Psychedelics, Safety and Clinical Trial Design

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Abstract:

Objectives: To investigate the safety of psychedelics for humans, to identify the limitations of the current evidence and to indicate how gaps and limitations may be addressed in future clinical trial design. **Methodology:** I completed a narrative review of the literature to investigate the safety profile and known adverse effects of psychedelics, with a specific focus on psilocybin and magic mushrooms. **Results:** Psychedelics can be accompanied by known adverse experiences, such as increased heart rate, blood pressure and breathing rate, headaches, and transient psychological distress. For some people, negative effects persist for days or weeks, usually depending on how long the transient distress lasts. Evidence for the empirical validation of Hallucinogen Persisting Perception Disorder (HPPD) is scant, and the diagnosis itself has come into question. The risks of negative experiences can be reduced by appropriate dosage, setting, preparation and support, as well as by not taking multiple doses or combining with other substances. Some medications do not mix well with psychedelics, including many anti-depressants. Psychedelics can be healing and beneficial, but they are powerful and often involve an ordeal, like many journeys. Clinical trials investigating psychedelics have established exclusion criteria to ensure appropriate subject selection and provide significant preparation, support and a setting to mitigate the known risks. Trials using psychedelics have established safety, tolerability and suggest efficacy; however, stage 3 clinical trials to establish effectiveness through a randomized control methodology are just now beginning. **Conclusion:** Psychedelics are relatively safe, with a low toxicity and risk profile; however, certain adverse experiences such as transient psychological distress and post-treatment headaches are common, and in some cases can be severe and persisting. Risks are mitigated through appropriate candidate selection, preparation, setting and support. The scientific literature is limited, and stage 3 clinical trials are needed to establish effectiveness for a wide range of potential treatment patients.

Background

There has been recent, significant increase in scientific publications concerning psychedelics. Some have proposed the combination of psychedelic dose administration with psychotherapy as a new paradigm of psychiatry (D. E. Nichols et al., 2017; Rucker et al., 2018). A recent scoping review on psilocybin-assisted therapy found that while 9 clinical trials investigating the

application of this psychedelic to a range of mental health disorders were completed between 2006 and 2016, there are currently 14 new registered psilocybin clinical trials in process, with significant increases in sample size (Shore et al. pre-pub, 2019). Psilocybin has recently been granted breakthrough therapy designation in the U.S. and U.K, and trials are now in stage 3 of regulatory drug approval processes (Rucker et al., 2018).

Psychedelics are categorized by their shared subjective experience of a significantly altered state of consciousness with profound alterations in perception, cognition and mood (Calvey & Howells, 2018; Rucker et al., 2018; Sellers et al., 2018; Studerus et al., 2011). Though originating in diverse chemical families, the various psychedelics demonstrate cross-tolerance, produce markedly similar effects in both animals and humans, and are understood to have common metabolic pathways, effecting common anatomical regions of the brain (Halberstadt, 2015; Sellers et al., 2018). Psychedelics share discriminative stimulative effects and selective agonism of serotonin-1 and 2 receptor subtypes. Classic psychedelics stimulate dopamine via D2 receptors and indirectly stimulate glutaminergic and GABAergic (gamma-aminobutyric acid) systems (David E Nichols, 2018). Psychedelics commonly stimulate $5HT_{2A}$ cortical layer V pyramidal neurons, triggering disruptive signalling pathways and cortical desynchronization across various key brain regions, creating a time-limited state of entropy and allowing for the loosening of rigid neurological and cognitive patterns (R. Carhart-Harris, 2016; Muthukumaraswamy et al., 2013; Rucker et al., 2018).

Psychedelics are divided into classic, and non-classic or atypical. Classic psychedelics include two structural types: indoleamines (lysergic acid diethylamide or LSD, dimethyltryptamine or DMT, and psilocybin from *Psilocybe* mushrooms) and phenylalkylamines (mescaline from peyote and modern synthetics such as the 2C-X family). Additional atypicals include dissociatives such as ketamine, entactogens such as MDMA, and the NMDA agonist and tryptamine ibogaine (Calvey & Howells, 2018; Halberstadt et al., 2017; David E Nichols, 2018; Sellers et al., 2018). This paper summarizes primarily the data concerning psilocybin, as that is the compound with the most robust recent history of clinical trial. To supplement the clinical

data pertaining to psilocybin and to ensure a comprehensive data set, the safety and risk literature on *Psilocybe* (magic) mushrooms, is also summarized.

Safety and Toxicity of Psychedelics

Serotonergic psychedelics possess relatively low physiological toxicity and have not been shown to lead to neurological deficits, organ damage or to cause genetic damage or birth defects (Gable, 2004; M. W. Johnson et al., 2008a; Strassman, 1984). Psychedelics have a low potential for abuse or dependence and have not been found to lead to compulsive drug seeking (Carbonaro et al., 2016; Johansen & Krebs, 2015; Krebs & Johansen, 2013a; Rucker et al., 2018). Animals do not reliably self-administer psychedelics (Fantegrossi et al., 2004; Rucker et al., 2016, 2018) Euphoria is not a consistent feature of the psychedelic experience, tolerance develops quickly and completely and there is no known withdrawal syndrome; psychological dependence appears to be rare with no indication of physical or psychological tolerance (Amsterdam et al., 2011; Rucker et al., 2018).

Psychedelics moderately increase pupil dilation, heart rate as well and both systolic and diastolic blood pressure and may result in transient hypertension, tachyarrhythmias and hyperthermia as well has having other physiological effects which may be considered adverse including: dizziness, weakness, impaired perception, impaired proprioception, tremors, nausea, drowsiness, paresthesia, blurred vision, dilated pupils and increased tendon reflexes (M. W. Johnson et al., 2008a; Sellers et al., 2018). Psychedelics affect time perception, synchronization and tapping tempo, and working memory which impairs driving and operation of machinery (Amsterdam et al., 2011). Other commonly reported subjective effects include visual and auditory hallucinations, synesthesia, interactions with entities/persons not physically present, past life experiences and experiences of *jamais vu.* (Carbonaro et al., 2016). Some known biologic effects of psychedelics such as increased corticotrophin, beta-endorphin, prolactin, cortisol, growth hormone, may have implications for clinical efficacy or safety after repeated dosing (Sellers et al., 2018). As well, due to the non-selective agonism of the 5HT2B receptor,

chronic microdosing may lead to ventricle heart disease, as a result of cardiac valvopathies and valvular hyperplasia (Kuypers et al., 2019).

Psychedelics are not regarded as promoting aggression or violence, dangerous behavior or suicide and accidental death under the influence of psychedelics is regarded as extremely rare (Johansen & Krebs, 2015; Krebs & Johansen, 2013a; Strassman, 1984). However, psychedelics can produce acute and (sometimes) persisting adverse psychological reactions (Johnson et al., 2008) (Strassman, 1984). Case reports document acute adverse effects of psilocybin in non-research settings including: short-term psychological distress and fear, individuals putting themselves at risk for harm, seeking medical help as well as persisting negative psychological or psychiatric problems (Carbonaro et al., 2016). Emergency room and poison control data also confirm that psilocybin ingestion is associated with seeking medical treatment; however, the incidence of psilocybin toxicity is extremely low relative to other substances used non-medically (Amsterdam et al., 2011; Carbonaro et al., 2016; Gable, 2004).

Psilocybin has peak effect on emotional excitation and sensitivity, heightened mood, and concentration in the early phase of drug metabolism (60–180min after drug intake). Effects such as dreaminess, dazed state, inactivation, and introversion were more pronounced in later phases (260–400min) (Studerus et al., 2011). Subjects tend to be more active, emotional, extroverted and cognitively impaired in the early phase of the psilocybin session relative to the later phase; derealization and depersonalization take precedence over visual hallucinations about 90–120min after drug intake. During the later phase, subjects increasingly turn inwards, appear absent-minded and show reduced facial expressions (Studerus et al., 2011).

The majority of published case reports of acute lethal toxicity due to psychedelics indicate the presence of other inebriants, most commonly alcohol (Gable, 2004). Studies which calculate safety ratios varied between various substances consistently demonstrate several hallucinogens as having the least direct physiological toxicity (Gable, 2004). The oral lethal dose (LD-50) value of psilocybin in rats is 280 mg/kg; 17 kg of fresh mushrooms (at average potency) would need

to be consumed by a human for a 50% chance of overdose(Amsterdam et al., 2011). Interactions which potentiate toxicity include alcohol and tobacco via their metabolic effect on monoamine oxidase (MAO) inhibiting enzymes (Amsterdam et al., 2011). Animals receiving doses of psilocybin exhibit dose-dependent irregularities in heart and breathing rate as well as mydriasis, piloerection, hyperglycaemia and hypertonia (Kuypers et al., 2019).

While their physiological safety is relatively well established, psychologically toxic reactions do occur, in part due to the demonstrated sensitive to context and setting found with psychedelics (Hartogsohn, 2017; Rucker et al., 2018; Strassman, 1984). Psychedelics often cause periods of confusion, disorientation, anxiety, fear, panic, dysphoria, paranoia and emotional turmoil during the immediate drug effects. Such adverse effects can last for a few days (M. W. Johnson et al., 2008b; Krebs & Johansen, 2012; Strassman, 1984). The most likely risk associated with psychedelics is the fabled commonly 'bad trip'. Distressing effects may be experienced somatically, sensorially, by the evocation of repressed psychological materials and memories, and at spiritual and metaphysical levels (M. W. Johnson et al., 2008b). In one survey of challenging psilocybin experiences (Carbonaro et al., 2016), 39% of respondents rated the experience as among the 5 most challenging experiences of their lives. Experiences of fear and paranoid delusions may lead to erratic and potentially dangerous behaviours, including aggression towards self or others (Strassman, 1984). Although very rare, in hazardous and unsupervised conditions, individuals under the influence of psychedelics have ended their lives by such acts as jumping from buildings (Gable, 2004; M. W. Johnson et al., 2008b; Strassman, 1984). Larger doses, taking larger doses than usual, alcohol and/or cannabis use associated with negative experiences (Carbonaro et al., 2016) .Younger people may also be more susceptible to adverse reactions (Strassman, 1984). Many psychedelic users report some brief visual abnormalities occurring after acute pharmacological effects wear off, but for only a small minority of users are these effects troubling or impairing enough to be considered clinically significant or warrant the diagnosis of Hallucinogen Persisting Perception Disorder, or HPPD, (M. W. Johnson et al., 2008a) and the empirical validity of the HPPD diagnosis itself has been questioned (Johansen & Krebs, 2015; Krebs & Johansen, 2012). HPPD phenomenon themselves

seem to be associated with poly drug use, preexisting psychiatric morbidities (Amsterdam et al., 2011) and other somatic symptom disorders (Johansen & Krebs, 2015; Krebs & Johansen, 2012).

Psychedelics have not been found to decrease mental health; the use of psychedelics may in fact be a protective factor associated with better mental health status (Johansen & Krebs, 2015). At population health levels, lifetime use of psilocybin or mescaline and past year LSD use were found to be associated with lower rates of serious psychological distress (Krebs & Johansen, 2013b). Lifetime psilocybin use was also significantly associated with lower rates of inpatient mental health treatment and psychiatric medication prescription, lower rates of panic attacks and lower rates of agoraphobia. No significant association was found between lifetime psychedelic use and greater risk of any negative mental health outcomes. No relation was found between lifetime use of psychedelics and any undesirable past year mental health outcomes, including serious psychological distress, mental health treatment or symptoms of panic disorder, major depressive episode, mania, social phobia, generalized anxiety disorder, agoraphobia, post- traumatic stress disorder, or non-affective psychosis. There were some associations between use of any psychedelic or use of specific psychedelics and lower rate of mental health problems (Johansen & Krebs, 2015; Krebs & Johansen, 2012).

The pharmacology of psychedelics is diverse and includes complex agonist and partial agonist/antagonist actions on 5HT2A, 5HT2C, 5HT1A, dopamine D_2, trace amine associate receptors 1 (TAAR), kappa receptors, various transporters (e.g., serotonergic, dopaminergic, norepinephrine), intracellular messengers, effects on gene expression and epigenetic regulators (Sellers et al., 2018). Such a wide range of pharmacologic mechanisms and targets raises the probability of unexpected acute and chronic off-target toxicity and an elevated risk of interactions with concurrent diseases and drugs that will vary for different psychedelics (Sellers et al., 2018).

Negative and Challenging Experiences

As part of a survey of challenging experiences after ingesting psilocybin mushrooms, 1993 individuals completed an online survey 39% of respondents rated it among the top five most challenging experiences of his or her lifetime (Carbonaro et al., 2016). Eleven percent put self or others at risk, 2.6% became physically aggressive, and 2.7% received medical help. Factors associated with increasing risk included dose, duration and difficulty of the experience, and not having social support and physical comfort. Of those whose experience occurred greater than 1 year before, a significant 7.6% sought treatment for enduring psychological symptoms. Three cases appeared associated with onset of enduring psychotic symptoms and three cases with attempted suicide. Despite difficulties, 84% endorsed benefiting from the challenging portions of their session and 34% described the experience as being among the top five meaningful experiences of their lives. 20.5% met the complete criteria of a mystical experience. The majority of participants reported that the social support and trust for others physically present (65%), physical comfort and safety of surroundings (75%), and emotional state (76%) before taking psilocybin was conducive to having a positive experience.

After the challenging session, 24% of these 1339 participants for whom one year had passed since their difficult experience reported experiencing one or more negative psychological states that lasted 1 week or longer and that the participant attributed to the chosen psilocybin session. The majority of those reporting symptoms (65%) reported more than one symptom (Carbonaro et al., 2016).

The duration of the challenging experience was positively related to the degree of difficulty of the experience and negatively related to personal meaning, spiritual significance, and enduring increased well-being. Therapeutic interventions during a challenging experience should be preferentially aimed at reducing the duration rather than the peak difficulty of the challenging experience (Carbonaro et al., 2016).

The median dose of dried psilocybin mushrooms reported was 4 g, and while there is wide variation in potency in cultivated *Psilocybe* mushrooms, 4 g of typically available dried *Psilocybe cubensis* is the approximate psychoactive equivalent to 25 mg of synthetic psilocybin, the moderate to high range of doses administered in multiple recent laboratory studies (Carbonaro et al., 2016; Roland R. Griffiths et al., 2016). Risks of harms related to psilocybin are dose-related (M. W. Johnson et al., 2008b; Studerus et al., 2010). Here, it must be pointed out that scientific trials utilize synthetic psilocybin, thought to be the primary psychoactive agent in magic mushrooms (and a prodrug to the more bioavailable psilocin), while the whole biomass of *Psilocybe* mushrooms contain an entourage of other important and potentially psychoactive compounds including psilocin, baeocystin, norbaeocystin, aerguinascin, norpsilocin and phenylethylamines, which carry an amphetamine chemical structure (Kuypers et al., 2019).

Another study which examined self-reports of negative outcomes of psilocybin users found that bad trips were more frequent in female users and are more likely to occur in unsupportive settings. The use of multiple doses of psilocybin in the same session or its combination with other substances was linked to the occurrence of long-term negative outcomes, while the use of mushrooms in single high doses was linked to medical emergencies (Bienemann et al., 2020).

A pooled analysis of acute, short- and long- term subjective effects of psilocybin in healthy humans across from eight double-blind placebo-controlled experimental studies conducted between 1999 and 2008 analyzed data from 110 healthy subjects who had received 1–4 oral doses of psilocybin (Studerus et al., 2011). Most subjects described their experience as pleasurable and enriching; acute adverse drug experiences included strong dysphoria and/or anxiety and panic but occurred only in the two highest dose conditions and only in a small proportion of subjects. All acute adverse events were managed by interpersonal support and none required urgent pharmacological intervention. Further, follow-up questionnaires indicated no subsequent drug abuse, persisting perceptual disorders, psychosis or other long-term impairments. However, twelve percent of subjects did report having experienced negative changes in psychological well-being and/or mental functioning after psilocybin. No incidences

of prolonged psychotic reactions or precipitations of schizophrenia-spectrum disorders were found in the 110 subjects studied.

High emotional excitability, younger age and being confined to brain-scan machine were the variables most associated with unpleasant or anxious reactions. Low baseline emotional excitability, high scores on the ability to experience absorption and having had few recent emotional problems were all associated with having a pleasant mystical-type experience. 22% of subjects in the high-dose condition met or exceeded the criteria for deep mystical or transcendent experiences (Studerus et al., 2011).

Drug, Set and Setting

Important for the planning of clinical trial research, results suggest that moderate doses of psilocybin given to healthy, high-functioning and well-prepared subjects in the context of a carefully monitored research environment is associated with an acceptable level of risk (Studerus et al., 2011). The high variability found within and between subjects of the pooled analysis indicate that psilocybin effects are not predicted by dose alone; other pharmacological variables such as plasma levels of psilocin, as well as non-pharmacological variables such as user expectations, personality structure, and the availability of interpersonal support, and the setting of the experience play determinant roles (Studerus et al., 2011).

Timothy Leary first identified the importance of set and setting during his psilocybin research at Harvard in the early 1960's. As Ido Hartogsohn points out, "no other group of drugs appears to be as plastic and responsive to conditions of set and setting as the psychedelics—mind-manifesting drugs whose very name points to their character as nonspecific reflectors of extra-drug conditions" (Hartogsohn, 2017).

The set and setting "hypothesis" holds that the set of the user (their expectations, mental and emotional state, psychological history) and the setting of the use (both the immediate physical setting but also the social environment and cultural values assigned to the drug) combine with

the basic potential pharmacology of the drug to together create the drug experience. The heavy influences of set and setting pose a significant challenge to modern pharmaceutical research and the prioritization of randomized controlled trials which seek to minimize, if not eliminate, extra-drug variables as confounding factors.

Research suggests that nonpharmacological variables are responsible for a major part of therapeutic benefits in a variety of accepted drug treatments beyond psychedelics (Hartogsohn, 2017) and the psychological supports provided in preparation to clinical psychedelic research settings remain a confounding factor and limitation of study findings (Rucker et al., 2018; Sellers et al., 2018).

Human Psychedelic Research: History and Challenges

Early psychedelic research, termed *psychotomimetic* (1940s-1950s) principally used LSD to mimic psychosis and to investigate the biochemical origins of mental illness. Later, European psychiatrists began to use low-dose LSD in combination with analysis, a model termed *psycholitic* therapy, while Canadian and American therapists used a model of high-dose*, peak psychedelic* therapy, to elicit dramatic emotional and psychological changes and were principally used in the treatment of alcoholism and neurosis (Krebs & Johansen, 2012). Early psychopharmacological research was extensive and produced over 10 000 scientific publications (Passie et al., 2008). More recently, 9 clinical trials have been completed using psilocybin in the treatment of a range of mental health conditions, including substance dependence, unipolar and treatment resistant depression, anxiety and depression as a result of terminal diagnosis, obsessive-compulsive disorder, and demoralization among long term AIDS survivors (Shore et al., in pre-pub, 2019)

While an extensive literature exists cataloging a multitude of naturally occurring plant-based and newly synthesized chemicals, most psychedelic research in humans has been conducted on only small, relative homogenous sample sizes and principally using synthetic derivatives such as psilocybin (Sellers et al., 2018). Further, trial methodology has been often descriptive, open-

labelled and uncontrolled (phase 1 and phase 2 of regulatory drug approval processes) (Rucker et al., 2018; Sellers & Leiderman, 2018). Further, the combination of psychedelic drug administration with extensive psychological counselling and support in preparation for the drug session significantly confounds study of the drug's therapeutic effect. The obvious behavioural effects of psychedelic drugs also impairs the ability of researchers to blind both participants and observers (M. W. Johnson et al., 2008b; Rucker et al., 2018; Sellers et al., 2018). Researchers have attributed the relative lack of rigour in the human studies has to the national and international regulatory restrictions on possession of and research with psychedelic compounds (Sellers et al., 2018). The minimal effective and maximum tolerated doses and optimal dosage of psilocybin remains unproven (Sellers et al., 2018).

By the Convention on Psychotropic Substances (1971) psychedelics tend to be regulated as Schedule 1 narcotics with the highest potential for abuse and no known medical indication (Rucker et al., 2018; Sellers et al., 2018; Sellers & Leiderman, 2018). While the scientific literature is largely at odds with such a classification, it is felt that the strict international control is not so much due to its (weak) potential for dependence as much as the relative risk of psychosis (Sellers et al., 2018). Clinical trials require exemptions from narcotics law to access psilocybin and other psychedelics, which is largely only approved for serious or unmet medical needs. As unmet need is defined as providing a therapy where none exists or way a novel treatment may be potentially superior to available therapies, it does appear that psychedelic research can gradually build the scientific case, meet regulatory drug approval standards and endpoints, and eventually result in the reclassification of at least some of the psychedelic substances (Rucker et al., 2018; Sellers & Leiderman, 2018).

Recent history does provide examples of drugs being reclassified from Schedule 1 to regulatory drug approval for medical use. Dronabinol (synthetic delta-9- tetrahydrocannabinol) is one such example, initially approved as an orphan drug for AIDS- related anorexia in 1985 and now approved for cancer chemotherapy related nausea and vomiting. Xyrem (sodium g-hydroxybutyrate) was approved for the treatment of cataplexy associated with narcolepsy in

2004 , and an extract of cannabis sativa has been licensed for medical application even in regimes of cannabis prohibition (Rucker et al., 2018).

Regulatory drug approval is generally a gradual process, as trials evolve historically from early investigative, open-labelled and uncontrolled trials to establish safety and tolerability (Stage One). Stage Two trials add more methodological rigour and slightly larger sample sizes to establish preliminary indications of therapeutic efficacy. Effectiveness is only established with Stage Three trials, which tend to be much larger, multi-site randomized controlled trials, with much more diverse patient populations. Given the profound and obvious behavioural effects of psychedelics and the imperative of blinded, unbiased and unconfounded RCTs for regulatory drug approval processes and as the gold standard for evaluating healthcare interventions (Schulz et al., 2010), RCTs with psychedelics face significant challenges.

Recent RCTs with psilocybin have shown significant effect sizes in trials for distress related to life threatening illness; however these studies provided extensive psychological support and gains were often noted even prior to psilocybin administration, and the impossibility of blinding creates expectancy effects for both researchers and subjects, potentially biasing outcome measurements and inflating effect sizes (Rucker et al., 2018; Sellers et al., 2018; Sellers & Leiderman, 2018). Due to regulatory controls, special licenses are required to process and administer Schedule I drugs in human trials, and strict security, control and monitoring protocols are necessary, requiring dedicated infrastructure (Rucker et al., 2018).
In planning future trials and charting the course for regulatory drug approval, two major indications present.

The most prescient initial focus may be unipolar depressive disorder, with treatment resistant depression a priority. Unipolar depression is rising in prevalence, chronic and unremitting, carries high socio-economic burden, has poorer outcomes in a wide variety of physical health problems and is associated with high risk of suicide (Rucker et al., 2018). As treatment resistance is (defined as failure to respond to at least two antidepressants) is common and

long-term, and as early trials have established safety, tolerance and early indications of efficacy, a large-scale Stage Three trial is now enrolling in the United Kingdom (Rucker et al., 2018). While depression may be a larger market with greater financial incentives, application of psychedelics to end of life and palliative care may gain easier approval as safety data requirements may not be as strict when life expectancy is limited and there may be considerable popular support (Rucker et al., 2018). The largest and most robust clinical psilocybin trials have been those focused on anxiety and depression resulting from terminal diagnoses (Roland R. Griffiths et al., 2016; Ross et al., 2016).

Determining the relative contribution of the psychedelic drug to its putative therapeutic effect is difficult, given the sensitivity to context and the provision of ancillary psychological supports. However it would be unethical to give psychedelics without at least a modern degree of preparation, psychological counselling and emotional support (Rucker et al., 2018). It has been suggested that carefully designed RCTs could actually examine how different contexts and supports interact with psychedelics (Rucker et al., 2018).

Psychedelic trial publications should at minimum provide a detailed description of the set and setting conditions of the trial, including reference to variables such as criteria for subject selection, researcher expectations, subject expectations, preparation activities, and physical setting characteristics. This will allow for separate trials to be compared and contrasted, allowing a more nuanced understanding of how the various aspects of set and setting function and interact in research settings (Hartogsohn, 2017). Good Clinical Practices form the basis for well-controlled studies, characterized by the ability “to distinguish the effects of the drug from other influences such as spontaneous change in the course of the a disease, placebo effect or biased observation” (Sellers et al., 2018).

In contrast to early hospital-based LSD research, contemporary settings for psilocybin research have been less clinical, and more comfortable for the user experience. Generally, modern experiments have taken place in comfortably furnished rooms, with sofas and pillows, aesthetic

features, and subjects were encouraged to relax, recline and listen to curated music through headphones. The social setting was non-threatening, staffed only by trained personnel with whom the subject had developed trust, and a framework for understanding and integration the experience is communicated. Contemporary studies with such settings have far fewer adverse effects than earlier, more constrictive and demanding psychotomimetic research program.

Based on available data, the incidence of adverse reactions to psychedelic drugs in contemporary research settings is low when subjects are carefully screened and prepared, supervised, followed up, and given moderate to high doses of pharmaceutical psychedelics (M. W. Johnson et al., 2008b; Strassman, 1984). Eight recent double-blind, placebo-controlled studies of psilocybin in healthy volunteers, with follow-up between 8 and 16 months, reported ‘‘no subsequent drug abuse, persisting perception disorders, prolonged psychosis or other long term impairment of functioning’’ (Johansen & Krebs, 2015), and two other recent clinical trials of psilocybin in 54 healthy volunteers found no evidence of lasting adverse effects (Krebs & Johansen, 2013b). No serious adverse events have been reported in recent randomized controlled trials of psilocybin, demonstrating that psychedelics can be administered safely in medical contexts (R. R. Griffiths et al., 2008; Johansen & Krebs, 2015; M. W. Johnson et al., 2008b; Sellers et al., 2018; Studerus et al., 2011).

Impersonal treatment and the necessity of performing structured tasks lead to intensified negative symptom severity, in early LSD trials, whereas support and freedom lessened both the frequency and duration of adverse experiences (Hartogsohn, 2017). Further and in contrast to contemporary trials providing individual-based psychedelic therapy alone, LSD trial subjects who had group experiences in a group demonstrated less sensory distortions’ and fewer disturbances of thought than those who had a solitary experience (Hartogsohn, 2017). Tests, required examination and exposure to non-therapeutic support personnel teaching resulted in intensification of negative symptoms; subjects who were with members of a peer group, who were not expected to produce anything, and who were not questioned except as a matter of support reported far fewer adverse effects (Hartogsohn, 2017; Strassman, 1984). Rigidity of

research, lack of concern for the emotional state of the subject, impersonal or investigative attitudes, and communication of nonacceptance led to greater negative response; support, familiarity with surroundings, flexibility in research design, acceptance and opportunity for personal expression led to significantly more favorable experiences (Hartogsohn, 2017; Matthew W. Johnson et al., 2018).

Adverse Experiences in Clinical Trials using Psychedelics and How to Manage Them

Manufacturers demonstrate safety, efficacy and quality of investigational drugs by clinical trial. Evaluating the risk profile of the proposed treatment involves safety analyses which identify untoward medical occurrences after exposure to the investigational drug (Allen et al., 2018). Such endpoints, known as adverse events or effects are assessed on an individual basis and also by aggregating data across trials to establish likelihood of adverse drug reactions (ADRs), those AE's which have a reasonable possibility of occurring (Allen et al., 2018).

Identifying, monitoring and reporting AEs may be more complex and time consuming than the processes involved in establishing the potential benefits; considerable variation still occurs in how trials collect and report on their AEs (Allen et al., 2013; Schulz et al., 2010). A recent Cochrane review established that more specific questioning of study participants leads to more AEs being reported, when compared to more open-ended general methods of enquiry. Severe AEs tend to be well reported by initial open enquiry, while less bothersome or clinically relevant AEs are only reported with subsequent, specific questioning. Best practice seems to suggest that open interviews, in addition to structured ratings, elicit the most comprehensive reporting of AEs (Allen et al., 2018) .

Adverse reactions to psychedelic drugs have been classified along a temporal continuum from acute to persisting to chronic (Strassman, 1984). Of importance within psychedelic research are delayed and/or persisting reactions which may occur between the two endpoints, such delayed panic reaction, (more rarely) psychosis, and the observed phenomenon of delayed headaches (M. W. Johnson et al., 2008b; Matthew W. Johnson et al., 2012; Strassman, 1984). The

likelihood of potential adverse effects in psychedelic trials will be related to dose, but also the quality of the overall experience, and will be modulated by careful screening and evidence-based eligibility requirements(M. W. Johnson et al., 2008b). Adverse effects related to psychedelics need to be understood not just for their incidence and frequency, but also their duration. Further, some conversation needs to occur which investigates the therapeutic functionality of at least some of the experiences considered adverse. The psychologically challenging nature of the psilocybin intoxication may at least play some role in the putative therapeutic effect.

Defining the Adverse Effects

Note: Appendix 1 contains a summary table of all AEs reported in contemporary psilocybin experiments, both clinical and those conducted with healthy volunteers, as well as adverse experiences reported by recreational users of psilocybe mushrooms. Table 2. Summarizes the known possible acute adverse effects, culled from the literature, of psilocybin and Psilocybe mushrooms while Table 3. Summarizes factors known to increase the likelihood and difficulty of adverse effects while Table 4. Presents possible contraindications and exclusion criteria for future trials of psychedelics.

Biologic Effects

Classical hallucinogens commonly exert dose-dependent physiological effects including pupil dilation, elevated temperature, increases in heart rate, systolic and/or diastolic blood pressure increase (M. W. Johnson et al., 2008b; Sellers et al., 2018). These effects signal pharmacological effect and may be important to monitor for patient safety. Clinical studies have not reported serious safety issues due to these physiologic effects, though some observed significant increases in blood pressure, which may pose a risk for subjects with untreated hypertension or related disorders (Sellers et al., 2018). Psilocybin increases respiratory rate and is associated with tachypnea and irregular respirations; these may be somewhat secondary to experiences of anxiety, but it is of note that the biomass of *Psilocybe* mushrooms does contain phenethylamines, which do have an amphetamine chemical structure (Kuypers et al., 2019). One of the few reports of psilocybin-associated mortality describes a patient who had unusual, irregular respiration prior to death (Sutter et al., 2014).

Classical psychedelics have extensive effect across the nervous system and may result in

headaches (during and after acute drug effect), mydriasis, altered perception, increased deep tendon reflexes, hyperreflexia and paresthesia as well as mydriatic pupils, facial flushing and diaphoresis. Electroencephalography (EEG) patterns from psilocybin studies show demonstrate cortical desynchronization, and increased beta wave activity along with decreases in both alpha and theta waves (Sutter et al., 2014).

Cardiovascular effects include tachycardia, and systolic hypertension, though these effects are not usually associated with life-threatening dysrhythmias., There has been one reported case of tako-tsubo cardiomyopathy associated with psilocybin ingestion (Sutter et al., 2014). Mild gastrointestinal effects are commonly reported with psilocybin consumption including nausea, vomiting and abdominal pain/cramps. Nausea without vomiting is most commonly reported, and to date there have been no reported cases of hepatic failure from the use of psilocybin in clinical settings (Sutter et al., 2014). Psilocybin results in decreased creatinine clearance and decreased clearance of inorganic phosphate; a few cases of both acute and chronic renal failure have been reported, but not in clinical settings and are thought to be due to misidentification of wild mushrooms (Sutter et al., 2014).

Recent psilocybin trials have demonstrated high incidence of dose-dependent acute and/or delayed headaches (M. W. Johnson et al., 2008b; Matthew W. Johnson et al., 2012). Headaches started a mean of 7 hours post drug administration. but were neither severe nor disabling, predisposition to headaches are not considered an exclusion criterion. Data also do not suggest that administering psilocybin during an ongoing headache poses any risk to safety. The underlying mechanism explaining psilocybin-induced headaches is unknown, but may be due to 5HT2A vasoconstriction, nitric oxide or glutamate release in the cortex, 5-HT2B agonism, alterations in neurologic inflammation signalling pathways or some combination thereof (M. W. Johnson et al., 2008b; Matthew W. Johnson et al., 2012).

Psychological Effects

Although psychedelics are relatively safe and have a low risk profile for addiction, their administration involves psychological experiences which pose unique risks. There is little risk that trials will leave participants physically or psychologically dependent. The most likely risk is distress/anxiety/panic during drug action and usually early in the timeline of drug effect (M. W. Johnson et al., 2008b; Strassman, 1984). Such psychological states can lead to potentially dangerous behavior; study subjects have attempted to leave study sites or have locked themselves inside a bathroom. Less common are any prolonged psychotic states triggered by psychedelics (M. W. Johnson et al., 2008b; Strassman, 1984).

Clinical observations suggest the possibility that unconscious or repressed psychological material may be recovered under drug effect. Such experiences may be challenging and may lead to psychological difficulties persisting after drug sessions. The cascade of images, sensations, emotions and unique perceptions may result in a breakdown in normal means of processing emotion and information, highlighting the importance of adequate preparation and selection criteria (Strassman, 1984). However, there are very few case reports of prolonged psychiatric symptoms following psilocybin or mescaline (Krebs & Johansen, 2013b).

Treatment of acute panic reactions involves reassuring and comforting the patient. A quiet, comfortable room which is aesthetically pleasing and with a minimum of distractions should be available (Roland R. Griffiths et al., 2016; M. W. Johnson et al., 2008b). Patients should not be left alone; the therapeutic standard is to have two monitors present throughout the session, preferably one of each gender but never both of the opposing gender. Most individuals can be "talked down" with reassurance or gentle touch, and a reminder that the experience is drug induced and time limited, and that the overall experience is safe (Strassman, 1984). For more severe agitation, rescue medications such as diazepam or other short-acting benzodiazepine should be available, in oral or parenteral form, and given under the supervision of psychiatrist (M. W. Johnson et al., 2008b). Major tranquilizers should be reserved for only those rare possible exceptions of severely agitated patients (Strassman, 1984). If rescue medications are

used, it may be necessary to arrange overnight stay and monitoring in the hospital or clinical research facility. Otherwise, participants can leave the research facility accompanied by a friend or relative once the clinical team is satisfied, and generally 8 hours after medication administration (Rucker et al., 2018).

Exclusion Criteria

Recent psilocybin trials have excluded volunteers with a current or a recent personal history of alcohol/drug dependence (excluding caffeine and nicotine), major depression or psychosis, current obsessive-compulsive disorder, dysthymic disorder, panic disorder, dissociative disorder, anorexia nervosa or bulimia nervosa (M. W. Johnson et al., 2008b). Family histories of psychotic disorders, bipolar disorder, obsessive-compulsive disorder or other serious mental health conditions have also been common exclusion criteria as have been personal or family history of certain personality disorders such as avoidance, narcissism. Individuals considered genetically susceptible, with a family history of severe psychiatric disease, are generally advised to abstain from the use of psychedelics. In schizophrenic patients the consumption of magic mushrooms may induce an acute psychotic state that necessitates hospitalization (Amsterdam et al., 2011).

Additional suggested exclusion criteria include personal history of repeated violence towards others, recent personal history of suicide attempt serious enough to require hospitalisation and current drug or alcohol dependence (unless this is the target for intervention) (Rucker et al., 2018). Some investigators have excluded individuals scoring high on the personality traits of rigidity and emotional lability, as these traits are significantly associated with negative experiences under psychedelics (M. W. Johnson et al., 2008b). Exclusion criteria should be applied judiciously but contextualized to individual trials. For example, trials specific to depression would not exclude those with a depressive diagnosis but may exclude those who require urgent care. Similarly, trials focusing on alleviating end of life distress may allow for the inclusion of those with mild co-morbid disorders (M. W. Johnson et al., 2008b).

Subject selection and screening

Psychedelic trial subjects should be in good general health as assessed by detailed medical history, physical examination, 12-lead ECG, blood chemistry profile, hematology and urine drug screening (M. W. Johnson et al., 2008b). Medication and drug use histories should be extensive. Concurrent medical exclusions due to drug interactions include patients on medications with perceptual effects such as tricyclic antidepressants, lithium, haloperidol, selective serotonin reuptake inhibitors, antipsychotics, MAO inhibitors (M. W. Johnson et al., 2008b; Sellers et al., 2018). Carefully structured psychiatric screening should be applied, and moderate to severe disorders excluded (Sellers et al., 2018). Concomitant psychiatric medications should be withdrawn, allowing sufficient washout time, for fluoxetine in particular (Rucker et al., 2018). Antagonists of the 5-HT2A receptor (mirtazapine and most antipsychotic drugs) attenuate response to psychedelics are contraindicated, as is benzodiazepines use (Rucker et al., 2018). Investigators are also encourage to assess the use of over-the-counter dietary supplements, and to exclude those taking potentially problematic substances which affect serotonergic function such as 5-hydroxytryptophan supplements and St John's Wort (M. W. Johnson et al., 2008b).

Pregnancy and breast-feeding women or those not practicing effective birth control are generally excluded from psychedelic trials, and given the cardiovascular effects of psilocybin, potential subjects with uncontrolled hypertension should also be excluded (M. W. Johnson et al., 2008b; Rucker et al., 2018). Medical screening should exclude those with serious neurological, renal, liver or cardiac disease and all participants should be registered with a local general or family practitioner with consent given to the sharing of their records(Rucker et al., 2018).

Safety and Physical Setting

Given the sensitivity to context demonstrated for psychedelics, an aesthetically pleasing environment is thought to decrease the probability of acute psychological distress. A living room-like setting, with comfortable furniture and a non-clinical aesthetic; comfortable, and

with the ability to control temperature, lighting and colours (M. W. Johnson et al., 2008b; Strassman, 1984). The environment should be designed to accommodate the perceptual changes and disorientation that can occur. The setting should be locked and secure, with no potentially dangerous objects. Windows should be double or triple paned, and locked. The session room should not have a telephone, or any extraneous sounds. There should be easy access to a private, unlockable bathroom (M. W. Johnson et al., 2008b; Sellers et al., 2018; Strassman, 1984).

Conclusion

Psychedelics, specifically psilocybin, are largely considered safe for human consumption, with low toxicity in comparison to other psycho-active substances. Decades of investigation have documented known risks and adverse effects. Of specific concern is the experience of transient anxiety and distress many will feel while under the influence of psychedelics. While not life-threatening, the "bad trip" can result in persisting negative symptoms. Psychedelics hold promise in the treatment of a various mental health conditions. Human psychedelic trials need to ensure risks are mitigated by selection of appropriate candidates and by the provision of a suitable setting and supports.

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References:

Allen, E. N., Chandler, C. I. R., Mandimika, N., & Barnes, K. (2013). Eliciting adverse effects data from participants in clinical trials. *Cochrane Database of Systematic Reviews*, *2013*(5). https://doi.org/10.1002/14651858.MR000039

Allen, E. N., Chandler, C. I. R., Mandimika, N., Leisegang, C., & Barnes, K. (2018). Eliciting adverse effects data from participants in clinical trials. *Cochrane Database of Systematic Reviews*, *2018*(1). https://doi.org/10.1002/14651858.MR000039.pub2

Amsterdam, J. van, Opperhuizen, A., & Brink, W. van den. (2011). Harm potential of magic mushroom use: A review. *Regulatory Toxicology and Pharmacology*, *59*(3), 423–429. https://doi.org/10.1016/j.yrtph.2011.01.006

Bienemann, B., Ruschel, N. S., Campos, M. L., Negreiros, M. A., & Mograbi, D. C. (2020). Self-reported negative outcomes of psilocybin users: A quantitative textual analysis. *PLoS ONE*, *15*(2), 1–15. https://doi.org/10.1371/journal.pone.0229067

Calvey, T., & Howells, F. M. (2018). An introduction to psychedelic neuroscience. *Progress in Brain Research*, *242*, 1–23. https://doi.org/10.1016/bs.pbr.2018.09.013

Carbonaro, T. M., Bradstreet, M. P., Barrett, F. S., MacLean, K. A., Jesse, R., Johnson, M. W., & Griffiths, R. R. (2016). Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *Journal of Psychopharmacology*, *30*(12), 1268–1278. https://doi.org/10.1177/0269881116662634

Carhart-Harris, R. (2016). 5-HT2A agonist drugs as new treatments in psychiatry. *European Neuropsychopharmacology*, *26*, S121. https://doi.org/10.1016/s0924-977x(16)30892-6

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The Lancet Psychiatry*, *3*(7), 619–627. https://doi.org/10.1016/S2215-0366(16)30065-7

Fantegrossi, W. E., Woods, J. H., & Winger, G. (2004). Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys. *Behavioural Pharmacology*, *15*(2), 149–157. https://doi.org/10.1097/00008877-200403000-00007

Gable, R. S. (2004). Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction*, *99*(6), 686–696. https://doi.org/10.1111/j.1360-0443.2004.00744.x

Griffiths, R. R., Richards, W. A., Johnson, M. W., McCann, U. D., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology*, *22*(6), 621–632. https://doi.org/10.1177/0269881108094300

Griffiths, Roland R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, *30*(12), 1181–1197. https://doi.org/10.1177/0269881116675513

Halberstadt, A. L. (2015). Recent Advances in the Neuropsychopharmacology of Serotonergic Hallucinogens. *Behav Brain Res.*, *277*, 99–120. https://doi.org/doi:10.1016/j.bbr.2014.07.016.

Halberstadt, A. L., Nichols, D. E., & Vollenweider, F. X. (2017). Behavioral Neurobiology of Psychedelic Drugs. In *Current Topics in Behavioral Neurosciences* (Vol. 2, Issue 2). https://doi.org/10.1007/7854_2009_7

Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law*, *3*, 205032451668332. https://doi.org/10.1177/2050324516683325

Johansen, P. O., & Krebs, T. S. (2015). Psychedelics not linked to mental health problems or suicidal behavior: A population study. *Journal of Psychopharmacology*, *29*(3), 270–279. https://doi.org/10.1177/0269881114568039

Johnson, M. W., Richards, W. A., & Griffiths, R. R. (2008a). Human hallucinogen research: Guidelines for safety. In *Journal of Psychopharmacology*. https://doi.org/10.1177/0269881108093587

Johnson, M. W., Richards, W. A., & Griffiths, R. R. (2008b). Human hallucinogen research: Guidelines for safety. *Journal of Psychopharmacology*, *22*(6), 603–620. https://doi.org/10.1177/0269881108093587

Johnson, Matthew W., Andrew Sewell, R., & Griffiths, R. R. (2012). Psilocybin dose-dependently

causes delayed, transient headaches in healthy volunteers. *Drug and Alcohol Dependence*, *123*(1–3), 132–140. https://doi.org/10.1016/j.drugalcdep.2011.10.029

Johnson, Matthew W., Griffiths, R. R., Hendricks, P. S., & Henningfield, J. E. (2018). The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. *Neuropharmacology*, *142*, 143–166. https://doi.org/10.1016/j.neuropharm.2018.05.012

Krebs, T. S., & Johansen, P. Ø. (2013a). Psychedelics and mental health: a population study. *PloS One*, *8*(8). https://doi.org/10.1371/journal.pone.0063972

Krebs, T. S., & Johansen, P. Ø. (2013b). Psychedelics and mental health: a population study. *PloS One*. https://doi.org/10.1371/journal.pone.0063972

Krebs, T. S., & Johansen, P. Ør. (2012). Lysergic acid diethylamide (LSD) for alcoholism: Meta-analysis of randomized controlled trials. *Journal of Psychopharmacology*, *26*(7), 994–1002. https://doi.org/10.1177/0269881112439253

Kuypers, K. P. C., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Pani, L., Soula, A., & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology*, *33*(9), 1039–1057. https://doi.org/10.1177/0269881119857204

Muthukumaraswamy, S. D., Carhart-Harris, R. L., Moran, R. J., Brookes, M. J., Williams, T. M., Errtizoe, D., Sessa, B., Papadopoulos, A., Bolstridge, M., Singh, K. D., Feilding, A., Friston, K. J., & Nutt, D. J. (2013). Broadband cortical desynchronization underlies the human psychedelic state. *Journal of Neuroscience*, *33*(38), 15171–15183. https://doi.org/10.1523/JNEUROSCI.2063-13.2013

Nichols, D. E., Johnson, M. W., & Nichols, C. D. (2017). Psychedelics as Medicines: An Emerging New Paradigm. *Clinical Pharmacology and Therapeutics*, *101*(2), 209–219. https://doi.org/10.1002/cpt.557

Nichols, David E. (2018). Chemistry and Structure - Activity Relationships of Psychedelics. In A. L. Halberstadt (Ed.), *Behavioural Neurobiology of Psychedelic Drugs* (pp. 1–43). Springer. https://doi.org/10.1007/7854

Passie, T., Halpern, J. H., Stichtenoth, D. O., Emrich, H. M., & Hintzen, A. (2008). The pharmacology of lysergic acid diethylamide: A review. *CNS Neuroscience and Therapeutics*,

14(4), 295–314. https://doi.org/10.1111/j.1755-5949.2008.00059.x

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology*, *30*(12), 1165–1180. https://doi.org/10.1177/0269881116675512

Rucker, J. J. H., Iliff, J., & Nutt, D. J. (2018). Psychiatry & the psychedelic drugs. Past, present & future. *Neuropharmacology*, *142*, 200–218. https://doi.org/10.1016/j.neuropharm.2017.12.040

Rucker, J. J. H., Jelen, L. A., Flynn, S., Frowde, K. D., & Young, A. H. (2016). Psychedelics in the treatment of unipolar mood disorders: A systematic review. *Journal of Psychopharmacology*, *30*(12), 1220–1229. https://doi.org/10.1177/0269881116679368

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. *Journal of Clinical Epidemiology*, *63*(8), 834–840. https://doi.org/10.1016/j.jclinepi.2010.02.005

Sellers, E. M., & Leiderman, D. B. (2018). Psychedelic Drugs as Therapeutics: No Illusions About the Challenges. *Clinical Pharmacology and Therapeutics*, *103*(4), 561–564. https://doi.org/10.1002/cpt.776

Sellers, E. M., Romach, M. K., & Leiderman, D. B. (2018). Studies with psychedelic drugs in human volunteers. *Neuropharmacology*, *142*, 116–134. https://doi.org/10.1016/j.neuropharm.2017.11.029

Shore, Ron., P. Ioudovski, S.McKeown, E. Dumont and C. Goldie (2019) Mapping Psilocybin Assisted Therapies: A Scoping Review. https://www.medrxiv.org/content/10.1101/2019.12.04.19013896v2

Strassman, R. J. (1984). Adverse reactions to psychedelic drugs. A review of the literature. *Journal of Nervous and Mental Disease*, *172*(10), 577–595. https://doi.org/10.1097/00005053-198410000-00001

Studerus, E., Gamma, A., & Vollenweider, F. X. (2010). Psychometric evaluation of the altered states of consciousness rating scale (OAV). *PLoS ONE*, *5*(8).

https://doi.org/10.1371/journal.pone.0012412

Studerus, E., Kometer, M., Hasler, F., & Vollenweider, F. X. (2011). Acute, subacute and long-term subjective effects of psilocybin in healthy humans: A pooled analysis of experimental studies. *Journal of Psychopharmacology*, *25*(11), 1434–1452. https://doi.org/10.1177/0269881110382466

Sutter, M. E., Chenoweth, J., & Albertson, T. E. (2014). Alternative drugs of abuse. *Clinical Reviews in Allergy and Immunology*, *46*(1), 3–18. https://doi.org/10.1007/s12016-013-8370-2

Appendices.

Table 1. Psilocybin Trials and Investigations, Documented Adverse Effects

Study	Sample Size	Indication	Substance / Dose	Adverse Effects (immediate)	Adverse Effects (delayed)
Carhart-Harris et al., 2017	20	Treatment Resistant Depression	Psilocybin, 10 mg & 25 mg	I patient became uncommunicative during drug session 15 (75%) transient anxiety lasting for minutes 5 (20%) transient nausea 3 (15%) transient paranoia	8 headaches lasting no longer than 1-2 days 5 sought and obtained psilocybin between 3 and 6 months post trial
Bogenshutz et al., 2015	10	Alcohol Dependence	Psilocybin 300mg/kg or 400mcg/kg	mild elevation of blood pressure # not specified 1 vomiting 1 diarrhea 1 insomnia	1 dropped out after first treatment
Bogenshutz et al., 2018	3/180	Alcohol Dependence	nor reported	nausea and abdominal pain (33%) 1 of 3 dropped out after first dose	
Grob et al., 2011	12	Life threatening disease	Psilocybin 200mcg/kg & Niacin 250 mg (control)	mild elevation of HR and diastolic BP	
Ross et al., 2016	29	life threatening disease	Psilocybin 300mcg/k & Niacin 250 mg (control)	statistically significant increases in BP/PR 28% headaches/migraines 14% nausea 17% transient anxiety 7% transient psychotic-like symptoms	
Griffiths et al., 2016	51	Life threatening cancer with anxiety and depression	Psilocybin 22mg/70kg or 30mg/70 kg & Psilocybin 1mg/70kg or 3mg/70 kg	34% high systolic BP at high dose 13% high diastolic BP at high dose 15% nausea and vomiting 21% physcial discomfort at high dose 32% psychological discomfort at high dose 26% anxiety (high dose) 1 headache 1 transient paranoid ideation (high dose)	2/11 delayed moderate headache after high dose session
Moreno et al., 2006	9	OCD	Psilocybin 25mcg/kg, 100mcg/kg, 200mcg/kg & 300mcg/kg	1 transient hypertension (mild) 2 dropped out after session 1 due to discomfort with hospitalization	
Johnson et al., 2014	15	Tobacco Addiction	Psilocybin 20mg/70kg or 30mg/70kg	10/42 (23.8%) sessions included strong or extreme feelings of fear, fear of insanity, or feeling trapped" mild increases in BP/HR	8/10 participants reported transient, mild post psilocybin headache
Studeris, 2011	110	pooled data from 1999-2008, healthy volunteers	Psilocybin 45-315mcg/kg	2 subjects had unusally intense reaction to low dose so were discontinued from study 1 subject experienced a tran- sient hypotonic reaction (systolic and diastolic blood pres- sure: 86/63mm/Hg) with dizziness, fainting and vomiting after having received 115mg/kg of psilocybin and was there- fore also excluded from further psilocybin experiments. 2 subjects dropped out after first dose extreme anxiety fear of loss of ego control negative memories emerging after 24 hours: fatigue headaches, head pressure or face pain lack of energy prolonged negative effects reported: (12%) reported in the follow-up questionnaire that they had experienced negative changes in psychological well-being and/or mental functions after the psilocybin experiment. However, 4 of those 11 said changes did not have to do with psilocybin, leaving 7 subjects or 8% emotional instability, anxiety, and depressive feelings (1) Concentration problems (2), mood swings (2), reactivation of old problems (1), memory problems (1), and being pensive and introverted (1) 1 sought psychiatric care due to emotional instability, anxiety, and depressive feelings, which he attributed to suppressedmemories, thoughts, and feel- ings that he had been confronted with during the psilocybin session	
Van Amsterdam, 2011	literature/ data review	naturalistic/recreational use	psilocybe mushrooms	tachycardia nausea anxiety restlessness impaired coordination impaired judgement of time or distance sense of unreality mild to moderate increase in breathing frequency, heart rate and BP depersonalization	
Carbonaro, 2016	1993	naturalistic/recreational use	psilocybe mushrooms	psychological distress putting self or others at risk of physical harm physical aggression or violence	
Kuypers, 2019	critique	alternative therapy	psilocybe mushrooms, microdosed	possibility of ventrical heart disease, cardiac valvulopathies, valvular hyperplasia, by chronic microdosing due to 5-HT2B agonism	

Table 2. Possible Acute Adverse Effects, Psilocybin & *Psilocybe* Mushrooms

Physiological	pupil dilation increased heart rate increased respiratory rate increased systolic pressure increased diastolic pressure facial flushing hyperreflexia dizziness/disequilibrium impaired coordination weakness tremors nausea vomiting abdominal pain drowsiness paresthesia blurred vision headache (acute & delayed)	**Cognitive**	altered time perception impaired tempo working memory deficits concentration problems impaired perception alterations in colour altered visuospatial perception impaired proprioception visual abnormalities auditory hallucinations synesthesia
Spiritual	past life experiences contact with spirits/entities	**Affective / Psychological**	acute anxiety panic fear paranoia heightened emotion past memory retrieval derealization depersonalization putting self or other at risk aggression

Sources: (Amsterdam et al., 2011; Hartogsohn, 2017; Johansen & Krebs, 2015; M. W. Johnson et al., 2008a; Krebs & Johansen, 2012; Studerus et al., 2011; Sutter et al., 2014)

Table 3. Risk Factors for Challenging or Negative Experiences with Psilocybin & *Psilocybe* Mushrooms

Past week emotional difficulty
High emotional excitability
Combining with other drugs, esp. alcohol
Multiple doses
Single high dose
Lack of interpersonal support
Non-supportive setting
Younger age
Necessity of performing structured tasks

References: (Amsterdam et al., 2011; Carbonaro et al., 2016; Gable, 2004; Johansen & Krebs, 2015; M. W. Johnson et al., 2008a; Strassman, 1984)

Table 4. Psilocybin Trial Exclusion Criteria

Psychiatric Conditions	Schizophrenia / Psychotic Disorders Bipolar Disorder Substance Use Disorder Obsessive-Compulsive Disorder Dysthymic Disorder Anxiety / Panic Disorder Dissociative Disorder Anorexia Nervosa Bulimia Suicidality Avoidance Narcissism History of repeated violence Family History (1st /2nd degree) major psychiatric disorder High rigidity scores High emotional lability scores
Health Conditions	uncontrolled hypertension pregnancy breast-feeding serious neurological disease serious renal or liver disease serious cardiac disease
Medications	SSRIs tricyclic antidepressants lithium haloperidol antipsychotics MAO inhibitors fluoxetine benzodiazepines Serotonin supplements St. John's Wort

References:

(M. W. Johnson et al., 2008a; Rucker et al., 2018; Strassman, 1984)(R. L. Carhart-Harris et al., 2016; Roland R. Griffiths et al., 2016; Ross et al., 2016)