DEPARTMENT OF HEALTH

Psilocybin Literature Overview

Introduction

There were six overarching conditions identified in the in initial search: Mood disorders (major depression disorder, bipolar type 2 disorder), anxiety disorders, obsessive-compulsive disorder, substance use disorders (alcohol use disorder, tobacco use disorder), migraine, cluster headache, and anorexia nervosa. Both major depressive disorder and bipolar type 2 disorder are categorized as mood disorders, and will be discussed together. Similarly, because mood and anxiety disorders were considered jointly in nearly all of the identified trials, and because these disorders often co-occur, they are presented together as well. To compare the efficacy of current standard treatments and psilocybin in these identified health conditions, we reviewed primary randomized controlled trials (RCTs) investigating the use of psilocybin as a treatment, along with meta-analyses and systematic reviews. However, there were no RCTs identified investigating psilocybin as a treatment for obsessive-compulsive disorder, tobacco use disorder, migraine, or anorexia nervosa, and so these conditions were not further explored.

Mood and Anxiety Disorders

Nine RCTs, as well as four publications with additional data from some of these trials, investigating mood and/or anxiety disorders were identified and analyzed[1-13]. Mood disorders included major depressive disorder, including treatment-resistant major depressive disorder, and bipolar type 2 disorder. Anxiety disorders typically included generalized anxiety disorder, but often included any DSM-diagnosed anxiety disorder. Some of these experiments were conducted in populations also experiencing life-threatening illnesses, such as cancer. A total of 597 participants were included from the nine RCTs. All of the included trials utilized a therapeutic component before and after the one, two, or sometimes three doses of psilocybin. Six studies provided one session with the drug, and three studies provided participants with two psilocybin sessions. One of these studies used a primary endpoint of one drug session, but allowed participants to have a second or third session if they chose. All trials had at least one preparatory psychotherapeutic session, along with one to three integrative post-treatment psychotherapy sessions.

Doses ranged from 1-3 milligrams (mg) as an active control to 10-30 mg as an experimental dose. Some studies dosed instead by body weight (BW), ranging from 0.2 mg/kg BW to 0.4 mg/kg BW. Only two of the included studies employed a true control, in which one group received only the placebo and never received psilocybin. Most either used active control doses, a wait-list control condition, or a crossover component, meaning that by the end of the trial all participants had received some dose of the drug. This is because, given the nature psilocybin, drug effects or lack thereof are often apparent, and difficult to control for. However, many of these studies (e.g., waitlist control trials and crossover studies) used a primary endpoint where only one group had received the drug. A waitlist controlled trial is one where one group receives the treatment immediately, while the other waits a certain amount of time to receive the drug. The effects of the drug are then compared between those who have received the

treatment and those who have not (yet). A crossover trial is one where one group receives the experimental drug and one group receives a placebo, then they go through the whole experiment. After this has concluded, the groups switch and the experiment is repeated. In both of these cases, the primary end point is before the control group has received psilocybin. However, long-term follow-up is not possible because all participants have received psilocybin by the end of the whole trial.

Of the 597 total participants, 370 received the experimental dose of psilocybin, while 518 received any dose (i.e., received an active control dose, were in the waitlist condition, or a crossover trial). Most studies measured depression through the Montgomery–Åsberg Depression Rating Scale (MADRS), comparing between baseline and endpoint scores within the treatment groups, as well as between the treatment groups. Other measurement scales included the Beck's Depression Inventory, the Hamilton Depression Rating Scale, the Hamilton Anxiety, Rating Scale, and the State-Trait Anxiety Inventory. All of the included studies ultimately indicated a beneficial effect of psilocybin, in conjunction with therapy, on measures of depression and anxiety. That is, all studies reported that psilocybin-assisted therapy resulted in a decrease in these symptoms from baseline to the endpoint of the studies, and most found that there were statistical differences in these decreases when comparing between the experimental and control groups.

Comparison of Efficacy, Mood and Anxiety Disorders

Major depressive disorder is typically treated with medications (antidepressants) and/or psychotherapy[14]. Psychotherapy is typically cognitive behavioral therapy (CBT), but can include other forms. Treatment-resistant depression is operationally defined as failure of at least two courses of treatment[7]. This type of depression is often treated with brain stimulation, including electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). Recently, a new form of treatment has been approved by the FDA, intranasal esketamine. Finally, antipsychotic or anticonvulsant medications may be taken in conjunction with standard antidepressants. Bipolar type 2 disorder can be treated with antidepressant medications, psychotherapy, or certain other mood stabilizers, like lithium or valproate[15]. However, while individuals with bipolar type 2 disorder were included in one study[12], there have been no RCTs designed to specifically investigate the use of psilocybin as a treatment for this condition. Anxiety disorders are typically treated with psychotherapy (CBT, others), medication (antidepressants, anti-anxiety medications, beta-blockers), or a combination of the two[16].

One RCT directly compared psilocybin-assisted therapy against a current standard medication for depression, and found that participants in both treatment groups improved equally, with no statistical difference[4] (see next section). Meta-analyses investigating the efficacy of psilocybin-assisted therapy as compared with a placebo condition can be found in the literature, all of which conclude that the treatment is statistically superior to a control condition[17-19]. However, no meta-analyses directly comparing this treatment against current standard treatments currently exist. In the meantime, discussions around meta-analyses for psilocybin-assisted therapy and those on current treatments are presented.

Direct Comparison of Efficacy of Psilocybin-Assisted Therapy and Standard Treatment

One RCT directly compared psilocybin-assisted therapy to a current standard treatment (the antidepressant medication escitalopram) for major depressive disorder (MDD)[4]. A total of 59 participants with MDD were assigned to either the psilocybin treatment group (n=30) or the escitalopram treatment group (n=29). The trial consisted of six visits over a period of six weeks, with two of these visits being drug treatment sessions. Participants received one session of psychological support 7-10 days before the start of the trial. In the first drug treatment session all participants, regardless of group, received psilocybin. While the psilocybin group received the full experimental dose of 25 mg, the escitalopram group only received 1 mg. This was to control for the effects of psilocybin. All participants were then given either placebo pills (psilocybin group) or escitalopram pills (10 mg; escitalopram group) to take daily until the next drug treatment session. Two follow-up visits occurred in the two weeks after this session. Three weeks after the session, participants returned for the second drug treatment session. Again, participants received either 25 mg or 1 mg of psilocybin, and were give more placebo or escitalopram pills, respectively, to take daily for the next three weeks until the final follow-up session.

Researchers analyzed the change in depressive symptomology between baseline and the end of the trial in the two groups, and statistically compared them. While depression scores decreased in both groups, there was no statistical difference between the two. The researchers also assessed both response and remission rates. Response was defined as a reduction of >50 % in the primary depression rating at the primary endpoint compared to baseline. Remission was defined as when a participant scored below a certain threshold on the depression scale used in the study. At the six week measurement, a response occurred in 70% of the participants in the psilocybin group and in 48% of those in the escitalopram group. Remission occurred in 57% of the psilocybin group and in 28% of those in the escitalopram group. Again, there were no statistical differences between these measurements.

The lack of difference between the two treatments in a head-to-head comparison suggests that psilocybin-assisted therapy is at least as efficacious as escitalopram, over a six week course of treatment. However, a placebo control condition was not included in the study.

Meta-Analyses, Psilocybin for Mood and Anxiety Disorders

Three meta-analyses were evaluated[17-19], all of which evaluated the RCTs included in the RCT portion of this current report, with the exception of one[12], as well as additional non-RCTs. All found that psilocybin produced beneficial effects on symptoms of both anxiety and depression, and these effects were statistically greater than the placebo condition. Furthermore, those in the psilocybin condition saw notable decreases in symptomology between baseline and the endpoint. One meta-analysis analyzed outcomes using effect sizes[19], which are a statistical measure of the magnitude of differences between two populations. This analysis used Hedge's g statistic. Effect sizes are typically considered small if they are 0.2 or less, medium if they are around 0.5, large if they are 0.8, very large if they are 1.2, and huge if they are 2.0 and above. Values can be negative, with the magnitude ranges being the same (i.e., the further away from 0, the greater the effect). The study calculated the difference in scores between baseline and the end of the treatment for each condition (psilocybin and control), and statistically compared these values. When comparing between the two conditions, they found large reductions in both depression (g=0.83) and anxiety (g=0.82) in response to psilocybin, as compared with the

control group. When looking just at the difference in scores between pre- and post-treatment in the psilocybin groups, there was again a very large reduction in depression (g=1.47) and anxiety (g=1.38).

Along with evaluating the change in depression and/or anxiety scores, many of these studies also assessed the response and remission rates. Response to the treatment was typically defined as a greater than 50% decrease in the measured depression or anxiety score relative to baseline, and remission was defined as a drop to or below a pre-defined (low) score on those same scales. One meta-analysis evaluating eight of the nine above RCTs, along with one non-RCT, calculated these values in depression scores, and determined that the response rate following psilocybin was 57%, as compared with 22% in those who were in control conditions. Similarly, remission rates were higher in those who received psilocybin (45%) versus those who were in the control conditions (14%)[17].

Meta-Analyses, Current Treatments for Mood Disorders

One meta-analysis evaluated 21 different antidepressants, versus placebo, in the efficacy of treatment for major depressive disorder[20]. A total of 522 double-blind, placebo-controlled RCTs, with a total of 116,477 participants, were analyzed. Of these, 87,052 participants received the intervention and 29,425 received a placebo. The study estimated summary odds ratios (ORs); an OR of 1 indicates no difference between drug and placebo, an OR above 1 favors the treatment, and an OR below 1 favors the placebo. Furthermore, an OR of 1.5 is considered a small effect size, while an OR of 2.5 indicates a medium effect size, and OR of 4 represent a high effect size. The study found that all of the analyzed antidepressants were more effective than placebo, with ORs ranging between 2.13 for the most-efficacious and 1.37 for the least efficacious, all of which are considered medium-low to low effect sizes. Another meta-analysis evaluated the effects of psychotherapy, with or without concomitant antidepressants, on MDD[21]. Again using ORs, they found that combined psychotherapy with antidepressants significantly outperformed antidepressants alone, and had an OR of 2.93, corresponding to a medium effect size. Combined psychotherapy with antidepressants resulted in an equal response to treatment compared with psychotherapy alone at six months, with an OR of 1.42, considered a low effect size.

Treatment-resistant depression (TRD), typically defined as MDD that does not respond to at least two different courses of treatment, may require further intervention (see above). A meta-analysis investigating the efficacy of electroconvulsive therapy (ECT) versus sham, placebo, or antidepressant therapy was evaluated[22]. Using ORs, the study found that the OR of a positive response to ECT was 4.77, which can be considered a large effect size, and was statistically better than placebo. The comparison of ECT versus antidepressants in general demonstrated a significant superior effect of ECT as well, with an OR of 3.72, considered medium-to-large. Another intervention for TRD is repetitive transcranial magnetic stimulation (rTMS). A meta-analysis investigating this treatment on response and remission rates in TRD was evaluated23. This study used risk ratios; the risk ratio (RR) compares the risk of a health event among one group (e.g., treatment group) with the risk among another group (e.g., control). In our case, a risk ratio of 1.0 indicates identical risk, whereas a number greater than one favors psilocybin, and less than one favors the control. This study found that the RR for response was 2.25, and the RR for remission was 2.78, both in favor of rTMS over sham treatment. Another type of

treatment used in TRD is atypical antipsychotic medications. A meta evaluating ORs in these types of treatments versus placebo was assessed[24], and all medications were found to be more effective than placebo, with ORs ranging from -0.43 to -0.27 (here, a negative OR indicated that the medication was favorable to placebo, but still considered a low effect size). Finally, TRD may, as of recently, be treated with intranasal esketamine. A meta-analysis investigating the efficacy of this treatment as an adjunct to current treatment, compared against a control condition, was assessed[25]. This study used effect sizes (see above), and found that adjunctive treatment with intranasal esketamine was significantly more effective than placebo, with an effect size of -0.24, indicating a small effect size.

Meta-Analyses, Current Treatments for Anxiety Disorders

In the treatment of anxiety disorders, a meta-analysis investigating the effect of CBT on anxiety was evaluated[26]. This study calculated the effect size between the changes in disorder symptoms from baseline to the end of treatment. Using Hedge's g (see above) the analysis indicated a medium effect size (g=0.56) of CBT on symptoms of anxiety. They also included measures of efficacy of CBT (without concomitant medication) on depressive symptoms, and found a small-to-medium effect size (g=0.31). Another meta-analysis investigating pharmacotherapy (without psychotherapy) as a treatment for anxiety disorders found that in general, pharmacotherapy has an effect size of 0.39 when comparing the difference in scores from baseline to the end of treatment between the treatment and control conditions[27]. A meta-analysis investigating the effects of psychotherapy and pharmacotherapy separately, as well as combined, was evaluated also[28]. Like the previous studies, this one compared the changes in anxiety symptomology from baseline to the end of treatment between the treatment and control conditions through effect sizes. In general, medications also were associated with a significantly higher effect size (d=2.02) than psychotherapies (d=1.22) in treating anxiety disorders. When psychotherapy and pharmacotherapy were combined the effect size was 2.12. All of these are considered very large to huge effect sizes.

Alcohol Use Disorder

One phase II, double-blind, placebo-controlled RCT investigating psilocybin, with a psychotherapeutic component, as a treatment for alcohol use disorder (AUD) was analyzed[29]. A total of 95 participants with a diagnosis of AUD were randomized to one of two groups, psilocybin (n=49) or placebo (diphenhydramine; n=46). All participants received four sessions of psychotherapy before treatment, two eight-hour sessions with the drug (separated by four weeks), and finally four non-drug follow-up psychotherapy sessions. Psilocybin doses were calculated by participant body weight (BW). During the first drug session participants received 25 mg/70kg BW, with the option to increase to 50 mg/70kg BW at the second session. The study assessed the percentage of heavy drinking days, the percentage of total drinking days, and the mean drinks per day over the following 32 weeks. By the end of this timeframe, the percentage of heavy drinking days was 9.7% for the psilocybin group and 23.6% for the control group; this was statistically different. The psilocybin group also had statistically fewer drinks per day than the control group, and neared a statistical difference for the percentage of total drinking days. One secondary outcome investigated was abstinence. While there was no

statistical difference in this measure between the psilocybin and control groups, there was a trend towards improvement following psilocybin.

Two systematic reviews[30,31] discussing the above-mentioned RCT, as well as one non-RCT[32], were analyzed. This non-RCT was a pilot study wherein all participants (n=10) received psilocybin-assisted therapy, following the same design as above. Like the RCT, this study found a statistically significant decrease in the percentage of total drinking days and the percentage of heavy drinking days when compared against baseline measurements. These measurements remained at this lower level 36 weeks after the treatment[32].

While there were some adverse effects in response to psilocybin treatment, these were considered mild-to-moderate. During treatment these were commonly anxiety and nausea or other gastrointestinal distress. Headaches occasionally occurred within 48 hours of treatment[29,32], along with some acute insomnia[32]. Psilocybin also resulted in a temporary increase in blood pressure and heart rate during treatment[29]. While there were no serious adverse effects associated with psilocybin treatment, one participant reported transient, passive suicidal ideation, which resolved without incident[32].

Comparison of Efficacy, Alcohol Use Disorder

Current treatments include three medications (naltrexone, acamprosate, and disulfiram) as well as cognitive behavioral therapy (CBT), which is often used in conjunction with medication[33]. There have been no meta-analyses directly comparing the efficacy of psilocybin as a treatment for AUD against current standard treatments, and therefore a 1:1 comparison of efficacy with the single RCT investigating psilocybin-assisted therapy cannot be made at the moment. However, we can make imperfect comparisons.

One meta-analysis evaluated the efficacy of several pharmacotherapies for treating alcohol use disorder, including naltrexone, acamprosate, and disulfiram[34]. This meta-analysis analyzed 118 RCTs, consisting of 20,976 participants. To compare the efficacy of these treatments against placebo conditions, they calculated the weighted mean difference (WMD); this measure describes the difference between the means of treatment groups, after weighing individual studies.

In looking at the percentage of heavy drinking days, the WMD comparing any dose of naltrexone against placebo found that , there was a mean of nearly 4% fewer heavy drinking days when using naltrexone, and a mean of just over 3% fewer heavy drinking days when using acamprosate[34]. A similar statistic was used in the psilocybin-assisted therapy study, though because this was a single study the measurement was simply the difference between means (unweighted). The mean difference in the number of heavy drinking days between the psilocybin and control groups was nearly 14%[29]. In looking at the percentage of any drinking days, the WMD indicated 4.5% fewer drinking days when receiving naltrexone and just over 8% fewer drinking days following acamprosate[34]. In comparison, psilocybin group had just over 13% fewer drinking days than the control condition[29]. Finally, evaluating the number of drinks per day, the WMD indicated that there was an average of almost one less drink per day in those receiving naltrexone as compared with placebo, while those who received acamprosate drank an average of 0.6 more drinks per day than those in the placebo group[34]. In the comparison of psilocybin versus control, the mean difference indicated that the psilocybin group drank an average of one drink less per day than the control group[29].

Another meta-analysis investigating the effect of combining pharmacotherapy with cognitive behavioral therapy (CBT) was analyzed[35]. The authors included 30 RCTs; 15 of these trials focused on AUD while the remaining 15 investigated either cocaine or opioid use disorders. The authors did not separate the analysis by type of substance use disorder, so the following statistics include results from those trials on cocaine and opioid use disorders. Furthermore, this meta-analysis evaluated the frequency of substance use as one unit, rather than isolating (for example) heavy drinking from total drinking. This study also used effect sizes (see Mood Disorders section for scale) rather than weighted mean differences. Comparing between CBT plus pharmacotherapy and usual care plus pharmacotherapy, the effect for CBT on posttreatment frequency of use outcomes was small but statistically significant (g=0.18)[35]. As a comparison, in the RCT, the percentage of total drinking days between the psilocybin and control groups resulted in an effect size of 0.4, in favor of psilocybin. Furthermore, the percentage of heavy drinking days following psilocybin versus the control group resulted in an effect size of 0.52. Additionally, in the meta-analysis, when looking at the quantity of substance use after treatment, the effects were small to moderate, but significant (g=0.28)[35]. Comparing the mean drinks per day between the psilocybin and control groups in the RCT, the effect size was 0.54, again in favor of psilocybin[29].

Cluster Headache

One exploratory, double-blind, placebo-controlled RCT investigating the use of psilocybin as a treatment for cluster headache was found[36]. A total of 16 participants were randomly assigned to either the psilocybin group (n=8) or the placebo group (n=8). Starting 14 days before the first experimental session, and lasting until the end of the experiment, participants kept a headache diary in which they logged the date, time, duration, and intensity of every cluster headache. Psilocybin was dosed by body weight (BW) (0.143 mg/kg BW), and treatment occurred over three 6-hour experimental sessions, each separated by approximately 5 days. While there was a reduction in attack frequency of cluster headache in the psilocybin group in the three weeks after the first session, there was no statistical difference in cluster headache frequency between the two groups. This was true for the measure of duration and intensity as well. Most frequent reports of adverse effects were mild-to-moderate and typically occurred during treatment. These included nausea and anxiety. Some participants also reported fatigue the following day. One participant experienced paranoia, but this resolved with staff support. Psilocybin increased blood pressure and heart rate, but there were no serious adverse effects reported.

The authors of this study conducted an extension experiment, in which 10 of participants returned for another psilocybin pulse regimen[37]. However, this extension was not an RCT; all participants received psilocybin this time (10 mg per session, for three sessions). While the authors reported a 50% decrease in cluster headache attack frequency at the end of this second round of treatment, the baseline attack frequency as measured at the start of the extension study was approximately double that measured in the initial study, a measurement that was statistically significant. Interestingly, the most frequently reported adverse effect both during treatment and in the following day was cluster headache. Otherwise, adverse effects were largely the same as the initial study, including cardiovascular effects[37].

Comparison of Efficacy, Cluster Headache

Cluster headaches are difficult to successfully treat, but are conventionally treated with triptan drugs, oxygen therapy, and non-invasive vagus nerve stimulation injections[38]. There have been no meta-analyses directly comparing the efficacy of psilocybin as a treatment for cluster headaches against current standard treatments. However, the single RCT identified found no statistical difference between psilocybin treatment and the control condition, therefore, we cannot compare the efficacy of psilocybin against current standard treatments for cluster headache at this time.

Overall Risks of Psilocybin as a Treatment

Risks in Clinical Trials

To review, while there were some adverse effects associated with psilocybin treatment in the RCTs, most effects were considered mild-to-moderate. The most commonly reported events during treatment were headache, nausea, dizziness, and fatigue. A recent meta-analysis concluded that these effects were statistically more likely to occur following psilocybin as opposed to the control condition[39]. Occasionally there were reports of anxiety, visual perceptual effects, migraine, and gastrointestinal effects. Negative effects appeared to be dose dependent; higher doses of psilocybin were associated a greater number and intensity of adverse effects. Only a few participants experienced more severe effects, including panic attack and paranoia; however, a single therapeutic dose of psilocybin is not statistically associated with paranoia[39].

While most adverse effects occurred only during the treatment and resolved on their own, headache was reported to linger for a few days after the treatment in most studies. These effects, particularly headache, were found to occur in studies of healthy individuals as well, and again were dose-dependent[40,41]. In the RCT that directly compared psilocybin to escitalopram (see above, Mood Disorders section), the percentage of patients who experienced anxiety, dry mouth, sexual dysfunction, or reduced emotional responsiveness were all higher in the escitalopram group than the psilocybin group[4].

Because these trials included individuals with treatment-resistant depression (TRD), there were a handful of reports of suicidal ideation, behavior, or self-injury, both in psilocybin and control groups. Individuals with TRD are often at an increased risk of suicidal ideation. Increased suicide risk with serotonergic antidepressant drugs has been a noted concern in the literature. Something to pay attention to, particularly regarding TRD, is that these individuals have been through several rounds of ineffective treatment, and may consider psychedelics as a last resort. Given the recent media hype around psychedelics as “cure-all” drugs, it is conceivable that if psilocybin-assisted treatment is perceived as being ineffectual as well, demoralization and hopelessness (and potentially further suicidal behavior) may ensue in this population[42].

In the RCTs, psilocybin treatment was found to increase blood pressure and heart rate as compared with the control condition, but these increases were considered mild and did not require medical intervention. However, more research regarding the effects of psilocybin with serotonin receptors in the cardiovascular system is necessary. Most RCTs have excluded participants with known cardiovascular disease, and therefore the effect of psilocybin in

serotonin-related cardiotoxicity is unclear. The potential for psilocybin to induce arrhythmia, as well as platelet aggregation, needs further investigation[43].

In healthy subjects, psilocybin administration has been suggested as use to model early psychosis or schizophrenia through the engagement of serotonin 2A receptors in particular regions of the brain[44,45], as well as mimicking the neural functional connectivity patterns of these psychotic and/or schizophrenic states[46,47]. However, a meta-analysis of the effects of psilocybin on "healthy" volunteers concluded that the administration of moderate doses of psilocybin was associated with an acceptable level of risk, with the side effects mirroring those seen in the above-mentioned RCTs[48]. Another RCT investigating the effects of the drug in healthy individuals found that psilocybin statistically reduced concentrations of certain pro-inflammatory cytokines, with some of these drops occurring immediately, and some of the decreased levels persisting up to a week after treatment[49]. The researchers hypothesized that the persisting effects of psilocybin on biomarkers of inflammation may play a part in the antidepressant effects of the drug.

Drug-Drug Interactions

Though interacting with the serotonin system, the use of psilocybin appears unlikely to result in serotonin toxicity, as psilocybin does not contain monoamine oxidase inhibitors[50]. Interestingly, pre-treatment with escitalopram appears to weaken the negative drug effects of psilocybin, including anxiety and adverse cardiovascular effects, with no effect on the positive mood effects of psilocybin[51]. However, SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) taken concurrently, or within three months of discontinuation, with psilocybin may weaken the overall effect of the drug[52]. An open-label, non-RCT investigated the efficacy of 25 mg of psilocybin (with a therapeutic component) adjunct to an SSRI[53], and found that participants reached clinically meaningful improvements in depression severity without any serious adverse effects. Certain antipsychotic medications (e.g., chlorpromazine), as well as GABAergic agents (e.g., benzodiazepines) have been shown to attenuate the drug effects of psilocybin[54,55].

Abuse Potential and Toxicity

Psilocybin does not appear to have great abuse potential; particularly, reports of acute elevations of anxiety in some patients are predictive of low abuse potential, as well as a sense of contentment following taking the drug. Together, these are not suggestive of a strong motivation for repeated and/or chronic use[56]. Physical dependence to and withdrawal from psilocybin have not been documented. Psilocybin carries a low risk of overdose toxicity. Poisoning from mushrooms containing psilocybin appears to be rare, though acute negative physiological and psychological reactions can occur[57,58]. The lethal dose in humans has been theoretically estimated to be approximately 1000 times an effective dose[59]. This corresponds to an amount that is likely not possible for an individual to consume when in the form of psilocybin-containing mushrooms. There are only very few reported cases of fatality following ingestion of psilocybin-containing mushrooms: one case of acute overdose poisoning occurred in an individual who had previously received a heart transplant[60] and another occurred after an individual ingested a large amount of psilocybin-containing mushrooms and jumped from a two story building[61].

Negative Effects Outside of the Clinic

While rare, two cases of Tako-Tsubo cardiomyopathy following the consumption of psychoactive fungi have been reported[62,63]. Two cases of rhabdomyolysis following ingestion of large amounts of psilocybin-containing mushrooms have also been reported; one occurred in an individual that experienced concurrent psilocybin-induced psychosis[64], and one occurred in an individual with hepatitis C, resulting in acute renal failure, posterior encephalopathy with cortical blindness, all of which were treated successfully[65]. However, a clinical trial investigating the pharmacokinetics indicated that, at clinical doses, renal clearance of intact psilocin accounted for less than 2% of the total clearance, suggesting that no dose reduction is needed for subjects with even mild-to-moderate renal impairment[66]. Similar to LSD, negative effects of psilocybin appear more likely to occur outside of a controlled environment, by those who are unexperienced or unprepared, or those with or predisposed to psychotic disorders[56]. A recent incident involving a pilot for Alaska Airlines further highlights the need for awareness of the "set and setting," referring to the mindset of the individual and the physical location, in taking this substance. If an individual is in a state of crisis or instability, psilocybin-containing mushrooms, without appropriate support, may further destabilize the individual[67]. In terms of emergency room visits, the only predictor associated with higher risk of emergency medical presentations is young age[68]. There was one report in the literature of an 18-year-old individual experiencing hallucinogen persisting perception disorder after consumption of psilocybin-containing mushrooms and cannabis together, which persisted for more than eight months before spontaneously resolving[69].

Risks of Current Standard Treatments

Adverse effects in response to standard treatments for major depressive disorder, anxiety disorders, and alcohol use disorder can be found in the LSD Literature Overview document (see April 2024 Task Force meeting materials), and so will not be summarized here.

An additional standard treatment for bipolar disorder, including bipolar type 2 disorder, is the use of mood stabilizers (e.g., lithium). Adverse effects of lithium treatment include tremor, nausea, fatigue, increased appetite, increased white blood-cell count, thirst, and increased frequency of urination. There are some reports of decreased cognitive functions. Lithium should not be used by individuals who have, or have had, acute myocardial infarction, acute kidney failure, or certain rare disorders of heart rhythm[70].

Treatment-resistant depression often employs additional attempts at treatment above antidepressants and psychotherapy. Other interventions include ECT, rTMS, and, as of recently, intranasal ketamine. Common acute adverse effects in response to ECT include headache, nausea, myalgia, and confusion; oftentimes these symptoms resolve on their own. Occasionally, retrograde amnesia may persist. Serious, but less common, adverse effects include cardiovascular, pulmonary, and cerebrovascular events[71]. Common adverse effects following rTMS include headache and scalp pain. More serious effects include seizures and hypomania, though the incidence of these more major adverse effects is low. Rarely, the procedure can result in transient increases in auditory threshold, the use of earplugs can mitigate this effect[72]. Finally, intranasal ketamine can result in dissociation, nausea, vertigo, dysgeusia, and dizziness[73].

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