Openness after 2 weeks	Could provide a window of increased openness for other intervention.	Haijen et al. (2018)
	-	Openness after 4 weeks		
Psilocybin, clinical	↓	Anxiety and impaired cognition	None	Russ et al. (2019a)
Higher Trait Absorption				
Classical psychedelic, recreational	↑	Stronger effects	None	Ott et al. (2005)
	↑*	Mystical experience	Increased efficacy	Haijen et al. (2018)
	↑*	Challenging experience	Increased efficacy	
	↑*	Visual effects	None	

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Psychedelic	Experiential Impact		Therapeutic Implication	Study
LSD, clinical	-↑**	Increased grapheme-color consistent synesthesia	None	Terhune et al. (2016)
Psilocybin, recreational	↑*	Mystical experience	Increased efficacy	Russ et al. (2019b, 2019a)
Ayahuasca, ceremonial	↑	Synesthesia experience	None	Bresnick & Levin (2006)
Obsessiveness				
LSD, clinical	↓[2]	Effects	Use higher dose	Baker (1964), Grof (Grof, 1975, p. 21)
Anxiety				
LSD, clinical	↑*	Openness 2 weeks following treatment	Possible increased efficacy	Carhart-Harris et al. (2016)
Trait Anxiety				
Classical psychedelic, recreational	-↓***	Well-being after 2 weeks	Possible reduced efficacy, though finding may be due to lower baseline well-being.	Haijen et al. (2018)
	↓***	Well-being after 4 weeks		
Depressive Symptoms				
LSD, clinical	↑**	Openness 2 weeks following treatment	Possible increased efficacy	Carhart-Harris et al. (2016)
Little Use of Positively Valenced Language				
Psilocybin, clinical	↑	Treatment response for depression (predictive with 85% accuracy)	Screen for this trait as a treatment indicator	Carrillo et al. (2018)
Higher Dissociation				
Ayahuasca, ceremonial	↑	Synesthesia	None	Bresnick & Levin (2006)
Psychopathy, Poor Marital History, and Lack of Guilt Feelings				
LSD, clinical	↑	Insight gained from experience	Possible increased efficacy	Eggert & Shagass (1966)

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Psychedelic	Experiential Impact		Therapeutic Implication	Study
Higher Attachment Anxiety				
Psilocybin, clinical	↑**	Mystical experience	Possible increased efficacy	Stauffer et al. (2021)
Higher Attachment Avoidance				
Psilocybin, clinical	↑**	Challenging experience	Possible increased efficacy	Stauffer et al. (2021)
Barriers to Peak Experience				
Psilocybin, recreational	- / ↓	Mystical experience	Possible decreased efficacy	Russ et al. (2019b, 2019a)
Family or Personal History of Substance Abuse				
Ketamine infusion	↑	Efficacy for bipolar depression	Increased efficacy	Permoda-Osip et al. (2014)
	↑*	Reduction in depressive symptoms 1- and 7-days following treatment	Increased efficacy	Niciu et al. (2014)
No Prior Suicide Attempts				
Ketamine infusion	↑*	Reduction in depressive symptoms 7 days following	Increased efficacy	Niciu et al. (2014)
Slower Processing Speed				
Ketamine infusion	↑*	Treatment response for depression	Increased efficacy	Murrough et al. (2013)
Higher Body Mass Index				
Ketamine	↑*	Reduction in depressive symptoms 1 day following	Increased efficacy	Niciu et al. (2014)
***rs6265* Gene Met Carrier**				
Ketamine	↓**	Reduction in depressive symptoms	Reduced efficacy	Laje et al. (2012)

Note. Symbol key on page 405. Independent variables are bolded. Some studies described in the text of this chapter were not included in this table due to little applicability to treatment selection.

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Chapter 11: Psychedelic-Assisted Therapies

This chapter summarizes the common treatment approaches used in psychedelic-assisted therapies. It is not intended to be a comprehensive guide to the practice of psychedelic-assisted therapies but rather to describe different treatment approaches referenced in the chapter following on psychedelic treatment targets. For this reason, many articles related to "psychotherapy" were excluded.

Ceremony as Therapy

When used in indigenous cultures, mescaline, psilocybin, ayahuasca, and ibogaine are typically taken in a ceremonial context (Alper et al., 2001; de Rios et al., 2002; Dobkin, 1968; Guzmán, 2008; Shonle, 1925; Trichter, 2010). Even among Westerners, this ceremonial format continues to be the dominant context in which ayahuasca is used (Trichter, 2010). Few references were found suggesting an alternate paradigm for ayahuasca treatment. Calvert (2013) suggests that in some circumstances, a referral be made for ayahuasca ceremonies as an adjunct to traditional psychotherapy. Only in a handful of studies has ayahuasca been administered as a treatment without religious or ceremonial aspects (Osório et al., 2015; Palhano-Fontes et al., 2019; Sanches et al., 2016; Zeifman et al., 2021).

Therapies Using Classical Psychedelics

Psycholytic Therapy

Psycholytic therapy is a psychodynamic therapy that is facilitated by repeated administration of low to moderate LSD in doses (Grof, 1970). The earliest known practice of psycholytic-like therapy was in 1931 by Baroni, an Italian psychoanalyst who used a combination of mescaline and *Datura stramonium* to intensify psychoanalysis

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(Passie, 1997, p. 10). However, the bulk of psycholytic therapy practice did not begin until the discovery of LSD in 1943 and its subsequent distribution (Passie, 1997). The first publication on LSD psycholytic therapy was not until 1954, when Sandison, Spencer, and Whitelaw published a paper titled *The therapeutic value of lysergic acid diethylamide in mental illness.* Sandison et al. administered LSD treatments in two-week intervals with doses ranging from 25 to 400 μg depending on clinical judgment. Between sessions, patients participated in individual and group therapy where the content of LSD sessions was discussed. They were also placed in wards with others who were participating in LSD sessions. Patients continued LSD sessions until treatment was judged to be complete, which took from two to 58 sessions.

S. Cohen and Eisner (1959) provide an early but refined description of psycholytic therapy using low doses of LSD in a psychoanalytic outpatient context. They describe weekly or biweekly sessions beginning with 25 μg LSD and progressing to 100 or 150 μg to minimize anxiety and side effects. The number of sessions ranged from 1 to 16, with an average of 4.6 psycholytic sessions among the 22 patients treated. During the LSD sessions, Cohen and Eisner observed "the enhancement of transference" toward the therapist and emphasized the quality of the relationship between therapist and patient (p. 616). Therapeutic interventions were directive and "personally involved" and mimicked techniques they used with schizophrenic patients. Patients commonly "reexperienced repressed events" that led to "anxiety and somatic distress" (p. 617). Therapists sought to provide insight into the psychogenesis of these overwhelming feelings and encouraged patients to surrender to the experience. They describe this

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process as resulting in an "integrative experience" that "involved a massive reduction in self-conflict" (p. 617).

Following these early pioneers, the most influential writer on psycholytic therapy has been Stanislav Grof, who researched psycholytic therapy at Spring Grove Hospital in Maryland from 1967 until 1973, when psychedelic prohibition interfered with continued research (Grof, 1975, p. 23). Grof has written several books about psycholytic therapy and continued to develop theories of the unconscious based on altered states achieved through Holotropic Breathwork (Grof, 1975, 1980; Grof & Grof, 2010). In addition to Grof's work, Gasser (1994) reports on psycholytic therapy research with MDMA and LSD that took place in Switzerland from 1988 to 1993.

Psychedelic Therapy

Psychedelic therapy is "derived from the observations of dramatic personality changes and religious conversions in LSD subjects" (Grof, 1970, p. 53). These therapies typically consist of a single overwhelmingly high dose of LSD (400–2,000 μg). In the present study, psychedelic therapies will refer to high-dose sessions with minimal intervention during the session.

Hopkins Psilocybin Treatment Protocol

The psilocybin psychedelic therapies performed at Johns Hopkins University for treating cancer-related distress, depression, and tobacco addiction use a high dose (20–30 mg/70 kg) and a non-directive approach to intervention during the drug session (Davis, Barrett, et al., 2021; Doss et al., 2021; Griffiths et al., 2006, 2016; M. W. Johnson et al., 2014). Rather than describing sitters as therapists, they are described in the literature as "monitors," highlighting the more passive role taken regarding intervention during the

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sessions (M. W. Johnson et al., 2008). Monitors meet with patients for several preparatory sessions prior to the psilocybin session(s), where the patients' history and current circumstances are reviewed. The session itself takes place in an "aesthetic living-room-like environment" (Griffiths et al., 2016, p. 1182), with music playing and the patient lying on a couch with an eye mask to support internal focus. Two monitors are present and supportive touch is sometimes provided. No explicit instructions are given to participants regarding the focus of their attention during the session outside of what has been already described. Following the session, patients participate in at least one integration session with the monitors and are monitored for safety (M. W. Johnson et al., 2008).

MAPS Protocol for MDMA-Assisted Psychotherapy for PTSD

The protocol developed through and used in the MAPS trials of MDMA-Assisted Psychotherapy for PTSD (Mithoefer et al., 2011, 2018; Oehen et al., 2012; Ot'alora G et al., 2018) is based on the principle that "…the therapeutic effect is not due simply to the physiological effects of the medicine; rather, it is the result of an interaction between the effects of the medicine, the therapeutic setting and the mindsets of the participant and therapists (Mithoefer, 2017, p. 6). The *MDMA-Assisted Psychotherapy Treatment Manual* (Mithoefer, 2017) describes protocols for creating a safe and therapeutic environment for MDMA-assisted therapy, preparing patients for the MDMA sessions, developing the therapeutic alliance, administering MDMA-assisted psychotherapy, and helping the patient to integrate the MDMA experience during the follow-up sessions. In the actual MDMA sessions, two co-therapists, typically one male and one female, engage in an inward-directed therapy "based on empathetic rapport and empathetic presence" (p. 7).

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Instead of providing directive interventions, therapists "encourage the participant to trust their inner healing intelligence" (p. 8). Therapists are instructed to "enable the processing of trauma rather than the avoidance of traumatic memories" while also respecting defenses that emerge and "address[ing] somatic manifestations of trauma that arise" (p. 8). These tasks often involve active intervention, with various therapeutic tools prescribed for this purpose, including "music, focused bodywork, [and] breathing" (p. 8).

Ketamine Therapies

Ketamine Infusion

Ketamine infusion refers to subanesthetic ketamine, typically given intravenously (IV) without accompanying psychotherapy. Ketamine infusion is the typical intervention given for treatment-resistant depression (Mathews & Zarate, 2013). In this treatment paradigm, the psychedelic effects of ketamine such as acute dissociation and psychotomimetic symptoms are classified by some as negative "side effects." However, the strength of the subjective effects of ketamine has been shown to be a mediator of symptom improvement in depression and bipolar disorder (Luckenbaugh et al., 2014).

Ketamine-Assisted Psychotherapy (KAP)

Ketamine-assisted psychotherapy (KAP) uses the psychedelic properties of low-dose ketamine to enhance the effects of psychotherapy, similar to psycholytic therapy (Bennett et al., 2022; Dore et al., 2019). For practical use in an office setting, ketamine is typically administered sublingually, intranasally, or intramuscularly. Two specific techniques of KAP are discussed below that have specific bodies of literature but are considered by the present author to be subsets of KAP.

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Ketamine Psychedelic Therapy (KPT). Krupitsky et al. (1992) developed a therapy for treating alcohol use disorder called "Affective Contra-Attribution," which would eventually be called Ketamine Psychedelic Therapy (KPT; Krupitsky & Grinenko, 1997). KPT is also referred to as Ketamine Psychedelic Psychotherapy in some literature (Kolp et al., 2014). KPT begins with preparatory psychotherapy sessions. Following that, 2–3 mg/kg IM ketamine combined with the anxiogenic bemegride, which "potentiates the negative emotional experiences and visions," and the drug aethimizol, which "promotes the fixing of experiences in the long-term memory" (Krupitsky et al., 1992, pp. 100–101). When the hallucinogenic effects of this combination are most intense, the patient is presented with the smell and taste of alcohol, with the goal of creating an aversive association (Krupitsky et al., 1992). Finally, group psychotherapy is given to patients to discuss their experiences during the treatment, which hopefully involves a negative aversive aspect.

Ketamine-Enhanced Psychotherapy (KEP). Ketamine-Enhanced Psychotherapy (KEP) was developed by Kolp to translate the work of Krupitsky to the cultural context of the U.S., given that Krupitsky worked in the Soviet Union and Russia (Kolp et al., 2006). Kolp et al. state that "As with Krupitsky's KPT technique, Kolp's KEP explicitly relied on the transpersonal effects of ketamine to facilitate psychotherapeutic change" (p. 405). Presumably different from Krupitsky's method is the lack of bemegride and aethimizol adjuncts in KEP. These compounds are not mentioned in either description found of KEP (Kolp et al., 2006, 2007).

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Group Psychedelic Therapies

Group therapies can provide unique benefits over individual therapy by providing opportunities to develop comfort in expressing difficult emotions, build social skills, and learn new ways of relating to others. In addition, group psychedelic therapy is appealing to reduce the cost of psychedelic therapies. In indigenous cultures, psychedelics have commonly been used in group settings. The widespread practice among indigenous peoples of administering psychedelics in groups for the purpose of healing underwrites the safety and potential efficacy of group psychedelic therapies in Western medicine (Trope et al., 2019). As evidence has borne out with Ayahuasca, traditional psychedelic rituals provide tangible psychological benefits (Barbosa et al., 2016; Bouso et al., 2012, 2018; Da Silveira et al., 2005; Grob et al., 1996; Ona et al., 2019; Uthaug et al., 2018).

Much of contemporary psychedelic research has been directed more toward individual therapies rather than group methods. However, this was not the case in the early psychedelic clinical research, when group protocols with LSD were common (Blewett & Chwelos, 1959; Cheek & Holstein, 1971; Hausner & Dolezal, 1963; Sandison, 1959; Slater et al., 1963; Spencer, 1961, 1963). Blewett (1971) commented on the advantages of administering psychedelics in groups versus ordinary group therapy. The “essential difference” noted was the speed at which the therapy progressed, with a faster establishment of trust, transference, emotions, self-awareness, and self-acceptance. However, this accelerated progression came with a heightened intensity that requires the presence of experienced therapists with stamina for extended group process.

In a review of group therapy studies using classical psychedelics [N=12], Trope et al. (2019) found no studies reporting serious adverse events such as suicide or prolonged

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psychosis among the 700 participants represented. While therapeutic outcomes varied, all seven group therapies for “neurotics” showed clinical improvements for more than 50% of participants. The authors also found compelling results among two of four inpatient programs for treating alcoholism, with those incorporating 12-Step methods alongside psychedelics being effective. In a Phase I clinical trial, 10 and 25 mg psilocybin was well-tolerated when administered in groups of six [*N*=89, 54% male, 46% female, age *M*=36.1, 81% White, 1% Black, 7% Asian, 5% mixed ethnicity, 7% other ethnicity] (Rucker et al., 2022). In addition, Stauffer et al. (2021) performed psilocybin group therapy for men with AIDS with positive results in endpoint measures, though the authors did not report on safety [*N*=18, age *M*=59.2, 78% White, 17% multiracial, 6% Black].

During the period when MDMA was legal and used therapeutically in the U.S. (1977–1985), there were several practitioners developing and applying MDMA group therapies (Passie, 2018). Qualitative outcome reports by clients were positive from the German psychiatrist, Friederike Fischer, who illegally administered MDMA, LSD, and 2-CB in groups until her arrest in 2009 (Sessa & Fischer, 2015). In Switzerland, group psycholytic therapies were conducted from 1988 to 1993 (Gasser, 1994). Among a group of 171 patients that took part in these therapies, 46.3% retrospectively reported good symptom improvement, 38.8% slight improvement, 5.8% no change, 4.2% slight deterioration, and 5% fluctuated between improvement and deterioration (Gasser, 1994).

Contemporary studies to develop new group psychedelic therapies are just resuming. Two studies have been published on administering psilocybin in group settings, both demonstrating safety and potential efficacy (B. T. Anderson et al., 2020; Smigielski et al., 2019). There were no studies found regarding ketamine group therapy, though it is

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unlikely that a group administration would pose safety concerns due to the sedating, internal focus of the experience.

Psychedelic-Assisted Couples Therapies

Of the eight psychedelics reviewed in this study, MDMA is the only one with a literature base supporting its use in couples therapy. Between 1977 and 1985, while MDMA remained legal, several dozen psychotherapists were regularly doing MDMA-assisted couples therapy (Passie, 2018). Passie (2018) reviewed the work of these pioneering couples therapists, the techniques they developed, and the indications and counterindications they identified.

MDMA has been applied as an adjunct to Cognitive Behavioral Conjoint Therapy (CBCT) for PTSD. CBCT is a manualized treatment intended to treat PTSD symptoms in the identified patient while also improving relationship functioning (Monson et al., 2008). In an uncontrolled trial, MDMA-facilitated CBCT showed large to very large improvements in relationship satisfaction ($p<.05$; patients: $d=0.82–1.22$; partners: $d=0.64–0.80$) and very large improvements in relationship happiness ($p<.001$; patients: $d=1.42–2.79$; partners: $d=1.30–1.78$) [$N=6$ couples, age $M=47$, Caucasian, heterosexual] (Monson et al., 2020). There were also large improvements ($p<.001$; $d=1.85–3.59$) in PTSD symptoms as rated by the patient, partner, and clinician. Finally, there were large to very large improvements in patient depression ($p>.05$; $d=1.50–2.53$), sleep ($p<.01$; $d=0.88–1.18$), emotion regulation ($p<.01$; $d=1.09–1.15$), and trauma-related beliefs ($p<.01$; $d=0.98–1.17$). These outcomes persisted at 3 and 6 months later. Importantly, all effect sizes in the study were equal to or larger than for CBCT without MDMA. Effect sizes for PTSD symptoms were also greater than with individual MDMA-assisted

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psychotherapy for PTSD. In a second analysis of the same pilot study, both partners had durable improvements in post-traumatic growth, relational support, and social intimacy following MDMA-facilitated CBCT (A. C. Wagner et al., 2021). Further, patients reported improved empathetic concern and psychosocial functioning, while their partners reported reduced conflict and behavioral accommodation.

In addition to CBCT, a recent theoretical article proposed using MDMA as an adjunct to evidence-based emotion-focused couples therapy for couples who have been impacted by trauma or PTSD (Almond & Allan, 2019). Outside of structured couples therapies, MDMA is sometimes used recreationally by couples as a means to support and improve their relationship (K. Anderson et al., 2019; Colbert, 2018). In a thematic analysis [*N*=8 couples], Colbert (2018) identified several major themes of MDMA use by couples: "different reason to relate to each other," "serving me in so many ways," "added depth to relationship," and "practice returning to MDMA experience." K. Anderson et al. (2019) analyzed three couple interviews, two diary interviews, and eight written diaries regarding couples' use of MDMA. The authors described the couples' MDMA use as "part of a spectrum of relationship 'work' practices" and "a unique kind of 'date night' that revitalizes couples' connection" (p. 10). The couples they studied tended to use MDMA in a protected and ritualistic environment away from other people to achieve these outcomes.

Regarding other psychedelics' applications to couples therapy, only one study was found. Edelson (2017) examined the impact of shared psilocybin experience on relationship satisfaction using a retrospective questionnaire [*N*=209; 48% male; age *M*=44; 80% White, 6% Asian/Pacific Islander, 6% Multi-racial, 3% Hispanic or Latino,

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1% Black, 0.5% Native American, 3% Other; 78% heterosexual, 16% bisexual, 3% gay/lesbian, 3% other]. The study found no significant differences in relationship satisfaction, empathy, and acceptance between those who had never had a psilocybin experience [*n*=46], those who had had a psilocybin experience separate from their partner [*n*=57], and those who had had a psilocybin experience together with their partner [*n*=106]. Still, 51.1% of participants described feeling "…closer or more connected to their partner during the [psilocybin] experience than they normally do" (p. 69), and 50.5% felt "…the experience had lasting, positive effects on their relationship" (p. 61).

Psychedelic Therapy Using Cognitive Behavioral Techniques

Sloshower et al. (2016) provide a rationale and theoretical framework for applying Acceptance and Commitment Therapy (ACT) to psilocybin-assisted therapy for depression. Walsh and Thiessen (2018) also propose that third-wave behavioral (TWBT) techniques, including ACT, Dialectical Behavior Therapy (DBT), and Mindfulness-Based Cognitive Therapy, may have potential as adjuncts to psychedelic-assisted therapies. They describe similarities in mechanisms of action and theoretical underpinnings between TWBT and psychedelic-assisted therapies and suggest that these similarities may indicate the potential for therapeutic synergies. These common mechanisms are listed to include enhanced mindfulness, emotional regulation, distress tolerance, and decentering. Luoma et al. (2019) further elaborate on specific ways in which ACT concepts can be integrated into psychedelic therapies. No trials were found applying TWBT to psychedelics.

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Microdosing

Microdosing is the practice of taking a low, sub-perceptual psychedelic dose with regular frequency for the purpose of achieving some psychological benefit. Microdosing was popularized by James Fadiman in his book *The Psychedelic Explorer's Guide* (Fadiman, 2011, p. 198). Since then, microdosing psychedelics has become common in non-clinical settings for self-treatment of psychiatric conditions and for cognitive enhancement (Hupli et al., 2019). In popular culture, as represented by a YouTube survey, there are purported benefits to microdosing mescaline, LSD, psilocybin, and DMT (Hupli et al., 2019). Studies of microdosing were excluded from this review to limit its scope.

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Chapter 12: Targets for Psychedelic-Assisted Therapies

This chapter provides a broad survey of what is known about the efficacy of treating psychological conditions using psychedelics therapies. In addition, new theoretical applications of psychedelics are translated from basic research. The aim is to highlight areas with high potential for effective psychedelic treatments. There is considerable research for conditions like depression and PTSD, which is summarized briefly rather than providing an exhaustive guide to technique. There were several reviews found examining the broad field of psychedelic treatments. Since the purpose of this study is similar, such reviews were excluded. Studies examining psychedelic microdosing were also excluded to limit the scope.

Developmental Conditions

Autism Spectrum Disorder

Classical Psychedelics. Many historical accounts used classical psychedelics to treat children with what would now likely be categorized as an autism spectrum disorder (ASD). Several reviews provide an overview of these early studies that began in the 1950s and continued through the early 1970s. The opinions of these authors on the body of literature are summarized below.

Mogar and Aldrich (1969) reviewed seven studies on treating autistic children with psychedelic drugs (mostly LSD; one study included psilocybin). They found consistent subjective reports of improved speech in mute subjects, greater emotional responsiveness, increased positive mood and laughter, and decreased “compulsive ritualistic behavior.” They comment that “The most effective results were obtained with at least 100 μg doses of LSD-25 given daily or weekly over relatively extended periods of

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time" (p. 50), referring to studies by Bender et al. (1962, 1963). Bender et al. (1962) describe substantial improvements in the perceptual organization among prepubescent "autistic schizophrenic" children with 100 μg daily LSD [*N*=14, age=6–10.5, 79% male, race N/R]. This is the same Bender that developed the Bender-Gestalt (L. A. Bender, 1938), a test measuring perceptual organization still in use, lending credibility to the validity of these findings. Contextualizing these results, Mogar and Aldrich conclude that "each of these studies contained serious therapeutic and experimental flaws" but that "the collective findings argue strongly for more extensive applications of psychedelic drugs in the treatment of autistic children" (p. 50).

Rhead (1977) extended the review of Mogar and Aldrich to include additional studies of "severely disturbed children" treated with psychedelics [*N*=91 children]. Based on these studies, Rhead concludes, "The physical and psychological safety of the responsible use of psychedelic agents with severely disturbed children seems to be relatively well established" (p. 97). They emphasize that psychedelics are not a "magical" treatment that will work with every child. Instead, the outcomes of psychedelic treatments in these children depend on the quality of the therapeutic relationship. Rhead also highlights the suggestion by Bender et al. (1966), borne from experience, that "[ongoing] LSD can be used to replace the traditional tranquilizers in the ward management of schizophrenic children, without the usual side effect of making them groggy and sleepy" (p. 98). Despite new generations of sedatives and antipsychotic drugs, this statement remains relevant as many of these drugs have serious side effects with long-term negative impacts.

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Finally, Sigafoos et al. (2007) reviewed studies using LSD to treat autism spectrum disorder (ASD) from 1959 to 1974. They conclude that due to weak methodologies, whether these studies show improvements in ASD is unknown. Most studies report findings as narrative descriptions rather than quantitative comparisons to a control group. In addition to describing the many positive reports of ASD treatment with LSD, Sigafoos also identified two publications that found LSD treatment ineffective. The first is a case of a 12-year-old child described as "schizophrenic" for whom "Rolo et al. [(1965)] found no evidence that LSD was of benefit to" (Sigafoos et al., 2007, p. 79). The second report is from Simmons et al. (1972), who, after initially having success treating two autistic children, had difficulty replicating an effective treatment with 17 additional children, many of whom "became completely immobile or preoccupied with certain objects" (Sigafoos et al., 2007, p. 79). While Sigafoos casts a pessimistic outlook on the potential of LSD in treating ASD based on these two reports, Rhead's comments regarding the role of the therapeutic relationship in treatment should be considered in evaluating these outcomes.

Much remains unknown about the efficacy of classical psychedelics in treating children with ASD. There appears to be enough evidence from early studies to indicate that such treatments have potential and are likely safe. Caution is certainly warranted in exploring any psychedelic treatment with children, and such investigations must proceed under modern ethical standards. The provisional findings by Bender et al. that LSD can support the development of cognitive-perceptual organization in children with ASD are compelling, as few interventions are currently available to treat these deficits. While the daily 100 μg LSD treatments given by Bender et al. may seem extreme, tolerance to LSD

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develops very rapidly. It is unlikely that subjective drug effects would persist for more than a week or two after beginning treatment. Notably, the children in some of Bender's studies attended school throughout LSD treatment. Finally, it is important to consider that the effects of LSD may differ in children compared to adults, as is true with other psychiatric drugs. Together, these early studies provide a potential avenue for treating ASD that may warrant further investigation.

Psilocybin. While most early studies used LSD to treat ASD-like presentations in children, a 1963 study by Fisher and Castile used 10–20 mg psilocybin, often combined with 50–400 µg LSD, to treat autistic children [*N*=12, age=5–13] (as reported by Mogar & Aldrich, 1969, original text not found). Following an average of 11 sessions, Mogar and Savage report outcomes as equally divided between 'excellent,' 'good,' and 'poor.' Doss et al. (2021) saw increased cognitive flexibility 1- and 4-weeks following 20 and 30 mg/70 kg psilocybin treatments for depression compared to a waitlist control (see Chapter 8 for more details). It is possible that this finding could translate to ASD treatment, given that deficits in cognitive flexibility are a prominent feature of ASD (D'Cruz et al., 2013; Van Eylen et al., 2011).

Ayahuasca. Aphantasia, the inability to form mental images, is associated with autistic traits and may be related to weaknesses in imagination and social skills in ASD (Dance et al., 2021). dos Santos et al. (2018) describe a case of a man with long-standing aphantasia who gained the ability to form mental visualizations through an ayahuasca ceremony. His improved ability to visualize remained durable following the experience. While the man attributed his aphantasia to a traumatic event in his childhood that was

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resolved during the ayahuasca experience, the case alludes to a possible way to resolve aphantasia that may occur with ASD.

MDMA. Danforth et al. (2018) performed a randomized, double-blind, placebo-controlled study to treat social anxiety in autistic adults using a sequence of two MDMA-assisted psychotherapy sessions [*N*=12, 83% male, age *M*=31.3, ethnic backgrounds "reasonably diverse," 25% non-heterosexual]. They found an effect size of *d*=1.4 on the Leibowitz Social Anxiety Scale following treatment and *d*=1.1 at 6-month follow-up.

Parker et al. (2017) found improvements in social functioning in autistic children following 4 weeks of twice-daily oxytocin treatment as measured by the Social Responsiveness Scale [*N*=32, 84% male, age=6–12, 44% White, 28% Asian]. This result is interesting given that MDMA causes oxytocin release and reopening of the critical period for social reward learning (Francis et al., 2016; Nardou et al., 2019). In non-autistic people, however, oxytocin administered alone does not produce the same prosocial effects as MDMA (Kirkpatrick, Lee, et al., 2014; Kuypers et al., 2014). Still, it is unknown whether the reductions in social anxiety seen with MDMA-assisted psychotherapy in autistic adults are dissociable from the effect of oxytocin alone.

Ketamine. Ketamine has been used to manage aggressive behavior in autistic children (Bachenberg, 1998; Rainey & van der Walt, 1998; S. Shah et al., 2009). Kastner et al. (2016) describe a case where an autistic and intellectually disabled 15-year-old male "…demonstrated a dramatic, albeit short-lived, remission of the core symptoms of autism following adventitious treatment with ketamine" (p. 121). Following a surgical procedure where ketamine and propofol were used as anesthesia, the child's parents reported that he

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"began speaking in full sentences and making eye contact" (p. 122). This effect lasted for 36 hours before symptoms returned to baseline.

Attention-Deficit/Hyperactivity Disorder and Executive Dysfunction

No research was found directly assessing the use of psychedelics to treat attention-deficit/hyperactivity disorder (ADHD). However, ADHD commonly co-occurs with other psychiatric conditions, including depression, anxiety, obsessive-compulsive disorder (OCD), and ASD, which may be treated with psychedelics, as discussed throughout this chapter. Specific considerations, however, are necessary with some psychedelics when treating these conditions with co-occurring ADHD or executive dysfunction.

Ayahuasca. Da Silveira et al. (2005) compared rates of DSM-III Attention Deficit Disorder (ADD) among ritual ayahuasca using adolescents [n=40] to matched controls [n=40]. In the ayahuasca group, ADD was less prevalent (2.5%; n=1) compared to controls (17.5%; n=7) in a result that approached significance (p<.057). This suggests that ritual ayahuasca use by adolescents or their parents could have some preventative role in the pathogenesis of ADD, a finding that warrants further investigation. In addition, ritual ayahuasca users show improved working memory and executive functions relative to controls in some studies, though these findings are mixed (see Chapter 8).

MDMA. There is evidence that chronic recreational use of MDMA can result in a long-term reduction in attention, working memory, processing speed, learning, and executive functions (see Chapter 8). However, the impact of clinical MDMA on neuropsychological functions is likely to be different given that it is given in a limited number of sessions, in controlled doses, and with pharmaceutical-grade medicine. The

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only study found regarding the neuropsychological impact of MDMA-assisted therapy (Mithoefer et al., 2011) found no significant differences between MDMA and placebo [*N*=20]. At long-term follow-up 17 to 74 months later (*M*=45.4), no participants felt their cognitive abilities had declined, while 68% felt that their cognition had improved (Mithoefer et al., 2013). Thus, MDMA-assisted therapy seems unlikely to have a long-term detrimental effect on ADHD or executive dysfunction symptoms when used to treat co-occurring conditions.

Ketamine. While there is no evidence for negative cognitive impacts with limited ketamine use, chronic clinical and recreational use of ketamine is associated with a decline in attention, working memory, processing speed, learning, and executive functions (see Chapter 8). In addition, there is evidence for reduced verbal learning and comprehension speed in the days following ketamine administration, along with mixed evidence regarding reduced verbal fluency. Together, these findings suggest caution in prescribing ongoing ketamine treatment in any patient, especially those with weaknesses in attentional, learning, and executive functioning.

Schizophrenia

Mescaline. Hoch (1951) reported that mescaline reactivated psychosis in schizophrenic patients who had already been treated successfully with psychosurgery [*N*=N/R]. Hoch et al. (1952) administered mescaline to 59 schizophrenic patients [41% male, age and race N/R]. They observed acute exacerbation of psychotic symptoms but did not conclude whether mescaline could help treat schizophrenia. Pennes (1954) also found that 400–600 mg of mescaline exacerbated symptoms in schizophrenic patients [*N*=55, 51% male, age M=33.5, race N/R].

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Denber and Merlis (1955a) administered mescaline (0.5 g IV) to 25 schizophrenic patients [72% female, age=18–51, race N/R], with 12 of 25 receiving 20 ECT sessions over an average of 6.5 weeks, followed by another mescaline session. From the single mescaline session, there was one complete remission resulting in discharge from the hospital and three temporary remissions, while symptoms were exacerbated in the remaining patients. In those that received subsequent ECT and another mescaline session, two patients had little response, while psychosis was reactivated in the remaining ten.

Denber and Merlis (1955b) gave 0.5 mg IV mescaline to 57 hospitalized patients[age=16–60, sex and race N/R]. Of those with an acute condition [*n*=40, 70% schizophrenia or psychosis, 17.5% "psychoneurosis," 5% manic], 45% showed 'complete remission of symptoms,' 17.5% were 'improved' or showed 'partial improvement,' 10% showed 'improvement with relapse,' and 27.5% were 'unimproved.' In those with a chronic condition [*n*=17, 88% schizophrenia or psychosis, 12% manic], none showed complete remission, 41% were 'improved' or showed 'partial improvement,' and 59% were 'unimproved.'

LSD. Without concurrent psychotherapy, LSD can worsen the symptoms of schizophrenia. Hoch et al. (1952) gave 10–120 µg LSD to 21 schizophrenic patients [41% male, age and race N/R]. They observed acute exacerbation of psychotic symptoms and came to no conclusions about the utility of LSD in treating schizophrenia. Pennes (1954) also found that 10–120 µg LSD exacerbated the symptoms of schizophrenic patients. However, there was some notable relaxation of tension during the LSD experience that was not present with mescaline [*n*=25, 51% male, age M=33.5, race N/R].

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When psycholytic LSD therapy is given to schizophrenic patients, the results are mixed, indicating a potentially efficacious therapy. Sandison and Whitelaw (1957) describe the outcomes of four patients diagnosed with "convalescent schizophrenia" and treated with LSD psychotherapy sessions. Among those, 50% were 'recovered,' 25% were 'moderately improved,' and 25% were 'not improved' after at least 6-month follow-up. Chandler and Hartman (1960) saw "marked improvement" in one patient diagnosed with DSM-I "Schizophrenic reaction, residual type" and treated with 50–150 µg LSD psycholytic therapy for an average of 6.2 sessions [*N*=110, 62% male, age=15–62, race N/R]. In a study of multi-session LSD treatments performed in Denmark during the 1960s [*N*=151], eight cases were designated as "schizophrenia and paranoid psychosis" according to the ICD-6 or ICD-8 used at the time (Larsen, 2017). Of those cases, 38% were improved, 25% were unchanged, and 38% deteriorated.

Stanislav Grof, a thought leader in psycholytic LSD therapy, describes successfully treating a 19-year-old male with schizophrenia (Grof, 1975, p. 237). As this case is used as an exemplary example in a book, presumably, Grof has had success treating other cases of schizophrenia through psycholytic therapy. In subsequent writing, Grof (1980) notes that "LSD work with severely disturbed individuals is a very demanding and intense process which requires special preparation and training. It should not be attempted by anyone who has not had sufficient experience of LSD sessions with 'normal' and neurotic individuals." (p. 257).

Finally, there is a trend toward long-term reduced symptoms of psychosis with LSD treatments in three studies (see Chapter 7 "Psychotic Symptoms"). While only two of these findings showed significance, the consistency of the trend across studies is

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notable. In addition, consistent decreases in paranoia were seen. These findings support the potential efficacy of LSD therapy in treating schizophrenia.

Psilocybin. In the concord prison experiments, Leary et al. (1965) saw a large but non-significant decrease in MMPI positive symptoms of psychosis (d_n=-0.80) along with a negligible change in paranoid symptoms (d_n=0.05) [n=19]. The large effect of psilocybin group treatment on positive symptoms of psychosis supports the notion that psilocybin therapy could have utility in treating schizophrenia. However, schizophrenic patients may also have acute negative reactions to psilocybin based on the drug's similarity to mescaline and LSD.

DMT. Böszörményi and Szára (1958) administered DMT (1.0–1.5 mg/kg IM) to 24 female schizophrenic patients [age and race N/R]. They observed an increase in thought disorder symptoms and psychotic preoccupations but not persistent changes in mood or behavior. They noted that psychotic patients had a less intense response to DMT than healthy controls. In paranoid patients, there was an attribution of DMT administration as a hostile act on the part of the doctors.

Jacob and Presti (2005) suggest that DMT could suppress symptoms of psychosis through agonism of the trace amine receptor, which produces a "calm and relaxed mental state" (p. 930). This effect is present even at low doses, suggesting the possibility of DMT microdosing as a treatment for psychosis.

Ayahuasca. Two studies of long-term change from ayahuasca ceremonies showed large decreases in psychotic and paranoid symptoms, though significance was not reached in one of the studies (p<.042; d_c=-0.43 to -0.48; p=NS, Δ=-48.8% to -50.8%; see

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Chapter 7). These studies demonstrate that ritual ayahuasca may have potential efficacy in treating schizophrenia.

Bilhimer et al. (2018) document a case of a 25-year-old male with a history of schizophrenia who was arrested and hospitalized after having broken several windows in his home, disturbing neighbors, and being discovered by police in front of his house fighting with a cat. Prior to this, he had ingested ayahuasca purchased from the internet, which was confirmed by the presence of 2000 ng/mL of DMT in his urine. While this case is alarming, it is likely to differ from the expected outcome of schizophrenic patients participating in supervised ayahuasca ceremonies.

MDMA. Passie (2018) describes the 1980s work of Phil Wolfson using MDMA to treat people in psychotic crisis. Wolfson used MDMA with psychotic patients with poor self-image or who struggled with trusting family members and clinicians, which hampered their ability to receive help. MDMA sessions would help these psychotic patients build trust and connection with others and view themselves in a new light. These changes tended to persist with intensity for several days in the "afterglow," sometimes persisting permanently. Sometimes, however, "...periods of closeness were followed by painful rebounds into isolation and alienation" (Passie, 2018, p. 8). Still, Wolfson saw with MDMA "…the possibility for a rapid and significant break with defensive structures that are a product of cumulative trauma and communicational disqualification" (Passie, 2018, p. 8). He suggested a course of therapy with acutely psychotic patients that included family-focused MDMA sessions every 5 days along with daily psychotherapy. Based on the findings of this review, such frequent MDMA administration risks excessive neurocognitive damage and is therefore not advisable (see Chapter 8).

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Ketamine. Acutely, Lahti et al. (1995) found that ketamine intensified psychosis in schizophrenic patients, with worsening positive (p<.01) but not negative symptoms [N=9, 56% male, age=22–53, 44% White, 33% Black, 22% Asian]. This effect was not blocked by the antipsychotic haloperidol [n=3]. In several patients, psychosis worsened for 8–24 hours following infusion and included persistent visual hallucinations. Malhotra et al. (1997), however, found that ketamine acutely worsens both positive (p<.001) and negative (p=.007) psychotic symptoms in schizophrenics [N=13, 77% male, age M=31.3, race N/R]. In a subsequent study, Lahti, Weiler, et al. (2001) again saw that ketamine increased only positive symptoms (p=.0001) of schizophrenia [N=17, 65% male, age M=31.6, 59% Caucasian, 29% African American, 12% Asian]. Together, it appears most likely that ketamine acutely increases positive symptoms in schizophrenics.

Despite exacerbated symptoms of psychosis when schizophrenics are given a ketamine infusion, Lahti, Warfel, et al. (2001) found that there is little distress and no long-term change in schizophrenic presentation caused by ketamine treatment compared to controls [N=50, 78% male, average age=35.2, 64% White, 20% African American, 16% Asian]. Given this lack of negative long-term impact of ketamine, it is reasonable to consider ketamine-assisted psychotherapy (KAP) to help treat schizophrenia. In support of this, Krupitsky and Grinenko (1997) saw a significant decrease in the positive symptoms of schizophrenia (p<.01; d_n=-0.46) and a non-significant decrease in paranoid symptoms (p>.05; d_n=-0.22) following KPT treatment for alcohol use disorder [N=111].

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Anxiety Disorders

General Anxiety

Here, "general anxiety" is used as a catch-all to summarize findings relevant to the treatment of non-specific anxiety, including treatment of patients with generalized anxiety disorder (GAD).

LSD. LSD shows robust and durable effects in reducing anxiety, both when administered on a one-time basis and as psycholytic therapy (see Chapter 7). However, in the only study examining the impact of an LSD session on trait Neuroticism, no effect was seen. Five early studies were found that treaded anxiety disorders through psycholytic LSD therapy (Chandler & Mortimer, 1960; Larsen, 2017; A. J. Martin, 1957; Sandison et al., 1954; Sandison & Whitelaw, 1957). Of 99 combined patients from these studies with known outcomes, 9% were reported to be 'recovered,' 67% as some degree of 'improved,' 15% as unchanged, and 9% as 'deteriorated.' All of the nine cases reported as 'deteriorated' were from a study of LSD treatments performed in Denmark during the 1960s (Larsen, 2017). Together, these studies, combined with quantitative studies showing that LSD can reduce anxiety, suggest that LSD therapies may have utility in treating anxiety disorders.

Psilocybin. In five of six modern clinical trials, psilocybin shows robust and durable effects in reducing anxiety and trait Neuroticism (see Chapter 7).

DMT. No human studies were found using DMT to treat anxiety. In rats, 10 mg/kg intraperitoneal (IP) DMT produced an acute anxiolytic effect 1 hour following injection (L. P. Cameron et al., 2018). It also enhanced fear-learning extinction. Microdosing DMT (1 mg/kg IP every 3 days) was also found to reduce anxiety in rodents

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and enhance fear extinction learning (L. P. Cameron et al., 2019). Jacob and Presti (2005) also suggest that DMT's agonism of the trace amine receptor may have an anxiolytic effect by producing a "calm and relaxed mental state" (p. 930). This effect may be present even at low doses and therefore could contribute to the effectiveness of DMT microdosing as an anxiety intervention.

Ayahuasca. In humans, ritual ayahuasca shows robust and durable effects in reducing anxiety and trait Neuroticism (see Chapter 7). In animals, dos Santos et al. (2016) found consistent anxiolytic effects with ayahuasca, harmine, and harmaline among 21 studies identified in a systematic review.

MDMA. Johansen and Krebs (2009) provide a neurobiological rationale for using MDMA to treat anxiety disorders. The mechanisms they suggest are: 1) strengthened therapeutic alliance due to oxytocin release; 2) improved emotional regulation and reduced avoidance due to increased regulating ventral medial PFC activity and decreased amygdala activity; and 3) enhanced extinction of fear associations and increased emotional engagement due to norepinephrine release and increased cortisol. They further describe that "…in a therapeutic setting, [MDMA] could provide a balance of activating emotions while feeling safe and in control, as described in case reports of MDMA-augmented psychotherapy" (p. 1). However, no studies of MDMA-assisted treatment of generalized anxiety were found in the literature. Building on this, Yazar-Klosinski and Mithoefer (2017) suggest that MDMA-assisted psychotherapy may help treat attachment-related anxiety by improving emotional regulation, reducing amygdala response to angry or fearful faces, and increasing the accuracy of perceived mental states in others.

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While not yet conclusive, two studies show long-term decreases in trait Neuroticism from MDMA-assisted psychotherapy for PTSD (see Chapter 7). There were also long-term increases in Openness to Experience, which may signify lessened anxiety related to new experiences.

Ketamine. Glue et al. (2018) examined the impact of once- or twice-weekly subcutaneous ketamine on symptoms of DSM-IV generalized anxiety disorder and social anxiety disorder in an uncontrolled, open-label trial [*N*=20, 50% male, age=18–65, race N/R]. There was a progressive decline in Fear Questionnaire (FQ) scores over time compared to baseline, which reached an asymptote after approximately 7.5 weeks of treatment. Similarly, pre-dose Hamilton Anxiety Scale (HAM-A) scores decreased from baseline to reach an asymptote around 3.5 weeks of treatment. Each ketamine dose decreased FQ and HAM-A scores by approximately 50% when measured 1 and 2 hours following. At follow-up at least 3 months after treatment, 25% of patients reported remission from anxiety, 40% reported partial reemergence of anxiety, 25% reported full reemergence of anxiety, while 10% continued ketamine treatment or dropped out.

Ketamine-Assisted Psychotherapy. Dore et al. (2019) examined the impact of -KAP on anxiety across several clinics in an uncontrolled, open-label trial [*N*=235 patients, 48.9% women, age *M*=42.7, race N/R]. KAP resulted in a significant decrease in anxiety compared to baseline as measured by the HAM-A ($p<.0001$; intake: $M\approx20$; w/ treatment: $M\approx15$). In contrast, Davis et al. (2021) found no significant effect of KAP in reducing anxiety symptoms based on a chart review of patients treated in an outpatient setting [*N*=18, 56% female, age *M*=45.22, 100% White].

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Specific Phobias

Classical Psychedelics. Moroz and Carhart-Harris (2018) suggest that the treatment of phobias using virtual reality exposure therapy (VRET) could be enhanced if combined with psychedelics. This hypothesis is based on: (1) existing evidence supporting the efficacy of VRET, (2) increases in efficacy seen when combining VRET with SSRIs, and (3) increases in cognitive flexibility, associative learning, and neural plasticity that has been shown with psilocybin (Carhart-Harris, Bolstridge, et al., 2016; Doss et al., 2021). These three enhancing effects of psilocybin are likely to apply to other classical psychedelics as well. No study to date has been completed using this method.

LSD. Sandison and Whitelaw (1957) describe the outcomes of three patients diagnosed with "phobic anxiety" and treated with LSD psychotherapy. Among those, outcomes were split evenly between 'recovered,' 'greatly improved,' and 'not improved' after at least 6-month follow-up. Chandler and Hartman (1960) saw, on average, "slight improvement" in three patients diagnosed with DSM-I "Psychoneurosis: Phobic reaction" and treated with 50–150 μg LSD psycholytic therapy for an average of 6.2 sessions [*N*=110, 62% male, age=15–62, race N/R].

MDMA. The suggestion of Moroz and Carhart-Harris (2018) to combine VRET with psychedelics could also apply to MDMA. MDMA produces acute decreases in fear-related amygdala reactivity (Feduccia & Mithoefer, 2018) and enhanced fear extinction learning (Doss et al., 2017; Hake et al., 2019; Young et al., 2015, 2017), factors that contribute to its effectiveness in supporting psychotherapy for PTSD. These effects could also enhance the efficacy of VRET in treating phobias.

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Social Anxiety

Classical Psychedelics. Though findings are mixed, there are several studies indicating that LSD, psilocybin, and ayahuasca can cause long-term increases in Extraversion (see Chapter 7). These same compounds also produce robust, long-term reductions in Neuroticism. These trait changes may also lead to reduced social anxiety, but this hypothesis needs to be validated through empirical study.

MDMA. MDMA has been used successfully to treat social anxiety in autistic adults (Danforth et al., 2018). It is possible that similar effects could be achieved in neurotypical people. This is supported by the finding by Mithoefer et al. (2018) that MDMA-assisted psychotherapy for PTSD significantly increased trait Extraversion at 12-month follow-up (p=.0002; d_c=0.51–1.14).

Ketamine. In an RCT, J. H. Taylor et al. (2017) found that a single 0.5 mg/kg IV ketamine infusion resulted in a significant reduction in social anxiety (p=.01) on the Liebowitz Social Anxiety Scale (LSAS) relative to placebo [N=18, 39% female, age M=29.72, 78% White, 11% Asian, 11% Hispanic]. While there was not a significant reduction (p=.95) in self-reported anxiety on a visual analog scale (VAS) relative to placebo, 89% of the treatment group and 53% of the placebo group had a VAS reduction of more than 50% (treatment response threshold). On the LSAS, 33% of the ketamine group saw a 35% or greater reduction of social anxiety in the 2 weeks following treatment, compared to 0% for placebo (p=.025). These improvements were durable at 2 weeks following infusion.

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Compulsive Disorders

Obsessive-Compulsive Disorder (OCD)

Serotonergic mechanisms are involved in the etiology of obsessive-compulsive disorder (OCD), and these mechanisms are a target of first-line treatment with SSRIs (Goddard et al., 2008). There is a genetic association between OCD and a promotor 5-HT_{2A} receptor polymorphism (Perrine, 1999). This type of functional promoter variant tends to alter transcription to lead to differences in serotonin receptor density. Perrine et al. (1999) link this genetic polymorphism to the purported efficacy of serotonergic psychedelics in treating OCD.

Classical Psychedelics. Several authors have suggested that the serotonergic mechanism of classical psychedelics could lead to effectiveness in treating OCD (Delgado, 2002; Perrine, 1999). Zghoul and Blier (2003) found that LSD enhanced the responsiveness of inhibitory neurons to serotonin in the orbitofrontal cortex (OFC) of rats both acutely and 24 hours following the last administration. This same inhibitory effect in the OFC is seen in the treatment of OCD with SSRIs (Hikari et al., 2022).

LSD. Several early studies used psycholytic LSD therapy to treat patients that were described as “obsessional” or diagnosed with “obsessional neurosis” (Chandler & Mortimer, 1960; Larsen, 2017; A. J. Martin, 1957; Sandison et al., 1954; Sandison & Whitelaw, 1957). Of 46 combined patients with known outcomes from these studies, 7% were reported to be ‘recovered,’ 63% as some degree of ‘improved,’ 15% as unchanged, and 15% as ‘deteriorated.’ All seven cases reported as ‘deteriorated’ were from a study of LSD treatments performed in Denmark during the 1960s (Larsen, 2017). Together, these studies indicate the potential for LSD psychotherapy to improve obsessional symptoms.

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Use With Children and Adolescents. K. Cameron (1961) describes the inpatient treatment of eight adolescent boys with severed obsessional symptoms using LSD-assisted psychotherapy [age=14–18, race N/R]. They concluded that LSD provided a "material advantage" in four cases, little value in three cases, and complicated the treatment in one case due to an "incautious increase of insights without expression of feeling" (p. 110).

Psilocybin. F. A. Moreno et al. (2006) performed an RCT administering psilocybin (1.75, 7, 14, and 21 mg/70 kg) to nine people with OCD [78% male, age=26–62, race N/R]. Across a total of 29 administrations, they found that psilocybin was well-tolerated, with the only adverse response being one incidence of transient hypertension. OCD symptom severity was significantly (p=.28) reduced 4-, 8-, and 24-hours following administration as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS). This effect was seen with all doses administered to a similar degree, with no significant dose-response effect found (p=.261). A reduction in YBOCS symptoms was seen in all participants, with magnitude ranging from 23%–100%. While a significant reduction in symptom severity was seen, this result must be taken with caution as there was no placebo control. The low 1.75 mg/70 kg dose was intended to be an active placebo; however, a similar effect was seen with this dose as well. This could mean that psilocybin is effective at treating OCD with a microdose, or it could mean that improvements seen in this study were entirely due to a placebo effect.

Wilcox (2014) reported on a case of significant OCD symptom reduction through psilocybin self-administration every 3 weeks. Larsen et al. (2017) also report on one case of improved OCD symptoms following psilocybin treatment.

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Ayahuasca. Ritual ayahuasca shows robust and durable effects in reducing OCD symptoms and trait Neuroticism based on four studies (see Chapter 7). However, no studies were found specifically examining the efficacy of ayahuasca in treating OCD.

MDMA. Though not conclusive, two studies show long-term decreases in trait Neuroticism from MDMA-assisted psychotherapy for PTSD (see Chapter 7). These improvements in Neuroticism may translate to improved OCD symptoms, but further research is needed.

Ketamine. Bloch et al. (2012) performed an open-label trial of 0.5 mg/kg IV ketamine infusion for treating refractory OCD [*N*=10, 60% male, age=18–64, race N/R]. They saw a significant reduction in OCD symptoms in the 3 days following ketamine treatment compared to baseline, but this reduction was not large enough to meet treatment response criteria. However, in four of seven patients with depression comorbid with OCD, there was a treatment response for depression. From within this trial, Niciu et al. (2013) describe two cases with increased anxiety and suicidal thoughts in the days following ketamine infusion.

In an RCT, Rodriguez et al. (2013) tested the efficacy of ketamine infusion in treating OCD symptoms in medication-free adults [*N*=15, 56% male, age *M*=34.2, 44% African American, 27% Caucasian, 19% Hispanic, 7% Asian]. They found that 1 week following treatment, 50% of the ketamine group showed a response versus 0% of the placebo group. Further, they found that ketamine effects on OCD symptoms lasted longer than a week ($p<.005$).

Finally, Rodriguez et al. (2016) tested whether 10 hours of exposure-based cognitive-behavioral therapy (CBT) could improve the efficacy of ketamine infusion in

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treating OCD symptoms in an open-label, uncontrolled trial [*N*=8, age=18–55, unmedicated, sex and race N/R]. They found that OCD symptoms were significantly lowered at 2-week (p<.0001; d_c=-2.64) and 4-week (p=.01; d_c=-0.93) follow-up compared to baseline. At the end of 2 weeks, when CBT was complete, 63% of participants showed a treatment response (Y-BOCS reduction ≥ 35%).

Body Dysmorphic Disorder

Body dysmorphic disorder (BDD) is etiologically related to OCD, though patients with BDD tend to have poorer insight than those with OCD (Hartmann et al., 2019; A. Malcolm et al., 2018, 2021). Ho et al. (2020) give theoretical grounds for using classical psychedelics and ketamine in disorders where body perception is distorted, such as anorexia nervosa and BDD. They argue that the profound changes in bodily self-awareness caused by psychedelics could help disrupt the entrenched body-image distortions that are present in these patients. To increase efficacy, Moroz, and Carhart-Harris (2018) proposed a psychedelic therapy using virtual reality to concurrently provide corrective feedback regarding body image. However, no study of this method was found in the literature.

LSD. LSD may have negative outcomes for treating BDD based on cases of negative outcomes with LSD for OCD that are described by Larsen et al. (2017).

Psilocybin. One case describes a Caucasian 27-year-old male, Mr. A, with BDD (Hanes, 1996). Three separate times, Mr. A, having self-administered psilocybin mushrooms, looked in the mirror and found "…that his appearance…had 'changed' and that he no longer looked deformed" (p. 188). Due to these experiences, Mr. A began to question whether "…his deformity was 'real'…" (p. 188). He subsequently began a

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fluoxetine trial that he found effective in treating depression and OCD. Three weeks after beginning fluoxetine, Mr. A felt less concerned with his appearance and had stopped compulsive mirror-checking. His condition remained stable after stopping medication 18 months later.

Anorexia Nervosa and Bulimia

There is phenomenological and tentative genetic evidence that anorexia nervosa is a compulsive disorder (Hinney et al., 2000; I. H. Mills & Medlicott, 1992; Perrine, 1999; Pigott et al., 1991; Speranza et al., 1999). Further, there is evidence that disturbances to the serotonergic system may contribute to the etiology of anorexia and bulimia (Bailer & Kaye, 2011). Given the effectiveness of psychedelics in treating OCD and reducing trait Neuroticism (see Chapter 7), it follows that psychedelics may have application in treating anorexia. Phenomenologically, Ho et al. (2020) argue that classical psychedelics and ketamine may help those with anorexia by disrupting entrenched body-image distortions.

LSD. Sandison and Whitelaw (1957) report that one patient treated with LSD psychotherapy sessions for anorexia nervosa was “not improved” when evaluated at least 6 months following treatment. However, in a study of LSD treatments performed in Denmark during the 1960s [*N*=151], the two cases of anorexia nervosa both had improved outcomes (Larsen, 2017).

Ayahuasca. Lafrance et al. (2017) explored the effect of ayahuasca ceremonies in 10 people with anorexia nervosa and six with bulimia through a thematic analysis of interviews [88% women, age=21–50, race N/R]. Participants reported improvements in mental health symptoms and shifts in body perception. While preparatory diets for some were reminiscent of disordered eating, ayahuasca purging was not experienced as

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triggering. A second thematic analysis, including some of the same authors found that ayahuasca helped facilitate "deep healing," "processing of intense emotions and/or memories," an "embodiment of love, self-love and self-care," and a "spiritual component to healing/recovery" for those with eating disorders [*N*=13, 92% women, age=21–49, race N/R] (Renelli et al., 2018). No quantitative studies related to eating disorder treatment with ayahuasca were found.

MDMA. In an RCT, Brewerton et al. (2022) saw a significant reduction in eating disorder symptoms following MDMA-assisted therapy (p=.03) compared to the same therapy with an inactive placebo [n=82; 62% female; 35% male, 2% non-binary; age M=41.00; 78% White, 8% Asian, 3% American Indian or Alaska Native, 2% Black or African American, 8% multi-racial].

Ketamine. In an uncontrolled trial, I. H. Mills et al. (1998) combined intermittent ketamine infusions at intervals of 5–21 days with an opioid antagonist twice daily to treat 15 patients with chronic and treatment-resistant anorexia, sometimes co-occurring with bulimia [female, age=24–42, race N/R]. Of these patients, nine responded to the treatment, meaning that either their compulsive eating stopped for 2 years, their weight rose to normal (or in one case close to normal) with stability, or their compulsive thirsting stopped. In the treatment responder group, compulsions were also significantly reduced (p=.0016; d_c=-1.86). In the non-responder group, there was no significant change in compulsions (p>.05, d_c=0.24). Of the five patients with amenorrhea in the responder group, four began menstruating again, with one returning to full regularity.

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Mood Disorders

Acute Suicidality

Mescaline and LSD. Horton (1973) suggests, based on three case reports, that mystical experiences induced by mescaline and LSD can provide a "…reliably soothing safeguard against their overwhelming loneliness and possible suicide" (p. 294) [female, 20, mescaline; male, 18, LSD; female, 18, LSD].

Psilocybin and Ayahuasca. Zeifman (2022) performed a meta-analysis of suicidality reduction in response to psychedelics that included five studies on psilocybin and two studies on ayahuasca. They saw a significant reduction in suicidality compared to baseline during the acute period (d=-1.48 to -1.72), which persisted into the next day (d=-2.18), the 8 weeks following (d=-1.50 to -1.64), at 3- to 4-month follow-up (d=-2.36), and at 6-month follow-up (d=-0.65).

Ayahuasca. Sanches et al. (2016) saw significantly reduced suicidal ideation (SI) following ayahuasca treatment for depression (p_t<.003) at 1 day (d_c=-2.20), 1 week (d_c=-1.58), 2 weeks (d_c=-2.13), and 3 weeks (d_c=-3.06) following treatment compared to baseline and measured by the Hamilton Depression Scale (HAM-D) suicidality item (data reported by Zeifman et al., 2022). Zeifman et al. (2019) also saw a trend toward reduced suicidality relative to placebo following a single session of ayahuasca for TRD (p=.088; d=0.48) that persisted at 7-day follow-up (d=0.67) [N=29, 72% female, age M=42.04, 59% Caucasian]. Zeifman et al. (2021) saw an immediate reduction in suicidality during acute ayahuasca (p<.001–.05; d_g=0.65–1.31) and 1 day (p<.001; d_g=1.62), 7 days (p<.001; d_g=1.57), 14 days (p<.001; d_g=1.53), and 21 days (p<.001; d_g=1.75) following, compared to baseline [n=15, 82% female, age M=42.71, Brazilian].

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MDMA. While clinical MDMA is not associated with increased suicidality, MDMA can produce a subacute mood depression that theoretically has the potential to increase suicidality. See Chapter 9 sections titled “Suicidality” and “Anxiety and Depression” for more details.

Ketamine. Wilkinson et al. (2018) performed a meta-analysis of individualized data from ten RCTs examining ketamine’s effect on treating SI compared to placebo or midazolam control [N=10 studies, 167 participants]. They found significant reductions in suicidality on clinician-administered rating scales 1-day following ketamine (p<.001; d=0.85) that were sustained 2 days (p<.001; d=0.85), 3 days (p<.001; d=0.67), and 7 days (p<.001; d=0.61) following. Self-report measures of suicidality were also significantly lower than controls 1 day (p<.001; d=0.73), 2 days (p<.001; d=0.84), and 3 days (p<.05; d=0.63), but not 7 days (p>.05; d=0.48) following. It is notable, that the lack of significance for self-report measures at 7 days following is largely due to reduced self-reported SI among controls rather than an increase in self-reported SI among the treatment group. This meta-analysis demonstrates that ketamine can rapidly reduce SI, with effects sustained for at least one week.

Depression

There is strong evidence linking neuronal atrophy in the prefrontal cortex to the pathophysiology of depression (Ly et al., 2018). Ly et al. found that LSD, ketamine, and DMT can counteract this neurite retraction, dendritic spine loss, and synaptic elimination, demonstrating one mechanism of psychedelic efficacy in treating depression.

LSD. In two early studies (Ludwig & Levine, 1965; Mogar & Savage, 1964), psycholytic LSD therapy showed robust and durable effects in reducing depressive

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symptoms with large effect sizes (see Chapter 7). Rucker et al. (2016) performed a systematic review of early studies (1943–1973) treating major depressive disorder (MDD) and dysthymia with psychedelics [*N*=19 studies]. Of the studies included, all involved LSD, though three combined mescaline with LSD. The authors found that despite methodological issues with the studies, 79.2% of the 423 patients treated were judged by clinicians to show improvement. In a study of LSD treatments performed in Denmark during the 1960s [*N*=151], five cases were designated as "depressive neurosis" according to the ICD-6 or ICD-8 (Larsen, 2017). Of those cases, two were improved, two were unchanged, and one deteriorated.

Use With Older Adults. Of two "older depressive patients" treated by Sandison et al. (1954) with LSD sessions (*M*=7.5), they report that both were 'recovered.' They also report that one older depressive patient with epilepsy was treated with six LSD sessions and 'recovered.'

Psilocybin. In the first modern study of psilocybin for depression, Carhart-Harris et al. (2016) performed an open-label uncontrolled trial using two doses of psilocybin (10 and 25 mg) [*N*=12, 50% male, age=30–64, 75% White, 17% Black, 8% Hispanic]. They saw a significant reduction in depressive symptoms 1 week (p=.002; d_g=3.1) and 3 months (p=.003; d_g=2) following treatment, relative to baseline. There were no serious adverse events. In a follow-up study with four additional participants [*N*=20], Carhart-Harris et al. saw durable improvements at 3 months (p<.001; d=1.5) and 6 months (p<.001; d=1.4) following treatment compared to baseline [70% male, age=27–64, 75% White, 15% Black, 5% Hispanic, 5% Asian]. Studying the same participants, Roseman et al. (2018) found that experiences of oceanic boundlessness (a component of mystical

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experience) and dread of ego dissolution during psilocybin mediated improvements in depressive symptoms (p=.002–.003).

Davis et al. (2021) performed an RCT examining the efficacy of 20 and 30 mg/70 kg psilocybin in treating depression compared to a waiting list control [N=24, 67% women, age M=39.8, 92% White]. They saw significant reductions in depressive symptoms the day following the first psilocybin treatment compared to baseline (p<.001; d=2.6). These improvements were sustained at 1 week (p<.001; d=2.5) and 4 weeks (p<.001; d=2.6) following treatment when compared to the control group. In a follow-up study, Gukasyan et al. (2022) found that these improvements were sustained at 3 months (d=2.0), 6 months (d=2.6), and 12 months (d=2.4) following treatment.

Finally, Carhart-Harris et al. (2021) performed a Phase 2 RCT comparing outcomes of treating major depression with two 25 mg doses of psilocybin versus the antidepressant escitalopram [N=59, 34% female, age M=41.3, 88% White]. With the pre-selected primary outcome measure at 6 weeks, treatment response occurred in 70% of the psilocybin group and 48% of the escitalopram group, while remission occurred in 57% of the psilocybin group and 28% of the escitalopram group. However, this did not represent a significant difference between the two groups (p=.17; d_c=0.37, favoring psilocybin), indicating that two-dose psilocybin therapy has equivalent efficacy to ongoing escitalopram treatment for depression. While not adjusted for multiple comparisons, all 12 secondary outcome measures favored psilocybin over escitalopram (p<.05) at 6 weeks following treatment. Thus, while the pre-registered primary outcome measure did not show psilocybin to be superior to escitalopram, the combined results suggest that

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psilocybin treatment is at least equivalent and perhaps superior to escitalopram according to secondary outcome measures.

DMT. No human trials were found for treating depression with DMT, though there are several involving ayahuasca. There is a trial underway at Imperial College London (Geddes, 2020). In rats, 10 mg/kg DMT IP produced an acute antidepressant response 30 minutes following injection and an acute anxiolytic effect 1 hour following injection (L. P. Cameron et al., 2018). It also enhanced fear-learning extinction. Microdosing DMT (1 mg/kg IP every 3 days) was also found to have an antidepressant-like effect in rats and to enhance fear-learning extinction (L. P. Cameron et al., 2019).

DMT may be effective in treating depression due to its weak agonism of the sigma-1 receptors (L. P. Cameron & Olson, 2018; Fontanilla et al., 2009). Sigma-1 agonism has been shown to contribute to the antidepressant effects of some tricyclic antidepressants, MAOIs, SSRIs, and newer generations of antidepressants (Fishback et al., 2010; Toyohara et al., 2012). In rodent models, selective sigma-1 receptor agonists produced antidepressant-like effects (Fishback et al., 2010). These effects were not seen when rodents were pretreated with a sigma-1 antagonist, indicating that there is a specific antidepressant effect of sigma-1 agonism (Fishback et al., 2010).

Ayahuasca. Ceremonial ayahuasca was associated with long-term reductions in depressive symptoms in four of five studies found, but significance was in only two of those studies (see Chapter 7). The same sigma-1 antidepressant mechanism that is present with DMT is likely to be present for ayahuasca, given that DMT is the main active ingredient (Inserra, 2018). Ayahuasca was found to modulate awakening salvatory cortisol response in patients with hypocortisolemia due to treatment-resistant depression,

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returning to normal 2 days after the session (de Menezes Galvão et al., 2018). In a systematic review, dos Santos et al. (2016) saw consistent antidepressant effects with ayahuasca, harmine, and harmaline in animals [*N*=21].

Osório et al. (2015) performed an open-label uncontrolled trial of ayahuasca treatment for depression in an inpatient psychiatric unit [*N*=6, 66% female, age=28–61, Brazilian]. They saw significant reductions in depressive symptoms compared to baseline 1, 7, and 21 days following ayahuasca, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS; $p<.01$). There were also significant decreases in HAM-D scores 1 and 21 days following ayahuasca ($p<.05$). There were no significant increases in symptoms of mania or hypomania.

Sanches et al. (2016) also performed an open-label uncontrolled trial of ayahuasca to treat recurrent MDD in volunteers from private psychiatric clinics [*N*=17, 82% women, age *M*=42.71, Brazilian]. They saw significant reductions relative to baseline in depressive symptoms 1, 7, 14, and 21 days following ayahuasca ($p<.001$) as measured by the MADRS and HAM-D. There were no increases in manic or hypomanic symptoms. In a qualitative follow-up study 5 years later, dos Santos et al. (2018) interviewed eight of the participants in the Sanches et al. study. In reflecting on the ayahuasca session, "most patients [6 of 8] believed that the experience was among the most important of their lives" (p. 22). However, all patients reported that the effects of ayahuasca on their depressive symptoms were "short-lived," and all remained on medication. Half of the group felt that "their symptoms remained stable" at follow-up.

Finally, Palhano-Fontes et al. (2019) performed an RCT examining the efficacy of ayahuasca in treatment-resistant depression [*N*=29, 28% male, age *M*=42.1, 59%

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Caucasian, 38% Pardo, 3% Black]. They saw significant improvements 1 day (p<.05; d=0.84), 2 days (p<.05; d=0.84), and 7 days (p<.0001; d=1.49) following ayahuasca treatment when compared to placebo and measured by the MADRS. On day 7, HAM-D response rates were higher in the ayahuasca group (p=0.04; 64% vs. 27%), and remission rates showed a trend toward improvement (p=.054; 36% vs. 7%). No follow-up beyond 7 days was found in the literature.

MDMA. Patel and Titheradge (2015) concluded that MDMA "offers a promising target as a rapid-onset agent" for treating unipolar depression based on a literature review (p. 179). Yazar-Klosinski and Mithoefer (2017) suggest that MDMA-assisted psychotherapy may be helpful in treating depression that is related to attachment insecurity due to improved accuracy of perceiving mental states in others, better emotional regulation, and reduced amygdala response to angry or fearful faces.

MDMA is also a sigma-1 agonist (Dunlap et al., 2018) and, therefore, may share the same antidepressant mechanism as DMT. However, it is unclear whether the antidepressant effects of sigma-1 agonism are durable or if they require ongoing treatments. If the latter is true, then sigma-1 agonism by MDMA is a moot point due to MDMA's toxicity with ongoing administration.

Ketamine. Ketamine has several potential antidepressant mechanisms. Ketamine changes clock gene expression, potentially regulating disrupted circadian rhythms present in depressed patients (Bunney et al., 2015). In addition, the antidepressant effects of ketamine may be mediated by changes to gut microbiome composition (Getachew et al., 2018; Qu et al., 2017; C. Yang et al., 2017). In patients treated for depression, one (R)-ketamine infusion increased 5-HT_{1B} serotonin binding in the hippocampus by 16.7%

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(p=.036) compared to placebo [N=30, demographics N/R] (Tiger et al., 2020). In addition, baseline 5-HT_{1B} binding in the ventral striatum correlated with more depressive symptom reduction in response to ketamine (p=.002, d_r=-1.68).

Ketamine Infusion. As ketamine infusion for depression has been widely studied, only the most recent meta-analyses are described here. Later in this section, findings regarding ketamine-assisted psychotherapy for depression are described.

Han et al. (2016) performed a meta-analysis of nine RCTs examining the efficacy of ketamine for treating major depressive disorder (MDD) [N=368 patients]. Compared to placebo, ketamine showed significant effectiveness 1 day (response: 47.9%; remission: 20.6%), 2 days (response: 47.9%; remission: 23.8%), and 7 days (response: 39.8%; remission: 26.2%) following treatment. Response was defined by more than 50% reduction in primary depression measure, while remission was defined by cutoff scores.

Xu et al. (2016) also performed a meta-analysis of RCTs using low- and very low-dose ketamine nasal spray to treat MDD [N=9 studies, 201 patients; 52% female, age M=46, race N/R]. Seven days following, remission rates were 24% with ketamine treatment versus 6% with control treatments (p=.02). There was also a significant response rate on day 7 (p=.001). Finally, they observed that low-dose ketamine (0.5 mg/kg IV) was more effective than very low-dose ketamine.

A third meta-analysis performed by Kraus et al. (2017) saw a response to ketamine in 59% of patients with unipolar depression 24 hours following infusion [n=12 studies, 226 patients; 53% female]. In all studies, ketamine was superior to placebo. However, relapse to depression occurred in 60%–92% of patients within 14–30 days, depending on the study. This reduction in efficacy after several days appears to be a

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consistent pattern with ketamine infusion for depression. This trend is confirmed by a meta-analytic finding by Kishmoto et al. (2016) that reductions in depressive symptoms from ketamine peaked 1 day following treatment (p<.001; d_g=-0.37) before declining to no longer have significant effects by days 10–12.

Since these meta-analyses, several additional RCTs have been published examining ketamine infusion's efficacy in treating depression (M.-H. Chen & Su, 2020; Fava et al., 2018; Su et al., 2017). These studies are consistent with the findings above. To conclude, ketamine infusion appears to provide rapid relief from depression, but these improvements are not durable beyond a week. Ketamine can be administered regularly to provide ongoing relief, but there are concerns about the negative neurocognitive effects ketamine can cause (see Summary Table 11). Thus, ketamine infusion is best seen as a short-term solution that can provide a window of opportunity for other interventions such as psychotherapy.

Ketamine-Assisted Psychotherapy. In an uncontrolled trial, Dore et al. (2019) examined the efficacy of ketamine-assisted psychotherapy (KAP) in treating depression across several clinics [N=235 patients, 48.9% women, age M=42.7, race N/R]. KAP resulted in a significant decrease in depression symptoms at the end of treatment compared to baseline (p<.0001; intake: M≈27; w/ treatment: M≈17). Davis et al. (2021) also found reduced depressive symptoms (p=.019; d=-0.53) in a chart review of patients treated with KAP in an outpatient setting [N=18, 56% female, age M=45.22, 100% White].

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Choice of Enantiomer. Hashimoto (2016) suggests that (*R*)-ketamine may be a better choice for use as an antidepressant due to having greater potency, longer-lasting antidepressant effects, and fewer psychotomimetic effects than (*S*)-ketamine.

Use With Children and Adolescents. Adolescents with treatment-resistant depression have been successfully treated using ketamine in a pilot study [*N*=13, 62% male, age=14–18, race N/R] (Cullen et al., 2018). Dwyer et al. (2017) also provide a case study describing the successful treatment of a 16-year-old boy with MDD and ADHD using ketamine.

Use With Older Adults. A series of four case studies by Szymkowicz et al. (2014) show little to no response to ketamine in the geriatric patients studied. Still, the side effects seen in these patients were mild. Iglewicz et al. (2015), however, found that for those in hospice care, ketamine improved depressive symptoms in 93% of cases for 3 days and 80% for up to 7 days [*N*=22, 55% male, age *M*=68, race N/R].

George et al. (2017) performed an RCT examining the efficacy of subcutaneous ketamine (series of 0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg sessions) in older adults with TRD compared to active placebo [*N*=16, 62.5% male, age *M*=65.6, race N/R]. Response or remission was seen in 69% of patients at some point during the trial, with efficacy increasing with higher doses ($p<.001$). Compared to placebo, all doses greater than or equal to 0.2 mg/kg showed significant symptom improvements ($p<.01$).

Use in Treating Depression With Psychotic Features. Zarrinnergar et al. (2019) describe the successful treatment of psychotic treatment-resistant depression with ketamine in a 15-year-old. The patient also had GAD, suicidality, and PTSD due to sexual abuse. Treatment involved six 0.5 mg/kg ketamine infusions over 3 weeks.

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Symptom measures progressively improved over the course of the infusions, though the patient denied improvement until 2 weeks following the final infusion. One month following ketamine treatment, the patient was discharged "with the absence of depressive, psychotic, or suicidal symptoms" (p. 2). Remission was sustained in the months following.

Bipolar Disorder

LSD. There is some inconclusive evidence that LSD can increase manic and hypomanic symptoms, indicating that caution is warranted when administering LSD to patients with bipolar disorder (see Chapter 9 section "Mania"). In one case, an accidental 1,100–1,200 μg LSD dose led to a significant reduction in symptoms of bipolar I disorder with psychotic features that had begun at 12 in a 15-year-old female (Haden & Woods, 2020). After the accidental dose, the patient behaved erratically for the next 6.5 hours, according to observers, before having a seizure. Upon awakening, she stated that "It's over," which she later clarified to mean that her bipolar disorder was cured. Mental health clinicians who had worked with her prior to the incident saw a dramatic change in her condition, reporting she was healthy and stable. She went off lithium 1 year later and reported being free from mental illness for the next 13 years until experiencing postpartum depression after having her first child.

DMT. In a case report, a 40-year-old male physician attempted to self-medicate long-standing, treatment-resistant depression that had been predicated single manic episode by using up to 1 g daily DMT (T. Brown et al., 2017). After 5 months and some improvement in depressive symptoms, he added 60 mg daily phenelzine (MAOI) alongside the 4–6 mg daily clonazepam he was already taking for sleep. Three weeks

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later, the patient presented at the hospital nonverbal and severely combative, requiring six security guards for restraint. When physical restraint failed, several chemical restraints were applied with minimal effect before the patient seized and was intubated. Treatment continued with lithium and clonazepam for mania and paliperidone for psychosis, with psychosis resolving after 7 days but hypomania persisting. This case demonstrates some potential for treatment using DMT for depression associated with bipolar disorder, given that the adverse reaction occurred only after adding an MAOI. The addition of an MAOI results in reduced DMT metabolism like with ayahuasca and increases the risk of adverse reactions to other drugs. The case also demonstrates a need for caution in applying such treatment to patients with bipolar I disorder.

Ayahuasca. dos Santos et al. (2017a) describe four cases of mania with psychotic features related to ayahuasca use, indicating that caution is warranted in treating patients with bipolar disorder using ayahuasca (see Chapter 9 section “Mania”). No trials, case studies, or theoretical evidence was found suggesting efficacy in treating bipolar disorder, and therefore ayahuasca does not appear to be a promising target for this condition.

MDMA. No cases of MDMA-induced mania were found in the literature, and recreational MDMA use shows no association with the development of bipolar disorder in adolescents or young adults (see Chapter 9 section “Mania”). However, there were no studies found suggesting that MDMA would have efficacy in treating bipolar disorder, though it may be useful in treating co-occurring PTSD that may contribute to symptoms of bipolar disorder.

Ketamine. Parsaik et al. (2015) performed a meta-analysis of the efficacy of ketamine in treating bipolar depression [n=3 studies, 69 patients]. They found a

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significant improvement in depressive symptoms following ketamine infusion compared to placebo (p<.0001; d_{SMD}=-1.01), with maximum improvement 40 minutes following. The studies were homogeneous in their findings, and they also showed reduced anhedonia and suicidality. Since the meta-analysis by Parsaik et al., several additional studies have been performed and are described below.

Saligan et al. (2016) studied the effects of ketamine in reducing fatigue among 36 patients with treatment-resistant bipolar disorder (I or II) who were medicated with lithium or valproate in an RCT [58% female, age M=46.7, race N/R]. They saw significantly reduced fatigue compared to placebo beginning at 40 min post-infusion (p<.01) and continuing at all time-points up to 3 days following (p<.001; day 2: d=-0.59). Seven, 10, and 14 days following, the difference was much smaller (day 7: d=-0.14), but there continued to be a significant reduction in fatigue among the ketamine group at day 10 (p<.05) and 14 (p<.01) compared to placebo.

Rybakowski et al. (2017) examined the impact of ketamine infusion on depressive symptoms in a group with treatment-resistant bipolar depression who were taking mood stabilizers [N=53, 75% female, age=22–81, race N/R]. Response to treatment was seen in 51% of participants at 7-day follow-up, with higher response rates among males than females (p=.031; 77% vs. 43%, respectively). Depressive symptoms showed significant reductions (p<.001) compared to baseline 1 day (d_c=-1.27), 3 days (d_c=-1.52), 7 days (d_c=-1.72), and 14 days (d_c=-1.76) following treatment.

Grunebaum et al. (2017) saw a trend toward reduced SI in patients with bipolar depression 1 day following 0.5 mg/kg ketamine infusion (p=.074; d=0.98) compared to midazolam control [N=16, age=18–65, 63% female, 13% non-white]. Compared to

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baseline, ketamine also reduced SI at 230 min (p=.017), 1 day (p=.008), and 1 week (p=.007) [n=7]. Follow-up at 2 weeks, 3 weeks, and 4 weeks did not show a significant reduction from baseline, with mean SI approximately midway between baseline and the first three measurements. At 5 weeks following, SI was again significantly reduced compared to baseline (p=.003). Finally, at 6 weeks following, there was no significant difference in SI, though mean SI remained lower than at 2–4 weeks. Examining these data, SI resembles a bipolar cycling pattern with SI substantially reduced in the week following ketamine, increasing in the next 3–4 weeks in what resembles a depressive period, then decreasing substantially at week 5 in what may be a manic or hypomanic period, and then finally increasing again to return to another depressive period at week 6. It is notable, however, that there is a qualitative trend in the data toward lower SI during these hypothesized depressive periods as time goes on. In addition, the possibility that ketamine may induce a normalized cycling pattern among bipolar patients may prove useful for treatment. While these observations are not validated through statistical analysis, they represent potentially fruitful hypotheses for further research.

Use With Children and Adolescents. Intranasal ketamine administered every 2–5 days has successfully been applied to treat children and adolescents with bipolar disorder with a fear of harm phenotype [N=12, 83% male, age=6–19, race N/R], though further research is needed in this area (Papolos et al., 2013, 2018).

Somatization/Conversion Disorders

LSD. Frederking (1955) commented that LSD doses as low as 20 µg "can have lasting effects on organic neurotic changes, especially in conditions associated with smooth-muscle cramps, such as chronic constipation and dysmenorrhea" (p. 265). Baker

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(1964) also categorized conversion disorders as among the "most favourable cases for LSD psychotherapy" based on experiences treating 150 patients using LSD (p. 1201). While no data is provided for these claims, it does suggest a possible treatment application.

Among four patients treated by Sandison et al. (1954) for "conversion hysteria" through LSD sessions (M=7.25), they reported one as 'recovered,' one as 'moderately improved,' and one as 'improved' but still in treatment, while one refused further treatment after the first LSD session. In a follow-up study that included the 30 original patients plus 64 more, Sandison and Whitelaw (1957) describe the outcomes of 12 patients diagnosed with "hysteria (all forms)" and treated with LSD psychotherapy. Among those, 8% were 'recovered,' 17% were 'greatly improved,' 33% were 'moderately improved,' and 42% were 'not improved' with at least 6-month follow-up.

Chandler and Hartman (1960) saw "some improvement" in two patients diagnosed with DSM-I "Psychoneurosis: Conversion reaction" or "Physiological disturbance, gastrointestinal type" and treated with 50–150 μg LSD psycholytic therapy for an average of 6.2 sessions [N=110, 62% male, age=15–62, race N/R].

LSD and Mescaline. Mogar and Savage (1964) saw non-significant changes compared to baseline following 200–700 μg LSD combined with 200–400 mg mescaline in MMPI hysteria (*Hy*), a measure of somatization symptoms. While these changes were not significant, the directions of change are interesting, with high-severity patients showing the largest improvement (d_n=-0.4; n=17), followed by moderate-severity patients (d_n=-0.2; n=18). In healthy normals, however, there was an increase in somatization symptoms (d_n=0.4; n=25).

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Ayahuasca. Compared to matched controls, Bouso et al. (2012) found moderately lower somatization symptoms among ritual ayahuasca users, though this result did not reach significance (p<.147; d_c=-0.36; n=127). Following a 3–9-month program treating SUDs with once to twice-weekly ayahuasca alongside other interventions, Fernández et al. (2014) saw a small and non-significant decrease in somatization symptoms (Δ=-15.4%; n=9).

Ketamine. Krupitsky and Grinenko (1997) saw a significant decrease in MMPI *Hy* (p<.05; d_n=-0.24) following 2.5 mg/kg IM KPT in treating 111 patients with alcohol use disorder [N=111].

Trauma- and Stressor-Related Disorders

Posttraumatic Stress Disorder

Classical Psychedelics. Regarding the treatment of posttraumatic stress disorder (PTSD) with classical psychedelics, there is relevance to Ann Shulgin's (1995) comment that "MDMA became a favorite tool of psychotherapists, [sic] because it can be given safely to people who are too emotionally fragile to benefit from any of the psychedelics" (p. 3). She further continues to describe the loss of control that can come with classical psychedelics, which "can be disturbing" (p. 3). While not all patients with PTSD would be considered "emotionally fragile," patients with PTSD tend to have emotional lability that may be acutely exacerbated by treatment with classical psychedelics.

Krediet et al. (2020) state that "many traumatized patients have been treated with classical psychedelics" based on the psycholytic treatment literature of the 1960s (p. 17). However, the concept of PTSD as we know it today did not exist until the DSM-III was released in 1980 (North et al., 2016). A rigorous study of these early treatments through

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the lens of contemporary trauma theory and diagnostic criteria could reveal how classical psychedelics can play a role in treating PTSD. Toward this possibility, there is evidence that classical psychedelics can be effective in treating symptoms that commonly co-occur with PTSD, including anxiety, depression, and suicidality (see respective sections in this chapter as well as Chapter 7). In further support, Krediet et al. (2020) outline a theoretical rationale for using classical psychedelics in treating PTSD, including enhanced fear extinction in animals, increased neuroplasticity, decreased amygdala reactivity, increased empathy, enhanced mindfulness, facilitation of insight, reduced emotional avoidance, increases in Openness, and facilitation of emotional breakthrough experiences. Together, there is sufficient rationale to warrant further investigation into the role that classical psychedelics can take in the treatment of PTSD.

Ayahuasca. Nielson and Megler (2013) provide theoretical justification and case studies supporting the use of ayahuasca for treating PTSD. They theorize that, like exposure therapy or EMDR, ayahuasca can help activate traumatic memories and allow for a change in how one reacts to those memories. When done in a safe and supportive environment, Nielson and Megler propose that the sympathetic activation triggered by ayahuasca could also help to support trauma healing by creating "the opportunity to identify, reorganize, and neutralize triggers" (p. 49). As further support, they cite the unpublished case studies of three veterans with PTSD who had positive outcomes from taking part in ayahuasca ceremonies in Peru.

Further supporting ayahuasca's use in treating PTSD, Inserra (2018) hypothesizes that the sigma-1 activating quality of DMT and the MAOI activity present in ayahuasca could have anti-amnesic effects. This would be beneficial to the treatment of PTSD as it

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could help elevate the repression of traumatic memories, making them available for processing and ordering in time. Corroborating this effect, Inserra cites accounts of people with PTSD who retrieved previously inaccessible traumatic memories with ayahuasca. Finally, in a qualitative study examining the impact of ayahuasca ceremonies on seven North American women, a core theme that emerged was "healing sexual abuse trauma" (Espinoza, 2013).

MDMA. Of the psychedelic therapies, MDMA-assisted psychotherapy (MDMA-PT) has the most established efficacy for treating PTSD, having received "Breakthrough Therapy" designation from the FDA (Mitchell et al., 2021). Amorosa and Workman (2016) performed a preliminary meta-analysis of MDMA-PT for PTSD [N=2]. They found that MDMA-PT had larger effect sizes than prolonged exposure therapy (PE) in treating PTSD based on both clinician-observed ratings (MDMA-PT: d_g=1.17; PE: d_g=1.08) and self-report ratings (MDMA-PT: d_g=0.87; PE: d_g=0.77). There were also lower dropout rates with MDMA-PT (12.7%) compared to PE (27.0%).

Since the preliminary meta-analysis by Amorosa and Workman, studies with MDMA-PT for PTSD have continued. In a combined analysis of six Phase 2 studies, Mithoefer et al. (2019) found that CAPS for DSM-IV (CAPS-IV) scores were significantly reduced (p<0.001; d=0.8) with 75–125 mg MDMA-PT compared to active controls of 0–40 mg MDMA-PT. Following two MDMA-PT treatments, 54.2% of participants no longer met CAPS-IV PTSD diagnostic criteria compared to 22.6% in the control group. In Phase 3 trials, Mitchell et al. (2021) saw significantly reduced PTSD symptoms from MDMA-PT (p<.0001; d=0.91) compared to placebo and measured by the CAPS for DSM-5 (CAPS-5) [N=90, 34.4% male, age M=41.0, 76.7% White, 8.9%

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Hispanic or Latino, 7.8% Asian, 2.2% Black or African American, 3.3% American Indian or Native Alaskan, 8.9% multi-racial]. An analysis by Avanceña et al. (2022) found that expanding access to MDMA-PT to U.S. patients with chronic or severe PTSD would avert 43,618–106,932 deaths and provide substantial health benefits whilst also being financially advantageous.

Use With Children and Adolescents. While clinical use of MDMA in children is controversial, the breakthrough effectiveness of MDMA-assisted psychotherapy for treating PTSD in adults suggests it could help relieve the suffering of abused and traumatized children (Sessa, 2017). There is an ethical balance between protecting children from unknown harms and striving toward new treatments that can provide relief from the relentless horrors of posttraumatic stress. For this reason, U.S. drug development standards specify that clinical trials extend to children and adolescents after safety and efficacy have been demonstrated in adults, in accordance with the Pediatric Research Equity Act (United States Food and Drug Administration, 2005). As such, the FDA has asked MAPS to perform trials for treating PTSD in adolescents using MDMA-assisted psychotherapy (R. Matthews, personal communication, September 21, 2019).

Ketamine. Feder et al. (2014) performed an RCT examining the effects of 0.5 mg/kg ketamine infusion on PTSD and related depressive symptoms [N=41, 46% female, age M=36.1, 56% Black, 17% White, 27% other]. They found that ketamine produced a rapid reduction in PTSD symptoms 24 hours following infusion compared to placebo (p=.02). However, there was no significant difference in PTSD symptoms between ketamine and placebo after 7 days (p=.20). Ketamine also reduced depressive symptoms

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throughout the 7 days following infusion (p=.046–.052). There were no serious adverse responses to ketamine nor elevations in psychotic or manic symptoms.

In a subsequent RCT, Feder et al. (2021) tested the efficacy of six 0.5 mg/kg ketamine infusions over the course of 2 weeks in a group of patients with chronic PTSD [N=30, 77% female, age M=38.9, 53% White, 17% Black, 17% Asian, 13% other]. At the end of 2 weeks, there was a significant improvement in PTSD symptoms compared to an active placebo (p=.004; d=1.13). In the ketamine group, 67% responded to treatment compared to 20% of the placebo group (p=.03). This response to treatment persisted up until a median of 27.5 days following the course of treatment.

Pradhan et al. (2017) performed a placebo-controlled RCT investigating whether a single 0.5 mg/kg ketamine infusion added to the efficacy of 12 sessions of Mindfulness-Based Extinction and Reconsolidation psychotherapy for treatment-resistant PTSD and associated depression [N=10]. The intervention was effective in both the ketamine and placebo groups, but there was no significant difference between the groups on any of the four outcome measures (p=.148–.800). In a similar study, Shiroma et al. (2020) performed an uncontrolled pilot study of 0.5 mg/kg ketamine infusion 24 hours prior to the first three weekly prolonged exposure sessions in a 10-week series treating PTSD in veterans [N=10, 70% male, age=24–72, race N/R]. At the end of treatment, they saw significant improvements in PTSD ($p\leq$.001; d=1.21–1.83) and depression (p=.001; d=1.35) symptoms compared to baseline.

Ketamine-Assisted Psychotherapy. Dore et al. (2019) examined the impact of KAP on anxiety and depression across several clinics in an uncontrolled trial [N=235 patients, 48.9% women, age M=42.7, race N/R]. They found reductions in anxiety and

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depression symptoms across the study population (see sections above) but also noted that the largest improvements occurred in those with developmental trauma. A chart review by Davis et al. (2021) found a trend close to significance toward reduced PTSD symptoms (p=.058; d=-0.48) and associated functional disability (p=.050; d=-0.52) in patients treated with KAP in an outpatient setting [N=18, 56% female, age M=45.22, 100% White]. In a case study, Halstead et al. (2021) saw significant improvement in PTSD symptoms related to racial trauma and childhood sexual abuse with KAP treatment in a 58-year-old African American woman.

Use With Children. Donoghue et al. (2015) describe remission of severe and ongoing aggression and emotional dysregulation in a 7-year-old boy with PTSD following ketamine anesthesia. These changes were sustained for some time, but his behavior returned to baseline after 13 days.

Adjustment Disorders

LSD. Chandler and Hartman (1960) saw, on average, "considerable improvement" among six patients diagnosed with DSM-I "Adult situational reaction" and treated with 50–150 μg LSD psycholytic therapy for an average of 6.2 sessions [N=110, 62% male, age=15–62, race N/R].

MDMA. The efficacy of MDMA-assisted psychotherapy for treating entrenched PTSD suggests that it could also support the treatment of adjustment disorder.

Ketamine. The efficacy of ketamine infusion in rapidly reducing anxiety and depression (see sections above) suggests that ketamine could support the remission of adjustment disorder, especially if combined with short-term psychotherapy.

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Grief

Beischel (2019) describes experiences of after-death communication (ADCs) as a normal and healthy part of grieving for many people. They summarize the literature in support of spontaneous ADCs as "beneficial and comforting" to those who are grieving and help "…create new, meaningful relationships between the bereaved and the deceased" (p. 5). In addition to ADCs occurring spontaneously, ADCs can also be facilitated through techniques like EMDR or with the assistance of spiritual practitioners or mediums. Beischel proposes that psychoactive substances can elicit spontaneous ADCs, or they can be used to intentionally occasion ADCs. Beischel notes the traditional use of ayahuasca and ibogaine for this purpose and cites reports of ADCs occasioned through LSD, DMT, and ketamine.

ADCs seem to be the main mechanism of action found in the literature by which psychedelics help with grief. Therefore, the capacity to produce ADCs is taken as evidence that a psychedelic may be able to assist with grief. There were few randomized controls found addressing the effect of psychedelics on grief.

Classical Psychedelics. Of the classical psychedelics, LSD, psilocybin, DMT, and ayahuasca are all associated with ADCs (see Chapter 6). Given mescaline's similarity to these psychedelics, it is also likely to facilitate ADCs, despite this phenomenology not being found in the literature. With ADCs as a mechanism, classical psychedelics may have a role in facilitating grief processing.

Ayahuasca. There is anecdotal evidence of ayahuasca being used in indigenous groups to induce ADCs and thereby assist in the grieving process (Beischel, 2019). Beischel provides references to indigenous descriptors of ayahuasca as "the vine of the

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dead," and its purpose is to connect with the "spirit world" to "enter into contact with the ancestors" (p. 19). This phenomenon of ayahuasca-induced ADCs is also validated by the thematic analysis of ayahuasca experiences by Wolff et al. (2019).

In an unrandomized trial, González et al. (2017) compared the impact of an ayahuasca ceremony compared to peer support on uncomplicated grief in 60 people [72% female, age M=44]. The ayahuasca group showed a significantly lower level of present grief than the peer-support control (p=.001; d_c=0.91) as measured by the Present Feelings Scale of the Texas Revised Inventory of Grief (TRIG; 40% Spanish version, 60% English version). The TRIG Past Feelings Scale was also lower in the ayahuasca group with a magnitude approaching significance, raising the possibility that ayahuasca may cause a reappraisal of past grief (p=.082; d_c=0.45). Experiential themes reported by participants related to grief included "emotional release," "biographical memories," and "contact with the deceased."

González et al. (2020) performed an observational study of 50 individuals who participated in indigenous Shipibo ayahuasca ceremonies for the purpose of resolving grief. Compared to baseline, participants' present grief as measured by the TRIG was significantly reduced (p<.001) at 15 days (d=0.84; n=39), 3 months (d=1.38; n=31), 6 months (d=1.16; n=29), and 12 months (d=1.39; n=27) following. While this cohort study does not prove ayahuasca's efficacy for treating grief, it does demonstrate that the results of the González (2017) study are likely to be durable.

MDMA. MDMA is not associated with ADC experiences. However, MDMA may facilitate grief processing through a reduction in avoidance with a similar mechanism to its efficacy for PTSD.

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Ketamine. While ketamine is not associated with ADCs, a case report demonstrates the role that ketamine treatment can have in processing grief. A 28-year-old male was brought to the hospital by family members 1 week following the death of his wife (Gowda et al., 2016). The patient had catatonic symptoms, had not been eating much, and was not engaging in personal care. After other treatment options were exhausted, IV ketamine infusion was given, and the patient progressively became more conversational before becoming sedated fully. Reporting on the experience, the patient described going to heaven in a chariot where he encountered his wife and had a conversation with her that led to feelings of tremendous relief. Following the experience, he was cheerful, communicative, and began eating again, changes that remained present 3 months later.

Ibogaine. Ibogaine is used by the Bwiti religious group of Gabon to initiate "spiritual contact with the dead" (Beischel, 2019, p. 17). ADCs have also been identified in studies of ibogaine phenomenology within a Western context. In a study of ibogaine experiences from people being treated for drug dependence [*N*=22], the theme of "meeting with deceased relatives" emerged (Schenberg et al., 2017). In another study of people who took ibogaine in a facilitated context for various clinical and spiritual reasons [*N*=20], the experiential theme of "ancestors and entities" emerged (Kohek et al., 2020).

Gender- and Sexuality-Related Dysphoria

There are many historical accounts of attempting to "cure" homosexuality and transgenderism using psychedelics (Abramson, 1955; Alpert, 1969; Ball & Armstrong, 1961; Chandler & Mortimer, 1960; A. J. Martin, 1961, 1962, 1967; Sandison et al., 1954; Sandison & Whitelaw, 1957). Since, as a society, we have come to recognize these traits

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not as disorders but rather as innate orientations, these applications are not reviewed. Instead, studies examining psychedelics' use in healing gender- and sexuality-related dysphoria are described here.

LSD and Psilocybin. Ludwig & Levine (1965) saw robust improvements in self-concept from LSD alone and with psychotherapy (d_c=0.82–2.03) [N=42]. Like LSD, psilocybin produces robust long-term increases in self-concept, self-acceptance, and pride (d_c=0.76–1.96) based on four studies (see Chapter 7). These findings support that LSD and psilocybin treatments may help with dysphoria related to gender and sexuality.

Ayahuasca. Cavnar (2014) performed a qualitative study of 17 self-identified gay and lesbian participants who, in the previous 3 years, had used ayahuasca in a ceremonial context. All participants felt that their ayahuasca experiences had helped to affirm their sexual orientation. There were no reports of ayahuasca ceremonies having negative effects on identity perception. Espinoza (2013) examined the qualitative impacts of ayahuasca ceremonies on the sexual and spiritual lives of seven North American women. Core themes that emerged included: "purification and support for reproductive health," "healing sexual abuse trauma," "transforming relationship with self," "empowered decision making," "enhanced intimacy with others," and "connecting with God."

MDMA and Ketamine. Both MDMA- and ketamine-assisted therapies have the potential to support healing from gender- and sexuality-related dysphoria based on the efficacy of these therapies in treating PTSD, anxiety, and depression (see sections above).

Sexual Disorders and Difficulties

LSD. Sandison and Whitelaw (1957) describe the outcomes of six patients diagnosed with "impotence" and treated with LSD psychotherapy sessions. Among those,

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17% were ‘recovered,’ 33% were ‘moderately improved,’ and 50% were ‘not improved’ after at least 6-month follow-up.

Ball and Armstrong (1961) describe treating a 46-year-old man who had engaged in compulsive frottage since he was a teenager. With LSD, he developed “an intense preoccupation with matters mystical” through what is described as a mystical experience according to Pahnke’s criteria (p. 232). While the LSD experience did not directly relate to the frottage compulsion, 8 months later, he had not engaged in frottage and had had only one fleeting impulse toward it.

Ball and Armstrong also report on a case of a 27-year-old man who had engaged in pedophilia with 8- to 10-year-old boys and had had no adult sexual relationships of any gender. His mother had died when he was young, and he had an intense relationship with his father in which they slept in the same bed until he was 25. He was treated with LSD, during which “…he became extremely disturbed, showing great anxiety, agitation, hyperactivity and fear” (p. 233). He became afraid he was going insane and suspicious of others, despite also feeling emotionally close to those around him. At the peak of the LSD experience, he stripped naked and expressed fears of losing his genitals to women. Soon after, he made sexual advances toward the female clinician who was present. Reflecting on the session, he “…felt himself to be part of a larger unity, developing a closer bond with God…” (p. 233). For 3 weeks following, he had heightened anxiety, for which he received mild sedatives and therapeutic reassurance. He then began engaging in adult heterosexual relationships for the first time in his life. Pedophilic interests continued but were much more easily controlled, and his long-standing dysphoria remitted.

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Ling and Buckman (1965) describe the treatment of a 33-year-old woman who, since being a child, had been frightened of sex and had no sexual desire as an adult. She was treated with six sessions of treatment with concurrent LSD (50–80 μg IM) and Ritalin (30–60 mg IV, in 2–3 doses). This drug combination was chosen to reduce the anxiety associated with LSD. The paper includes verbatim descriptions of the sessions by the patient in which she describes uncovering memories of a childhood sexual assault. In uncovering this memory across several LSD/Ritalin sessions, she recalled both the horror and the pleasure of the experience. Following the sixth session, she felt a sense of tranquility and was able to have intercourse with her husband and achieve orgasm. Six months later, she reported no inhibitions regarding sex.

MDMA. In a survey on MDMA's effect on sexual function, 35% of females and 37% of males responded yes to the question, "Do you feel that MDMA has helped you overcome any sexual inhibitions or concerns?" [*N*=76, 51% male, 49% female, age=20–63, race N/R] (Buffum & Moser, 1986). Those females who responded yes shared significant comments that included (p. 358):

"Used it to forgive my childhood molestations and clear pelvic blocks."

"Lessening of armor/resistance."

"MDMA helped me to determine that I'm bisexual."

"Has enabled me to enjoy sex more."

"I feel more relaxed and open since." / "To relax more."

"More awareness of my physical feelings."

"Jealousy had reduced due to the love shared in tricky sexual scenes."

Those men responding yes also shared comments:

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> "More sensitive to one's own and other's levels of sensuality—better sensual communication."
>
> "Allowed for more sensuality—less purely sexual."
>
> "More receptive to my partner's love and sensuality toward me."
>
> "More relaxed to just let things happen."
>
> "It's easier to ask for sexual activity."
>
> "More open"

One male who had responded yes, clarified that MDMA had helped his wife but that the effects were temporary, resulting in her taking MDMA every 2 weeks.

Ketamine. Long-term recreational ketamine use is associated with erectile dysfunction and bladder cystitis that is linked to lowered female sexual function (see Chapter 5 section "Sexual Dysfunction"). These findings suggest that ongoing clinical ketamine treatments may reduce sexual function, though no studies were found on this topic. Ketamine-assisted psychotherapy could be useful in treating sexual paraphilias in a similar manner to the cases described with LSD above, given ketamine's association with mystical experience (see Chapter 6). Further, ketamine infusion combined with psychotherapy could support the treatment of sexual aversion, given its short-term efficacy in reducing PTSD symptoms (see "Posttraumatic Stress Disorder" above).

Substance Use Disorders

Mescaline and LSD. Chandler and Hartman (1960) saw, on average, "some improvement" among 17 patients diagnosed with DSM-I "Sociopathic disorder: Addiction, alcohol and/or narcotic"[9] and treated with 50–150 μg LSD psycholytic therapy

[9] The DSM-I classified addiction as a sociopathic personality disorder (American Psychiatric Association, 1952, p. 7).

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for an average of 6.2 sessions [*N*=110, 62% male, age=15–62, race N/R]. Among two LSD treatments for "abuse of alcohol and medicine" in Denmark during the 1960s, one was improved and the other unchanged (Larsen, 2017). Finally, C. M. Smith (1958) and Baker (1964) note that substance-abusing patients require higher doses of LSD for effective treatment. Smith writes that the same is true of mescaline.

Ayahuasca. Traditionally, ayahuasca has been used to handle addiction in both the Santo Daime and UDV traditions (Labate et al., 2010). Neither of these traditions, however, use ayahuasca to formally 'treat' addiction; rather, healing of addiction is aligned culturally with the goals of "spiritual healing" and "spiritual evolution" (p. 210). Labate et al. cite several small studies related to the handling of substance use disorders within UDV. However, most of these studies are published in Spanish and therefore not included in the present review. Labate et al. (2014) examined the impact of Santo Daime membership on substance abuse through a retrospective survey [*N*=83, 49% male, age=18–40, Brazilian]. Of the sample, 41 met the author's criteria for a history of substance dependence, with 90% reporting recovery from one or more substances while only 10% reported continued dependence. Of those with a substance dependence history, 27% reported recovery from alcohol dependence, 24% from cocaine, 19% from tobacco, 8% from crack cocaine, and 5% from other substances.

Labate et al. (2010) also describe two SUD treatment centers using ayahuasca in Peru and Brazil, respectively. The first, called Takiwasi, was founded in 1992 and has since treated over 700 patients. In an uncontrolled pilot study examining the efficacy of treatment at Takiwasi [*N*=211], 31% were feeling 'well,' 23% 'better,' and 23% 'the same or worse,' with outcome data missing for the remaining 23% (Giove, 2002, as reported by

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Labate, 2010). The second center is called the Institute of Applied Amazonian Ethnopsychology (IDEAA). Fernández and Fábregas (2014) describe the treatment protocol of the center and examine the qualitative experiences of patients treated through their method. The treatment involves daily yoga and meditation, individual psychotherapy, community involvement, and ayahuasca sessions 1–2 times per week.

Fernández et al. (2014) performed an uncontrolled pilot study examining the efficacy of IDEAA in 13 patients over the course of 3 to 9 months, nine of whom were diagnosed with substance abuse and/or dependence [62% male, age *M*=35, race N/R]. They saw improvements in traits related to addiction following treatment, including impulsiveness (p=.042), "anticipatory worry" (p=.029), "responsibility" (p=.021), and overall positive psychological symptoms (p=.029) compared to baseline. They did not, however, report substance abuse outcomes.

G. Thomas et al. (2013) performed an observational study of 12 participants in a 4-day retreat focused on addiction and stress that included group counseling and two ayahuasca ceremonies [indigenous Canadian, age and sex N/R]. They saw reductions in self-reported use of substances approaching or reaching significance between the month preceding baseline and the month preceding 6-month follow-up for alcohol (p=.091; 50% reported use at baseline to 20% at follow-up), cocaine (p=.003; 60% to 0%), and tobacco (p=.057; 81.8% to 63.6%) use [n=11]. There was no significant change in cannabis (p=.958; 45.5% to 45.5%) or opiate use (p=N/R; 9.1% to 9.1%). While these results are encouraging, they should be taken with caution as the study lacked a control group.

MDMA. Given the effectiveness of MDMA in treating PTSD and the association between PTSD and substance use disorders, it follows that MDMA-assisted

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psychotherapy may have applications in treating SUDs (Bogenschutz & Pommy, 2012).Greer and Tolbert (1986) administered MDMA to 29 subjects in their home environments with various therapeutic goals. At follow-up, 50% reported a reduction in substance use, while only three reported an increase [*n*=28]. Follow-up time was between 2 months and 2 years following the MDMA session, with most around 9 months. Because this was an uncontrolled study with only retrospective self-report data, no definitive causal benefit can be shown, but it does indicate a promising avenue for further research. MDMA-assisted psychotherapy so far does not show an association with increased substance use, including the use of MDMA outside the therapeutic context (Mithoefer et al., 2013).

Ibogaine. Schenberg et al. (2014) looked retrospectively at outcomes from 75 people treated with ibogaine for alcohol (64%), cannabis (81%), snorted cocaine (83%), injected cocaine (8%), and crack cocaine (68%) abuse [89% male, age *M*=33.7, 72% polydrug users, race N/R]. Ibogaine treatment resulted in a median abstinence period of 5.5 months for those treated with one session and 8.4 months for those treated multiple times. There was a significant effect of the number of ibogaine sessions on the period of abstinence ($p<.001$). There was also a significant increase in the duration of abstinence periods following ibogaine treatment compared to pretreatment.

dos Santos et al. (2017b) reviewed human studies of ibogaine's efficacy in treating addiction [*N*=8]. Of those studies, seven were case series suggesting that one dose of ibogaine can significantly reduce drug withdrawal, craving, and relapse from a mix of substances for a period of 24 hours up to weeks or months. The one RCT included in the review (Glue et al., 2016) is described below under Opioid Use Disorder.

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Belgers et al. (2016) performed a meta-analysis of ibogaine studies with animal models [*N*=27]. They found a robust effect of ibogaine in reducing drug self-administration, with the most substantial effects seen 0–24 hours following administration (*d*=-2.42; *n*=29 comparisons), with continued efficacy at 24–72 hours (*d*=-1.14; *n*=13 comp.) and >72 hours (*d*=-0.92; *n*=9 comp.) [*n*=8 studies]. There was no effect of ibogaine seen on conditioned place preference in rats [*n*=3 studies]. Based on two studies, ibogaine decreased drug-induced dopamine release in rats (*d*=-1.14).

Alcohol Use Disorder

Garcia-Romeu et al. (2019) performed a retrospective online survey of people with alcohol use disorder (AUD) who had reduced or stopped alcohol use following a psychedelic experience in a non-clinical setting [*N*=343, 78% male, 89% White]. Prior to the experience, 72% of the sample met the criteria for severe AUD, according to their retrospective report. Following their experiences, 83% no longer met the criteria for AUD. Psilocybin was attributed to alcohol cessation or reduction in 36.2% of cases, LSD in 37.9%, ayahuasca in 7.9%, DMT in 5.0%, and another psychedelic, including peyote and San Pedro in 13.1%.

Mescaline and LSD. C. M. Smith (1958) reported on 24 patients treated with mescaline (0.5 g) and LSD (200–400 μg) as adjuncts to an AUD treatment program that included psychotherapy, occupational therapy, and recreational therapy. At follow-up 2 months to 3 years later (*M*=1 year), 25% were ‘much improved,’ 25% ‘improved,’ and 50% ‘unchanged.’ Those who were ‘much improved’ were abstinent or “drinking only in small quantities.” Those who improved showed a “definite reduction in alcohol intake.”

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The authors note that Alcoholics Anonymous programs were “invaluable” in the treatment process.

Mescaline. There are anecdotal reports from Native American communities that mescaline is effectively used in treating alcoholism (de Rios et al., 2002; L. Lu et al., 2009). Albaugh and P. O. Anderson (1974) describe a treatment program for alcoholism among Native Americans that involved peyote ceremonies through the Native American Church. However, no outcomes were reported. Garcia-Romeu et al. (2019) identified 45 cases of successful alcohol cessation or reduction that were retrospectively attributed to “Other (e.g., peyote, San Pedro)” in an online survey of naturalistic psychedelic use.

LSD. There is a long history of LSD treatment for alcoholism, but early studies suffered from methodological flaws (Dyck, 2006). In a meta-analysis of modern RCTs for treating alcoholism with LSD [*N*=6 studies], Krebs and Johansen (2012) found that there were significant benefits for alcohol use and misuse at initial (OR=1.96), 2- or 3-month (OR=1.85), and 6-month (OR=1.66) follow-up. At 12-month follow-up, however, there were no significant benefits for alcohol misuse [*n*=4 studies]. Regarding alcohol abstinence, there was a significant effect at initial (OR=2.07) and “short-term” (OR=1.80) but not “medium-term” follow-up [*n*=3 studies].

Psilocybin. Bogenschutz et al. (2015) performed an open-label uncontrolled trial treating alcohol dependence with one to two psilocybin sessions alongside Motivational Enhancement Therapy and preparatory/integration sessions related to the psilocybin experiences [*N*=10, 60% male, age=25–56, 40% Hispanic, 30% White, 20% Native American/Alaska Native, 10% African American]. The proportion of drinking or heavy drinking days showed no significant change during the first 4 weeks of treatment, which

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was prior to the psilocybin sessions. However, after psilocybin, in weeks 5 through 12, there were significant decreases in percent drinking days (p=.009; d_c=-1.15) and percent heavy drinking days (p=.008; d_c=-1.16) relative to baseline. These changes were largely maintained 36 weeks later (p=.007–.018; d=-1.040 to -1.187). The intensity of effects in the first psilocybin session was predictive of change in drinking in weeks 5–8 (r=.76–.89). No significant treatment-related adverse events occurred.

Meinhardt et al. (2021) identified one mechanism for psilocybin's efficacy in treating AUD. The authors determined that impairments in cognitive flexibility seen in alcohol-dependent rats were linked to reduced mGluR2 expression in the prefrontal cortex. They further determined that mGluR2 knockout rats were vulnerable to excessive alcohol seeking. Finally, the authors demonstrated that psilocybin could restore mGluR2 expression, improve cognitive flexibility, and reduce alcohol-seeking behavior.

DMT. Garcia-Romeu et al. (2019) found 17 cases of alcohol cessation or reduction that were retrospectively attributed to DMT. No other evidence was found regarding DMT's effectiveness in treating alcohol use disorder, though Halpern (1996) suggests that DMT may have practical utility in treating addiction due to its short duration and ability to be administered in an office setting.

Ayahuasca. Garcia-Romeu et al. (2019) found 27 cases of alcohol cessation or reduction that were retrospectively attributed to ayahuasca. In mice, ayahuasca prevents the development of alcohol addiction (Oliveira-Lima et al., 2015).

MDMA. Sessa (2018) that following its success in treating PTSD, MDMA may be useful in treating AUD, given the association between AUD and early traumatic experiences. Sessa points out that compared to other psychedelics, there are few reports

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of people attributing alcohol cessation to MDMA experiences. Further, mystical-type experience occurs only in 10%–15% of first-time MDMA compared to 80%–90% with classical psychedelics. In other psychedelics, mystical experience has been shown to be a mediator in addiction treatment outcomes. However, Sessa also points out that in addition to being effective at treating PTSD, MDMA can also facilitate feelings of empathy and self-compassion that could be helpful in building insight about alcohol use and its impact. In addition, Sessa highlights that MDMA is better tolerated than other psychedelics and may be a better choice for patients that would be overwhelmed by classical psychedelics in a non-therapeutic manner.

Ketamine. Krupitsky et al. (1992) examined the efficacy of 3.0 mg/kg KPT (see Chapter 11) in treating AUD compared to a non-psychedelic aversive conditioning control treatment [*N*=186, male, age *M*=36.1, Russian, duration of alcohol withdrawal syndrome *M*=5.6 years]. Among the treatment group, 69.8% were abstinent 1 year following treatment compared to 24% in the control group. Krupitsky and Grinenko (1997) compared the efficacy of 2.5 mg/kg IM KPT in treating AUD to a conventional treatment control [*N*=211, male, age *M*=37.4, Russian, duration of alcohol withdrawal syndrome *M*=6.0 years]. Of the treatment group, 65.8% sustained alcohol abstinence for more than 1 year compared to 24% of the control group. It is important to note that treatment groups were not randomized.

Kolp et al. (2006) report retrospectively on the outcomes of using Ketamine-Enhanced Psychotherapy (KEP; see Chapter 11) combined with group therapy to treat AUD in a private practice setting [*N*≈70, male and female, age=21–64, race N/R]. The study was uncontrolled and tested five different treatment designs involving one or two

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ketamine sessions and 10–90 hours of weekly group therapy. Approximate 1-year abstinence rates ranged from 25% to 70%. However, none of the treatment conditions varied the number of ketamine administrations while holding constant the amount of psychotherapy. For this reason, it is unclear what role ketamine sessions played in treatment efficacy.

In an RCT, Rothberg et al. (2020) found that ketamine infusion resulted in a significant reduction in at-risk drinking frequency ($p<.05$; OR≈0.2) when given alongside a 5-week motivational enhancement therapy program to alcohol-dependent adults [N=40, 52.5% female, age M=53.0, 70.3% White, 13.5% Black or African American, 5.4% Asian, 10.8% multiracial]. They also found that mystical effects mediated the effect of ketamine on at-risk drinking ($p<.05$), while dissociative effects did not ($p=.742$). Midazolam infusion was used as the control condition.

Wong et al. (2015) tested the safety and efficacy of ketamine as an adjunct to benzodiazepines for managing alcohol withdrawal [N=23, 60.9% male, age median=50.0, 87% Caucasian]. Ketamine was shown to be safe for this application and reduced required benzodiazepine doses. Finally, ketamine may be more effective as an antidepressant ($p=.03–.09$) in those with a family history of AUD [N=26, 54% male, age=18–65, race N/R] (Phelps et al., 2009). Given that depression can contribute to alcohol use, this finding indicates a potential pathway to AUD treatment through treating a concomitant disorder.

Ibogaine. Rezvani et al. (1995, 1997) found that ibogaine attenuated alcohol intake in alcohol-preferring rats. Schenberg et al. (2014) looked retrospectively at outcomes from 75 people treated with ibogaine for abuse of various substances, with 48

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cases involving alcohol [89% male, age *M*=33.7, 72% polydrug users, race N/R]. Ibogaine treatment resulted in a median abstinence period of 5.5 months for those treated with one session and 8.4 months for those treated multiple times.

Barsuglia et al. (2018) propose a sequential regimen of ibogaine followed by 5-MeO-DMT for treating alcohol use disorder. They hypothesize that the two drugs may have additive effects given that serotonergic psychedelics such as 5-MeO-DMT tend to occasion mystical experiences that positively mediate substance abuse treatment outcomes. Conversely, Barsuglia et al. (2018) claim that ibogaine does not produce mystical experiences despite being effective on its own for treating AUD. This may not be entirely accurate, however, as Heink et al. (2017) found that experiences of oceanic boundlessness were 49.7% greater with ibogaine than with 22.05 mg/70 kg psilocybin. Barsuglia et al. describe one case treated with their suggested regimen that was successful for AUD, with abstinence 1 month following and mild alcohol use 2 months following.

Opioid Use Disorder

In opioid-using cis- or trans- female sex workers, psychedelic use significantly moderated suicide risk (p=.036) during a 7-year study period [*N*=340, median age=36, 35% Indigenous, 23% gender or sexual minority] (Argento et al., 2018). Those who used psychedelics (mescaline, LSD, psilocybin, DMT, or MDMA) concurrently with opioids had an adjusted hazard ratio for suicide of 0.64 compared to 2.59 for those who used opioids without psychedelics.

LSD. C. Savage and McCabe (1973) performed an RCT evaluating the efficacy of 300–450 μg LSD combined with approximately 24 hours of preparatory psychotherapy to treat chronic heroin users who were on parole [*N*=74, 100% male, age *M*=28.6, 76%

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Black]. The control condition was an outpatient treatment program that included urine monitoring and weekly group therapy, to which the treatment group was transferred after the 6-week LSD therapy program. Complete abstinence for 1 year was significantly higher among the treatment group (p=.05; 25% vs. 5%). However, three treatment group members relapsed briefly but then sustained abstinence for the 1-year study program resulting in a total abstinence rate of 33% in the treatment group if those patients are included. It is important to note that the treatment group received approximately 24 hours of (presumedly individual) psychotherapy during the first 6 weeks of release, compared to 6 group therapy sessions for the control group. The difference in therapy received by the two groups confounds the findings, as the effects could be due to more hours of psychotherapy rather than LSD treatment.

A 49-year-old woman with chronic pain foot and morphine addiction (40–80 mg/day) acquired through medical pain management accidentally snorted 55,000 μg LSD thinking it was cocaine (Haden & Woods, 2020). Within an hour, she began vomiting, which continued for the next 12 hours. During this time, she was unable to communicate and "blacked out" while her roommate cared for her. For the 12 hours following, she felt "pleasantly high" and infrequently vomited, though her roommate described her sitting still in her chair frothing at the mouth with eyes open, closed, or rolled back in her head. The woman returned to "normal" another 12 hours later for a total duration of 36 hours. The following day, she no longer had foot pain and therefore discontinued morphine. For 5 days, her pain subsided, and she had no withdrawal symptoms. Her pain returned, but she was able to treat the pain effectively with 10–20 mg morphine daily and 25 μg LSD every 3 days. Approximately 3 years later, the woman discontinued morphine and other

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pain medications completely, as she believed that her pain was sufficiently reduced. She experienced no physiological withdrawal symptoms but did experience increased anxiety, depression, sensitivity to others' experiences, and social withdrawal.

Ketamine. In an RCT, Krupitsky et al. (2002) examined the efficacy of KPT for treating heroin addiction in individuals who had a 34.6-month mean duration of addiction prior to detoxification [N=70, 79% male, age M=22.3, Russian]. Ten hours of preparatory psychotherapy were given before a single KPT session, which was followed by an additional 5 hours of psychotherapy. Both the treatment and control groups received the same protocol, except that the treatment group received 2.0 mg/kg of IM ketamine while the control group received 0.2 mg/kg. The treatment group had significantly higher abstinence rates at 1- and 2-month follow-up (p<.01) as well as at 3-, 4-, 5-, 6-, 9-, 10-, 11-, 12-, 15-, 18-, 21-, and 24-month follow-up (p<.05). At 24-month follow-up, the treatment group was approximately 17% abstinent while the control group was approximately 3% abstinent. During the KPT experience, the treatment group also had substantially more hallucinogenic effects than the control condition.

In a second RCT, Krupitsky et al. (2007) replicated their prior study treating heroin dependence with KPT but varied the number of KPT sessions, with the treatment group receiving three sessions while controls received one [N=53, 83% male, age M=22.6, duration of heroin abuse M=37.7 months, Russian]. Abstinence rates were significantly higher during the 1-year follow-up period in the treatment group than in controls (p<.01). At one year, 50% of the treatment group was abstinent compared to 22.2% of the control group (p<.05).

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Finally, Jovaiša et al. (2006) performed an RCT using subanesthetic ketamine infusion (0.5 mg/kg/hr) to attenuate the effects of opiate withdrawal prior to administering opioid antagonists [*N*=50, 14% female, age *M*=23.1, duration of opiate abuse *M*=4.0 years, race N/R]. They found that ketamine attenuated opiate withdrawal signs at the first and second hours of anesthesia ($p<.05$) compared to controls, but not in the third hour. There were no significant differences between groups in abstinence rates, aftercare retention, or health or social/family life improvement 4 months after treatment.

Ibogaine. Alper et al. (1999) retrospectively examined 33 cases of heroin detoxification with ibogaine that were performed in non-medical settings [67% male, age *M*=27.3, 97% Caucasian, 3% Surinamese]. For 75.8% of patients, opioid withdrawal was resolved without drug-seeking behavior within 24 hours and was sustained during the 72-hour observation period. In 12.1% of patients, there was drug-seeking behavior despite having no withdrawal signs, while 6.1% of patients showed only attenuated withdrawal signs but maintained abstinence. A single patient (3.0%) had continued withdrawal signs and drug-seeking behavior. There was one fatality 19 hours following ibogaine administration. The authors suggest this death may have involved surreptitious heroin use, though their rationale for their suspicion is not described.

Glue et al. (2016) performed an RCT examining the efficacy of noribogaine in discontinuing methadone maintenance therapy [*N*=27, 78% male, age *M*=41.2, 74% White, 19% Maori, 7% other]. They found no difference in time to resume methadone between those given noribogaine (60–180mg) and placebo. There was a non-significant trend toward decreased opioid withdrawal among the treatment group. There were no

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serious adverse events seen in the study. The doses of noribogaine used, however, were quite low compared to what is typically used to treat substance use disorders.

T. K. Brown and Alper (2017) performed a prospective study of 30 people undergoing ibogaine treatment (1,540 ± 920 mg) for opioid dependence (oxycodone and/or heroin, used *M*=29.0 of previous 30 days) [83% male, age *M*=29.0, 90% Caucasian, 3% Hispanic, 7% other]. Opioid withdrawal symptoms were significantly decreased at 76.5 ± 30 hours following treatment ($p<.001$). At 1 month follow-up, 50% of participants reported no opioid use in the prior 30 days, and other drug use was significantly reduced ($p<.001$; $d_c=-3.41$) [$n=20$]. At 3-, 6-, 9-, and 12-month follow-up, reduced drug use was sustained ($p<.001$; $d_c=-2.32$, -3.29, -2.50, and -2.54, respectively).

Davis et al. (2017) performed an online survey of 88 patients who received ibogaine treatment for chronic opioid use. Of these people, 30% reported no opioid use since treatment, 41% had been abstinent for at least 6 months, and 48% reported decreased use compared to baseline. Seventy percent of those surveyed had relapsed following treatment, though some did achieve abstinence following relapse.

B. J. Malcolm et al. (2018) looked at opioid withdrawal and cravings during a week-long detoxification program with 18–20 mg/kg ibogaine in an uncontrolled, open-label study [*N*=50, 39% female, age=19–51, 77.5% White, 5% Asian, 17.5% other]. Compared to baseline, 78% of patients showed no clinical signs of opioid withdrawal, 79% reported minimal cravings, and 68% reported mild subjective withdrawal symptoms. While these results are impressive, they must be cautiously interpreted as there was no control group or long-term follow-up.

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Stimulant Use Disorders

Ayahuasca. Cruz and Nappo (2017) examined the qualitative experiences of 40 people who had reduced crack cocaine use through ayahuasca ceremonies. The authors found evidence that "ayahuasca, in a religious context, may have therapeutic value for crack cocaine dependence treatment" (p. 1). In a retrospective survey, Labate et al. (2014) identified 13 people who attributed recovery from cocaine abuse to Santo Daime membership among a sample of 83.

Ketamine. In an RCT, Dakwar et al. (2014; 2014) found that 24 hours following infusion, ketamine increased motivation to stop using crack cocaine (p=.012; Δ≈+60%) and reduced cue-induced craving (p=.012; Δ≈-60%) among crack cocaine-dependent individuals [N=8, 87.5% male, age M=47.5, 87.5% African American, 12.5% Hispanic, cocaine frequency M=22 days/month]. Motivation to stop cocaine was significantly greater with treatment conditions (p<.001) compared to placebo in an effect that was mediated by greater mystical effects (p<.005). Greater mystical effects were associated with the higher 0.71 mg/kg dose tested as opposed to the lower 0.41 mg/kg dose (p=.027). In a second RCT, Dakwar et al. (2017) found that ketamine given more than 24 hours prior reduced participants choosing cocaine now over money later by 67% compared to placebo [N=20, 55% male, age M=48.6, 75% African American, 20% Hispanic, 5% White, cocaine frequency M=9.8 days/month].

In animals, Belujon et al. (2016) found that ketamine can reverse the effects of amphetamine withdrawal on amygdala-driven dopamine neuron attenuation in rats. Ketamine also reduced cocaine-induced *egr-1* mRNA expression in the rat forebrain (Jouvert et al., 2002).

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Ibogaine. Schenberg et al. (2014) looked retrospectively at outcomes from 75 people treated with ibogaine for abuse of various substances, with 62 cases involving snorted cocaine, 51 cases involving crack cocaine, and 6 cases involving injected cocaine [89% male, age *M*=33.7, 72% polydrug users, race N/R]. Ibogaine treatment resulted in a median abstinence period of 5.5 months for those treated with one session and 8.4 months for those treated multiple times.

Tobacco Cessation

Classical Psychedelics. In a retrospective online survey of people who quit using tobacco [*N*=358], M. W. Johnson et al. (2017) found that of the psychedelics, psilocybin was most commonly ($p<.05$) with quitting or reducing tobacco usage [85.5% male, age *M*=31.1, 86% White, 7% mixed race, 2% American Indian/Alaska Native, 2% Asian, 4% other]. Those that reduced tobacco use went from a mode of 300 cigarettes/month to a mode of 1 cigarette/month. Of the psychedelics examined (LSD, psilocybin, DMT, ayahuasca, and others, including mescaline), quitting tobacco through an LSD experience was most associated with relapse to prior tobacco use ($p<.05$), but this outcome occurred only in 41% of cases, while 36% quit completely and 23% reduced their use. Those who relapsed to tobacco use rated their psychedelic experience as having "significantly lower personal meaning and spiritual significance" compared to those who quit or reduced use (p. 1). All participants rated withdrawal symptoms from quitting as significantly less severe compared to prior attempts to quit.

Mescaline. M. W. Johnson et al. (2017) identified one person who attributed quitting tobacco to the psychedelic category "Other (morning glory, mescaline, peyote,

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San Pedro)" and seven people who attributed reducing smoking due to an experience with a psychedelic in this category in a retrospective online survey [*N*=358].

LSD. In the same survey, M. W. Johnson et al. (2017) found 57 people who attributed quitting and 36 people who attributed reducing tobacco use due to an LSD experience.

Psilocybin. M. W. Johnson et al. (2014) performed an open-label, uncontrolled pilot study of psilocybin treatment for tobacco addiction [*N*=15, 67% male, age *M*=51, daily cigarettes *M*=19, quit attempts *M*=6, race N/R]. Participants attended four weekly CBT for smoking cessation sessions prior to the target quit date when they were administered 20 mg/70 kg psilocybin. They continued weekly meetings with staff and received psilocybin doses (20–30 mg/70 kg) at week 7 and optionally at week 13. Participants met with staff the day following each psilocybin session and weekly following the final psilocybin session for a total of 19 sessions. Six months following, 80% of participants showed biologically-verified 7-day abstinence. The authors note that most smoking cessation therapies have a cessation rate of less than 35% at 6-month follow-up.

Analyzing the same participants, M. W. Johnson, Garcia-Romeu, et al. (2015) found that mystical experiences, retrospective ratings of spiritual significance, and retrospective ratings of personal meaning mediated smoking cessation outcomes. While nine of 15 participants had complete mystical experiences, such experiences occurred both in the abstinent group and those who continued smoking at the 6-month follow-up. In a long-term follow-up study with the same participants, M. W. Johnson et al. (2016) found that 67% of participants were abstinent at 12 months [*n*=15], while 60% of

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participants were abstinent at 16- to 57-month follow-up [*n*=12]. At 12 months following treatment, 86.7% of participants rated their psilocybin experiences as "among the five most personally meaningful and spiritually significant experiences of their lives" (p. 1).

DMT. M. W. Johnson et al. (2017) identified seven people who attributed quitting tobacco and six people who attributed reducing tobacco following a DMT experience in a retrospective online survey [*N*=358].

Ayahuasca. In the same survey, M. W. Johnson et al. (2017) found eight people who attributed quitting tobacco and four people who attributed reducing tobacco due to an ayahuasca experience.

Ibogaine. Ibogaine may have theoretical utility in tobacco cessation, given that it can reduce the rewarding effects of nicotine. Acutely, ibogaine antagonizes the nicotinic acetylcholine receptors (Wasko et al., 2018). When ibogaine is given to rats, 22 hours later, dopamine release from nicotine is attenuated in the nucleus accumbens (Benwell et al., 1996). This effect, however, is not seen 2 hours following ibogaine.

Personality Disorders

Very little recent research has focused on psychedelic-assisted treatments of personality disorders (PDs), though some historical accounts do exist. Note that the literature search for this study only included antisocial PD and borderline PD, though some studies were found related to other PDs.

LSD. In a study of LSD treatments performed in Denmark during the 1960s [*N*=151], 53 cases were designated as "character neurosis" according to ICD-6 or ICD-8 criteria (Larsen, 2017). Of those cases, 16 were improved, 10 were unchanged, 17 deteriorated, and 10 had an unknown outcome. In addition, two cases were diagnosed

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with “personality disorder,” one of which deteriorated while the outcome of the other is unknown. Baker (1964) states that “near-psychotic patients” require higher doses of LSD for effective treatment based on experiences treating 150 patients with various presentations. This description suggests patients that might fall into personality-disordered categories.

Paranoid Personality Disorder

LSD. Chandler and Hartman (1960) saw, on average, “slight improvement” among three patients with DSM-I paranoid PD treated with 50–150 μg LSD psycholytic therapy for an average of 6.2 sessions [*N*=110, 62% male, age=15–62, race N/R]. Supporting the potential efficacy of LSD therapy for treating paranoid PD, two studies of psycholytic LSD therapy show long-term reductions in paranoia (see Chapter 7 under “Paranoia and Delusions”).

Psilocybin. In the concord prison experiments, Leary et al. (1965) saw negligible change in MMPI paranoia (*Pa*; d_n=0.05) [*n*=19].

DMT. Böszörményi and Szára (1958) administered DMT (1.0–1.5 mg/kg IM) to 24 female schizophrenic patients [age and race N/R]. Among paranoid patients, there was an attribution of DMT administration as a hostile act on the part of the doctors.

Ayahuasca. Two studies of long-term change from ayahuasca ceremonies showed large decreases in paranoid symptoms, though significance was not reached in one of the studies (p<.008; d_c=-0.48; p=NS, Δ=-50.8%; see Chapter 7). These studies demonstrate that ritual ayahuasca may have efficacy in treating paranoid PD.

MDMA. Passie (2018) describes the 1980s work of Phil Wolfson, who used MDMA to treat people in psychotic crises. Wolfson found that MDMA could help

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patients to trust clinicians and family members. A similar effect could be seen in patients with paranoid PD.

Ketamine. Krupitsky and Grinenko (1997) saw a non-significant decrease in MMPI paranoia ($p>.05$; d_n=-0.22) when using KPT to treat alcohol use disorder [N=111]. Because the effect size is not particularly large, this does not support ketamine's potential efficacy in treating paranoid PD, though further research could show otherwise.

Schizoid Personality Disorder

After treating one patient with "schizoid personality" through LSD sessions, Sandison et al. (1954) report that the patient was "moderately improved." Chandler and Hartman (1960) saw, on average, "some improvement" among ten patients diagnosed with DSM-I schizoid personality disorder and treated with 50–150 μg LSD psycholytic therapy for an average of 6.2 sessions [N=110, 62% male, age=15–62, race N/R]. Leuner (1961) adapted Sandison et al.'s methodology to treat eight inpatients diagnosed as "schizophrenic borderline cases," a label similar to schizoid personality disorder [demographics N/R]. They reported three of these cases to be 'recovered,' two to be 'greatly improved,' and three to be 'moderately or not improved.'

Improvements seen in these patients could be related to increased Extraversion seen acutely under LSD and long-term (see Chapter 6 and Chapter 7). Similar acute effects occur with MDMA and ketamine, while similar long-term effects occur with psilocybin, ayahuasca, and MDMA. Given that MDMA, like LSD, increases Extraversion acutely and long-term, it may be a good candidate for treating schizoid PD.

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Antisocial Personality Disorder

Hendricks et al. (2014) found that diagnosis of hallucinogen use disorder was associated with less likelihood of parole non-compliance (p=.0002; OR=0.60, 95% CI=0.46–0.79) in people on parole from a felony charge [N=25,622, 71% male, age=15–85, 60% African American, 39% Caucasian, and 1.5% other]. Odds were adjusted to account for a range of confounding variables.

Hendricks et al. (2018) found that those with lifetime classical psychedelic use had a significantly reduced likelihood of past year larceny/theft (aOR=0.73), assault (aOR=0.88), property crime arrest (aOR=0.78), or violent crime arrest (aOR=0.82) [N=480,000]. Lifetime use of other drugs was, on the other hand, associated with an increased risk of these outcomes. Hendricks et al. conclude that these results indicate a "protective effect of psilocybin for antisocial criminal behavior" and advocate for research with classical psychedelics in forensic settings (p. 10). However, the associations found by Hendricks et al. are not causative. Thus, the results cannot be extrapolated to indicate that classical psychedelics can reduce criminal behavior.

LSD. Among six patients described as "psychopaths" and treated with LSD psychotherapy in a day-hospital setting, A. J. Martin (1957) described 50% as 'recovered,' 33% as 'greatly improved,' 17% as 'slightly improved,' and none as 'not improved.' The dose was initially 25–50 μg, with additional given until "optimum reaction was obtained."

Among two patients treated by Sandison et al. (1954) for "psychopathic personality with depressive features" through LSD sessions (M=7), they reported one to be 'recovered' and one to be 'improved' but still in treatment. In a follow-up study that

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included 30 patients from the original study plus 64 more who had been treated since, Sandison and Whitelaw (1957) report on the outcomes of six patients diagnosed with "psychopathic personality" and treated with LSD psychotherapy sessions. With at least 6 months following treatment, they described 0% as 'recovered,' 17% as 'greatly improved,' 50% as 'moderately improved,' and 33% as 'not improved.'

Chandler and Hartman (1960) saw, on average, "some improvement" among three patients diagnosed with DSM-I "Sociopathic disorder: Antisocial reaction" and treated with 50–150 μg LSD psycholytic therapy for an average of 6.2 sessions [*N*=110, 62% male, age=15–62, race N/R].

Baker and Buck (1977) administered 500 μg LSD to 30 patients in a maximum-security mental hospital, all of whom were motivated to receive the treatment and received informed written consent from next of kin. Patients reported the experience to be "exceedingly beneficial" and felt "they had obtained important insights into themselves" (p. 312). However, staff and other patients "…could not see this subjectively reported benefit translated into an improved mental state or behavior" (p. 312). No patients were observed to worsen.

Psilocybin. Leary et al. (1965) performed a famous study examining the impact of psilocybin on recidivism, which is known as the "Concord Prison Experiment" [*N*=32, male, age *M*≈21–22, race N/R]. Treatment involved two 20–70 mg group psilocybin sessions along with 6 weeks of bi-weekly group meetings. Compared to baseline, there was a reduction approaching significance in MMPI psychopathic deviance (*Pd*; $p>.05$; $d_n=-0.82$). There were improvements on the California Personality Inventory in self-control (*Sc*; $p<.01$; $d_n=0.69$), responsibility (*Re*; $p<.01$; $d_n=0.97$), tolerance (*To*; $p<.01$;

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d_n=0.86), and other scales. However, they found that the program did not reduce recidivism in the 18–26 months the participants' release from prison, with 59% having returned to prison. This figure is compared to a 56% expected recidivism base rate from a prior study at Concord Prison. Contextualizing this finding, Riedlinger and Leary (1994) report that only 32% returned to prison in the first 10 months following release. They also note that those released did not have the halfway house support that was suggested both by the prisoners and the research team and that most returned to prison for parole violations rather than new crimes.

In a follow-up to the Concord Prison Experiments, Doblin (1998) examined the criminal justice records of 21 of the original subjects and interviewed two subjects and three of the researchers. Doblin found discrepancies among the published recidivism statistics in the original series of papers by Leary and others. In particular, the time frame of the recidivism base rate of 56% that was used as a comparison by Leary was at 30 months following release, while statistical comparisons to this figure were made at 10 months and 18–26 months. Doblin was able to locate the recidivism base rate at 10 months from the same study that was used as a control, which turned out to be 34.3%, very similar to the 32% in the experimental group. In the criminal records that Doblin was able to recover [*n*=21 of 32], the recidivism rate was 71% at 30 months, higher than the comparison base rate of 56%. Doblin determined that of those whose criminal records he was able to recover, 38% returned to prison for a new crime, 33% returned to prison for parole violations, and 29% did not return to prison, statistics that differed from Leary's findings and aligned with recidivism trends at Concord Prison. Thus, it appears that the treatment was not successful in reducing recidivism rates, though psychological

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change garnered by the program could have significant effects on quality of life and perhaps propensity toward re-offense if additional supports are provided after release.

Ayahuasca. Frecska (2008) describes a case of a 43-year-old Caucasian male who had been convicted twice of manslaughter for the murder of his abusive stepfather and his employer and sentenced to a total of 17 years in prison. After his release, he was discharged to a homeless shelter where Frecska followed up with him twice a week. The patient met DSM-IV criteria for antisocial disorder and had an IQ of 136. He showed no remorse toward those whom he had killed, though he did show some remorse toward the families. He felt that life was futile, had a chronically dysthymic mood, and was deemed "not eligible for dynamic or cognitive-behavioral psychotherapy." Several pharmacotherapy trials did not help his condition. He decided to participate in three ritual ayahuasca sessions. During those sessions, he had a series of "meaningful thoughts and deep moral insights," including an entity telling him to "Just slow down, behaving hastily is what has given you the most trouble in life" (p. 97). He also was confronted by this same entity about his lies and misdeeds. One month following the third ayahuasca session, he began to show progress in the rehabilitation program of the homeless shelter he had been living in for 3 years and was discharged 6 months later.

Romero (2015) provides a journalistic account of a Brazilian program to make ayahuasca ceremonies available to prison inmates. No quantitative findings of the program were reported, but individual accounts of pro-social accounts are described.

MDMA. Recreational MDMA has been shown to bias perception of facial expressions toward being evaluated as more aggressive in the 4 days following MDMA use, though this bias does not persist long-term (Curran et al., 2004; Hoshi et al., 2016;

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Tomlinson et al., 2016). Lifetime recreational use of MDMA/ecstasy in the U.S. is associated with more self-perceived aggression and higher rates of violent crime (see Chapter 9 section titled “Violent Behavior”). However, this association may not be due to MDMA, and even if it is, it may not be present with clinical MDMA. Further, there is an association between violence and PTSD (E. L. Barrett et al., 2014; Gillikin et al., 2016; Ternes et al., 2019; Trevillion et al., 2015), a condition that MDMA-assisted therapy has been shown to be effective in treating (see above section titled “Posttraumatic Stress Disorder”). Thus, MDMA therapy may help those classified as having antisocial personality disorder when their condition stems from trauma.

Borderline Personality Disorder

Borderline personality disorder (BPD) has a high rate of co-occurrence with substance use disorders (Alcohol: 48.1%, Other drugs: 45.9%) (Zeifman & Wagner, 2020). Further, people with BPD are also more likely to have instances of violence or aggression. Finally, those with BPD have very high rates of attempted suicide (70.6%–83.6%), completed suicide (5.9%), and non-suicidal self-injury (65%–80%). Those with BPD also have a high co-occurrence of complex PTSD, with 52.8% found to have experienced childhood/adolescent physical abuse (Golier et al., 2003). In considering BPD treatment, treating these co-occurring conditions must also be considered.

A core symptom and treatment target with BPD is emotional dysregulation. Zeifman and Wagner (2020) suggest that this symptom of BPD may be improved with psychedelics, citing observational studies showing reduced emotional dysregulation following ayahuasca ceremonies and lower emotional dysregulation correlated with

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lifetime psychedelic use. Further, they assert that decreases in affective symptoms and Neuroticism from psychedelics may translate into improved emotional regulation.

Zeifman and Wagner (2020) also described the ways in which mindfulness and identity development are incorporated into contemporary treatments for BPD. They suggest that psychedelics could be useful in treating BPD due to their tendency to increase mindfulness and help develop an individual sense of identity. Finally, they describe the improvements in social functioning seen with psychedelics and the possible translation of this effect to those with BPD.

Mescaline and LSD. Pennes (1954) attempted to treat patients with "pseudoneurotic schizophrenia" using mescaline and 10–120 μg LSD without concurrent psychotherapy [*n*=20, age *M*=35.8, sex and race N/R]. According to Frankenburg (2005), "many of these subjects probably would have met DSM-IV criteria for BPD and/or schizotypal personality," given that pseudoneurotic schizophrenia referred to extremely anxious and agitated patients with phobias but no hallucinations, delusions, or thought disorder. Pennes found that such patients tended to respond poorly to mescaline and LSD, with symptoms intensifying.

One case of LSD treatment for "borderline psychosis" was present in a study of LSD treatment in Denmark during the 1960s [*N*=151] (Larsen, 2017). In this case, symptoms were characterized as "unchanged." Chandler and Hartman (1960) saw "some improvement" in a person diagnosed with DSM-I "emotionally unstable personality" and treated with 50–150 μg LSD psycholytic therapy for an average of 6.2 sessions [*N*=110, 62% male, age=15–62, race N/R].

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Ayahuasca. Reduced emotional dysregulation seen following ayahuasca ceremonies provides a compelling theoretical argument for its application to treating BPD (Zeifman & Wagner, 2020). In an observational study, Domínguez-Clavé et al. (2019) compared the effects of ayahuasca ceremonies in 12 people with BPD-like traits and 33 controls without BPD-like traits [60% women, age M=40.9, race N/R]. The BPD-like group showed decreases in lack of control (p=.024; d_c=-0.80) and emotional interference (p=.049; d_c=-0.76). In the BPD-like group, there was no significant change in mindfulness or decentering. In contrast, the non-BPD group showed significant improvements in both these areas.

Because the BPD-like group in the Domínguez-Clavé et al. study had far fewer participants than the non-BPD group, there was far less statistical power to detect change. Thus, it is useful to look at effect sizes in conjunction with p to observe trends toward significance. Table 44 summarizes the pre- to post- outcome measures comparison for the BPD-like group. When examined in this fashion, it appears that several more FFMQ-SF scales showed improvements with Moderate to Very Large effect sizes that approached significance: Observing (p_t=.021; d_c=1.10), Describing (p_t=.11; d_c=0.25), and Non-Reacting (p_t=.13; d_c=0.88). Together, this shows that there may be potential for treating BPD with ayahuasca but that some traits relevant to therapeutic outcomes may be more difficult to change in those with BPD than in those without.

Ketamine. In treating 64 patients with AUD and a personality disorder using KPT, Ivanov et al. (1995) observed that the treatment was least effective in those with BPD [n=23] (reported by Krupitsky & Grinenko, 1996).

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Table 44

Effect of Ayahuasca on Twelve People with BPD-like Symptoms

Measure	d_c	*Descriptor*	*p*	p_t
Difficulties in Emotion Regulation Scale (DERS)				
Emotional Non-Acceptance	-0.07	Small	0.08	**0.87**
Emotional Interference	-0.76	Large	0.049*	0.088
Emotional Awareness	0.22	Moderate	0.96	0.60
Lack of Clarity	-0.19	Small	0.36	0.66
Lack of Control	-0.80	Large	0.024*	0.075
Five Facet Mindfulness Questionnaire–Short Form (FFMQ-SF)				
Observing	1.10	V. Large	0.97	**0.021***
Describing	0.25	Moderate	0.11	0.56
Awareness	0.48	Moderate	0.89	0.27
Non-reacting	0.88	Large	0.13	0.053
Non-judging	0.66	Large	0.26	0.13
Experiences Questionnaire (EQ):	0.40	Moderate	0.50	0.35

Note. Adapted from Domínguez-Clavé (2019). p_t values were computed by the present author using a *t*-test that was not adjusted for multiple comparisons. This computation was done because of a discrepancy between the high computed effect size of FFMQ-SF Observing and the very high *p*-value reported in the study. It is believed that the reported *p*-values for this parameter and DERS Emotional Non-Acceptance may be mistakes, and the computed p_t-values are bolded for this reason.

* $p < .05$

Summary of BPD Treatment With Psychedelics. Table 45 summarizes studies on the treatment of BPD with psychedelics, alongside psychedelic effects on the BPD symptoms and comorbidities. The following symbols are used in the table:

+++ Well-validated treatment efficacy that must include multiple RCTs.

++ Good but not yet conclusive evidence of treatment efficacy. May include multiple uncontrolled trials, a single RCT, or one uncontrolled trial along with traditional use.

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+	Likely treatment efficacy based on traditional uses, three or more case studies, or a single uncontrolled trial.
⊕⊕	Decent chance of treatment efficacy based on weak findings from multiple uncontrolled trials or several historical trials with descriptive outcome reports rather than quantitative outcome measures.
⊕	Possible treatment efficacy based on one or two case studies, weak findings from an uncontrolled trial, or quantitative evidence of related psychological change.
○	Possible treatment efficacy based on theory or animal studies.
◌	Possible efficacy due to shared mechanism with another psychedelic.
⊖	Caution is warranted due to a possible negative outcome despite potential treatment efficacy.
∅	Evidence showing a lack of effectiveness.
××	Contraindicated based on a single uncontrolled trial, RCT, or epidemiological study showing acute negative reactions or deterioration following treatment.
-	No research, case studies, or theoretical justification was found for using a psychedelic for a given indication.

For BPD symptoms, the following symbols are used:

↑	Statistically significant increase
↓	Statistically significant decrease
∅	No significant change
$\varnothing^{\uparrow}$	No significant change, but a directional trend
[2]	The number of references that demonstrate a finding. If not shown, only one study is referenced.

With BPD symptoms, effect sizes are shown using the following conventions:

	Small or Tiny effect size [no asterisk] ($d \leq 0.2$)
*	Moderate effect size ($d = 0.21–0.5$)
**	Large effect size ($d > 0.5$)
***	Very Large effect size ($d > 1.0$)

Table 45

Effects of Psychedelics on BPD Symptoms and Co-Occurrences

Relevant Literature Domain	Mescaline Session	LSD Session	LSD Psycholytic	Psilocybin Session	DMT Session	Ayahuasca Ritual	Aya. Tx	MDMA PT	Ketamine Infusion	Ket. KAP	Ibogaine Tx
BPD-Specific Psychedelic Treatment Literature	××	××	× / ⊕	-	-	+	-	-	-	∅	-
BPD Symptoms (from Summary Table 9)											
Emotional regulation	∅↑	-	-	-	-	-	∅↑	-	-	-	-
Neuroticism	-	∅	-	↓**[2] / ∅	-	↓**[2] / ∅↓*	-	↓**[2]	-	-	-
Mindfulness	-	-	-	↑**	-	-	↑	-	-	-	-
Identity development	-	-	-	-	-	-	-	-	-	-	-
Self-concept/pride	-	↑***	-	↑***[3]	-	-	-	-	-	-	-
Self-compassion/acceptance	-	-	-	↑	-	∅	-	-	-	-	-
Common BPD Co-Occurrences (from Summary Table 16)											
Violence/aggression (antisocial PD tx as proxy)	◌	⊕⊕	⊕⊕	+	-	⊕	◌	○	-	-	-
Acute suicidality	⊕	⊕	⊕	+++	-	-	+++	⊖	+++	○	-
SUDs	++	+++	⊕⊕	++	+	++	+	+	++	++	++
PTSD	○	○	○	○	○	+	○	+++	+++	+	-
Combined Support for Treating BPD	×× / ○	×× / ○	× / ⊕	⊕	○	+	○	⊕⊕	⊕⊕	∅ / ○	○

Note. PT = assisted-psychotherapy; KAP = ketamine-assisted psychotherapy; Tx = treatment.

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Histrionic Personality Disorder

Ketamine. Ivanov et al. (1995) found that KPT was "less effective" in those with histrionic personality disorder [*n*=21] (reported by Krupitsky & Grinenko, 1996).

Narcissistic Personality Disorder

Naturalistic use of mescaline, LSD, psilocybin, or ayahuasca is associated with lower narcissism, though a causative link is yet to be demonstrated (van Mulukom et al., 2020). See the Chapter 7 section titled "Narcissism" for more details.

Avoidant Personality Disorder

Avoidant PD is a severe manifestation of social phobia and anxiety that significantly impacts interpersonal functioning (Herbert et al., 1992; Hummelen et al., 2007; S. M. Turner et al., 1986). Thus, treatments for social anxiety and specific phobias are expected to translate to treating avoidant PD. Regarding psychedelics, MDMA and ketamine have been shown to have some efficacy in treating social anxiety, while LSD, psilocybin, and ayahuasca are hypothesized to have potential efficacy based on theory. In treating phobias, Sandison and Whitelaw (1957) treated three patients using psycholytic LSD therapy with mixed success. In addition, there is theoretical justification for combining virtual reality exposure therapy with classical psychedelics, MDMA, and ketamine to treat phobias. See sections on "Social Anxiety" and "Specific Phobias" above for more details. Finally, Ivanov et al. (1995) observed that KPT was "very effective" in treating 20 patients with avoidant personality disorder (reported by Krupitsky & Grinenko, 1996).

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Aging

Ameliorating Age-Related Decline

Aday, Bloesch, et al. (2020) makes several theoretical arguments for using psychedelics to attenuate changes in cognition and affect related to aging. In structuring their arguments, the authors present the persistent effects of psychedelics coupled with a corresponding domain of functional decline seen in aging. These arguments are summarized and critiqued in Table 46. There does appear to be a strong argument for using psychedelics to help with some aspects of age-related decline, with some caveats noted in the table.

Table 46

Attenuating Age-Related Decline Through Psychedelics

Domain of Age-Related Decline	Rationale for Psychedelics (Adey et al., 2020)	Comment and Critique
Creativity	Psychedelics may have creativity-enhancing properties.	None.
Executive functioning	Long-term ayahuasca use is linked to better executive functioning.	This statement is supported regarding ayahuasca, though some findings are mixed. Ayahuasca may negatively impact verbal learning. Long-term MDMA and ketamine negatively impact executive functions. See Summary Table 11 "*Long-Term Neuropsychological Effects of Psychedelics*"
Cognitive decline	Psychedelics stimulate neuroplasticity, and enhanced neuroplasticity has been shown to improve executive function.	The aging process may result in a state of over-plasticity that results in a state of cortical instability that causes new plastic changes to decay rapidly (Cisneros-Franco et al., 2018). The study cited by Adey et al. (Selemon, 2013) is specifically linking neuroplasticity in adolescence to improved executive function. *The risk that psychedelics may impact the stability of neural systems in older adults should be investigated further.*
Reduced Openness	Psychedelics consistently increase Openness to Experience.	None.

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Domain of Age-Related Decline	Rationale for Psychedelics (Adey et al., 2020)	Comment and Critique
Empathy	Psychedelic use has been shown to increase empathy.	The study cited regarding declining empathy in old age (Grühn et al., 2008) found that longitudinal studies do not show a decline in empathy with old age. Rather, cross-sectional studies find that older generations show less empathy, which is likely to be a cohort effect, not an age-related phenomenon. Regardless, increases in empathy are generally a good thing.
Increased pessimism	Psychedelic therapy has been shown to reduce pessimism.	None.
Increased rates of depression and suicide	Psychedelics are being successfully used to treat depression and suicidality.	Geriatric patients may not respond to ketamine infusions for treating depression based on a series of four case studies (Szymkowicz et al., 2014). More research is needed to confirm this finding, and other psychedelic treatments may work for treating geriatric depression.
Fewer meaningful experiences	Psychedelic experiences are often rated as among the most meaningful experiences in a person's life.	None.
End-of-life distress and palliative care	Psychedelics have been successfully used to reduce end-of-life distress.	None.
Higher rates of opioid abuse	Psychedelic users had a 40% lower risk of abusing opioids in the past year.	While this is an encouraging finding, causality was not found in the study cited (Pisano et al., 2017). Further, Pisano et al. saw only a 27% lower risk of past-year opioid dependence among psychedelic users. In many cases, this is likely due to opioid dependence for medical reasons, which is a scenario that is even more likely in an aging population. Still, there is promise in psychedelics helping to reduce opioid dependence and abuse in older adults.

Psilocybin. Stamets (2021) saw increased finger tapping speed with psilocybin microdosing in people over 55 but not those under 55 (see Chapter 8 "Psychomotor Functioning"). This finding is significant because reduced finger tapping speed is indicative of early-stage dementia (Almkvist & Bäckman, 1993; G. Müller et al., 1991).

Ketamine. While ketamine infusion can be used safely and effectively in older adults, there is some question about whether long-term ketamine treatment may have

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increased neurocognitive impact in this population (see Chapter 5 section titled "Older Adulthood"). Thus, caution is warranted when considering ongoing ketamine treatment in older adults.

Rational Suicidality

Hendricks and Grob (2016) argue that classical psychedelics may provide an effective treatment for rational suicidality in elderly people. This type of suicidality tends to be due to discounting future life as painful, isolated, declining, and ultimately futile. Hendricks and Grob enumerate the evidence that classical psychedelics have the potential to reduce rational suicidality by occasioning significant and mystical experiences, increasing positive and altruistic attitudes toward life, reducing existential anxiety and depressive symptoms, improving the management of chronic pain, and treating substance abuse (since substance abuse is associated with suicide in general). Together this provides a promising avenue for increasing *raison d'être* in the elderly and thereby decreasing the rationale for suicide. Given the occurrence of mystical experiences with ketamine (see Chapter 6) and the effectiveness of ibogaine in treating substance abuse (see above), Hendricks and Grob's argument may be extended to include these compounds.

Palliative Care and Existential Anxiety

Byock (2018) extends the argument of Hendricks and Grob (2016) to include psychedelics in applied palliative care. He contends that emotional, existential, and spiritual suffering is common in palliative patients and often does not respond to existing treatments. Byock advocates for careful screening of patients eligible for psychedelic treatment, excluding those with "disorganized or diminished ego strength," such as with

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personality disorders or schizophrenia, perhaps excepting the use of MDMA in these patients (p. 3).

LSD. Moderate- to high-dose LSD has been used to treat cancer-related distress beginning in the 1960s and continuing through the 1980s, with early studies showing promising results (Grof et al., 1973; Kast, 1966, 1967; Kast & Collins, 1964; Kurland, 1985; Kurland et al., 1972; Pahnke et al., 1969, 1970; W. Richards et al., 1972). However, these early studies have weak methodologies compared to modern medical standards (Reiche et al., 2018).

Since those early studies, one RCT crossover trial was performed by Gasser et al. (Gasser et al., 2014, 2015), treating 12 patients suffering from anxiety associated with life-threatening diseases with 200 μg LSD [N=11, 64% male, age=39–64, race N/R]. At 2-month follow-up, there were significant reductions in both state (p=.021; d=1.2) and trait anxiety (p=.033; d=1.1) compared to placebo. These improvements were sustained 12 months later compared to baseline. There were no serious adverse events related to treatment, nor were there any adverse effects lasting more than 1 day.

Psilocybin. Grob et al. (2011) performed an RCT crossover pilot study for treating cancer-related distress with 14 mg/70 kg psilocybin in 12 adults [demographics N/R]. There was a decrease in trait anxiety from baseline that reached significance at 1 month (p<.01) and 3 months (p<.05) but did not reach significance at any other monthly measurements taken up to 6 months following treatment, despite a decreasing trend. There was no significant difference between psilocybin and placebo in state or trait anxiety in the first two weeks following treatment. Regarding depression, there was a decrease approaching significance (p=.06–.08) between psilocybin and placebo in the two

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weeks following treatment. BDI scores trended toward a decrease from baseline in the months following but only reached a significant difference at 6 months (p<.05).

Ross et al. (2016) performed an RCT crossover trial of 21 mg/70 kg psilocybin for cancer-related distress in 29 patients [62% women, age=22–75, 90% Caucasian]. They saw immediate reductions the day following treatment in anxiety (p<.05; d=0.80–1.20) and depression (p<.01; d=1.10–1.23) compared to control. Improvements relative to placebo continued up until cross over at 7-weeks (anxiety: p<.01, d=1.07–1.29; depression: p<.05, d=0.82–0.98). These improvements were sustained 6.5 months later relative to baseline, with clinically significant reductions in depression or anxiety present in 60–80% of participants.

Griffiths et al. (2016) also performed an RCT crossover trial of 22 or 30 mg/70 kg psilocybin for cancer-related distress compared to 1 or 3 mg/70 kg psilocybin active placebo [N=51, 49% female, age M=56.3, 94% White, 4% Black/African American, 2% Asian]. At 5 weeks following treatment, the psilocybin group showed significant reductions in two of four measures of anxiety (p<.001, .05; d=0.50–1.23) and all three measures of depression (p<.001, .01, .05; d=0.40–1.33) compared to placebo. The two measures of anxiety that did not show a significant difference were reduced on average in the treatment group compared to placebo. These improvements were sustained 6 months later relative to baseline (p<.001; anxiety: d=1.20–3.40; depression: d=1.63–2.98).

In a review of studies examining psilocybin for cancer-related distress [N=4], Bahi (2019) found that no serious adverse events occurred among the 79 participants in the Ross et al. and Griffiths et al. studies. Grob et al. (2011) also reported no adverse effects among their 12 participants.

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DMT. The similarity seen between DMT experience and near-death experience (Timmermann et al., 2018) may allow for an experience of simulated death that could potentially help to relieve anxiety related to life-threatening diseases. However, no studies were found examining the effect of DMT to treat this indication.

MDMA. Wolfson et al. (2020) saw a reduction in anxiety approaching significance (p=.056; d_g=1.03) among those treated with MDMA-PT for anxiety due to life-threatening illness compared to placebo and measured by STAI-Trait anxiety [N=18, 77.8% female, age M=54.9, 83.3% White/Caucasian].

Ketamine. Kolp et al. (2007) describe two cases where 150 mg IM Ketamine-Enhanced Psychotherapy (KEP; see Chapter 11) was used to treat death anxiety through "death rehearsal" in a hospice care setting. For a 62-year-old female with breast cancer, KEP was a pleasant and meaningful experience that helped to alleviate her persistent pain and recurrent panic attacks. She remained comfortable until her death 7 months later. In a 46-year-old male with pancreatic cancer, the KEP session was very unpleasant as "a strong fear of non-existence completely overwhelmed" him, and he experienced death repeatedly from different causes (p. 10). In follow-up sessions, the patient described "…his horror of disintegration all through his frightening experience of stepwise regression from existence to non-existence," and felt that there was no existence beyond death (p. 10). He died an unpleasant death 2 weeks later, possibly from an accidental overdose of CNS depressant medication.

Iglewicz et al. (2015) found that for those in hospice care, ketamine infusion improved depressive symptoms in 93% of cases from administration up to the third day

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following [*N*=22, 55% male, age *M*=68, race N/R]. In 80% of cases, depression symptoms were also improved during the period 4 to 7 days following administration.

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Summary of Psychedelic-Assisted Treatment Targets

Summary Table 16 summarizes treatment indications for different psychedelics using the following symbols:

+++	Well-validated treatment efficacy that must include multiple RCTs.
++	Good but not yet conclusive evidence of treatment efficacy. May include multiple uncontrolled trials, a single RCT, or one uncontrolled trial along with traditional use.
+	Likely treatment efficacy based on traditional uses, three or more case studies, or a single uncontrolled trial.
⊕⊕	Decent chance of treatment efficacy based on weak findings from multiple uncontrolled trials or several historical trials with descriptive outcome reports rather than quantitative outcome measures.
⊕	Possible treatment efficacy based on one or two case studies, weak findings from an uncontrolled trial, or quantitative evidence of related psychological change.
○	Possible treatment efficacy based on theory or animal studies.
◌	Possible efficacy due to shared mechanism with another psychedelic.
⊖	Caution is warranted due to a possible negative outcome despite potential treatment efficacy.
∅	Evidence showing a lack of effectiveness.
⊗	Possible contraindication due to the likelihood of negative reactions based on theoretical evidence or a single case study.
×	Contraindicated based on two or more case studies showing acute negative reactions or deterioration following treatment.
××	Contraindicated based on a single uncontrolled trial, RCT, or epidemiological study showing acute negative reactions or deterioration following treatment.
×××	Contraindicated based on multiple uncontrolled trials, RCTs, or epidemiological studies showing acute negative reactions or deterioration following treatment.
-	No research, case studies, or theoretical justification was found for using a psychedelic for a given indication.

Summary Table 16

Psychedelic Treatment Targets

Treatment Target	Mescaline Session	LSD Session	LSD Psycholytic	Psilocybin Session	DMT Session	Ayahuasca Ritual	Aya. Tx	MDMA PT	Ketamine Infusion	Ket. KAP	Ibogaine Tx
Developmental Conditions											
Autism spectrum disorder	◌	○	⊕⊕	⊕⊕	-	⊕	○	++	⊕	○	-
ADHD and executive dysfunction	-	-	-	-	-	⊕⊕	○	-	⊖	-	-
Schizophrenia	×××	××	⊕⊕	⊗ / ⊕	× / ○[μ]	⊕ / ⊖	○	⊕	×××	⊕	-
Anxiety Disorders											
General anxiety	◌	++	++	++	○	++	○	⊕	+	⊕	-
Specific phobias	○	○	⊕⊕	○	-	-	○	○	-	-	-
Social anxiety	◌	○	○	○	-	○	○	⊕	+	○	-
Compulsive Disorders											
OCD	○	○	⊕⊕	++	◌	++	○	○	++	+	-
Body dysmorphic disorder	○	○	⊕	⊕	○	○	○	○	○	○	-
Anorexia and bulimia	○	○	+ / ⊖	○	○	+	○	++	+	○	-
Mood Disorders											
Acute suicidality	⊕	⊕	⊕	+++	-	-	+++	⊖	+++	○	-
Depression	◌	++	++	+++	○	⊕	++	○	+++	++	-
Bipolar disorder	-	⊖ / ⊕	-	-	⊕	⊖	⊖	∅	+++	○	-

Summary Table 16

Psychedelic Treatment Targets, Continued

Treatment Target	Mescaline Session	LSD Session	LSD Psycholytic	Psilocybin Session	DMT Session	Ayahuasca Ritual	Aya. Tx	MDMA PT	Ketamine Infusion	Ket. KAP	Ibogaine Tx
Somatization/conversion disorders	⊕	+	⊕⊕	◌	-	⊕	○	-	-	⊕	-
Trauma and Stressor-Related Disorders											
PTSD	○	○	○	○	○	+	○	+++	+++	+	-
Adjustment disorder	◌	◌	+	◌	◌	◌	◌	○	○	○	-
Grief	○	○	○	○	○	++	○	○	⊕	○	+
Gender and Sexuality-Related Disorders											
Gender/sexuality-related dysphoria	◌	⊕	⊕	⊕	-	+	○	○	-	○	-
Sexual disorders & difficulties	◌	⊕	+	◌	-	◌	◌	⊕	××	○	-
Substance Use Disorders											
General	++	+++	⊕⊕	++	+	++	++	+	++	++	++
Alcohol use disorder	++	+++	-	++	+	+	+	○	++	++	+
Opioid use disorder	-	+	-	-	-	-	-	-	+	++	++
Stimulant use disorders	-	-	-	-	-	+	-	-	++	○	+
Tobacco cessation	+	+	-	++	+	+	-	-	○	○	○
Personality Disorders (PD)											
Paranoid PD	-	-	⊕	∅	⊗	○	-	⊕	-	-	-
Schizoid PD	-	-	+	-	-	-	-	○	-	-	-

Summary Table 16

Psychedelic Treatment Targets, Continued

Treatment Target	Mescaline Session	LSD Session	LSD Psycholytic	Psilocybin Session	DMT Session	Ayahuasca Ritual	Aya. Tx	MDMA PT	Ketamine Infusion	Ket. KAP	Ibogaine Tx
Antisocial PD	◌	⊕⊕	⊕⊕	⊕	-	⊕	◌	○	-	-	-
Borderline PD	×× / ○	×× / ○	× / ⊕	⊕	○	+	○	⊕⊕	⊕⊕	∅ / ○	○
Histrionic PD	-	-	-	-	-	-	-	-	-	∅	-
Narcissistic PD	○	○	○	○	-	○	○	-	-	-	-
Avoidant PD	○	○	⊕⊕	○	-	-	○	⊕	+	○	-
Aging											
Age-related decline	○	○	○	○	○	○	○	○	⊖	○	○
Rational suicidality	○	○	○	○	○	○	○	-	○	○	○
Palliative care and existential anxiety	○	++	○	+++	○	○	○	⊕	+ / ⊖	○	×××

Note. Symbol key on page 510. Session = psychedelic therapy (high-dose, 1–3 sessions, minimal intervention during the session); Psycholytic = psycholytic therapy, where a moderate dose of LSD is given as an adjunct to psychodynamic psychotherapy; Ritual = ceremonial use, typically ongoing; Tx = treatment in a clinical environment or treatment program; PT = assisted psychotherapy; Infusion = IV administration of subanesthetic ketamine without psychotherapy; KAP = ketamine-assisted psychotherapy; ADHD = attention-deficit/hyperactivity disorder.

[μ] Potential efficacy shown with microdosing.

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Chapter 13: Planning Psychedelic-Assisted Treatments

At present, the idea of treatment planning with psychedelics is aspirational. In the United States, very few psychedelics can be legally administered. However, as psychedelics become medically available, it is essential to have decision-making frameworks for guiding clinical judgment on psychedelic-assisted treatment decisions. For this reason, a heuristic for treatment planning was developed to assist clinicians in applying the material summarized in this review.

Treatment Planning Process

Appendix C contains a document titled “Treatment Planning Worksheet for Psychedelic-Assisted Therapy” that can be used to structure decision-making when planning psychedelic therapies. Corresponding to that worksheet, the seven steps below elaborate on the worksheet instructions and link to the relevant summary tables throughout this review.

In each section of the worksheet, it is acceptable to use either the detailed symbols used in the summary tables, or the simplified symbol set designated in the worksheet and elaborated as follows:

×	Contraindication or dangerous medication interaction
/	Caution or additional considerations needed
++	Strong treatment indication
+	Provisional treatment indication
–	Known negative treatment response
?	More information is needed

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The suggested treatment planning process involves the sequential consideration of the following factors according to the treatment planning worksheet:

1. Medical Risk Factors

Consider risks related to the patient's age and pregnancy status by consulting Summary Table 3 "*Life Stage and Psychedelic Safety*." Then use Summary Table 4 "*Medical Risk Factors and Contraindications*" to identify any medical risk factors present for the patient and list them on the worksheet. A physician should be consulted regarding medical conditions, risk factors, or psychedelic treatments with minors, pregnant people, or older adults.

2. Drug and Medication Interactions

List current medications or drugs taken by the patient and examine any potential interactions. This review covers only a few common interactions with psychiatric medications (Summary Table 4) and does not provide an extensive review of drug interactions. Other medical references should be consulted regarding hazardous drug interactions with psychedelics. In addition, it is always prudent to perform a Google search of any drug interaction to identify any other known hazards. Finally, a physician should be consulted regarding any medication or drug interactions.

3. Developmental Factors

Next, identify any psychological risk factors for the patient using Summary Table 14 "*Psychological Risk Factors*." Add these factors to the treatment planning worksheet.

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4. Summarize Risk

Review each column on page 1 of the treatment planning worksheet. Choose the most severe risk factor to represent the overall risk of each psychedelic. If no risk factors were identified, use "✓" or "○" to indicate no risk factors for the psychedelic.

5. Presenting Problem(s)

Use Summary Table 16 "*Psychedelic Treatment Targets*" to determine the treatments relevant to the patient's presenting problem(s) and fill these into the worksheet.

6. Influencing Factors

Examine any patient factors influencing psychedelic experience and treatment outcomes by referencing Summary Table 15 "*Patient Factors Affecting Psychedelic Experience and Outcome*." Summarize any relevant influencing factors in the treatment worksheet.

7. Rank Treatment Options

First, transfer the summarized risk from page 1 of the worksheet. Any psychedelic treatment contraindicated due to risk factors should be marked with an "×" in ranking. Otherwise, clinical judgment should be used to rank-order each psychedelic by examining relative risk, efficacy regarding presenting problems, and influence of personality factors. Any risk or efficacy considerations should be noted.

Patient Consultation Regarding Treatment Plan

Treatment planning performed with the treatment planning worksheet should be considered preliminary until consulting with the patient to finalize a treatment plan. Fortunately, the different psychedelic treatments are flexible enough that there are likely

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to be multiple options for any patient treated. Optimal treatment efficacy for any psychological intervention occurs only with patient confidence and motivation. These factors are crucial to psychedelic treatments, given the overwhelming nature of the experience. The ethical application of such challenging treatments requires particular attention to informed consent and patient autonomy.

In discussing treatment options with the patient, several factors should be addressed:

1. **Risks associated with each treatment option:** The risks associated with different treatment options should be described to the patient alongside the benefits. In addition to the risks already enumerated in the worksheet, Summary Table 5 "*Long-Term Medical Risks Associated with Psychedelics*" should be referenced to examine long-term risks associated with proposed treatments. Further, Summary Table 12 "*Acute and Subacute Psychological Risks of Psychedelics*" and Summary Table 13 "*Risk of Long-Term Psychopathogenesis from Psychedelics*" can help communicate a complete understanding of psychedelic risks. However, reference to any risk factors in these tables requires care and caution to prevent excessive patient anxiety regarding risk.
2. **Phenomenological experience of psychedelic treatment options:** While it is difficult if not impossible to communicate a psychedelic experience to someone without experience with a dramatically altered state, an attempt should be made to explain what different treatment experiences may involve. In addition to being an important part of informed consent, this begins to prepare the "set" factor of the psychedelic treatment by mentally preparing the patient for the experience.

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3. **Cultural congruence of psychedelic treatment options:** It is important to discuss with the patient the cultural congruence, or incongruence, of a psychedelic treatment with the patient's identities. When possible and desired, psychedelic treatment should align with the patient's cultural background.

Together these steps can help build the therapeutic alliance throughout the treatment planning process by supporting self-determination and respecting cultural identities. In addition, this strategy begins to mentally prepare the patient for an intense but ultimately rewarding treatment experience.

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Chapter 14: Discussion and Conclusion

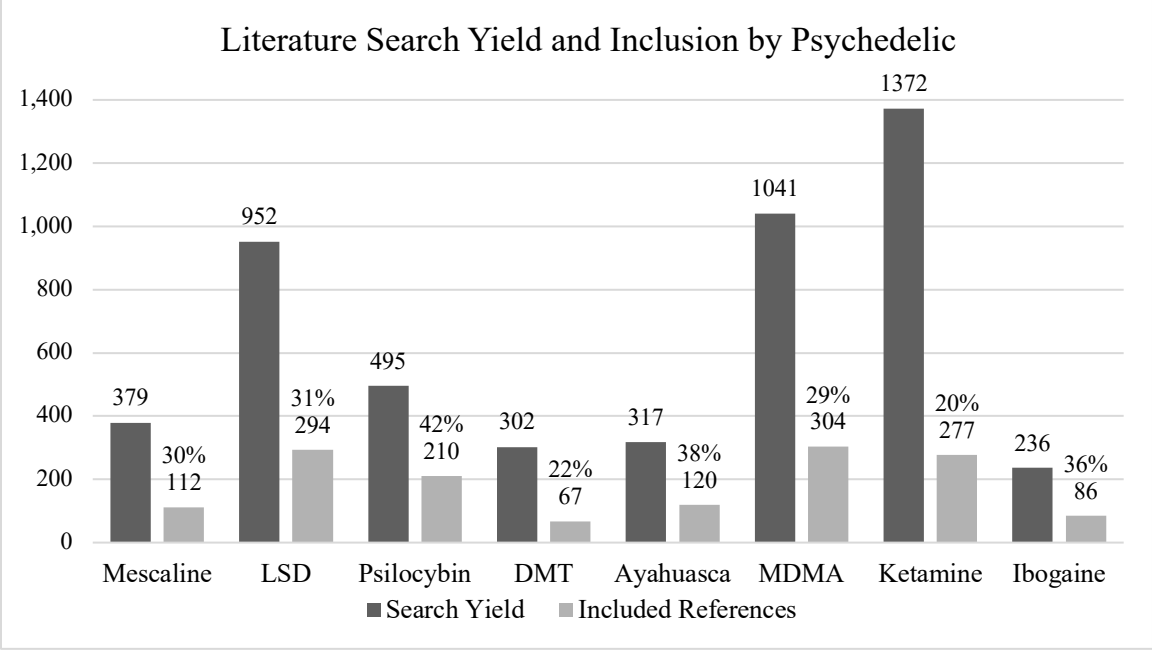
This review covered a broad swath of the psychedelic literature, synthesizing findings into a format that supports clinical decision-making regarding the use of psychedelic therapies. This chapter describes the process of completing this review, summarizes its findings, and discusses limitations and future directions.

Literature Review

The systematic literature search consisted of 1024 Google Scholar searches, which yielded a total of 4,409 references that were selected for further review. Of these, 1,164 references were ultimately included in this review for an overall inclusion rate of 26%. Figure 1 shows the inclusion statistics by psychedelic. Regarding DMT, note that the initial search yield includes articles on 5-MeO-DMT, all of which were excluded from the review, leading to a relatively low inclusion rate (22%).

Figure 1

Literature Search Yield and Inclusion by Psychedelic



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Summary of Findings

This study summarizes much of the literature related to psychedelic-assisted treatment using eight psychedelics with the object of translating this knowledge into treatment planning decisions. For most literature domains, summary tables were developed to provide a condensed overview of existing knowledge (see Table of Tables). A process for psychedelic-assisted treatment planning is described in Chapter 13, drawing on these tables. In addition to this literature synthesis, translational insights arose for each of the psychedelics studied. These insights are described below.

Mescaline

No treatment targets were identified where mescaline would be more effective than LSD or psilocybin. Given that mescaline's long duration makes it impractical, there is little justification for further research in mescaline therapy. However, indigenous mescaline ceremonies appear to have therapeutic benefits like those of LSD and psilocybin. For clinicians evaluating indigenous people for psychedelic treatment, mescaline should be considered an option when it is culturally congruent. When possible, this treatment should be done in collaboration with indigenous practitioners due to their unique knowledge of the substance and traditional practices around it. In addition, there is a good chance that colonialism and cultural appropriation themes arise in the session. These themes could result in a negative transference toward a non-indigenous practitioner that interferes with treatment. Finally, culturally congruent psychedelic treatment provides an avenue for developing cultural identity and building cultural affiliation, improving treatment outcomes.

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LSD

Historical evidence shows that psycholytic LSD therapy can treat many conditions, including depression, anxiety, phobias, OCD, conversion disorders, personality disorders, and schizophrenia (see Summary Table 16). However, these findings are yet to be validated according to modern medical standards, not for lack of potential but rather prohibition and related cultural aversion to LSD. Psycholytic LSD therapy deserves more research attention for treating severe mental health conditions such as personality disorders, complex co-occurring disorders, and sexual paraphilias(see respective sections in Chapter 12).

LSD is uniquely suited to facilitating psycholytic therapy compared to psilocybin due to its tendency to increase Extraversion and outward focus (see Chapter 6 "Introversion, Extraversion, Spontaneity, and Silliness"). In contrast, psilocybin tends to be more sedating and inward-focused. This may be due to LSD having dopaminergic effects while psilocybin does not, along with psilocybin's stronger agonism of the 5-HT_{2C} receptors, an action associated with sedation (see Chapter 3). These properties make low-dose LSD uniquely suited for active intervention during the experience, allowing for therapeutic work in the transference using psychodynamic techniques. Through meta-analysis, long-term psychodynamic therapy has been shown to be superior in treating patients with complex disorders who show high relapse rates with less intensive therapies (Leichsenring & Rabung, 2011; Shedler, 2010). Psycholytic therapy draws on the same mechanisms as psychodynamic psychotherapy but adding low-dose LSD accelerates the emergence of deep psychological material (Grof, 1980, p. 27). Psycholytic therapies can shorten the duration of psychodynamic psychotherapy in achieving sustained remission

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from complex disorders. As has been done historically, psycholytic therapies can also be administered in groups, further improving efficiency (see Chapter 11 “Group Psychedelic Therapies”). Thus, psycholytic therapy represents a potential avenue to increase clinical capacity for treating refractory conditions.

Another early application of LSD therapy was in autism spectrum disorder (ASD) intervention in children (see Chapter 12 “Autism Spectrum Disorder”). While published studies were primarily observational, many children were documented to have improved with LSD, particularly when given daily or weekly for extended periods with doses of 100 μg or higher. Some of the improvements described include substantial improvements in perceptual organization, reducing ritualistic behavior, increasing emotional responsiveness and mood, and facilitating speech in mute children. Despite methodological weaknesses in these studies, the concordance of reports between different practitioners suggests that LSD therapies may provide tangible developmental benefits to children with ASD. Strong caution is warranted in considering future LSD research with children, especially those with developmental disorders. However, few interventions are available to alter the developmental course of ASD, particularly the neuropsychological deficits such as perceptual organization. LSD therapy may show promise in improving the developmental trajectory of children with ASD, provided new research proceeds carefully and in line with modern ethical standards.

Finally, high-dose LSD psychedelic therapy can treat alcohol use disorder (AUD) and holds promise for treating other addictions (see Chapter 12 “Alcohol Use Disorder”). However, current evidence does not support efficacy for AUD beyond 6 months.

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Psilocybin

Psilocybin treatment has robust efficacy across various indications, including depression, suicidality, anxiety, OCD, alcohol use disorder, tobacco cessation, and anxiety related to life-threatening diseases (see Summary Table 16). Outcomes tend to improve with higher doses (see Chapter 10 "Dose"). Overall, psilocybin has the largest body of research supporting its safety and efficacy across many indications. The clinical findings regarding psilocybin's safety and efficacy are straightforward relative to other psychedelics. The brevity of this paragraph reflects this straightforwardness rather than psilocybin's lack of utility. Based on this review, psilocybin is expected to continue to play a substantial role in psychedelic medicine.

DMT

Very few known clinical applications were found for DMT. That said, a handful of case reports from naturalistic users attribute a DMT experience to their cessation of alcohol or tobacco use (see Chapter 12 "Substance Use Disorders"). There is also a theoretical argument supporting that DMT microdosing could help treat schizophrenia, but this theory awaits empirical validation (see Chapter 12 "Schizophrenia").

One promising theoretical application for DMT may be preparing patients for successful treatment with other psychedelics. Psychedelic-induced mystical experience strongly predicts symptom improvement across treatment targets (see Chapter 7 "Spirituality and Mysticism"). A personal "tendency to reject information that is not easily explained through rational, logical, and scientific processes" (Russ et al., 2019b, p. 4) was negatively correlated to mystical experiences from psilocybin (see Chapter 10 "Barriers to Peak Experience"). While a second study did not find significance in this

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association, the possibility of this effect existing holds, in part because it is theoretically parsimonious. In patients that hold rigidly logical and scientific beliefs, Sola suggests that the all-encompassing intensity and ineffability of DMT experience may provide an opportunity to gain a broader epistemological perspective (E. Sola, personal communication, December 7, 2020). In addition to expanding the worldview of these patients through DMT experience, this change in belief system may also improve the efficacy of subsequent psilocybin treatment by facilitating increased mystical experience.

Ayahuasca

Ritual ayahuasca use is associated with fewer symptoms of anxiety, OCD, PTSD, grief, and substance abuse (see Summary Table 16). As a psychiatric treatment, ayahuasca is robust in reducing suicidality and depressive symptoms (see Chapter 12 "Mood Disorders"). Treatment centers in South America also use ayahuasca to support substance abuse recovery. However, the efficacy of these programs has only been demonstrated through uncontrolled trials with mixed findings (see Chapter 12 "Substance Use Disorders"). Finally, one observational study found that ceremonial ayahuasca can reduce some symptoms of borderline personality disorder (see Chapter 12 "Borderline Personality Disorder"). Across studies, ayahuasca has shown a good safety record with no long-term adverse medical or psychological effects seen in humans (see Summary Table 5 and Summary Table 13). Neurocognitively, ritual ayahuasca shows beneficial effects in all domains except for verbal learning, which shows some impairment in two of three studies (see Summary Table 11).

One surprising area where ayahuasca may be beneficial is in treating ADHD (see Chapter 12 "Attention-Deficit/Hyperactivity Disorder and Executive Dysfunction"). Da

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Silveira et al. (2005) found that attention deficit disorder prevalence among ritual ayahuasca users was only 2.5% compared to 17.5% in matched controls, with the difference approaching significance ($p<.057$; $N=80$). Other studies have also shown superior working memory and executive functions in ritual ayahuasca users compared to controls, though these findings are mixed (see Chapter 8). While this is far from conclusive evidence, these findings warrant further investigation as few interventions exist that can improve attention and executive functions outside of ongoing stimulant treatment. If ayahuasca can indeed reduce these neurological deficits associated with ADHD or prevent these deficits from developing in the first place, this would represent a major therapeutic breakthrough.

MDMA

MDMA-assisted psychotherapy has robust efficacy in treating PTSD, as established in Phase 3 FDA trials (see Chapter 12 "Posttraumatic Stress Disorder"). MDMA experience also tends to be gentler and easily tolerated than other psychedelics, making it ideal for emotionally vulnerable patients or as an introductory experience. Strong findings support MDMA-assisted therapy for social anxiety in ASD, which may also extend to treating social anxiety in neurotypical patients (see Chapter 12 "Autism Spectrum Disorder"). There is also some evidence for MDMA's application in treating generalized anxiety, phobias, and avoidant personality disorder (see Chapter 12 sections "Anxiety Disorders" and "Avoidant Personality Disorder"). In addition, recreational MDMA users report experiences that led to overcoming sexual inhibitions and sexual trauma (see Chapter 12 "Sexual Disorders and Difficulties"). This ties into MDMA's

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historical use in couples therapy, which has gained contemporary research support as a part of PTSD treatment (see Chapter 11 “Psychedelic-Assisted Couples Therapies”).

Another promising clinical application for MDMA is in building a therapeutic alliance with patients who present with paranoia and schizoid traits (see Chapter 12 sections “Schizophrenia,” “Paranoid Personality Disorder,” and “Schizoid Personality Disorder”). These patients are commonly resistant to treatment due to difficulty trusting clinicians. MDMA is reported to help these patients gain trust in clinicians, though the ethical implications of using MDMA in this way must be weighed carefully.

Chronic recreational MDMA shows neurotoxicity that causes long-term cognitive deficits (see Chapter 5 “Neurotoxicity” along with Summary Table 10). Only one study was found regarding the neurocognitive effects of clinical MDMA (Mithoefer et al., 2011). While this study found no long-term impact, the extensive evidence of MDMA neurotoxicity warrants further investigation. Most likely, pure clinical MDMA administered in reasonable doses and across a limited number of sessions has negligible neurocognitive effects compared to its therapeutic benefits. However, this should be borne out through research rather than conjecture.

Several harm reduction strategies applicable to MDMA therapy were identified in this review. MDMA’s neurocognitive impact can be minimized by avoiding body temperature elevation (see Chapter 5 sections “Neurotoxicity,” “Temperature Dysregulation and Hyperthermia,” and “Astrogliosis and Associated Neuroplasticity Inhibition”). Elevations in body temperature can be avoided by administering MDMA in a cool environment, monitoring for increased body temperature, and using the R(–) enantiomer instead of racemic or S(+)-MDMA. Temperature increases can also be

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prevented through pretreatment with cannabinoids, carvedilol (a beta-blocker), clomethiazole and pentobarbital (sedatives), and CGS (adrenergic-2A receptor agonist). In addition, avoiding caffeine before MDMA can also reduce neurotoxicity (Khairnar et al., 2014). Finally, pretreatment with beta-blockers can minimize cardiovascular risks by attenuating MDMA-induced heart rate and blood pressure increases. As the beta-blocker carvedilol is safe and preserves the subjective effects of MDMA, it appears to be an excellent drug for harm reduction (Hysek et al., 2012).

Ketamine

This review suggests that ketamine is under-utilized as a safe and highly effective first-line treatment for depression and suicidality (see Chapter 12 section "Mood Disorders"). Currently, ketamine's only formal indication is for treatment-resistant depression, meaning that several other pharmacotherapies such as SSRIs are tried first. This paradigm is backward, as ketamine has the potential to rapidly reduce depressive symptoms and suicidality in unipolar and bipolar depression. In this way, ketamine can provide a functional window for non-pharmacological intervention. On the other hand, SSRI treatments take weeks to become effective, require daily doses, and have many harmful side effects. SSRIs also interact with serotonergic psychedelics and MDMA, restricting psychedelic treatment options (see Chapter 5 "Serotonin Syndrome"). While the anti-depressant effects of ketamine infusion decline after a week, ketamine-assisted therapy may provide more long-lasting effects. Initial treatment with ketamine could also improve mindset to facilitate treatment with psilocybin, which shows robust long-term efficacy for depression.

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This review also highlights concerns about the adverse effects of frequent and ongoing ketamine treatments. Chronic recreational ketamine use has been linked to bladder cytosis, abdominal pain, sexual dysfunction, and fertility decline (see Summary Table 5). Long-term ketamine use has also been linked to neurocognitive damage in clinical and recreational contexts (see Summary Table 11). In addition, there is substantial evidence for ketamine's addictive potential, which is particularly relevant to self-administered ketamine nasal sprays (see Chapter 9 "Abuse Potential of Psychedelics").

For treating conditions other than mood disorders, ketamine-assisted psychotherapies show promise for treating conditions as diverse as OCD, PTSD, and substance use disorders (see Summary Table 16). Like with depression, ketamine rapidly reduces PTSD symptoms with declining efficacy in the days following infusion. Again, this can provide a window for other interventions, even if it does not ameliorate symptoms long-term. Finally, ketamine-assisted therapy may effectively treat avoidant personality disorder based on one observational study with 20 patients (see Chapter 12 "Avoidant Personality Disorder").

Ibogaine

Ibogaine shows substantial promise as a treatment for addiction, given its remarkable ability to, in many cases, completely attenuate withdrawal symptoms. Ibogaine therapies lead to relatively low relapse rates, especially when several sessions are given. However, ibogaine's fatal cardiovascular risk is exceptionally high, with therapeutic doses commonly exceeding what is considered safe by pharmaceutical standards (see Table 1). This risk may be deemed acceptable for treating severe and life-threatening addictions, but it is far from ideal. As alternatives, the primary metabolite of

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ibogaine, noribogaine, and the ibogaine analog, 18-methoxycoronaridine (18-MC), have similar antiaddictive properties but far less toxicity (see Chapter 5 section on "Fatal Toxicity"). These drugs represent ideal targets for future research. In addition, the safety of ibogaine may be improved by examining and implementing indigenous methods of preparation for initiation, which often include several days of stress-reducing activities that may also reduce cardiovascular risk.

Outside of treating addition, the only other therapeutic target identified for ibogaine is in processing grief (see Chapter 12 "Grief"). Ibogaine is used indigenously to make spiritual contact with the dead. Experiences of after-death communication (ADCs) are documented in its phenomenology. Such experiences are empirically linked to grief resolution (Beischel, 2019). Other psychedelics, however, are also linked to ADCs and carry less risk. As with mescaline, cultural congruence is a determiner in whether ibogaine is a good choice for a patient.

Psychedelics and Graceful Aging

One relatively unexplored area where psychedelics may benefit people is to support graceful aging (see Chapter 12 "Aging"). Aday, Bloesch, et al. (2020) provide theoretical justification for using psychedelic therapies for ameliorating age-related cognitive decline and psychological distress (see Table 46). For the most part, this review supports their reasoning. A particularly notable finding by Stamets (2021) is increased finger-tapping speed among people over 55 who microdose psilocybin, given that slowed finger-tapping speed is a marker of early-stage dementia. Hendricks and Grob (2016) also describe why classical psychedelics may help reduce rational suicidality through reasoning supported by this review. Finally, there is strong support for psilocybin and

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LSD treatment to treat anxiety due to life-threatening diseases, with applications in palliative care (see Chapter 12 “Palliative Care and Existential Anxiety”).

Genetic Screening Prior to Psychedelic Treatment

Unexpectedly, several genetic variables relevant to psychedelic treatment were uncovered in this review. Since these factors are not well-known within the psychedelic research community, they are summarized here. While genetic screening is an extra hurdle, for some psychedelics, it should be performed as a matter of safety, while for others, it can influence treatment efficacy. Given the popularity of commercial gene sequencing, many patients already have access to their genetic data, which could be used for screening purposes.

CYP2D6. MDMA and ibogaine are metabolized by the CYP2D6 enzyme, which is genetically deficient in 7%–10% of Caucasians (see Chapter 3). Poor *CYP2D6* metabolizers will be more sensitive to these drugs. Poor metabolization is particularly of concern with ibogaine, where the safety ratio is extremely low. Thus, screening is recommended for the *CYP2D6* poor metabolizer gene before ibogaine treatment.

CYP2B6*6. Those with the *CYP2B6*6* gene variant metabolize ketamine more slowly and, therefore, require a lower dose (see Chapter 3). This gene is common in African, African American, and some Asian populations. Since ketamine has a relatively high safety ratio, this is unlikely to be a safety concern, but this factor may be significant in treatment planning.

rs6265. The efficacy of ketamine in treating depression is reduced in *rs6265* Met carriers, who make up approximately 40% of the population (see Chapter 10 “Genetic Differences”). The one human study found on this phenomenon saw a substantial impact

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from *rs6265* polymorphism. Those with the dominant genotype (Val/Val) showed 41% improvement in symptoms, while symptom improvement was only 24% for Met carriers (Laje et al., 2012).

Limitations

This study has several major limitations. First, being an extensive review, the depth of inquiry into any topic is superficial. Other guides are necessary to guide the specifics of any psychedelic-assisted therapy. Further, a lack of in-depth review could have led to false conclusions in some areas, despite the author's efforts to prevent this.

Next, this review is limited in the breadth of psychedelic-assisted treatments reviewed. 5-MeO-DMT was not covered in this review and may have potential treatment applications (Davis et al., 2019; Hesselink & Hesselink, 2018). Further, the range of MDMA analogs described by Alexander and Ann Shulgin (1991), including the *2C*-series, were not investigated. Also not investigated were *Salvia divinorum* and *2,5*-Dimethoxy-*4*-iodoamphetamine (DOI). Finally, psychedelic microdosing was not examined, which may hold promise for many conditions (Bornemann, 2020; Fadiman, 2011; Lea et al., 2020; Polito & Stevenson, 2019; Szigeti et al., 2021).

Another limitation of this study is the exclusions made to limit its scope. The review of neuroscience is cursory at best, with the entirety of neuroimaging and animal studies excluded, along with the impacts of psychedelics on emotional processing and neuroscience of treatment mechanisms. As these domains are likely to have strong translational value, this represents a major area for future study. Drug interactions were also excluded, as was the treatment of organic disorders with psychedelics, despite promising applications for these disorders. Finally, the literature search only included

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antisocial and borderline personality disorders; therefore, there may be additional extant literature regarding other personality disorders that were not covered.

Quantitatively, this study included a preliminary meta-analysis comparing studies based on computed effect sizes. This meta-analysis is considered preliminary because it does not meet contemporary meta-analytic standards in medicine (Kepes et al., 2013):

1. No formal analysis of methodological quality was performed, though study quality was considered throughout the review.
2. The heterogeneity of findings was not assessed quantitatively.
3. Combined effect size and confidence intervals were not computed.

In addition, the effect sizes of psychedelic treatments for different conditions were not compared against one another or to conventional treatments. Finally, the potential for computational errors must be acknowledged. Effect size computations were performed by a single author and not audited by an external reviewer.

Finally, this review is limited by the discrete timepoints at which literature searches took place (February 29 to June 10, 2020). Articles published after the searches were complete were omitted unless discovered organically and deemed important enough to be added post hoc. Science marches forward, and as with any review, this synthesis is out of date already, even before its publication.

Future Directions

In addition to the areas for future research already identified in this chapter, there are several further promising directions for this research. First, the author plans to develop this dissertation into a reference volume for clinicians. This book will help to support the assessment of psychedelic treatment options and the planning of psychedelic-

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assisted treatments. Another potential future project is developing an assessment instrument to measure personality factors relevant to psychedelic effects, identified by this review. This instrument would support clinicians in treatment planning by providing individualized insight into the factors relevant to psychedelic-assisted treatment.

Aspirationally, this assessment and treatment planning method could be tested through a multi-arm trial. Patients of varying and mixed diagnoses could be assigned to different psychedelic-assisted therapies using the present methodology or assigned to a treatment-as-usual control group. The combined efficacy of psychedelic-assisted treatment could then be evaluated against conventional treatment. In addition, the treatment arms could be compared individually to treatment-as-usual to yield valuable insights regardless of the overall outcome of the study.

Regarding future research opportunities, the curious researcher need only look to the summary tables to identify areas with a dearth of literature (see Table of Tables). The "Summary of Findings" above also suggests several promising areas for future research.

Conclusion

As expected, choosing between psychedelic therapies is an extraordinarily complex task, with factors to consider that span biological, psychological, and clinical domains of knowledge. This dissertation has yielded a systematic method to wrangle this complexity, as described in Chapter 13. This method uses tabular literature summaries to allow clinicians to integrate research into treatment planning decisions rapidly. To the author's knowledge, no other system exists for this purpose. The literature review and synthesis process has yielded novel insights into potential psychedelic treatment indications and uncovered fertile grounds for future research.

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With psychedelic-assisted therapies reentering mainstream medical practice, heuristics for making treatment decisions will become increasingly important. This is especially true as psychedelic treatments are applied in treating real-world patients who do not present with the "pure" DSM diagnoses studied in clinical trials. Further, this review has uncovered a dizzying array of risk factors that are important to consider in selecting treatments but may be unknown to many clinicians, even those experienced with psychedelic treatments. Together, this system can assist clinicians in planning psychedelic-assisted treatments that maximize effectiveness while minimizing risk based on the available evidence base.

Finally, this synthesis highlights the need for medical access to the full range of psychedelic medicines. The body of literature shows that each psychedelic has unique and valuable properties that may be ideal for one patient yet harmful to another. Clinicians need a variety of treatment options to serve patients best. The astonishing effectiveness of psychedelic-assisted treatments across conditions suggests a promising route toward meeting the systemic mental healthcare challenges we face today. Legal reform is necessary to unlock this potential and support growth toward our collective well-being. While not a panacea, psychedelics have an essential role in the future of mental healthcare. The author hopes this study will provide a meaningful step toward improved social wellness and mental health treatment through psychedelic medicine.

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Appendix A: Literature Search Results

The following tables document the Google Scholar searches performed to obtain literature for this review. Each search consists of a concatenation of a "topic keyword" shown in the left column and the name of one of the psychedelics reviewed listed in the top row. For formatting purposes, this matrix of keyword searches has been split into two tables. Table 47 includes mescaline, LSD, psilocybin, and DMT (Actual search term "dimethyltryptamine" for disambiguation). Table 48 includes ayahuasca, MDMA, ketamine, and ibogaine. For each search, three comma-separated values are provided:

- The total number of results returned,
- The number of search results examined for relevance,
- The number of references included for further review (with full text available).

Finally, the date of each search is indicated by a case-sensitive alphabetical superscript following the comma-separated values. Table 49 maps superscripts to the date of the respective literature search.

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Table 47

Literature Search Results (Mescaline, LSD, Psilocybin, DMT)

Topic Keyword	Mescaline	LSD	Psilocybin	DMT*
Pharmacology	13100, 20, 8 [G]	83700, 20, 10 [h]	6760, 20, 11 [h]	7560, 20, 16 [i]
Acetylcholine	2860, 30, 19 [H]	17200, 10, 5 [h]	1930, 10, 3 [h]	1750, 10, 4 [i]
Adrenaline	2160, 20, 9 [H]	7530, 10, 4 [h]	1020, 10, 3 [h]	875, 10, 7 [i]
Cortisol	1630, 20, 9 [H]	13200, 10, 3 [h]	1650, 20, 17 [h]	750, 10, 7 [i]
Dopamine	7860, 20, 15 [G]	33600, 10, 6 [a]	5,830, 10, 7 [h]	4790, 10, 5 [i]
Dose	16500, 30, 29 [G]	147000, 20, 12 [h]	9090, 20, 18 [h]	7370, 20, 15 [i]
Epinephrine	2,170, 20, 13 [H]	9630, 10, 2 [k]	1070, 10, 5 [k]	896, 10, 5 [k]
GABA	2820, 20, 10 [H]	21500, 20, 8 [h]	2870, 10, 7 [h]	1990, 10, 3 [i]
Glutamate	2860, 30, 18 [H]	27000, 10, 6 [h]	2,950, 10, 5 [h]	2140, 10, 7 [i]
Opioid receptors	3110, 20, 3 [H]	14900, 10, 2 [k]	2820, 10, 6 [k]	1930, 10, 8 [k]
Oxytocin	599, 20, 4 [H]	5410, 20, 0 [a]	846, 10, 4 [h]	392, 10, 2 [i]
Pharmacokinetics	2840, 20, 15 [G]	12900, 20, 10 [h]	2420, 20, 14 [h]	1790, 20, 13 [i]
Serotonin	8030, 40, 33 [H]	38100, 15, 11 [h]	7230, 20, 17 [h]	6620, 20, 12 [i]
Phenomenology	3090, 30, 8 [H]	8730, 50, 31 [F]	3050, 30, 21 [F]	1290, 30, 24 [F]
Neuroscience	4790, 30, 16 [H]	49900, 50, 39 [F]	4920, 30, 24 [F]	3440, 30, 29 [F]
Behavior	16900, 50, 40 [H]	191000, 30, 27 [s]	10800, 30, 28 [A]	6590, 40, 29 [D]
Connectome harmonics	31, 30, 22 [H]	81, 20, 12 [s]	137, 30, 26 [B]	38, 20, 15 [D]
Dreaming	6340, 20, 9 [H]	8370, 20, 12 [s]	1790, 20, 9 [B]	1450, 30, 15 [D]
EEG	3060, 30, 21 [H]	17800, 20, 16 [s]	2940, 30, 16 [B]	1240, 30, 20 [D]
Empathy	2960, 20, 6 [H]	13600, 10, 3 [s]	2670, 20, 13 [B]	756, 20, 10 [D]
Entropic brain	267, 30, 24 [H]	782, 20, 18 [s]	441, 30, 24 [B]	460, 30, 26 [D]
Fear	9690, 30, 16 [H]	60900, 20, 17 [s]	6710, 40, 32 [B]	2360, 30, 24 [D]
Functional connectivity	1440, 40, 35 [I]	14300, 30, 24 [s]	2360, 40, 33 [B]	761, 30, 28 [D]
Gender	4680, 20, 4 [I]	80700, 10, 0 [s]	4200, 10, 6 [s]	1280, 20, 13 [s]
Gene expression	6120, 20, 13 [I]	97300, 20, 10 [s]	5810, 30, 19 [B]	2920, 20, 17 [D]
Learning	12800, 40, 30 [I]	126000, 30, 17 [s]	7130, 20, 9 [B]	3840, 30, 22 [D]
Metabolism	7910, 30, 25 [I]	121000, 30, 20 [t]	5120, 20, 12 [B]	5400, 30, 27 [D]
Microbiome	46, 20, 5 [I]	3750, 10, 0 [t]	172, 10, 2 [t]	63, 10, 2 [t]
Neuroimaging	1510, 30, 21 [I]	10200, 50, 40 [t]	2810, 30, 24 [B]	975, 30, 24 [D]
Neurons	6820, 30, 21 [I]	54600, 40, 30 [F]	5860, 30, 28 [F]	4870, 30, 23 [F]
Neuroplasticity	374, 20, 10 [I]	4010, 20, 4 [t]	715, 20, 13 [B]	361, 20, 17 [D]

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Topic Keyword	Mescaline	LSD	Psilocybin	DMT*
Neuroprotection	642, 10, 3 [I]	14500, 10, 0 [t]	662, 20, 1 [C]	691, 20, 9 [D]
Neuropsychology	2140, 20, 12 [I]	7500, 10, 0 [t]	2430, 30, 14 [C]	1060, 30, 18 [D]
Attention	15500, 10, 5 [I]	187000, 20, 12 [t]	10300, 30, 27 [C]	4380, 20, 17 [D]
Cognition	8460, 20, 8 [I]	62700, 40, 32 [t]	8620, 30, 27 [C]	3480, 30, 22 [D]
Executive functioning	2990, 20, 7 [I]	23300, 20, 6 [t]	2880, 30, 20 [C]	819, 20, 13 [D]
Intellectual functioning	4900, 20, 8 [I]	21100, 20, 14 [t]	3370, 20, 12 [C]	989, 20, 12 [D]
Information processing speed	3060, 10, 3 [I]	39200, 20, 3 [L]	3000, 20, 13 [L]	795, 20, 13 [L]
Memory	10800, 20, 14 [I]	96500, 30, 18 [t]	8290, 20, 17 [C]	3150, 20, 14 [D]
Verbal	5480, 20, 12 [I]	43700, 30, 26 [t]	3640, 30, 22 [C]	1090, 20, 13 [D]
Psychotomimetic	3560, 30, 18 [I]	7130, 50, 35 [t]	2560, 30, 23 [C]	1780, 30, 21 [D]
Sensory processing	3070, 20, 9 [I]	41500, 20, 11 [t]	3380, 30, 28 [C]	1300, 30, 20 [D]
Auditory processing	2090, 20, 8 [I]	14800, 30, 19 [t]	2370, 30, 27 [C]	830, 20, 13 [D]
Dissociation	3690, 30, 16 [J]	27300, 20, 11 [t]	2940, 20, 11 [C]	1880, 30, 22 [D]
Emotional processing	3930, 20, 14 [J]	22800, 30, 20 [t]	4220, 30, 27 [C]	1460, 30, 23 [D]
Interoception	503, 20, 11 [J]	1920, 20, 8 [t]	534, 20, 11 [C]	317, 20, 12 [D]
Olfaction	1830, 20, 5 [J]	16800, 10, 4 [t]	1350, 10, 2 [C]	943, 20, 4 [D]
Sensorimotor processing	561, 20, 7 [J]	5300, 20, 12 [t]	809, 20, 20 [C]	354, 20, 11 [D]
Time perception	13100, 20, 15 [J]	84000, 20, 16 [C]	10400, 20, 15 [C]	3570, 30, 28 [D]
Visual processing	4150, 30, 14 [J]	53600, 30, 22 [t]	4560, 30, 28 [C]	1580, 30, 27 [D]
Sex	9280, 20, 12 [J]	104000, 20, 7 [t]	6320, 20, 4 [C]	2240, 20, 17 [D]
Sleep	9790, 20, 9 [J]	48900, 20, 9 [t]	6710, 20, 8 [C]	2900, 30, 27 [D]
Social interaction	9220, 20, 12 [J]	75800, 30, 16 [t]	6570, 20, 14 [C]	2960, 30, 20 [D]
Personality Change	8490, 40, 27 [J]	46900, 50, 38 [F]	6600, 30, 26 [F]	1950, 30, 26 [F]
Clinical Research	13600, 50, 39 [J]	153000, 50, 41 [F]	12100, 30, 28 [F]	5960, 30, 24 [F]
ADHD treatment	1310, 20, 2 [J]	8620, 20, 4 [F]	1510, 20, 3 [F]	433, 20, 7 [F]
Adolescents	7260, 20, 4 [J]	41400, 30, 10 [C]	5500, 30, 2 [C]	1570, 20, 9 [C]
Aging	2430, 20, 6 [J]	56300, 30, 11 [b]	2150, 20, 7 [b]	941, 20, 8 [c]
Antisocial personality disorder	1380, 20, 2 [J]	8080, 20, 7 [b]	1020, 20, 6 [c]	1110, 10, 1 [e]
Anxiety	10700, 30, 23 [J]	59500, 20, 6 [a]	8310, 40, 31 [c]	4000, 20, 11 [e]
Social anxiety	8510, 20, 12 [J]	41100, 10, 0 [a]	6930, 20, 12 [c]	2480, 20, 14 [e]

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Topic Keyword	Mescaline	LSD	Psilocybin	DMT*
Autism	1520, 20, 6 [J]	9000, 20, 4 [a]	1260, 20, 10 [c]	600, 20, 3 [c]
Bipolar disorder	1940, 20, 2 [J]	15100, 20, 3 [a]	2170, 20, 14 [c]	952, 20, 8 [e]
Body dysmorphic disorder	126, 10, 2 [J]	923, 10, 3 [d]	169, 20, 6 [c]	247, 10, 3 [d]
Borderline personality disorder	996, 20, 4 [J]	5780, 20, 6 [g]	845, 20, 9 [g]	1060, 20, 1 [g]
Children	11500, 20, 10 [J]	106000, 30, 21 [b]	7560, 30, 9 [b]	2300, 20, 6 [b]
Cluster Headaches	1130, 20, 8 [J]	4730, 10, 4 [a]	1270, 20, 14 [c]	420, 20, 12 [e]
Couples therapy	3110, 10, 4 [J]	14900, 30, 5 [b]	2460, 20, 6 [c]	778, 10, 3 [e]
Death Anxiety	6660, 20, 10 [J]	29000, 20, 6 [a]	5590, 30, 21 [c]	2060, 20, 18 [e]
Depression treatment	11800, 20, 18 [J]	76000, 30, 9 [a]	9490, 50, 44 [c]	4760, 20, 13 [e]
Eating disorders	4220, 10, 2 [J]	20300, 20, 0 [d]	3,390, 20, 9 [d]	1130, 10, 7 [d]
Epilepsy	3580, 20, 15 [J]	16300, 20, 8 [C]	2800, 20, 6 [C]	1220, 20, 9 [C]
Family therapy	9350, 20, 6 [J]	48300, 30, 1 [b]	5330, 30, 21 [c]	3270, 20, 11 [e]
Grief	1890, 20, 4 [J]	9020, 20, 4 [g]	1010, 20, 13 [g]	331, 20, 14 [g]
Group Therapy	13000, 30, 21 [J]	77000, 20, 11 [a]	6670, 30, 25 [c]	5060, 20, 13 [e]
Healthy normals	645, 20, 14 [J]	3300, 20, 10 [b]	427, 20, 12 [c]	264, 20, 12 [e]
Immunomodulation	444, 10, 2 [J]	8680, 20, 1 [b]	654, 20, 2 [b]	81, 20, 9 [b]
Microdosing	185, 30, 15 [J]	709, 30, 18 [a]	320, 30, 21 [c]	177, 20, 13 [e]
Obsessive compulsive disorder	2070, 30, 19 [J]	10700, 10, 5 [a]	2210, 20, 17 [c]	890, 20, 9 [e]
Pain Management	5680, 20, 7 [K]	29300, 20, 6 [d]	3440, 20, 7 [c]	1480, 20, 6 [d]
Post traumatic stress disorder	3890, 20, 8 [K]	19100, 20, 2 [a]	20700, 20, 10 [c]	5210, 20, 11 [e]
Psychotherapy	5780, 30, 20 [K]	20300, 30, 16 [a]	5,270, 30, 27 [c]	1830, 30, 18 [e]
Review	16500, 20, 14 [K]	314000, 30, 21 [a]	12400, 40, 28 [c]	6420, 20, 14 [e]
Schizophrenia treatment	6770, 20, 14 [K]	28800, 30, 15 [a]	5370, 20, 8 [c]	2870, 20, 14 [e]
Sexuality	9660, 20, 9 [K]	15300, 30, 10 [b]	1540, 20, 4 [b]	2260, 20, 9 [b]
Homosexuality	2000, 10, 2 [K]	6360, 20, 8 [b]	1100, 20, 1 [b]	230, 20, 1 [b]
Somatization disorder	2250, 20, 12 [K]	11900, 30, 21 [C]	2060, 20, 14 [C]	18600, 10, 4 [C]
Substance use disorder treatment	11600, 20, 15 [K]	41100, 30, 19 [a]	25100, 30, 22 [c]	17300, 20, 16 [e]
Alcoholism	7900, 30, 19 [K]	32000, 30, 14 [a]	5680, 30, 17 [c]	2030, 20, 13 [e]
Tobacco cessation	1280, 20, 4 [K]	6420, 20, 5 [b]	1200, 20, 14 [c]	395, 20, 12 [e]
Tourette syndrome	455, 20, 5 [K]	2440, 10, 1 [C]	423, 10, 2 [C]	529, 10, 0 [C]

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Topic Keyword	Mescaline	LSD	Psilocybin	DMT*
Traumatic brain injury treatment	4850, 20, 4 [K]	22500, 20, 1 [C]	20000, 10, 4 [C]	7350, 10, 1 [C]
Risk	12300, 20, 6 [K]	170000, 30, 13 [C]	10100, 30, 27 [C]	3820, 30, 21 [C]
Abuse potential	10100, 20, 6 [K]	53300, 10, 4 [k]	8030, 20, 19 [l]	3290, 20, 16 [p]
Accidental injury	3070, 20, 3 [K]	10100, 10, 3 [k]	1390, 10, 0 [l]	535, 10, 3 [p]
Astrogliosis	103, 20, 8 [J]	2760, 10, 0 [C]	91, 10, 2 [J]	108, 10, 1 [C]
Cardiovascular risk	2810, 20, 8 [K]	35200, 10, 0 [k]	2580, 20, 17 [l]	1180, 10, 8 [p]
Chromosome damage	1170, 20, 12 [K]	20200, 20, 19 [k]	1010, 10, 4 [l]	459, 10, 8 [p]
Cystitis	172, 10, 0 [K]	1190, 10, 0 [q]	180, 10, 0 [q]	87, 10, 3 [q]
Developmental risk	9390, 20, 5 [K]	37400, 20, 5 [k]	7710, 10, 8 [l]	2980, 20, 9 [p]
Fatality	1780, 30, 11 [K]	3930, 20, 6 [p]	1580, 20, 4 [p]	568, 10, 4 [p]
Overdose	5290, 20, 8 [K]	22100, 20, 6 [p]	4110, 10, 4 [p]	1250, 20, 12 [p]
Flashbacks	1900, 30, 16 [K]	5220, 20, 15 [k]	1960, 10, 7 [l]	523, 10, 4 [p]
Harm reduction	5030, 20, 2 [K]	32200, 20, 1 [r]	4700, 20, 8 [r]	1500, 10, 5 [r]
Hallucinogen persisting perception disorder	4520, 20, 17 [K]	11400, 20, 16 [l]	8450, 20, 12 [m]	2370, 20, 14 [p]
Hyponatremia	363, 10, 6 [K]	1300, 10, 1 [p]	262, 10, 4 [p]	85, 10, 1 [p]
Induced psychosis	7990, 30, 30 [K]	22700, 20, 13 [l]	6150, 20, 18 [m]	3080, 20, 15 [p]
Interactions	8640, 30, 21 [K]	182000, 20, 13 [l]	6360, 20, 19 [m]	6820, 20, 16 [p]
Long-term risk	6480, 20, 8 [K]	90200, 20, 11 [l]	6180, 20, 18 [m]	2090, 20, 14 [p]
Mania	3330, 20, 4 [K]	10100, 10, 2 [l]	1450, 10, 6 [m]	1040, 20, 15 [p]
Negative experiences	10300, 20, 14 [K]	47400, 20, 16 [l]	8660, 20, 19 [m]	2930, 20, 18 [p]
Bad trip	5550, 30, 11 [K]	19000, 20, 14 [l]	2950, 20, 13 [m]	1120, 20, 13 [p]
Nystagmus	929, 20, 2 [K]	2940, 10, 2 [r]	776, 10, 4 [r]	227, 10, 3 [r]
Paralysis	2530, 20, 12 [K]	13100, 20, 12 [K]	1740, 20, 7 [L]	681, 20, 3 [L]
Parkinson's	2820, 20, 7 [K]	9750, 10, 0 [C]	2570, 20, 3 [C]	1490, 20, 12 [C]
Psychiatric risk	7610, 20, 13 [K]	44400, 20, 9 [p]	6900, 20, 19 [p]	2570, 10, 6 [p]
Respiratory depression	4000, 20, 11 [K]	22700, 10, 4 [l]	3100, 20, 9 [m]	1280, 20, 8 [p]
Rhabdomyolysis	658, 20, 7 [K]	2160, 10, 1 [p]	590, 10, 3 [p]	220, 10, 5 [p]
Safety	7890, 20, 10 [K]	104000, 20, 15 [r]	6500, 20, 20 [r]	2620, 20, 16 [p]
Seizure	6450, 20, 14 [K]	23400, 10, 6 [l]	4530, 10, 2 [m]	1990, 20, 6 [p]
Serotonin syndrome	3970, 30, 23 [K]	17100, 10, 5 [l]	3510, 10, 9 [m]	2820, 20, 10 [p]
Sexual dysfunction	2520, 20, 11 [K]	21000, 10, 1 [r]	2350, 10, 4 [r]	945, 10, 5 [r]
Sexual misconduct	278, 20, 3 [K]	2310, 10, 0 [p]	203, 10, 3 [p]	49, 20, 2 [p]

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Topic Keyword	Mescaline	LSD	Psilocybin	DMT*
Suicide	5910, 20, 13 K	31400, 20, 9 l	3920, 20, 16 m	1560, 20, 10 p
Temperature dysregulation	351, 10, 6 K	7440, 10, 1 l	342, 10, 3 m	192, 20, 3 p
Teratogen	728, 20, 11 K	5350, 20, 18 l	522, 10, 3 m	236, 20, 5 p
Toxicity	9730, 30, 20 K	89100, 20, 5 l	3970, 20, 17 m	3960, 20, 9 p
Violence	8580, 20, 7 K	39800, 20, 3 p	4520, 20, 6 p	1380, 20, 13 p

Note. *Actual search term “dimethyltryptamine” for disambiguation.

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Table 48

Literature Search Results (Ayahuasca, MDMA, Ketamine, Ibogaine)

Topic Keyword	Ayahuasca	MDMA	Ketamine	Ibogaine
Pharmacology	4540, 20, 17 [i]	21800, 20, 15 [i]	194000, 20, 16 [j]	4340, 20, 11 [b]
Acetylcholine	525, 10, 2 [i]	5750, 10, 9 [i]	45400, 20, 19 [k]	1510, 10, 7 [i]
Adrenaline	344, 10, 4 [i]	1950, 10, 6 [i]	13700, 10, 1 [k]	370, 10, 1 [i]
Cortisol	602, 20, 19 [i]	4120, 20, 17 [i]	23800, 10, 8 [k]	281, 10, 4 [i]
Dopamine	1940, 20, 13 [i]	22900, 20, 17 [i]	80500, 20, 20 [k]	3030, 20, 18 [b]
Dose	4460, 20, 20 [i]	29400, 20, 14 [i]	380000, 20, 10 [k]	4280, 20, 17 [i]
Epinephrine	251, 10, 7 [k]	2950, 10, 5 [k]	31400, 10, 5 [k]	428, 10, 6 [k]
GABA	1010, 10, 7 [i]	11200, 10, 9 [i]	70300, 10, 8 [k]	1460, 10, 8 [i]
Glutamate	979, 20, 16 [i]	11600, 10, 9 [i]	99300, 20, 15 [k]	1870, 10, 8 [i]
Opioid receptors	969, 10, 6 [k]	10200, 10, 7 [k]	50400, 10, 8 [k]	2030, 10, 7 [k]
Oxytocin	243, 10, 1 [i]	2430, 20, 19 [i]	12900, 10, 3 [k]	279, 10, 0 [b]
Pharmacokinetics	1180, 20, 16 [i]	11900, 20, 16 [i]	66700, 20, 10 [k]	1490, 20, 11 [i]
Serotonin	2800, 10, 8 [i]	22200, 20, 18 [i]	64900, 20, 17 [k]	2840, 20, 19 [i]
Phenomenology	2530, 30, 26 [F]	3070, 30, 27 [F]	7520, 40, 30 [F]	447, 30, 26 [F]
Neuroscience	3750, 30, 29 [F]	16900, 30, 26 [F]	156000, 50, 46 [F]	2210, 30, 29 [F]
Behavior	7040, 40, 38 [E]	29900, 40, 34 [x]	197000, 40, 36 [u]	3820, 30, 29 [x]
Connectome harmonics	42, 30, 24 [E]	30, 20, 13 [x]	129, 30, 21 [u]	5, 5, 2 [x]
Dreaming	1580, 30, 19 [E]	1170, 20, 6 [x]	2740, 30, 10 [v]	654, 30, 23 [x]
EEG	1210, 30, 26 [E]	4830, 40, 31 [y]	34100, 30, 26 [v]	504, 20, 17 [x]
Empathy	1590, 30, 27 [E]	4550, 40, 34 [y]	4280, 20, 10 [v]	353, 20, 14 [x]
Entropic brain	313, 30, 25 [E]	242, 30, 23 [y]	473, 30, 23 [v]	86, 20, 16 [x]
Fear	4400, 30, 23 [E]	13000, 30, 26 [y]	38500, 30, 26 [v]	1220, 20, 16 [x]
Functional connectivity	1510, 40, 38 [E]	3690, 20, 15 [y]	33300, 50, 48 [v]	338, 20, 14 [x]
Gender	3260, 10, 6 [s]	17300, 30, 23 [s]	51300, 20, 11 [s]	856, 10, 9 [s]
Gene expression	3520, 20, 13 [E]	17800, 30, 27 [y]	199000, 40, 40 [v]	2150, 20, 16 [x]
Learning	5170, 20, 19 [E]	19600, 50, 48 [z]	97800, 40, 38 [v]	2480, 20, 19 [x]
Metabolism	2070, 30, 25 [E]	19500, 30, 19 [z]	172000, 30, 13 [v]	2850, 20, 17 [x]
Microbiome	97, 10, 4 [t]	206, 20, 7 [t]	3710, 20, 4 [t]	21, 10, 0 [t]
Neuroimaging	1160, 40, 40 [E]	6630, 40, 34 [z]	26600, 50, 45 [v]	442, 20, 10 [x]
Neurons	2800, 30, 21 [F]	19400, 30, 29 [F]	190000, 40, 36 [F]	2850, 30, 27 [F]
Neuroplasticity	300, 30, 20 [E]	2060, 20, 15 [z]	14500, 30, 21 [v]	205, 20, 11 [x]

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Topic Keyword	Ayahuasca	MDMA	Ketamine	Ibogaine
Neuroprotection	384, 20, 13 [E]	5790, 20, 19 [z]	43000, 30, 24 [v]	930, 20, 8 [x]
Neuropsychology	1210, 30, 27 [E]	7000, 40, 34 [z]	16800, 40, 29 [w]	438, 20, 11 [x]
Attention	6950, 30, 24 [E]	25700, 30, 25 [z]	111000, 30, 28 [w]	2520, 20, 17 [x]
Cognition	6250, 30, 27 [E]	20600, 30, 26 [z]	65000, 40, 37 [w]	2230, 20, 15 [x]
Executive functioning	1290, 30, 29 [E]	8180, 40, 36 [A]	19300, 40, 37 [w]	482, 20, 8 [x]
Intellectual functioning	2490, 30, 22 [E]	3610, 30, 26 [A]	13000, 30, 20 [w]	500, 20, 10 [x]
Information processing speed	1010, 30, 24 [L]	5780, 30, 27 [L]	26200, 30, 28 [L]	477, 10, 4 [L]
Memory	4750, 30, 27 [E]	20900, 50, 47 [A]	122000, 50, 49 [w]	2100, 20, 17 [x]
Verbal	3290, 30, 25 [E]	8390, 40, 38 [A]	23300, 30, 25 [w]	487, 20, 13 [x]
Psychotomimetic	797, 20, 13 [E]	1910, 20, 11 [A]	12400, 30, 22 [w]	568, 20, 13 [x]
Sensory processing	1510, 30, 29 [E]	5640, 30, 30 [A]	65900, 30, 28 [w]	624, 20, 9 [x]
Auditory processing	919, 30, 28 [E]	4370, 50, 49 [A]	30900, 40, 35 [w]	358, 20, 12 [x]
Dissociation	1550, 30, 25 [E]	6310, 30, 24 [A]	49000, 30, 22 [w]	1080, 20, 16 [x]
Emotional processing	2130, 30, 29 [E]	8430, 50, 47 [A]	26600, 40, 39 [w]	674, 20, 16 [x]
Interoception	261, 30, 21 [E]	915, 30, 18 [A]	2360, 20, 4 [w]	143, 20, 13 [x]
Olfaction	587, 20, 7 [E]	3930, 20, 10 [A]	20300, 20, 12 [w]	490, 20, 7 [x]
Sensorimotor processing	324, 20, 15 [E]	1640, 30, 24 [A]	15000, 30, 26 [w]	168, 10, 0 [x]
Time perception	6410, 20, 16 [E]	16300, 20, 16 [A]	44800, 20, 14 [A]	1600, 20, 19 [C]
Visual processing	2010, 30, 29 [E]	7020, 50, 49 [A]	63400, 50, 45 [w]	761, 20, 18 [x]
Sex	3530, 20, 17 [E]	20500, 30, 23 [A]	107000, 30, 25 [u]	1370, 20, 16 [x]
Sleep	3330, 20, 19 [E]	14000, 50, 45 [A]	61500, 30, 20 [u]	1530, 20, 15 [x]
Social interaction	5550, 20, 15 [E]	18500, 50, 45 [A]	46600, 30, 28 [u]	1750, 20, 18 [x]
Personality Change	3280, 30, 29 [F]	10900, 30, 27 [F]	16900, 30, 25 [F]	887, 30, 26 [F]
Clinical Research	5330, 30, 25 [F]	32900, 30, 28 [F]	328000, 40, 32 [F]	3630, 30, 27 [F]
ADHD treatment	427, 20, 3 [F]	5730, 20, 19 [F]	8970, 20, 17 [F]	475, 20, 8 [F]
Adolescents	2480, 20, 18 [C]	14300, 30, 15 [C]	25300, 20, 10 [C]	1010, 10, 3 [C]
Aging	1090, 30, 16 [c]	8840, 30, 22 [c]	78200, 20, 10 [c]	738, 20, 9 [b]
Antisocial personality disorder	265, 20, 9 [g]	2860, 20, 7 [d]	2250, 10, 1 [e]	175, 20, 2 [b]
Anxiety	3960, 30, 26 [g]	21300, 30, 19 [d]	67200, 30, 17 [e]	2290, 30, 17 [b]
Social anxiety	3420, 30, 20 [g]	15700, 20, 15 [d]	32000, 20, 12 [e]	1500, 20, 13 [b]

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Topic Keyword	Ayahuasca	MDMA	Ketamine	Ibogaine
Autism	451, 20, 3 [c]	3290, 20, 13 [c]	13500, 30, 16 [c]	444, 20, 5 [b]
Bipolar disorder	714, 20, 18 [g]	6240, 20, 5 [d]	30000, 80, 66 [e]	598, 20, 11 [b]
Body dysmorphic disorder	36, 10, 5 [d]	317, 20, 5 [d]	1160, 10, 1 [d]	33, 10, 1 [d]
Borderline personality disorder	304, 20, 14 [g]	2020, 20, 10 [g]	3020, 20, 6 [g]	163, 10, 4 [g]
Children	4760, 20, 5 [b]	18900, 20, 7 [b]	115000, 20, 4 [b]	1370, 20, 7 [b]
Cluster Headaches	497, 10, 5 [g]	1760, 20, 5 [c]	5970, 20, 9 [d]	301, 10, 2 [b]
Couples therapy	1340, 10, 4 [g]	4410, 50, 22 [d]	16000, 10, 4 [e]	501, 20, 6 [b]
Death Anxiety	2690, 20, 15 [g]	12200, 20, 6 [d]	27100, 20, 12 [e]	1300, 20, 16 [b]
Depression treatment	3820, 40, 34 [g]	22900, 30, 19 [d]	135000, 100, 86 [e]	2780, 30, 23 [b]
Eating disorders	1550, 20, 13 [d]	7210, 20, 5 [d]	19300, 20, 12 [d]	744, 20, 9 [d]
Epilepsy	1,110, 20, 16 [C]	5590, 20, 6 [C]	36900, 40, 33 [C]	924, 20, 16 [C]
Family therapy	2650, 20, 18 [g]	13000, 20, 11 [d]	75200, 10, 5 [e]	2690, 20, 16 [b]
Grief	790, 20, 11 [g]	1230, 30, 12 [g]	2130, 30, 18 [g]	165, 10, 5 [g]
Group Therapy	3290, 20, 20 [g]	17400, 20, 18 [d]	186000, 20, 8 [e]	3620, 20, 14 [b]
Healthy normals	115, 20, 7 [g]	498, 20, 15 [d]	2260, 30, 23 [e]	53, 20, 2 [b]
Immunomodulation	210, 30, 15 [b]	2170, 20, 14 [b]	18900, 20, 11 [b]	242, 20, 8 [b]
Microdosing	217, 20, 11 [g]	241, 20, 16 [d]	862, 20, 7 [e]	78, 20, 6 [b]
Obsessive compulsive disorder	835, 20, 17 [g]	4390, 20, 8 [d]	10100, 30, 25 [e]	592, 20, 4 [b]
Pain Management	1460, 20, 7 [d]	9450, 20, 1 [d]	73500, 20, 10 [e]	1190, 20, 16 [d]
Post traumatic stress disorder	1750, 20, 17 [g]	21,400, 30, 18 [d]	29700, 30, 26 [e]	1160, 20, 10 [b]
Psychotherapy	2910, 20, 19 [g]	6590, 50, 37 [d]	9710, 30, 19 [e]	1070, 30, 20 [b]
Review	9080, 40, 28 [f]	40300, 50, 29 [c]	309000, 50, 25 [d]	3870, 30, 26 [b]
Schizophrenia treatment	1860, 20, 18 [g]	10900, 20, 15 [d]	40100, 20, 8 [e]	1310, 20, 14 [b]
Sexuality	1190, 20, 2 [b]	3230, 20, 9 [b]	3390, 20, 6 [b]	1260, 20, 7 [b]
Homosexuality	795, 20, 4 [b]	2600, 20, 2 [b]	1120, 20, 2 [b]	103, 20, 4 [b]
Somatization disorder	895, 20, 16 [C]	3990, 20, 12 [C]	14400, 20, 14 [C]	1980, 20, 15 [C]
Substance use disorder treatment	3930, 50, 47 [g]	23,900, 20, 10 [d]	51800, 30, 24 [e]	4060, 40, 35 [b]
Alcoholism	2320, 30, 24 [g]	14300, 20, 9 [d]	13900, 20, 10 [e]	1800, 20, 12 [b]
Tobacco cessation	397, 20, 13 [g]	3240, 20, 8 [d]	5080, 10, 1 [e]	631, 20, 8 [b]
Tourette syndrome	81, 10, 0 [C]	1160, 10, 4 [C]	3720, 20, 9 [C]	199, 10, 0 [C]

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Topic Keyword	Ayahuasca	MDMA	Ketamine	Ibogaine
Traumatic brain injury treatment	2130, 10, 9 [C]	10100, 10, 6 [C]	51500, 30, 25 [C]	1350, 10, 6 [C]
Risk	5630, 30, 24 [C]	32500, 30, 20 [C]	197000, 30, 11 [C]	2650, 30, 28 [C]
Abuse potential	3430, 20, 18 [p]	28300, 20, 13 [n]	44000, 20, 11 [q]	2800, 20, 18 [o]
Accidental injury	755, 10, 0 [p]	5260, 20, 8 [n]	12000, 20, 13 [q]	305, 10, 1 [o]
Astrogliosis	63, 10, 4 [C]	1140, 20, 17 [C]	9670, 20, 7 [C]	143, 20, 8 [C]
Cardiovascular risk	972, 20, 17 [p]	10300, 20, 14 [n]	72200, 20, 13 [q]	935, 20, 19 [o]
Chromosome damage	355, 10, 6 [p]	1810, 10, 5 [n]	19300, 20, 9 [q]	289, 10, 4 [o]
Cystitis	90, 10, 0 [q]	371, 10, 5 [q]	5880, 20, 14 [q]	46, 10, 2 [q]
Developmental risk	4390, 20, 16 [p]	20500, 20, 14 [n]	54500, 20, 16 [q]	2220, 20, 18 [o]
Fatality	447, 20, 10 [p]	5870, 20, 15 [p]	10300, 20, 6 [q]	399, 20, 19 [p]
Overdose	1250, 20, 15 [p]	11300, 20, 11 [p]	58700, 20, 10 [q]	926, 20, 19 [p]
Flashbacks	687, 10, 5 [p]	2720, 20, 14 [n]	2340, 20, 16 [q]	231, 10, 5 [o]
Harm reduction	2440, 10, 7 [r]	13000, 20, 6 [r]	22900, 20, 13 [q]	871, 10, 7 [r]
Hallucinogen persisting perception disorder	1830, 20, 17 [p]	9840, 20, 16 [n]	4120, 20, 16 [q]	771, 10, 7 [o]
Hyponatremia	55, 10, 0 [p]	1590, 20, 15 [o]	4260, 10, 0 [q]	35, 10, 2 [o]
Induced psychosis	2310, 20, 20 [p]	10900, 20, 17 [o]	26400, 20, 19 [q]	1310, 20, 20 [o]
Interactions	4520, 20, 15 [p]	21600, 20, 17 [n]	177000, 30, 25 [r]	3810, 20, 18 [o]
Long-term risk	2620, 20, 18 [p]	19600, 20, 13 [n]	103000, 20, 16 [r]	1670, 20, 18 [o]
Mania	739, 10, 10 [p]	2960, 20, 14 [n]	8520, 20, 15 [r]	477, 20, 11 [o]
Negative experiences	4680, 10, 7 [p]	19200, 20, 12 [n]	23100, 20, 14 [r]	1620, 20, 18 [o]
Bad trip	1750, 20, 9 [p]	2890, 20, 7 [o]	2180, 20, 10 [r]	486, 20, 15 [o]
Nystagmus	107, 10, 6 [r]	1500, 10, 8 [r]	6340, 10, 6 [r]	98, 10, 2 [r]
Paralysis	810, 20, 6 [L]	2410, 30, 26 [L]	32900, 30, 23 [L]	413, 20, 14 [L]
Parkinson's	1250, 20, 11 [C]	4300, 20, 6 [C]	24400, 20, 10 [C]	1230, 10, 3 [C]
Psychiatric risk	2910, 20, 17 [p]	20900, 20, 12 [o]	44000, 20, 19 [r]	1780, 20, 16 [p]
Respiratory depression	776, 20, 16 [p]	7080, 10, 6 [o]	52000, 20, 11 [r]	920, 20, 18 [o]
Rhabdomyolysis	118, 10, 6 [p]	2860, 20, 15 [o]	4810, 20, 9 [r]	87, 10, 2 [p]
Safety	3350, 20, 15 [p]	19100, 20, 17 [r]	132000, 20, 18 [r]	1980, 20, 20 [r]
Seizure	1690, 20, 8 [p]	7040, 20, 8 [o]	42600, 20, 19 [r]	1310 , 20, 17 [p]
Serotonin syndrome	1080, 20, 18 [p]	11100, 20, 14 [o]	28400, 10, 5 [r]	1440, 20, 20 [p]
Sexual dysfunction	706, 10, 8 [r]	8350, 10, 7 [r]	29700, 10, 8 [r]	682, 10, 8 [r]
Sexual misconduct	68, 10, 2 [p]	451, 10, 1 [o]	281, 10, 1 [r]	26, 10, 0 [p]

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Topic Keyword	Ayahuasca	MDMA	Ketamine	Ibogaine
Suicide	1660, 20, 16 [p]	9160, 20, 5 [o]	19800, 20, 19 [r]	820, 20, 13 [p]
Temperature dysregulation	103, 10, 8 [p]	1900, 20, 19 [o]	20200, 10, 8 [r]	177, 10, 2 [p]
Teratogen	113, 10, 8 [p]	1140, 20, 11 [o]	5540, 20, 11 [r]	120, 10, 0 [o]
Toxicity	1770, 20, 17 [p]	18200, 20, 19 [o]	112000, 20, 18 [r]	2950, 30, 27 [p]
Violence	4980, 20, 10 [p]	13200, 10, 2 [o]	15500, 20, 14 [r]	849, 10, 0 [p]

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Table 49

Superscripts for Literature Search Dates

Superscript	Search Date	Superscript	Search Date
a	2/29/20	A	5/18/20
b	3/13/20	B	5/19/20
c	3/14/20	C	5/20/20
d	3/15/20	D	5/23/20
e	3/22/20	E	5/24/20
f	3/23/20	F	5/25/20
g	3/24/20	G	6/2/20
h	3/31/20	H	6/3/20
i	4/8/20	I	6/4/20
j	4/10/20	J	6/5/20
k	4/11/20	K	6/9/20
l	4/12/20	L	6/10/20
m	4/14/20		
n	4/17/20		
o	4/20/20		
p	4/21/20		
q	4/22/20		
r	4/27/20		
s	5/4/20		
t	5/5/20		
u	5/6/20		
v	5/9/20		
w	5/11/20		
x	5/12/20		
y	5/13/20		
z	5/14/20		

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Appendix B: Literature Organization, Inclusion, and Exclusion

Table 50 tallies the total number of results found relevant to each respective combination of topic and psychedelic. Results are listed in the form "# / #" to indicate first the number of relevant articles and second the number of articles excluded after closer inspection. For instance, "3 / 1" would indicate three relevant and included articles and one article that met exclusion criteria after closer review. The following abbreviations are used in the table:

- \- No research found/null
- NS Not searched
- X Excluded

Table 50

Literature Organization, Inclusion, and Exclusion

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
0. History (NS)	3 / 6	3 / 14	2 / 5	-	3 / 17	3 / 6	1 / 0	1 / 3
3. Pharmacology								
General	1 / 16	1 / 21	1 / 16	3 / 20	3 / 8	3 / 26	5 / 25	7 / 7
Endogenous (excluded)	NS	NS	NS	X / 10	NS	NS	NS	NS
Metabolics (excluded)	X / 19	X / 16	X / 4	X / 11	-	X / 5	-	-
Pharmacokinetics	0 / 3	2 / 3	0 / 6	0 / 10	2 / 6	3 / 16	3 / 15	3 / 5
Acetylcholine	3 / 3	4 / 0	-	1 / 0	-	5 / 2	2 / 20	3 / 3
Cortisol	2 / 0	3 / 0	-	-	1 / 0	4 / 8	3 / 8	2 / 0
Dopamine	2 / 10	3 / 22	3 / 0	4 / 1	1 / 0	7 / 41	7 / 28	6 / 21
Epinephrine	3 / 12	5 / 6	3 / 2	1 / 1	-	3 / 4	3 / 4	-
GABA	1 / 0	1 / 2	-	-	1 / 0	2 / 2	3 / 12	-
Glutamate	2 / 2	5 / 6	3 / 3	1 / 0	-	3 / 9	3 / 39	3 / 9
Opioid receptors	-	-	-	3 / 0	0 / 1	2 / 1	4 / 7	1 / 4
Oxytocin	-	-	-	-	-	11 / 8	0 / 1	-
Serotonin	3 / 22	6 / 50	3 / 15	2 / 21	2 / 6	15 / 76	13 / 4	1 / 8
Animal behavior (excluded)	X / 53	X / 64	X / 21	X / 39	X / 8	X / 62	X / 52	X / 16
Metabolism (excluded)	X / 4	X / 5	-	-	-	X / 9	X / 25	X / 4

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
4. Neuroscience								
General	1 / 3	0 / 5	0 / 3	0 / 3	1 / 3	1 / 0	2 / 3	-
Neurons	0 / 10	0 / 7	0 / 2	0 / 2	-	1 / 0	0 / 11	-
Neuroplasticity	-	3 / 2	3 / 0	1 / 1	2 / 0	14 / 3	11 / 17	5 / 0
Neuroprotection	-	-	-	2 / 2	1 / 0	-	4 / 30	-
Gene expression (excluded)	X / 2	X / 10	X / 1	X / 1	-	X / 28	X / 53	X / 3
Neuroimaging								
Entropic brain	-	10 / 6	11 / 5	-	1 / 1	-	2 / 9	-
Connectome harmonics	-	3 / 4	1 / 2	-	-	-	-	-
EEG (excluded)	X / 14	X / 26	X / 14	X / 5	X / 9	X / 11	X / 40	X / 3
Functional connectivity, acute/subacute (excluded)	-	X / 26	X / 21	-	X / 7	X / 4	X / 38	-
Localized neuroimaging (excluded)	X / 6	X / 6	X / 14	X / 6	X / 7	X / 8	X / 36	X / 1
Long-term brain change (excluded)	X / 1	X / 2	X / 2	X / 1	X / 1	X / 27	X / 15	-
Affective Neuroscience								
Emotional processing	X / 1	X / 7	X / 13	X / 2	X / 3	X / 23	X / 10	-
Fear	0 / 7	2 / 7	3 / 3	0 / 4	0 / 1	3 / 8	7 / 14	1 / 0
Gut Microbiome	0 / 1	1 / 1	1 / 0	-	1 / 0	1 / 2	4 / 2	1 / 0

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Sensory processing (semi-excluded)								
General	1 / 3	2 / 4	1 / 3	0 / 2	1 / 2	0 / 2	-	-
Auditory	0 / 5	1 / 10	0 / 4	0 / 10	1 / 3	2 / 9	0 / 31	-
Visual	1 / 10	8 / 26	6 / 16	1 / 5	2 / 6	3 / 8	6 / 10	-
Olfaction & taste	1 / 0	1 / 0	1 / 0	-	-	1 / 0	5 / 9	-
Sensorimotor	0 / 4	6 / 7	2 / 1	0 / 4	0 / 1	4 / 8	2 / 12	1 / 0
Dissociation	2 / 0	2 / 1	0 / 1	0 / 5	-	1 / 1	6 / 7	-
Interoception	-	-	-	0 / 1	-	1 / 2	1 / 4	-
Sexuality & reproduction	1 / 1	2 / 0	-	-	-	4 / 5	2 / 0	3 / 0
Dreaming (semi-excluded)	1 / 6	6 / 8	5 / 4	3 / 4	2 / 1	1 / 0	1 / 5	-
Sleep (excluded)	X / 2	X / 15	X / 3	X / 4	X / 1	X / 30	X / 14	X / 1
Learning & memory (excluded)	X / 9	X / 11	X / 8	X / 4	X / 7	X / 50	X / 57	X / 4
5. Medical Risks								
General	1 / 6	6 / 11	3 / 4	3 / 3	0 / 5	6 / 10	3 / 7	3 / 7
Fatality	3 / 0	3 / 1	5 / 0	1 / 0	2 / 2	X / 20	X / 10	3 / 2
Hazardous drug interactions	X / 28	X / 31	X / 4	X / 21	X / 5	X / 52	X / 76	X / 14
Serotonin syndrome	0 / 1	2 / 1	1 / 0	-	-	4 / 7	-	-
Toxicity & neurotoxicity	5 / 5	2 / 4	3 / 3	1 / 1	3 / 4	20 / 112	7 / 27	8 / 8
Long-term risk	-	0 / 2	-	-	1 / 4	15 / 43	8 / 6	-

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Alzheimer's	NS	NS	NS	NS	NS	NS	1 / 0	NS
Apoptosis	NS	NS	NS	NS	NS	NS	3 / 1	NS
Astrogliosis	-	-	-	-	-	5 / 2	1 / 0	2 / 0
Cardiovascular	3 / 0	6 / 2	6 / 1	-	1 / 0	20 / 3	5 / 14	13 / 2
Chromosome damage	1 / 2	2 / 29	-	-	1 / 0	1 / 0	3 / 0	-
Headaches	NS	NS	1 / 0	NS	NS	NS	NS	NS
Hyponatremia	-	-	-	-	-	14 / 2	-	-
Cystitis	-	-	-	-	-	1 / 0	3 / 22	-
Nystagmus	2 / 0	2 / 0	2 / 0	-	-	1 / 0	2 / 2	-
Oxidative stress	NS	NS	NS	NS	NS	2 / 0	NS	NS
Paralysis	0 / 1	1 / 0	-	-	-	2 / 0	-	-
Parkinson's	-	-	-	-	-	4 / 3	-	0 / 1
Pneumomediastinum & pneumatosis	NS	NS	NS	NS	NS	2 / 0	NS	NS
Respiratory depression	1 / 0	2 / 1	-	0 / 2	-	1 / 1	4 / 7	-
Rhabdomyolysis	1 / 0	1 / 0	1 / 0	1 / 0	1 / 1	10 / 0	1 / 1	-
Seizure	1 / 3	6 / 0	1 / 0	-	1 / 0	5 / 0	1 / 2	3 / 1
Coma	NS	1 / 0	NS	NS	NS	NS	NS	NS
Temperature dysregulation	-	3 / 3	0 / 1	-	0 / 2	23 / 23	-	-
Teratogenicity	6 / 0	4 / 18	2 / 0	1 / 0	6 / 1	3 / 20	6 / 9	1 / 0

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Developmental risk	0 / 1	3 / 2	-	-	4 / 4	6 / 21	6 / 21	-
Sexual dysfunction	1 / 0	2 / 0	1 / 0	-	1 / 0	8 / 6	5 / 1	-
Aging	1 / 1	6 / 2	4 / 2	1 / 1	2 / 1	1 / 1	7 / 2	-
6. Phenomenology								
Reviews	-	0 / 1	-	-	-	1 / 0	1 / 0	-
IPA	-	-	2 / 0	-	1 / 0	1 / 0	-	1 / 0
Thematic analysis	1 / 0	1 / 0	2 / 0	2 / 0	6 / 0	2 / 1	1 / 0	3 / 0
Narrative (excluded)	X / 4	X / 7	X / 3	X / 3	X / 8	X / 2	X / 5	X / 2
Quantitative	1 / 0	3 / 10	6 / 4	5 / 2	1 / 2	11 / 5	11 / 3	-
Psychotomimetic	9 / 5	11 / 20	6 / 5	4 / 10	0 / 1	2 / 1	18 / 72	-
Dream-like	1 / 0	2 / 0	1 / 0	1 / 0	1 / 0	1 / 0	1 / 0	1 / 0
Ego-dissolution	1 / 1	1 / 3	2 / 2	1 / 1	1 / 2	-	0 / 1	1 / 0
Out-of-body	-	-	-	-	-	-	1 / 0	-
Time perception	1 / 0	5 / 1	3 / 4	-	1 / 0	-	2 / 2	1 / 0
Purging	NS	NS	NS	NS	1 / 1	NS	NS	NS
Negative experiences	4 / 4	5 / 12	8 / 3	3 / 4	1 / 2	2 / 1	2 / 6	-
Empathy	-	1 / 0	3 / 1	-	-	7 / 3	-	-
Social interaction	0 / 4	3 / 5	1 / 3	0 / 4	-	10 / 28	0 / 4	-
Spirituality, mysticism, & religion	1 / 3	3 / 13	12 / 13	6 / 9	4 / 14	5 / 1	2 / 2	1 / 0

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
7. Psychological Change								
Personality Change	8 / 2	20 / 13	20 / 3	6 / 4	17 / 6	5 / 1	4 / 1	-
Healthy normals	-	0 / 3	0 / 1	1 / 2	2 / 2	-	1 / 0	-
Rorschach	0 / 2	3 / 0	-	-	-	-	-	-
8. Neuropsychology & Cognition								
General	2 / 0	1 / 3	-	-	4 / 1	6 / 12	-	-
Cognition	-	4 / 0	2 / 0	-	2 / 0	5 / 21	11 / 5	1 / 0
Intellectual functioning	-	4 / 2	-	0 / 1	-	0 / 3	1 / 0	-
Attention	-	5 / 2	3 / 3	-	-	4 / 5	3 / 2	1 / 0
Memory	-	5 / 0	3 / 0	-	2 / 0	17 / 37	18 / 2	1 / 0
Executive functions	-	1 / 0	1 / 0	-	3 / 0	6 / 15	4 / 0	-
Verbal Processing	-	5 / 1	1 / 1	-	1 / 0	2 / 3	5 / 0	-
Psychomotor & Processing Speed	-	4 / 0	1 / 0	-	-	1 / 4	2 / 0	-
Creativity (excluded)	X / 7	X / 9	X / 9	-	X / 3	-	-	-
9. Psychological Risks								
Psychiatric risk	4 / 0	3 / 1	2 / 0	-	4 / 0	12 / 32	4 / 1	-
Suicide	2 / 0	5 / 0	3 / 0	-	-	2 / 2	2 / 0	-
Violence	5 / 9	7 / 10	7 / 2	2 / 3	3 / 0	7 / 4	11 / 1	-
Accidental injury	-	1 / 0	-	-	-	4 / 3	6 / 0	1 / 0

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Abuse potential	1 / 4	2 / 7	3 / 2	2 / 0	3 / 3	7 / 18	9 / 21	-
Flashbacks	2 / 1	5 / 15	1 / 0	0 / 1	-	2 / 0	1 / 1	-
Hallucinogen persisting perception disorder (HPPD)	2 / 1	9 / 20	4 / 2	-	-	3 / 1	1 / 0	1 / 0
Psychosis	3 / 2	13 / 14	2 / 1	2 / 2	2 / 1	2 / 7	3 / 1	1 / 0
Mania	-	2 / 0	-	-	1 / 0	-	11 / 4	1 / 0
Therapy abuse	-	-	-	-	1 / 0	4 / 0	1 / 0	-
10. Factors Influencing Psychedelic Experience								
Personality-dependence	-	8 / 1	12 / 1	-	2 / 0	1 / 1	5 / 2	-
Sex differences	-	2 / 0	0 / 1	0 / 1	-	7 / 16	9 / 21	1 / 0
11. Psychedelic-Assisted Therapies								
Dose	2 / 14	3 / 12	4 / 4	2 / 4	0 / 1	1 / 9	2 / 4	-
Safety	1 / 0	2 / 0	2 / 0	2 / 0	2 / 2	1 / 0	3 / 16	1 / 2
Harm reduction	-	-	-	-	0 / 1	13 / 12	3 / 4	-
Psychotherapy	5 / 3	14 / 25	3 / 5	-	4 / 4	11 / 11	3 / 1	1 / 4
Group therapy	-	10 / 1	5 / 1	1 / 0	4 / 2	1 / 0	-	1 / 0
Couples therapy	-	0 / 1	1 / 1	-	-	8 / 4	-	-
Family therapy	-	-	-	-	-	-	-	-
Microdosing	X / 1	X / 28	X / 14	X / 1	-	X / 1	X / 1	-

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
12. Treatment Indications								
Reviews	1 / 2	3 / 4	1 / 9	1 / 5	1 / 8	0 / 6	1 / 3	0 / 1
Children & adolescents	1 / 1	10 / 1	1 / 1	-	1 / 0	1 / 0	11 / 22	-
Organic Disorders (excluded)								
Cancer	NS	NS	NS	NS	X / 1	NS	NS	NS
Epilepsy	X / 3	X / 6	X / 2	X / 3	-	X / 1	X / 44	-
Headaches	-	X / 9	X / 2	X / 3	-	-	X / 6	-
Immunomodulation	X / 1	X / 7	X / 1	X / 7	X / 3	X / 19	X / 21	X / 7
Pain Management	X / 1	X / 5	X / 3	X / 2	X / 3	X / 1	X / 58	X / 2
Parkinson's disease	-	-	X / 1	X / 1	X / 10	X / 1	X / 11	-
Tourette syndrome	-	X / 1	X / 1	-	-	-	X / 1	-
Traumatic brain injury	-	X / 1	-	X / 1	-	X / 3	X / 17	-
Developmental Conditions								
ASD	-	11 / 1	1 / 1	-	-	3 / 4	5 / 0	-
ADHD	-	0 / 1	-	-	1 / 0	-	-	-
Schizophrenia	5 / 2	8 / 4	-	1 / 0	1 / 0	1 / 0	4 / 3	-
Anxiety Disorders								
Anxiety	0 / 2	7 / 5	2 / 7	4 / 0	3 / 8	3 / 2	3 / 10	-
Social anxiety	-	-	-	-	-	2 / 1	1 / 1	-

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Compulsive Disorders								
OCD	2 / 1	9 / 6	5 / 3	-	-	-	4 / 16	-
Eating disorders	1 / 0	3 / 1	3 / 1	1 / 1	3 / 2	1 / 2	2 / 0	-
Body dysmorphic disorder	-	4 / 1	3 / 0	-	-	1 / 0	2 / 0	-
Depression								
Treatment	-	7 / 12	8 / 14	4 / 1	6 / 14	2 / 0	27 / 85	-
Suicidality	3 / 0	2 / 0	4 / 0	1 / 0	4 / 1	2 / 0	2 / 22	-
Neuroscience (excluded)	NS	X / 1	X / 9	X / 2	X / 5	NS	X / 42	NS
Social defeat stress model (excluded)	-	-	-	-	-	-	X / 9	-
ECT (excluded)	-	-	-	-	-	-	X / 12	-
Animal models (excluded)	-	X / 1	X / 3	X / 2	X / 3	-	X / 11	-
Bipolar disorder	-	2 / 0	-	1 / 0	-	-	13 / 19	-
PTSD	0 / 1	4 / 3	1 / 1	0 / 1	2 / 0	19 / 18	11 / 25	-
Somatization disorder	-	2 / 2	-	-	0 / 1	-	-	-
Substance Use Disorders								
General	3 / 3	2 / 5	2 / 6	1 / 1	9 / 26	3 / 2	2 / 3	6 / 20
Alcohol use disorder	4 / 2	6 / 20	3 / 3	2 / 0	2 / 1	2 / 1	6 / 4	4 / 1
Opioid use disorder (NS)	NS	4 / 0	1 / 0	1 / 0	NS	1 / 0	3 / 2	7 / 14

Table 50

Literature Organization, Inclusion, and Exclusion, Continued

Topic	Mescaline	LSD	Psilocybin	DMT	Ayahuasca	MDMA	Ketamine	Ibogaine
Stimulant use disorders (NS)	NS	NS	NS	NS	1 / 1	NS	5 / 0	3 / 9
Tobacco cessation	1 / 0	1 / 0	4 / 1	1 / 0	1 / 1	-	-	1 / 0
Personality Disorders								
Antisocial personality disorder	2 / 1	9 / 1	8 / 2	0 / 2	3 / 0	7 / 7	2 / 0	-
Borderline personality disorder	2 / 0	3 / 0	1 / 0	1 / 0	2 / 0	-	4 / 5	-
Sexual disorders	2 / 0	12 / 2	2 / 0	1 / 6	4 / 1	2 / 1	1 / 2	-
End-of-Life Care								
Death anxiety & palliative care	0 / 1	13 / 4	6 / 14	1 / 0	-	1 / 0	2 / 9	-
Grief	-	-	-	1 / 0	3 / 0	-	2 / 1	1 / 0

Note. Headings are bolded and italicized for clarity.

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Appendix C: Treatment Planning Worksheet

(See following page)

Treatment Planning Worksheet for Psychedelic-Assisted Therapy

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Patient Name: _____ Clinician: _____

Age: _____ Date: _____

	Mesc.	LSD	Psil.	DMT	Aya.	MDMA	Ket.	Ibog.	Notes
1. Medical Risk Factors	List any medical risk factors present. Mark X if a psychedelic is contraindicated, / if precautions need to be taken, and ? if more information is needed.								
Age:									
Neurodev Dx:									
2. Drug/Med. Interactions	List all current medications. Mark X if there is a dangerous interaction, / if there is an interaction that needs to be considered, and ? If more information is needed.								
3. Psych. Risk Factors	List developmental factors. Mark X if psychedelic is contraindicated, / if considerations need to be made, and ? If more information is needed.								
4. Summarize Risk	Look down each column. Choose most severe mark ordered: X, /, ?. If none put ✓.								

Patient Name: _____ Date: _____

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	Mesc.	LSD	Psil.	DMT	Aya.	MDMA	Ket.	Ibog.	Notes
5. Presenting Problem(s)	List presenting problems. Mark ++ for indication, + for provisional indication, ⊖ if caution needed, X if contraindicated, and ? for more info. needed.								
6. Influencing Factors	List known patient traits that impact psychedelic experience and outcomes. Note impacts relevant to different psychedelic treatment options.								
Sex/Gender:									
7. Rank Treatment Options	Copy risk summary from page 1. For ranking, put an X for any medically contraindicated psychedelic. Rank order psychedelic treatment options based on presenting problems, psychedelic therapy indications, and personality factors.								
Risk Summary (p. 1):									
Ranking:									

	Notes Regarding Treatment Options
#1:	
#2:	
#3:	

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Appendix D: Abbreviations

Organizations

DEA: The United States Drug Enforcement Agency

FDA: The U.S. Food and Drug Administration

MAPS: The Multi-Disciplinary Association for Psychedelic Studies

UDV: União do Vegetal

U.S.: The United States

Research Methods and Statistical Reporting

RCT: Randomized controlled trial

aOR: Adjusted odds ratio

N/C: No change

N/R: Not reported

NS: Not significant; referring to statistical significance

OR: Odds ratio

SD: Standard deviation

wOR: Weighted odds ratio

Drugs

5-HT: 5-hydroxytryptamine

18-MC: 18-methoxycoronaridine

5-MeO-DMT: 5-methoxy-*N,N*-dimethyltryptamine

CGS: 2-[p-(2-carboxyethyl) phenethylamino]-5'-*N*-ethylcarboxamido adenosine

DLH: *D,L*-homocysteic acid, a potent NMDA receptor agonist

DMT: *N,N*-Dimethyltryptamine

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DOI: *2,5*-Dimethoxy-*4*-iodoamphetamine

LSD: Lysergic-acid diethylamide

MAOI: Monoamine oxidase inhibiter

MDMA: 3,4-methylenedioxymethamphetamine

SSRI: Selective serotonin reuptake inhibitor

Drug Administration

IV: Intravenous

IM: Intramuscular

IN: Intranasal

IP: Intraperitoneal

SC: Subcutaneously

Neurotransmitters, Receptors, and Transporters

5-HT: Serotonin

5-HT$_x$: Serotonin receptor *x*

ACh: Acetylcholine

AChE: Acetylcholinesterase enzyme

cAMP: Cyclic adenosine monophosphate

DA: Dopamine

D$_x$: Dopamine receptor X [1-5]

DAT: Dopamine transporter

GABA: Gamma aminobutyric acid

GAT: Glutamate transporter

Glu: Glutamate

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nAChR: Nicotinic acetylcholine receptors

mAChR: Muscarinic acetylcholine receptor

MAO: Monoamine oxidase

NE: Norepinephrine

NET: Norepinephrine transporter

NMDA: *N*-methyl-D-aspartate

PCP: Phencyclidine receptor

SERT: Serotonin transporter

TAAR: Trace amine-associated receptor

Neuroanatomy

[B]: Prefix specifying bilateral (e.g., "[B]ACC")

[L]: Prefix specifying left hemisphere (e.g., "[L]ACC")

[R]: Prefix specifying right hemisphere (e.g., "[R]ACC")

ACC: Anterior cingulate cortex

AI: Anterior insula

Amg: Amygdala

AUD: Auditory network

BA#: Broadmann area (BA), followed by identifying number (#)

dmPFC: Dorsomedial prefrontal cortex

dlPFC: Dorsolateral prefrontal cortex

DMN: Default mode network

dmPFC: Dorsomedial prefrontal cortex

DRN: Dorsal raphe nucleus

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FC: Functional connectivity

FO: Frontal operculum

flPFC: Frontolateral prefrontal cortex

FPN: Frontoparietal network, also known as central executive network (CEN) or the lateral frontoparietal network (L-FPN).

Hipp: Hippocampus

lFP: Left frontoparietal network

LGN: Lateral geniculate nucleus

LH: Left hemisphere

mPFC: Medial prefrontal cortex

mTL: Medial temporal lobe

NA: Nucleus accumbens

PAR: Parietal cortex network

PCC: Posterior cingulate cortex

PFC: Prefrontal cortex

PHG: Parahippocampal cortex

PHG: Parahippocampal gyrus

PI: Posterior insula

POP: Posterior opercular network

rFP: Right frontoparietal network

RH: Right hemisphere

SN: Substantia nigra

SM: Sensorimotor

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TL: Temporal lobe

TPN: Task-positive network

V1: Primary visual cortex

VC: Visual cortex

VisO: Occipital pole network

VisL: Lateral visual network

vmPFC: Ventral medial prefrontal cortex

vlPFC: Ventral lateral prefrontal cortex, also known as the inferior frontal gyrus.

VTA: Ventral tegmental area

Neuroimaging

DTI: Diffusion tensor imaging

fMRI: Functional magnetic resonance imagery

EEG: Electroencephalogram

BOLD: Blood-oxygen-level-dependent imaging

LORETA: Low-resolution electromagnetic tomography

PET: Positron emission tomography

RSFC: Resting-state functional connectivity

SPECT: Single-photon emission computed tomography

Psychological and Neuropsychological Measures

5D-ASC: 5-Dimension Altered States of Consciousness Rating Scale

11D-ASC: 11-Dimension Altered States of Consciousness Rating Scale

ASPIRES: Assessment of Spirituality and Religious Sentiments Scale

BDI: Beck Depression Inventory

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BEES: Balanced Emotional Empathy Scale

BFI: Big Five Inventory

BPRS: Brief Psychiatric Rating Scale

CADSS: Clinician-Administered Dissociative States Scale

CANTAB: Cambridge Neuropsychological Test Automated Battery

CAPS: Clinician-Administered PTSD Scale

CEQ: Challenging Experience Questionnaire

CIIS: Creative Imagination Scale

CPI: California Psychological Inventory

DASS: Depression, Anxiety, and Stress Scale

DASS-21: Depression, Anxiety, and Stress Scale, 21-item version

DERS: Difficulties in Emotion Regulation Scale

DES: Dissociative Experiences Scale

DPES: Dispositional Positive Emotion Scale

DSES: Daily Spiritual Experience Scale

DTS: Death Transcendence Scale

EETS: Emotional Empathic Tendency Scale

EPI: Eysenck's Personality Inventory

ES: Empowerment Scale

FFMQ: Five Facet Mindfulness Questionnaire

FFMQ-SF: Five Facet Mindfulness Questionnaire–Short Form

FMS: Faith Maturity Scale

FQ: Fear Questionnaire

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GQ-6: Gratitude Questionnaire, Six Item Form

HADS: Hospital Anxiety and Depression Scale

HAM-A: Hamilton Anxiety Scale

HAM-D: Hamilton Depression Scale

HS: Hope Scale

HVLT: Hopkins Verbal Learning Test

IOS: Inclusion of Others in the Self scale

IRIC: Interpersonal Reactivity Index for Couples

IVE: Impulsiveness, Venturesomeness, and Empathy questionnaire

LAP-R: Life Attitude Profile–Revised

LCI-R: Life Changes Inventory, Revised

LOT-R: Revised Life Orientation Test

LSI: Plutchik's Life Style Index

MAAS: Mindfulness Questionnaire Mindful Attention Awareness Scale

MEQ: Pahnke-Richards Mystical Experience Questionnaire

MET: Multifaceted Empathy Test

MMPI: Minnesota Multiphasic Personality Inventory

MMPI-2: Minnesota Multiphasic Personality Inventory, Second Edition

MADRS: Montgomery-Åsberg Depression Rating Scale

MODTAS: Modified Tellegen Absorption Scale

MPI: Eysenck's Maudsley Personality Inventory

MRS: Mood Rating Scale

MS: The Mysticism Scale

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MQL: McGill Quality of Life survey

NR-6: Nature Relatedness Scale, Short Form (6-item)

NEO-FFI: NEO Five-Factor Inventory

NEO-PI: NEO Personality Inventory

NEO-PI-R: Revised NEO Personality Inventory

OAV: Altered States of Consciousness Rating Scale

O-LIFE: Oxford-Liverpool Inventory of Feelings and Experiences

PANAS-X: Positive and Negative Affect Schedule–Expanded Form

PCET: Penn Conditional Exclusion Test

PCT: Picture Concept Task

PDI: Peter's Delusion Inventory

PDS-P: Paranoid Depression Scale

PEP: Psychiatric Evaluation Profile

PEQ: Persisting Effects Questionnaire

PHLMS: Philadelphia Mindfulness Scale

POI: Personal Orientation Inventory

POMS: Profile of Mood States

RBMT: Rivermead Behavioral Memory Test

RMHI: Rand Mental Health Inventory

ROCFT: Rey-Osterrieth Complex Figure Test

SCL-90-R: Symptom Checklist-90-Revised

SOC: Stockings of Cambridge

SOCQ: States of Consciousness Questionnaire

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SOI: Spiritual Orientation Inventory

SSQ: Schizotypal Symptomatology Questionnaire

SSR: Scale of Social Responsibility

SVO: Social Value Orientation

STAI: Spielberger Trait Anxiety Inventory

SWBS: Spiritual Well-Being Scale

TAS: Tellegen Absorption Scale

TFS: Trait Forgiveness Scale

TCI: Temperament and Character Inventory

TCI-R: Temperament and Character Inventory-Revised

TMT-A: Trail Making Test Part A

TMT-B: Trail Making Test Part B

TPQ: Tridimensional Personality Questionnaire

WAIS: Wechsler Adult Intelligence Scale (First Edition)

WAIS-[II/III/IV]: Wechsler Adult Intelligence Scale, [Second/Third/Fourth] Edition

WAIS-R: Wechsler Adult Intelligence Scale Revised

WCST: Wisconsin Card Sorting Test

WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

WISC: Wechsler Intelligence Scale for Children

WMS: Wechsler Memory Scale

WPPSI: Wechsler Preschool and Primary Scale of Intelligence

YBOCS: Yale-Brown Obsessive Compulsive Scale.

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YMRS: Young Mania Rating Scale

Diagnostic Abbreviations

ADHD: Attention-deficit hyperactivity disorder

ASD: Autism spectrum disorder

DIP: Drug-induced psychosis

GAD: Generalized anxiety disorder

NOP: Naturally occurring psychosis

OCD: Obsessive-compulsive disorder

MDD: Major depressive disorder

PTSD: Post-traumatic stress disorder

TRD: Treatment-resistant depression

Therapeutic Techniques

CBT: Cognitive behavioral therapy

ECT: Electroconvulsive therapy

MDMA-PT: MDMA-assisted psychotherapy