Selected references regarding therapeutic benefits of various psychedelic compounds
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Aday, J. S., et al. (2020). "Long-term effects of psychedelic drugs: A systematic review." Neurosci Biobehav Rev. **113:179-189.**(doi): 10.1016/j.neubiorev.2020.1003.1017. Epub 2020 Mar 1016.

Research into the basic effects and therapeutic applications of psychedelic drugs has grown considerably in recent years. Yet, pressing questions remain regarding the substances' lasting effects. Although individual studies have begun monitoring sustained changes, no study to-date has synthesized this information. Therefore, this systematic review aims to fill this important gap in the literature by synthesizing results from 34 contemporary experimental studies which included classic psychedelics, human subjects, and follow-up latencies of at least two weeks. The bulk of this work was published in the last five years, with psilocybin being the most frequently administered drug. Enduring changes in personality/attitudes, depression, spirituality, anxiety, wellbeing, substance misuse, meditative practices, and mindfulness were documented. Mystical experiences, connectedness, emotional breakthrough, and increased neural entropy were related to these long-term changes in psychological functioning. Finally, with proper screening, preparation, supervision, and integration, limited aversive side effects were noted by study participants. Future researchers should focus on including larger and more diverse samples, lengthier longitudinal designs, stronger control conditions, and standardized dosages.

Andersen, K. A. A., et al. (2021). "Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies." Acta Psychiatr Scand. **143**(2): 101-118. doi: 110.1111/acps.13249. Epub 12020 Dec 13241.

OBJECTIVE: To conduct a systematic review of modern-era (post-millennium) clinical studies assessing the therapeutic effects of serotonergic psychedelics drugs for mental health conditions. Although the main focus was on efficacy and safety, study characteristics, duration of antidepressants effects across studies, and the role of the subjective drug experiences were also reviewed and presented. METHOD: A systematic literature search (1 Jan 2000 to 1 May 2020) was conducted in PubMed and PsychINFO for studies of patients undergoing treatment with a serotonergic psychedelic. RESULTS: Data from 16 papers, representing 10 independent psychedelic-assisted therapy trials (psilocybin = 7, ayahuasca = 2, LSD = 1), were extracted, presented in figures and tables, and narratively synthesized and discussed. Across these studies, a total of 188 patients suffering either cancer- or illness-related anxiety and depression disorders (C/I-RADD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD) or substance use disorder (SUD) were included. The reviewed studies established feasibility and evidence of safety, alongside promising early data of efficacy in the treatment of depression, anxiety, OCD, and tobacco and alcohol use disorders. For a majority of patients, the therapeutic effects appeared to be long-lasting (weeks-months) after only 1 to 3 treatment session(s). All studies were conducted in line with guidelines for the safe conduct of psychedelic therapy, and no severe adverse events were reported. CONCLUSION: The resurrection of clinical psychedelic research provides early evidence for treatment efficacy and safety for a range of psychiatric conditions, and constitutes an exciting new treatment avenue in a health area with major unmet needs.

Arkell, T. R., et al. (2022). "Effects of psychotropic drugs on ocular parameters relevant to traffic safety: A systematic review." Neurosci Biobehav Rev. **141:104831.**(doi): 10.1016/j.neubiorev.2022.104831. Epub 102022 Aug 104820.

Driving is a complex neurobehavioural task necessitating the rapid selection, uptake, and processing of visual information. Eye movements that are critical for the execution of visually

guided behaviour such as driving are also sensitive to the effects of psychotropic substances. The Embase (via Ovid), EBSCOHost, Psynet, Pubmed, Scopus and Web of Science databases were examined from January 01st, 2000 to December 31st, 2021. Study selection, data extraction and Cochrane Risk of Bias (RoB2) assessments were conducted according to PRISMA guidelines. The review was prospectively registered (CRD42021267554). In total, 36 full-text articles examined the effects of six principal psychotropic drug classes on measures of oculomotor parameters relevant to driving. Centrally depressing substances affect oculomotor responses in a dose-dependent manner. Psychostimulants improve maximal speed, but not accuracy, of visual search behaviours. Inhaled Δ-9-tetrahydrocannabinol (THC) increases inattention (saccadic inaccuracy) but does not consistently affect other oculomotor parameters. Alterations to composite ocular parameters due to psychoactive substance usage likely differently compromises performance precision during driving through impaired ability to select and process dynamic visual information.

Bilbao, A. and R. Spanagel (2022). "Medical cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications." BMC Med. **20**(1): 259. doi: 210.1186/s12916-12022-02459-12911.

BACKGROUND: Medical cannabinoids differ in their pharmacology and may have different treatment effects. We aimed to conduct a pharmacology-based systematic review (SR) and meta-analyses of medical cannabinoids for efficacy, retention and adverse events. METHODS: We systematically reviewed (registered at PROSPERO: CRD42021229932) eight databases for randomized controlled trials (RCTs) of dronabinol, nabilone, cannabidiol and nabiximols for chronic pain, spasticity, nausea /vomiting, appetite, ALS, irritable bowel syndrome, MS, Chorea Huntington, epilepsy, dystonia, Parkinsonism, glaucoma, ADHD, anorexia nervosa, anxiety, dementia, depression, schizophrenia, PTSD, sleeping disorders, SUD and Tourette. Main outcomes and measures included patient-relevant/disease-specific outcomes, retention and adverse events. Data were calculated as standardized mean difference (SMD) and ORs with confidence intervals (CI) via random effects. Evidence quality was assessed by the Cochrane Risk of Bias and GRADE tools. RESULTS: In total, 152 RCTs (12,123 participants) were analysed according to the type of the cannabinoid, outcome and comparator used, resulting in 84 comparisons. Significant therapeutic effects of medical cannabinoids show a large variability in the grade of evidence that depends on the type of cannabinoid. CBD has a significant therapeutic effect for epilepsy (SMD - 0.5[CI - 0.62, - 0.38] high grade) and Parkinsonism (- 0.41[CI - 0.75, - 0.08] moderate grade). There is moderate evidence for dronabinol for chronic pain (- 0.31[CI - 0.46, - 0.15]), appetite (- 0.51[CI - 0.87, - 0.15]) and Tourette (- 1.01[CI - 1.58, - 0.44]) and moderate evidence for nabiximols on chronic pain (- 0.25[- 0.37, - 0.14]), spasticity (- 0.36[CI - 0.54, - 0.19]), sleep (- 0.24[CI - 0.35, - 0.14]) and SUDs (- 0.48[CI - 0.92, - 0.04]). All other significant therapeutic effects have either low, very low, or even no grade of evidence. Cannabinoids produce different adverse events, and there is low to moderate grade of evidence for this conclusion depending on the type of cannabinoid. CONCLUSIONS: Cannabinoids are effective therapeutics for several medical indications if their specific pharmacological properties are considered. We suggest that future systematic studies in the cannabinoid field should be based upon their specific pharmacology.

Breeksema, J. J., et al. (2020). "Psychedelic Treatments for Psychiatric Disorders: A Systematic Review and Thematic Synthesis of Patient Experiences in Qualitative Studies." CNS Drugs. **34**(9): 925-946. doi: 910.1007/s40263-40020-00748-y.

INTRODUCTION: Interest in the use of psychedelic substances for the treatment of mental disorders is increasing. Processes that may affect therapeutic change are not yet fully understood. Qualitative research methods are increasingly used to examine patient accounts; however,

currently, no systematic review exists that synthesizes these findings in relation to the use of psychedelics for the treatment of mental disorders. OBJECTIVE: To provide an overview of salient themes in patient experiences of psychedelic treatments for mental disorders, presenting both common and diverging elements in patients' accounts, and elucidating how these affect the treatment process. METHODS: We systematically searched the PubMed, MEDLINE, PsycINFO, and Embase databases for English-language qualitative literature without time limitations. Inclusion criteria were qualitative research design; peer-reviewed studies; based on verbalized patient utterances; and a level of abstraction or analysis of the results. Thematic synthesis was used to analyze and synthesize results across studies. A critical appraisal of study quality and methodological rigor was conducted using the Critical Appraisal Skills Programme (CASP). RESULTS: Fifteen research articles, comprising 178 patient experiences, were included. Studies exhibited a broad heterogeneity in terms of substance, mental disorder, treatment context, and qualitative methodology. Substances included psilocybin, lysergic acid diethylamide (LSD), ibogaine, ayahuasca, ketamine and 3,4-methylenedioxymethamphetamine (MDMA). Disorders included anxiety, depression, eating disorders, post-traumatic stress disorder, and substance use disorders. While the included compounds were heterogeneous in pharmacology and treatment contexts, patients reported largely comparable experiences across disorders, which included phenomenological analogous effects, perspectives on the intervention, therapeutic processes and treatment outcomes. Comparable therapeutic processes included insights, altered self-perception, increased connectedness, transcendental experiences, and an expanded emotional spectrum, which patients reported contributed to clinically and personally relevant responses. CONCLUSIONS: This review demonstrates how qualitative research of psychedelic treatments can contribute to distinguishing specific features of specific substances, and carry otherwise undiscovered implications for the treatment of specific psychiatric disorders.

Campos, D. A., et al. (2022). "A Systematic Review of Medical Cannabinoids Dosing in Human." Clin Ther. **44**(12): e39-e58. doi: 10.1016/j.clinthera.2022.1010.1003. Epub 2022 Nov 1018.

PURPOSE: This systematic review assesses currently available clinical information on which cannabinoids and what range of doses have been used to achieve positive effects in a diversity of medical context. METHODS: The data were collected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol guidelines. Inclusion criteria were articles that assessed administration of any cannabinoid to any clinical population, reported in the ClinicalTrials.gov or PubMed databases, that involved a comparison with other treatment or placebo and a result measurement to assess the effectiveness or ineffectiveness of the cannabinoid. Exclusion criteria were review or letter; articles not in the English language; not full-text articles; not a clinical trial, case report, case series, open-label trial, or pilot study; administration in animals, in vitro, or in healthy participants; cannabinoids administered in combination with other cannabinoids (except for cannabidiol [CBD] or tetrahydrocannabinol [THC]) or as whole cannabis extracts; no stated concentration; inhalation or smoke as a route of administration; and no results described. The articles were assessed by the risk of bias. FINDING: In total, 1668 articles were recovered, of which 55 studies met the inclusion criteria for 21 diseases. Positive effects were reported in clinical studies: 52% with THC (range, 0.01-0.5 mg/kg/d [0.62-31 mg/d]), 74% with CBD (range, 1-50 mg/kg/d [62-3100 mg/d]), 64% with THC-CBD (mean, 1:1.3 mg/kg/d [ratio, 1:1]), and 100% with tetrahydrocannabivarin (THCV) (0.2 mg/kg/d). IMPLICATIONS: THC, CBD, and THCV can regulate activity in several pathologies. New studies of cannabinoids are highly encouraged because each patient is unique and requires a unique cannabinoid medication.

Haikazian, S., et al. (2023). "Psilocybin-assisted therapy for depression: A systematic review and meta-analysis." Psychiatry Res. **329:115531.**(doi): 10.1016/j.psychres.2023.115531. Epub 112023 Oct 115511.

The aim of this review was to determine the effect of psilocybin on depressive symptoms in patients diagnosed with life-threatening illnesses or major depressive disorder. Systematic searches were conducted to search for randomized clinical trials and open-label trials that evaluated depression symptoms after psilocybin therapy. Data was pooled using a random-effects model. The primary outcome was the standardized mean difference (SMD) in depression severity, determined by calculating the change in depression ratings from baseline to the primary endpoint in the psilocybin arm versus the control arm. The literature search yielded 1734 studies, and 13 studies (n = 686) were included in either qualitative and/or quantitative analyses. The meta-analysis included 9 studies (pooled n = 596) and yielded a large effect size in favour of psilocybin (SMD = -0.78; p<0.001). Risk ratios for response and remission were large and significant in favour of psilocybin. A review of open-label trials showed robust decreases in depressive symptoms following psilocybin administration. These findings provide preliminary evidence for antidepressant efficacy with psilocybin-assisted psychotherapy, however, further studies are needed to evaluate safety and efficacy and to optimize treatment protocols.

Hovmand, O. R., et al. (2023). "Risk of bias in randomized clinical trials on psychedelic medicine: A systematic review." J Psychopharmacol. **37**(7): 649-659. doi: 610.1177/02698811231180276. Epub 02698811231182023 Jul 02698811231180274.

BACKGROUND: The classical psychedelics, psilocybin, peyote, ayahuasca/N,N-dimethyltryptamine, and lysergic acid diethylamide are considered promising new treatments for psychiatric illnesses, such as depression, anxiety, addiction, and obsessive-compulsive disorders. However, their profound and characteristic subjective effects raise concern for distinctive biases in randomized clinical trials. METHODS: We performed a systematic literature search to identify all clinical trials on classical psychedelics with patient populations to examine descriptive data and determine the risk of bias. Two independent reviewers searched three databases (PubMed, Embase, and APA PsycNet) and extracted information on study design, study population, use of active or inactive placebo, dropouts, evaluation of blinding of intervention, and reporting of expectancy and therapeutic alliance. RESULTS: We included 10 papers reporting on 10 unique trials. The trials generally included populations that were predominantly white and highly educated. The trials had small samples and considerable dropout. Blinding was either unsuccessful or not reported regardless of type of placebo. Few trials published protocols, statistical analysis plans (SAPs), and outcomes relating to psychotherapy fidelity. All trials but one were rated as high risk of bias. CONCLUSION: Successful blinding of intervention is a significant challenge in this field. To better accommodate this, we suggest that future trials use a parallel-group design and utilize an active placebo on a psychedelic-naïve population. Future trials should publish trial protocol and SAPs, use clinician-rated outcomes accessed by a blinded rater, evaluate blinding of intervention, and consider measuring expectancy and therapeutic fidelity.

Ko, K., et al. (2023). "Psychedelic therapy for depressive symptoms: A systematic review and meta-analysis." J Affect Disord. **322:194-204.**(doi): 10.1016/j.jad.2022.1009.1168. Epub 2022 Oct 1017.

BACKGROUND: Psychedelic therapy shows promise for Major Depressive Disorder, especially when treatment-resistant, as well as life-threatening illness distress. The objective of this systematic review, inclusive of meta-analysis, is to examine recent clinical research on the therapeutic effects of classic psychedelics on depressive symptoms. METHODS: Fourteen psychedelic therapy studies, utilising psilocybin, ayahuasca, or LSD, were systematically reviewed. For the meta-analysis, standardised mean differences were calculated for seven randomised

controlled trials. RESULTS: The systematic review indicated significant short- and long-term reduction of depressive symptoms in all conditions studied after administration of psilocybin, ayahuasca, or LSD, with psychological support. In the meta-analysis, symptom reduction was significantly indicated in three timepoints out of four, including 1-day, 1-week, and 3-5 weeks, supporting the results of the systematic review, with the exception of the 6-8 weeks follow-up point which was less conclusive. LIMITATIONS: The absence of required data for 2 studies necessitated the less precise use of graphical extraction and imputation. The small sample size in all but one study negatively affected the statistical power. None of the studies had long-term follow-up without also utilising the cross-over method, which did not allow for long-term results to be included in the meta-review. CONCLUSIONS: This review indicates an association between psychedelic therapy and significant reduction of depressive symptoms at several time points. However, the small number of studies, and low sample sizes, calls for careful interpretation of results. This suggests the need for more randomised clinical trials of psychedelic therapy, with larger and more diverse samples.

Ledwos, N., et al. (2023). "Therapeutic uses of psychedelics for eating disorders and body dysmorphic disorder." J Psychopharmacol. **37**(1): 3-13. doi: 10.1177/02698811221140009. Epub 02698811221142022 Dec 02698811221140014.

BACKGROUND: Clinical use of psychedelics has gained considerable attention, with promising benefits across a range of mental disorders. Current pharmacological and psychotherapeutic treatments for body dysmorphic disorder (BDD) and eating disorders (EDs) have limited efficacy. As such, other treatment options such as psychedelic-assisted therapies are being explored in these clinical groups. AIMS: This systematic review evaluates evidence related to the therapeutic potential of psychedelics in individuals diagnosed with BDD and EDs. METHODS: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we conducted a systematic review of all study designs published to the end of February 2022 that identified changes in ED/BDD symptom severity from psychedelics using validated measures to assess symptom changes. RESULTS: Our search detected a total of 372 studies, of which five met inclusion criteria (two exploratory studies, two case reports, and one prospective study). These were included in the data evaluation. Effects of psychedelics on BDD and various ED symptoms were identified mostly through thematic analyses and self-reports. CONCLUSIONS: Our findings highlight that more research is needed to determine the safety and efficacy of psychedelics in BDD and EDs and we suggest avenues for future exploration.

Linguiti, S., et al. (2023). "Functional imaging studies of acute administration of classic psychedelics, ketamine, and MDMA: Methodological limitations and convergent results." Neurosci Biobehav Rev. **154:105421.**(doi): 10.1016/j.neubiorev.2023.105421. Epub 102023 Oct 105425.

Functional magnetic resonance imaging (fMRI) is increasingly used to non-invasively study the acute impact of psychedelics on the human brain. While fMRI is a promising tool for measuring brain function in response to psychedelics, it also has known methodological challenges. We conducted a systematic review of fMRI studies examining acute responses to experimentally administered psychedelics in order to identify convergent findings and characterize heterogeneity in the literature. We reviewed 91 full-text papers; these studies were notable for substantial heterogeneity in design, task, dosage, drug timing, and statistical approach. Data recycling was common, with 51 unique samples across 91 studies. Fifty-seven studies (54%) did not meet contemporary standards for Type I error correction or control of motion artifact. Psilocybin and LSD were consistently reported to moderate the connectivity architecture of the sensorimotor-association cortical axis. Studies also consistently reported that ketamine administration increased

activation in the dorsomedial prefrontal cortex. Moving forward, use of best practices such as pre-registration, standardized image processing and statistical testing, and data sharing will be important in this rapidly developing field.

Ona, G. and J. C. Bouso (2020). "Potential safety, benefits, and influence of the placebo effect in microdosing psychedelic drugs: A systematic review." Neurosci Biobehav Rev. **119:194-203.**(doi): 10.1016/j.neubiorev.2020.1009.1035. Epub 2020 Oct 1015.

Microdosing psychedelic drugs-that is, taking sub-behavioral doses of lysergic acid diethylamide (LSD) or psilocybin-is a growing practice in Western societies. Taken mainly for creative or mood-enhancing purposes, thousands of users are increasingly being exposed to (micro)doses of psychedelic drugs. In this systematic review, we searched the available evidence from human studies, focusing our results in terms of three main axes: efficacy, safety, and the influence of the placebo effect in microdosing practices. While the available evidence has some strengths (e.g. large sample sizes, robust methodologies) there are also remarkable limitations (e.g. gender bias, heterogeneity of dosing schedules and drugs used). Highly contradictory results have been found, showing both the benefits and detriments of microdosing in terms of mood, creative processes, and energy, among other regards. This review provides a general overview of the methods and approaches used, which could be useful for improving future studies.

Polito, V. and P. Liknaitzky (2022). "The emerging science of microdosing: A systematic review of research on low dose psychedelics (1955-2021) and recommendations for the field." Neurosci Biobehav Rev. **139:104706.**(doi): 10.1016/j.neubiorev.2022.104706. Epub 102022 May 104721.

The use of low doses of psychedelic substances (microdosing) is attracting increasing interest. This systematic review summarises all empirical microdosing research to date, including a set of infrequently cited studies that took place prior to prohibition. Specifically, we reviewed 44 studies published between 1955 and 2021, and summarised reported effects across six categories: mood and mental health; wellbeing and attitude; cognition and creativity; personality; changes in conscious state; and neurobiology and physiology. Studies showed a wide range in risk of bias, depending on design, age, and other study characteristics. Laboratory studies found changes in pain perception, time perception, conscious state, and neurophysiology. Self-report studies found changes in cognitive processing and mental health. We review data related to expectation and placebo effects, but argue that claims that microdosing effects are largely due to expectancy are premature and possibly wrong. In addition, we attempt to clarify definitional inconsistencies in the microdosing literature by providing suggested dose ranges across different substances. Finally, we provide specific design suggestions to facilitate more rigorous future research.

Rodrigues, L. S., et al. (2022). "Effects of ayahuasca and its alkaloids on substance use disorders: an updated (2016-2020) systematic review of preclinical and human studies." Eur Arch Psychiatry Clin Neurosci. **272**(4): 541-556. doi: 510.1007/s00406-00021-01267-00407. Epub 02021 Apr 00429.

Ayahuasca is a hallucinogenic/psychedelic traditionally used for ritual and therapeutic purposes. One such therapeutic use is related to Substance Use Disorders (SUDs). A previous systematic review of preclinical and human studies published until 2016 suggested that ayahuasca and its alkaloids have therapeutic effects in the treatment of SUDs. To conduct an update of this previous review. A systematic review of quantitative studies which analyzed the effects of ayahuasca and its alkaloids on drug use (primary outcome) and other measures (secondary outcomes) related to SUDs was conducted, including articles from 2016 to 2020. Nine studies (four preclinical, five observational) were included in the review. Preclinical studies in rodents reported reductions in amphetamine self-administration and anxiety, and in alcohol- and methylphenidate-induced

conditioned place preference. Observational studies among healthy ritual ayahuasca users and patients with SUDs reported reductions in drug use, anxiety, and depression, and increases in quality of life and well-being. We replicated the findings of the previous review suggesting that ayahuasca and its alkaloids have therapeutic effects in the treatment of SUDs. However, translation of preclinical data to humans is limited, observational studies do not allow us to infer causality, and there is a lack of standardization on ayahuasca doses. Although promising, randomized, controlled trials are needed to better elucidate these results. The PROSPERO ID for this study is CRD42020192046.

Rosenblat, J. D., et al. (2023). "The Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Report: Serotonergic Psychedelic Treatments for Major Depressive Disorder." Can J Psychiatry. **68**(1): 5-21. doi: 10.1177/07067437221111371. Epub 07067437221112022 Aug 07067437221111317.

OBJECTIVE: Serotonergic psychedelics are re-emerging as potential novel treatments for several psychiatric disorders including major depressive disorder. The Canadian Network for Mood and Anxiety Treatments (CANMAT) convened a task force to review the evidence and provide a consensus recommendation for the clinical use of psychedelic treatments for major depressive disorder. METHODS: A systematic review was conducted to identify contemporary clinical trials of serotonergic psychedelics for the treatment of major depressive disorder and cancer-related depression. Studies published between January 1990 and July 2021 were identified using combinations of search terms, inspection of bibliographies and review of other psychedelic reviews and consensus statements. The levels of evidence for efficacy were graded according to the Canadian Network for Mood and Anxiety Treatments criteria. RESULTS: Only psilocybin and ayahuasca have contemporary clinical trials evaluating antidepressant effects. Two pilot studies showed preliminary positive effects of single-dose ayahuasca for treatment-resistant depression (Level 3 evidence). Small randomized controlled trials of psilocybin combined with psychotherapy showed superiority to waitlist controls and comparable efficacy and safety to an active comparator (escitalopram with supportive psychotherapy) in major depressive disorder, with additional randomized controlled trials showing efficacy specifically in cancer-related depression (Level 3 evidence). There was only one open-label trial of psilocybin in treatment-resistant unipolar depression (Level 4 evidence). Small sample sizes and functional unblinding were major limitations in all studies. Adverse events associated with psychedelics, including psychological (e.g., psychotomimetic effects) and physical (e.g., nausea, emesis and headaches) effects, were generally transient. CONCLUSIONS: There is currently only low-level evidence to support the efficacy and safety of psychedelics for major depressive disorder. In Canada, as of 2022, psilocybin remains an experimental option that is only available through clinical trials or the special access program. As such, Canadian Network for Mood and Anxiety Treatments considers psilocybin an experimental treatment and recommends its use primarily within clinical trials, or, less commonly, through the special access program in rare, special circumstances.

Schimmers, N., et al. (2022). "Psychedelics for the treatment of depression, anxiety, and existential distress in patients with a terminal illness: a systematic review." Psychopharmacology (Berl). **239**(1): 15-33. doi: 10.1007/s00213-00021-06027-y. Epub 02021 Nov 00223.

BACKGROUND: Terminally ill patients may experience existential distress, depression, or anxiety, limiting quality of life in the final stage. Existing psychotherapeutic or pharmacological interventions have (time) limited efficacy. Psychedelic treatment may be a safe and effective alternative treatment option. AIM: Systematically review studies on psychedelic treatment with and without psychotherapy for existential distress, depression, and anxiety in terminally ill patients. METHODS: Medline, PsycINFO, and Embase were searched for original-data studies on

the treatment of depression, anxiety, and existential distress with classical or a-typical psychedelics in patients with a terminal illness, using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. RESULTS: A total of 1850 records were screened, and 33 articles were included in this review: 14 studies on classical psychedelics (DPT, LSD, and psilocybin) and 19 studies on atypical psychedelics (MDMA and ketamine). Results of early pre-post studies are promising but have serious methodological flaws. Recent (controlled) trials with LSD, psilocybin, ketamine, and MDMA are of higher methodological quality and indicate positive effects on existential and spiritual well-being, quality of life, acceptance, and reduction of anxiety and depression with few adverse and no serious adverse effects. CONCLUSIONS: Both classical and a-typical psychedelics are promising treatment options in patients with terminal illness. To draw final conclusions on effectiveness and safety of psychedelics, we need larger high-quality studies for classical psychedelics and MDMA. Ketamine studies should pay more attention to existential dimensions of well-being and the psychotherapeutic context of the treatment.

Sharma, R., et al. (2023). "Psychedelic Treatments for Substance Use Disorder and Substance Misuse: A Mixed Methods Systematic Review." J Psychoactive Drugs. **55**(5): 612-630. doi: 610.1080/02791072.02792023.02190319. Epub 02792023 Mar 02791018.

Renewed interest in psychedelic substances in the 21(st) century has seen the exploration of psychedelic treatments for various psychiatric disorders including substance use disorder (SUD). This review aimed to assess the effectiveness of psychedelic treatments for people with SUD and those falling below diagnostic thresholds (i.e. substance misuse). We systematically searched 11 databases, trial registries, and psychedelic organization websites for empirical studies examining adults undergoing psychedelic treatment for SUD or substance misuse, published in the English language, between 2000 and 2021. Seven studies investigating treatment using psilocybin, ibogaine, and ayahuasca, alone or adjunct with psychotherapy reported across 10 papers were included. Measures of abstinence, substance use, psychological and psychosocial outcomes, craving, and withdrawal reported positive results, however, this data was scarce among studies examining a wide range of addictions including opioid, nicotine, alcohol, cocaine and unspecified substance. The qualitative synthesis from three studies described subjective experience of psychedelic-assisted treatments enhanced self-awareness, insight, and confidence. At present, there is no sufficient research evidence to suggest effectiveness of any of the psychedelics on any specific substance use disorder or substance misuse. Further research using rigorous effectiveness evaluation methods with larger sample sizes and longer-term follow-up is required.

Smith, K. W., et al. (2022). "MDMA-Assisted Psychotherapy for Treatment of Posttraumatic Stress Disorder: A Systematic Review With Meta-Analysis." J Clin Pharmacol. **62**(4): 463-471. doi: 410.1002/jcph.1995. Epub 2021 Nov 1028.

This article discusses current literature on the use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD). MDMA, the intended active ingredient in illicit Ecstasy or Molly products, is a psychedelic that causes an elevated mood, feeling of bonding, and increased energy. In MDMA-assisted psychotherapy, patients are subjected to 2 or 3 multihour sessions of therapy with a team of psychiatrists. The dosing of MDMA is used to allow the therapist to probe the underlying trauma without causing emotional distress. The use of MDMA-assisted psychotherapy treatment reduced patient's Clinician-Administered PTSD Scale (CAPS) scores from baseline more than control psychotherapy (-22.03; 95%CI, -38.53 to -5.52) but with high statistical heterogeneity. MDMA-assisted psychotherapy enhanced the achievement of clinically significant reductions in CAPS scores (relative risk, 3.65; 95%CI, 2.39-5.57) and CAPS score reductions sufficient to no longer meet the

definition of PTSD (relative risk, 2.10; 95%CI, 1.37-3.21) with no detected statistical heterogeneity. While therapy was generally safe and well tolerated, bruxism, anxiety, jitteriness, headache, and nausea are commonly reported. While MDMA-assisted psychotherapy has been shown to be an effective therapy for patients with PTSD with a reasonable safety profile, use of unregulated MDMA or use in the absence of a strongly controlled psychotherapeutic environment has considerable risks.

van Amsterdam, J. and W. van den Brink (2022). "The therapeutic potential of psilocybin: a systematic review." Expert Opin Drug Saf. **21**(6): 833-840. doi: 810.1080/14740338.14742022.12047929. Epub 14742022 Mar 14740332.

INTRODUCTION: Psychedelic drugs were used quite extensively before their prohibition in 1968 which delayed research. However, since the 1990s, studies on the potential therapeutic benefits of psychedelics have rapidly increased. AREAS COVERED: This systematic review provides an overview of the clinical effects of psilocybin in the treatment of a variety of mental disorders. Only (randomized) clinical trials were selected. A total of 11 studies (15 publications) were selected, including seven randomized controlled trials (eight publications) and four single arm open-label studies (seven publications). In total, 488 patients were included in the selected studies: 333 patients treated with psilocybin and 155 patients treated with (active) placebo. In nine studies, psychotherapeutic support was provided as an integral part of the psilocybin treatment. The findings of these studies collectively show that psilocybin has a positive benefit-risk balance in the treatment of various mental disorders with an immediate and prolonged effect following 1-3 doses of psilocybin and a few (serious) adverse events. EXPERT OPINION: Psilocybin - mostly combined with psychotherapy or psychotherapeutic support - shows a promise as a treatment for various (treatment-resistant) mental disorders. Larger double-blind RCTs with objective (long-term) outcomes are needed to confirm these findings before standard clinical use of psilocybin can be considered.