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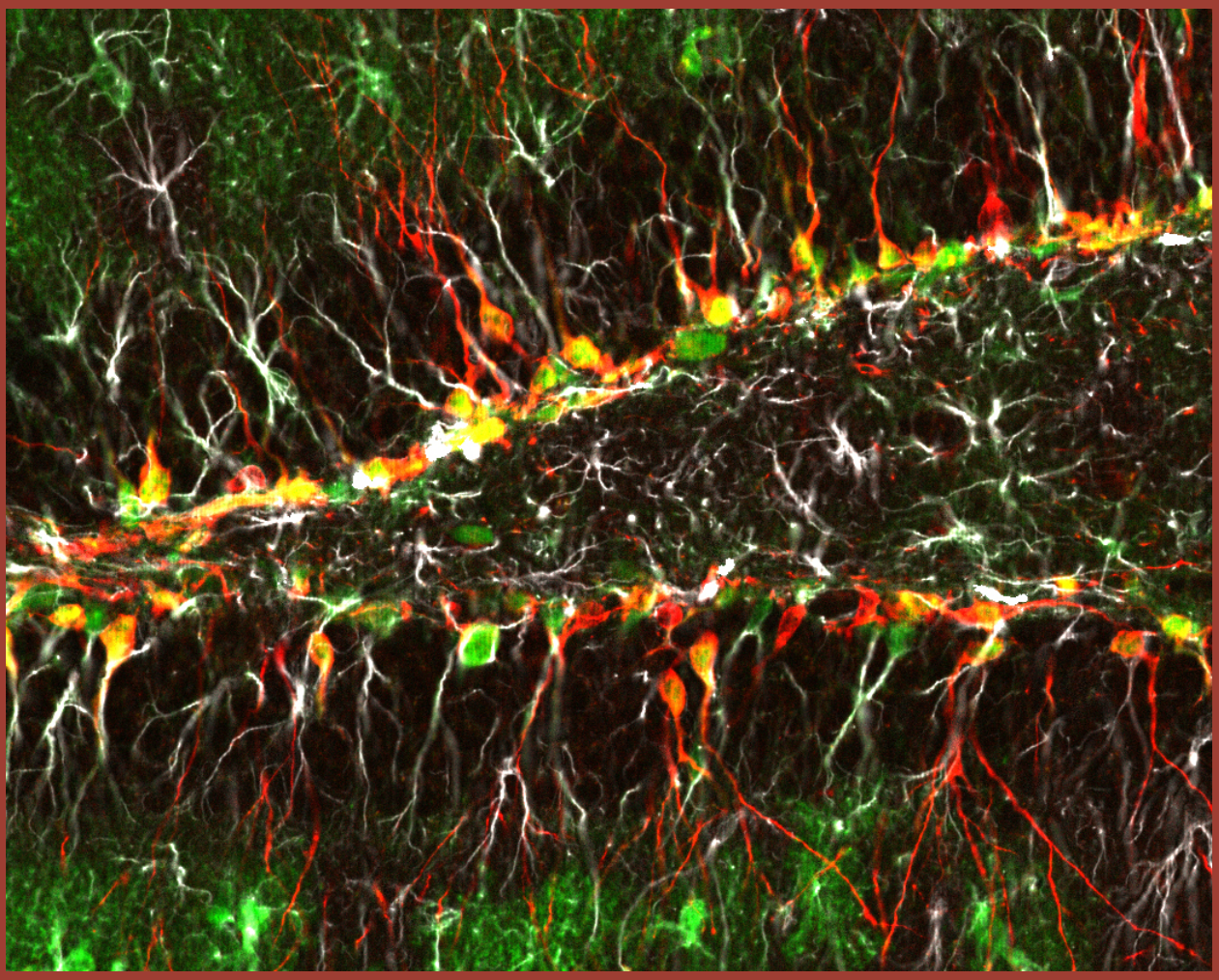

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Enhancing Methodological Rigor in Controlled Trials of Psychedelics

Christine K. Moore, PhD; Julia D Forte, MSc; Natalia E Drosopoulou, PhD; Henry J Riordan, PhD

Abstract:
There has recently been a resurgence in the clinical development of pharmacologic treatments for psychiatric disorders, exemplified by a renewal of psychedelic research. Given the unmet need for new therapies in psychiatry and encouraging positive results from initial psychedelic clinical trials, there is tremendous enthusiasm and promotion of their potential for a variety of indications. Though promising, this enthusiasm has been ahead of a general acceptance of rigorous clinical trial methodology and optimization of study designs to show treatment effects and sufficient characterization of safety. Importantly, although psychedelics are largely considered to have a favorable safety profile, their pharmacology is complex, and their use is not without risk. Only recently have clinical trials in major depression, treatment-resistant depression, post-traumatic stress disorder, and other indications been undertaken in efforts to replicate earlier proof-of-concept trials. These well-controlled clinical trials in larger patient samples are needed to further characterize which patients might be predisposed to adverse reactions, which patient characteristics might predict response, and the optimal treatment setting. This paper outlines the need for conducting psychedelic clinical trials with more rigor, not only to substantiate efficacy but also to characterize their safety. As there is increasing demand for sites that can conduct these trials, this paper also summarizes considerations for implementing psychedelic trials with rigor and efficiency while accounting for site and patient practicalities, including a discussion of appropriate patient enrollment, the ideal site profile, and suggested safety

We are fortunate to be in the midst of a "renaissance" in neuroscience drug development characterized by a renewed interest in pharmacotherapies aimed at the central nervous system (CNS) [1]. This revitalization has been driven by increasing knowledge of the pathophysiology of neuropsychiatric diseases, encouragement from regulatory agencies that are inspiring innovative approaches to drug development, and funding sources for development that have been both diversified and increased. This resurgence of CNS clinical trials should ultimately improve the quality and extent of life for those afflicted with mental health disorders, particularly given the tremendous unmet medical need in psychiatry specifically, which has only been exacerbated by the COVID-19 pandemic [2].

This recent resurgence in psychiatry is exemplified by an ever-growing interest and renewal of psychedelic clinical research. The psychedelic market is expected to grow from an estimated $2 billion in 2019 to $10 billion by 2027 [3], with over 70 organizations with psychedelic drug development programs underway and beginning to advance toward larger Phase 3 trials. Several distinguished academic institutions globally have dedicated psychedelic research centers or programs; some examples include Yale and Johns Hopkins in the United States and Imperial College and King's College in the United Kingdom, with a growing number of research sites entering the space. Psychedelic research efforts were initially funded primarily by non-traditional sources such as philanthropic gifts and non-profit organizations—a shift in

traditional psychiatric drug development once heavily reliant on industry, although industry and federal agencies are now also heavily invested [4]. Regulatory agencies are encouraging psychedelic development efforts as well. The US Food and Drug Administration (FDA) granted breakthrough designation for MDMA-assisted therapy for post-traumatic stress disorder (PTSD) in 2017, followed by similar designations for two psilocybin-based compounds in 2019, one for treatment-resistant depression and one for major depressive disorder (MDD). Similarly, the UK Medicines & Healthcare products Regulatory Agency (MHRA) granted fast-track status for dimethyltryptamine (DMT)-assisted therapy for major depressive disorder in 2021, and in 2022 the Minister of Health in the Netherlands endorsed more research in psychedelic therapy [5]. Further, the US Drug Enforcement Agency (DEA) has accelerated the once onerous process of granting licenses for research with Schedule 1 compounds [6] and reversed its decision to categorize five different psychedelic substances as Schedule 1 after considerable public and researcher pushback [7].

These efforts have helped give rise to an abundance of encouraging data from recent psychedelic research across several psychiatric indications. In one study, a single dose of psilocybin produced substantial and clinically meaningful decreases in depressed mood and anxiety and increased quality of life in 51 patients with cancer-related distress[8]. Further, treatment effects were durable, with an overall rate of clinical response at 6 months for depression and anxiety of 78% and 83%, respectively. In a pooled analysis across six Phase 2 trials of MDMA in patients with chronic PTSD who had previously failed to respond to pharmacotherapies or psychotherapies, 54.2% of patients no longer met PTSD diagnostic criteria one to two months after two experimental sessions, compared to 22.6% in the control group, with a large effect size (Cohen's *d* of 0.8) [9]. After a third dose, symptoms on average improved further. In patients with moderate or severe MDD, psilocybin-assisted therapy produced robust, rapid, and sustained antidepressant effects after two sessions; 71% of patients continued to show a clinically significant response for up to 8 weeks, again with very large effect sizes (Cohen's d =2.6) [10]. Psilocybin has also shown promise for addiction, specifically in smoking cessation and alcohol use disorder [11,12]. Results have also been encouraging with ayahuasca, as seen in a preliminary report from a small sample of patients with a current depressive episode, noting clinically meaningful reductions in depressive symptoms three weeks after a single dose [13]. These studies, however, have mainly been in a small number of patients, but efforts to replicate results in larger samples are underway.

Given such results, it is not surprising that public interest and enthusiasm for using psychedelics to treat mental health disorders has grown at a staggering speed, albeit with some healthy skepticism toward pharmaceutical industry involvement, given that the drug class is deemed natural and used by Indigenous people for millennia. While it would be foolish not to both respect and learn from those with generational knowledge of these compounds, formal, rigorous testing is necessary, especially for (although not limited to) psychedelic substances that have been manipulated or are manufactured synthetically to minimize potential adverse effects.

Need for Rigorous Clinical Trial Methodology

Although psychedelics are considered to have a favorable safety profile, their pharmacology is complex, and their use is not without risk. Classic psychedelics including psilocybin, lysergic acid diethylamide (LSD), mescaline, and DMT, act as agonists at the

serotonin 2A receptors (5-HT_{2A}), which is similar to the mechanism of action for many antipsychotics and antidepressants. Serotonin (5-hydroxytryptamine, 5-HT) mediates a wide range of bodily functions, the more well-known being regulation of emotion/mood and memory, but also platelet aggregation and wound healing, gastrointestinal function, sexual function, and bone health. There are 14 distinct mammalian 5-HT receptor subtypes, which are divided into seven families (5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, and 5-HT7) distributed mainly in the central nervous system but also heavily expressed in the liver, kidney, heart, and fundus of the stomach [14]. LSD primarily acts on the 5-HT family of receptors but has non-specific interactions across several receptor types. Both psilocin (the active metabolite of psilocybin) and LSD are potent 5-HT_{2B} agonists; activation of 5-HT_{2B} receptors can cause cumulation of potentially serious side effects such as valvular heart disease with chronic use over time. Other psychedelics such as ibogaine and MDMA act on different pathways; for example, MDMA is an analog of phenethylamine and works via serotonin release rather than 5-HT_{2A} agonism, which causes psychoactive effects that only partially overlap with classic psychedelics [15].

Psychedelics also vary in their duration of action. LSD, for example, dissociates from the receptor very slowly and its effects are relatively long-lasting—12 to 36 hours depending on dose, with subjective effects not necessarily correlating with pharmacokinetics and lasting much longer. Conversely, DMT has a much shorter duration of effect, 30 to 90 minutes. Ayahuasca and psilocybin also have an intermediate duration of action (6 to 8 hours) and, along with LSD, are challenging to scale and control dose, thus limiting the ability to end a negative adverse reaction should one occur.

Serious adverse effects after using psychedelics in unsupervised settings are well documented. For example, MDMA toxicity has been associated with seizures, hyperthermia, acute kidney injury, and rhabdomyolysis, with some cases leading to death [16]. LSD and psilocybin commonly cause nausea, vomiting, headaches, agitation, and tachycardia [17]. Some patients may also experience heightened anxiety or panic, mood volatility, or psychosis-like symptoms during a "bad trip" that can linger or even exacerbate suicidality. Well-controlled clinical trials in larger patient samples are needed to help identify which patients might be predisposed to adverse reactions, what patient characteristics might predict response, and what the durability of response may be, at what dose, duration of treatment, and importantly, what kind of therapy (if any) should accompany dosing. It is also imperative to determine which medications may interact with psychedelics to make more informed risk/benefit judgments at the individual patient level. The purpose of performing such clinical trials is not only to substantiate the efficacy of putative compounds but to address these types of questions and ultimately to protect patients who would otherwise be exposed to undue risk. It should be noted, however, that although rigorous clinical trials are necessary, there remains the need for balance with expeditious patient access to potentially beneficial treatments; it is precisely for that reason that regulatory agencies have created fast-track programs.

Given the public enthusiasm to use these substances, there is some urgency to both initiate and expand larger studies in the psychedelic space. In the US, states are already beginning to legalize access to psilocybin for mental health treatment, despite insufficient evidence supporting the practice [18]. Research with ketamine for mood disorders began much the same way and there are applicable similarities in terms of cautions and pitfalls. Small academic studies of ketamine for treatment-resistant depression were

completed then followed by a National Institute of Mental Health study in 2006; about 300 clinical trials have since been conducted and the first "ketamine clinic" was opened in the US in 2012 [19]. Although ketamine has been approved by the FDA as an anesthetic for nearly five decades, the lack of patent protection and prolific off-label use makes it unlikely that larger Phase 3 trials required for approval in a psychiatric indication or post-marketing surveillance studies that would address longer-term safety and effectiveness will ever be completed [20]. There are likely now 800 to 1000 ketamine clinics in North America alone using off-label or "proprietary blends" of ketamine for depression, with wide-ranging inconsistencies in screening patients, medical oversight, dosing, and frequency of infusions [21].

The popularity of ketamine clinics was at least partially fueled by the approval of intranasal esketamine (SPRAVATO®) in the US, UK, and Europe for treatment-resistant depression in March of 2019. Though esketamine is derived from racemic ketamine, they are not the same drug—there is no FDA-approved dosing regimen, no data supporting the conversion of esketamine nasal spray and compounded ketamine nasal spray, and compounded ketamine is often used at different doses and higher frequency than currently approved for SPRAVATO®. It should be noted that SPRAVATO® was also approved with a required Risk Evaluation and Mitigation Strategy (REMS) due to its potential for sedation, dissociative properties, and abuse and misuse. This program requires certification of pharmacies and healthcare settings and administration only in a medically supervised healthcare setting with appropriate monitoring. The FDA has more recently issued a health alert after a concerning number of case reports of psychiatric adverse events associated with off-label use of ketamine, and after becoming aware that some pharmacies compound nasal spray formulations of ketamine either alone or in combination with other ingredients [22].

Optimizing the Conduct of Clinical Trials of Psychedelics

Given the tremendous interest in psychedelic drugs, the need for rigorous clinical trial methodology, and the increasing demand for sites that can conduct controlled psychedelic clinical trials, the remainder of this paper will summarize considerations for optimizing study conduct. While clinical trials in psychiatry are by nature complex, psychedelic trials in psychiatric indications can be even more complex and there is no uniform approach to follow. Logistically, conducting large, global clinical trials of psychedelics intended for registration can be challenging but is quite achievable. Considerations follow for implementing psychedelic trials with rigor and efficiency while accounting for site and patient practicalities, including a discussion of appropriate patient enrollment, the ideal site profile, and suggested safety monitoring for psychedelic clinical trials. It should be noted that some of these considerations vary by compound and the treatment model employed; this discussion is intended to be broad and may not apply to all psychedelic compounds and treatment models.

Enrolling the right patient population

There are always indication-specific considerations in psychiatric trials to ensure proper diagnosis of the condition under study, exclusion of comorbidities, history of response (or lack thereof) to previous treatments, and requirements for symptom severity and stability over time. All of these are equally relevant in psychedelic trials and should be contemplated in terms of individual patient safety and to help ensure trial assay sensitivity (i.e., the ability of a trial to detect treatment differences if they actually exist). For example,

although the literature is not clear on how previous experience with psychedelics may influence subsequent experiences and treatment response, careful determination of a patient's previous psychedelic use pattern is warranted prior to enrollment in a clinical trial and whether that use was recreational in nature or part of a medical treatment plan. It is also important to characterize their subjective experience. Patients who did not respond to prior psychedelic use in a medical treatment setting, who experienced worsening symptoms or significant anxiety during treatment, or who developed active suicidal ideation after treatment should be excluded from participating in a clinical trial of a similar drug. Patients who used psychedelics recreationally within the last few years should also be excluded if their use patterns are consistent with substance abuse.

Patients with mood disorders and other mental health conditions are vulnerable by nature. Psychedelic studies perhaps draw an even more vulnerable patient population—patients have often tried many other treatment options unsuccessfully and see participation in a psychedelic trial as a "last resort." Patients are also becoming increasingly savvy "consumers" and are acutely aware of the clinical trial space and what is required for enrollment. Some may feign or deny specific symptoms or even purposefully achieve certain scale scores to qualify for enrollment. In the face of such expectations or behavior, it is challenging for the research site staff to strike the right balance in managing patient expectations of benefit and providing therapeutic support required within the study protocol with the ability to objectively determine if study medication is efficacious and maintaining clinical equipoise.

Of note, not all research sites are equally skilled in diagnosing psychiatric conditions and relevant comorbidities. Incorporating a structured clinical interview (e.g., the SCID or MINI) can be useful not only for diagnostic specificity, but also for standardizing diagnostic methods across investigative sites and correctly identifying salient comorbid disorders in an individual patient. Adequate severity and stability of symptoms should also be considered formally in protocol entry criteria. For example, in trials for MDD or treatment-resistant depression (TRD), there are typically minimum severity requirements as measured by the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS), or similarly with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) in PTSD trials to avoid ceiling and floor effects and enhance the ability to detect change with treatment. It is not enough to have adequate symptoms, but they should also be relatively persistent. Stability of symptoms can be guaranteed by assuming that there should not be significant changes (improvement or decline) in key symptoms over relatively short periods of time on successive measures, which could be accomplished by excluding those with more than a 20% or 30% change in a severity score (e.g., HAM-D, CAPS-5, MADRS, etc.) between screening and baseline. Patients with higher levels of variability are more likely to have external sources driving this instability and are more likely to respond to non-specific effects independent of treatment and therefore heighten "placebo" response.

Other sources of non-specific treatment effects include rater inflation or exaggerated judgment of symptom severity by the clinician (subconsciously or overtly) to qualify a potential patient to meet study entry criteria. Rater inflation can result in an artificial improvement of symptoms post-baseline reflecting regression to the mean. For example, when using a high HAM-D score for inclusion purposes, a decrease in score the next time the scale is administered would be expected even with no treatment. This decrease is because statistical regression to the mean

acknowledges that severe or higher scores are more likely to have positive measurement error, while less severe or lower ones are more likely to have negative measurement error. As measurement error is, by definition, uncorrelated with the true measurement of the underlying construct, the measurement error of any two independent measures of the same construct should be zero. There are several ways to help avoid rater inflation, including the use of one scale for entrance purposes (e.g., the Hospital Anxiety and Depression Scale for Depression [HADS-D] or even a Clinical Global Impressions [CGI]) followed by a separate independent scale for baseline (e.g., the HAM-D) and then using change scores from that baseline measure as an efficacy outcome, which ultimately helps reduce placebo response. Alternatively, using a combination of self-report and investigator-reported measures with some measure of congruence has been shown to be helpful. Additionally, blinding patients (as well as site staff) to all cardinal entry criteria can decrease the possibility of rater inflation of scores for inclusion purposes; appropriate and efficient randomization can be accomplished through the use of an algorithm via an automated system. When blinding these entry criteria, sites are merely informed that there will be a minimal level of severity and stability during the screening period and that sites will be notified if the patient is eligible for randomization or not. Finally, the use of independent centralized raters blinded to the study visit of individual patients can prevent biased inflation of ratings.

A history of treatment resistance should also be carefully evaluated, with the definition of treatment resistance clearly defined in the study's protocol, typically operationalized as less than a 30 to 50% response to at least two treatment agents of different classes taken over an adequate period with ostensible compliance. Patients with a current or lifetime history or family history of any psychotic disorder, bipolar disorder, or personality disorder should also be excluded from participating in a psychedelic trial for both safety and efficacy reasons. Additionally, unless there are strong data indicating that there are no drug-drug interactions of consequence with other serotonergic agents, the use of serotonergic medications is generally discontinued prior to study entry.

Practically Managing "Placebo" Response

Control groups in clinical trials allow discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors (e.g., natural progression of disease, patient expectations, or other treatment) and are required by regulatory agencies for the evaluation of safety and efficacy [23]. An adequate and well-controlled trial, as defined by regulatory agencies, could utilize a placebo control, no treatment, a different dose or regimen of the study treatment, or a different active treatment. Given the extensive and recognizable effects of psychedelics, these trials often do not include a true "placebo" control and instead often employ a very low dose of the test treatment or even a different active control that causes some physiologic response (e.g., niacin or methylphenidate) that is intended to aid in blinding. Regardless of the control used, patient and site expectations of benefit can have substantial impact on assay sensitivity of the overall trial. Most psychedelic study protocols incorporate preparatory sessions for trial procedures as well as the overall psychedelic experience (what to expect, what patients may or may not experience), which are critical. This training should also be extended to family members/caregivers, as family members can influence the response of the patient on efficacy measures. The requirement for caregivers in a psychedelic study varies,, depending on the compound and local country requirements. Competent authorities in some countries

mandate patient caregivers so that they are aware of worsening of patient symptoms during the washout period of SSRIs, for example, and to accompany the patient home after their dosing day. In addition, some study protocols also include caregiver assessments for an independent observer review of how the study drug has affected the patient.

During the consent process, patients are routinely told they may or may not receive active study drug and that if they do receive active treatment, it is uncertain whether it will work—and that this is the purpose of studying it in a clinical trial. For psychedelic studies in particular and given the profound mystical experience that can accompany psychedelic use, it should be further explained that change may occur in the absence of a complete mystical experience. Further, sites should encourage a "research" and, as much as possible, not a "therapeutic" partnership with patients in order to establish a true sense of clinical equipoise at the site in which site staff does not have a predisposition to study drug effect (i.e., the purpose of a patient's participation is to help determine if a treatment is efficacious, rather than to themselves improve). An assessment of site staff beliefs and expectations regarding clinical practice versus research should be incorporated, as well as a standardized training program on practical methods of standardizing patient interactions that will limit non-specific treatment effects. Site staff also need training on managing their own expectations of treatment success. Demanding that site staff interactions with patients be controlled and not inappropriately and unintentionally create a nonspecific supportive treatment environment that heightens placebo response is especially tricky in the psychedelic setting because in many instances therapy is by design part of the treatment. For this reason, the therapist (sometimes referred to as a facilitator, supporter, or moderator) providing support during and after dosing should be a separate clinician from the one providing efficacy ratings for the study. An independent rater, blinded to the patient's experience during dosing sessions, should complete efficacy assessments in these trials. Those raters should be evaluated on their qualifications to rate and have experience both with the patient population and the assessments used and undergo specific training on using those assessments in the context of the protocol for that specific study. Using remote centralized raters through phone or video contact with subjects is an alternative option that can be more efficient and further decrease variability in study outcomes.

Proper Safety Monitoring

Proper safety monitoring in a psychedelic clinical trial is multifaceted and should be in place both during and after dosing sessions. Prior to dosing sessions, careful preparation of patients regarding the session is essential. During dosing sessions when patients are most vulnerable, the setting should provide a safe environment that can accommodate privacy, particularly in the event of a difficult experience. Real-time access to an on-call physician or clinician (often a psychiatrist) responsible for safety should be maintained in case the patient requires rescue medication or additional psychiatric support. Anxiety can often occur and can be significant but transient; sustained psychotic reactions or loss of reality are rare. Participant consent permitting, sessions should be videotaped and reviewed in a timely manner by independent reviewers, which protects both the patient and the therapists/facilitators. Of note, regulatory agencies may also request a review of videotaped sessions. Physiologically, safety monitoring by qualified, trained staff that can provide medical oversight should include an evaluation of cardiovascular effects (QT prolongation, tachycardia), respiratory depression, sedation or impairment, and

although rare, serotonergic toxicity, seizures, or hallucinogen persisting perception disorder. Frequent acute physiologic effects also include nausea and vomiting. Patients with valvular heart disease, uncontrolled hypertension, or arrhythmias or who are taking other serotonergic agents, MAOIs, lithium, atypical antipsychotics, or tricyclic antidepressants should not participate in earlier phase trials. Psychiatric adverse events of interest include psychosis or delirium and suicidal ideation, and those with a prior history or familial history of psychosis or severe mental illness should not participate. Nearly all psychiatric clinical trials have been required to formally and prospectively assess and actively monitor the occurrence of treatment-emergent suicidal ideation [24]. For psychedelic trials, this should also include a formalized, written plan of action (e.g., hospitalization, initiation of other treatment, referral, etc.) at the individual site level in the event suicidal ideation occurs. Data alerts should also be established for suicidality measures included in the protocol (Columbia-Suicide Severity Rating Scale [C-SSRS], MADRS, HAM-D scores) with active surveillance of those data by either the sponsor or study medical monitor.

Following dosing, patients can remain vulnerable for an extended period, and therefore post-dose integration sessions are important--crucial depending on the type of psychedelic. Sites should also be aware of the potential disappointment and worsening of symptoms if patients report feeling "no different" after treatment. Follow-up contact with patients should occur between clinic visits, with any symptom worsening documented along with whether those changes are due to the treatment itself, patient expectations of treatment, or if related to the natural course of illness. Once the clinical trial has concluded, adequate aftercare needs to be in place, whether with the established therapist or referral elsewhere. Therapy may come to an abrupt halt from the patient's perspective after the last study visit, which is of particular importance in psychedelic trials as patients have likely formed a bond with their therapist after many hours of partnership for the trial. Offering an open-label extension where all patients can access active study drug for an extended period is helpful in these cases and is also a successful way of aiding recruitment and mitigating against potential drop-outs of patients who were not randomized to active treatment. Ethics committees and Institutional Review Boards may also look favorably on offering patients extended open-label treatment as it not only allows patients access to active study drug but also permits more extensive safety evaluation.

Choosing the Right Sites

In addition to having the competencies related to appropriate safety monitoring, sites should have experience in the psychiatric indication under study, as well as experience in running clinical trials intended for registration in a "good clinical practice" setting. Ideally, sites would also have experience in psychedelic research (even better in a range of psychoactive agents), but this is infrequent. Aside from the requirements for traditional psychiatric clinical trials, psychedelic trials also require:

- Adequate resources, with few overlapping, competing trials. The main source of competition is often for scarce resources and capacity within a given site, although competing for the same patient population should also be considered,
- Sites with specialized, qualified, and trained therapists (or facilitators, moderators) that are separate from the investigator responsible for overall patient safety. Two therapists, one male and one female, are ideal.

- Additional independent efficacy raters, qualified and trained to rate scales being used in the study. Alternatively, centralized raters not on staff at the site may be used, which is often a more efficient approach that aids in minimizing unwanted variance in assessments.
- Recent experience with a range of Schedule 1 (or comparable) controlled substances, with adequate and secure storage. A separate pharmacist may be required if the drug storage location is off site.
- Suitable space for dosing rooms, with the ability to adjust the setting (furniture, lighting, audio) to specific protocols or to handle group dosing, if required.
- Importantly, the ability to recruit patients with established patient referral pathways in place, ideally ones who are well known to the investigator or referring physician. Sites that have a combination of their own clinic patients and additional patients through referrals tend to be the most successful. A tailored approach for each site is the most helpful way to boost recruitment, and establishing the patient recruitment pathway early on is key. Site-based referral pathways are more productive than broad direct-to-patient outreach campaigns for finding suitable patients whilst also mitigating the potential to overload sites with ineligible patients.

The geographic location of the site can also be important from a regulatory and timeline perspective. In some countries, the lengthy and cumbersome controlled substance licensing process can be started in parallel with ethics committee submissions as soon as sites are selected.

Given the tremendous increase in psychedelic trials, many more competent sites are needed. Of note, it is easier to train sites established and experienced doing regulated clinical trials which may not be experienced with psychedelics than to upskill those experienced with psychedelics on regulatory requirements conforming to International Conference on Harmonization Good Clinical Practice standards. One possible solution is to select known sites or site networks experienced with Phase 1 psychiatric trials that have an inpatient unit and infrastructure already in place and train them in the methods specific to psychedelic compounds and research setting. Having a blend of sites will greatly improve recruitment because experienced sites have clear and established patient pathways at the outset. Sites with previous psychedelic experience mitigate the risk of delays to site activation due to Schedule 1 licensing complexities and therapist recruitment, ultimately leading to delayed start-up timelines.

Summary

One clear illustration of the renewed interest in drug development for psychiatric disorders is the tremendous growing interest in psychedelics, hailed as potential treatments for anxiety, depression, and addiction – indications that have exhibited a recent rise in prevalence but with available treatments characterized by only modest efficacy with significant side effects. Recently both regulatory and funding agencies have demonstrated their willingness to both support and speed the approval of psychedelic treatments. Many pharma/biotech companies have taken advantage of these events and now find themselves in possession of promising albeit limited initial safety and efficacy data in small proof-of-concept studies. This encouragement for further development and the accompanying demand for more sites that can reliably and systematically conduct controlled clinical trials of psychedelics makes it imperative that drug

developers optimize study parameters. Specifically, sponsors should drive best practices surrounding proper patient and site selection, appropriate safety monitoring, training on apposite efficacy assessments and drug-related subjective effects, and management of "placebo" response in a rigorously controlled trial setting -- all while ensuring assay sensitivity and clinical equipoise. Only with the application of these effective and practical clinical trial methodologies can the conduct of large, global clinical trials of psychedelics intended for registration be ensured.

AUTHOR INFORMATION

Conflicts of Interest:
All authors are salaried employees of Worldwide Clinical Trials, an international, full-service, contract research organization that specializes in clinical research activities in support of the pharmaceutical industry. Relationships exist with multiple (>100) pharmaceutical companies as part of the company's primary business activity.

Send correspondence to Christine K Moore, PhD (christine.moore@worldwide.com)

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Viewpoint

Mechanistic actions of psychedelics on neurogenesis: Re-building the tapestry of consciousness

Mohan Muvvala, D.O., Harika Sandhu, D.O., Ezra Klein, D.O

Abstract:
Throughout history, many naturally occurring psychedelic substances have been recognized for their ability to alter emotions, cognition, and perception. These same compounds have recently been studied to better understand their role in adult neurogenesis. Adult neurogenesis is the creation of new neurons beyond fetal development in specific brain regions, which are then integrated into existing neural circuitry. These adult-born neurons play a key role in understanding how psychedelics can help promote healthier brain activity and lead to reversible effects for neurodegenerative conditions. Recent implicative studies of adult neurogenesis have shown its significance in the areas of Alzheimer's, Post Traumatic Stress Disorder, Schizophrenia, stress, and various other non-neurotypical conditions. This literature review will focus on what has already been discovered about adult neurogenesis through the use of LSD, Ayahuasca, and Peyote, as well as the future use of psychedelics in a clinical setting.

Keywords: LSD, ayahuasca, peyote, psychedelic, therapeutics, neurogenesis, depression

INTRODUCTION

According to the World Health Organization (WHO), neurological disorders are a major concern for public health, and many rural populations have taken charge of providing treatments by pulling resources from their naturally occurring environment. This concept of ethnobiological treatment has proven itself positively among populations. Thus, WHO is beginning to stress the importance of inspecting these traditional medicinal plants and seeing if any of the compounds being used can be utilized in the prevention and treatment of psychological illnesses worldwide [1]. One such study was conducted on a rural population in Chota Nagpur Plateau, India--a place full of plant, animal, and population diversity in terms of indigenous communities. The results of this study reported 65 knowledgeable and traditional medicine men and 47 traditional formulations from plants and animals to use against 13 neurological and psychological disorders [2].

Given this knowledge, there has been an interest in studying naturally-occurring psychedelics and similar synthetically produced psychedelics that diverse cultures across the globe have used. There has been a particular interest in serotonergic psychedelics, as serotonin is implicated in many prevalent mental disease states such as Major Depressive Disorder, anxiety, and addiction. The mechanism of therapy proposed by existing literature shows that a psychedelic compound's efficacy lies in "destabilizing networks in the brain and amplifying neurons," allowing the brain to "reset" itself [2]. This phenomenon is referred to as neurogenesis. Both interconnectivity and neurogenesis play a role: Interconnectivity or neuroplasticity is the ability for the brain to form new connections and pathways from already established neurons and adapt based on learning and injury. Neurogenesis on the other hand is the ability to form new neurons and from those neurons, create new connections. Furthermore, psychedelics show promise in treating inflammatory diseases, with some mechanisms of action being more advantageous than existing anti-inflammatory agents currently on the market.

A study conducted in 2015 sampled 130,000 adults in the United States to see if there was a correlation between psychedelic use and mental health issues. Researchers concluded that there was no such link between the two. Additionally, psychedelic use is not prone to addiction or excessive use, furthering the interest in researching psychedelic compounds to be used as therapeutic drugs [3]. Aside from the physical remodeling of the brain induced by psychedelic compounds, psychotherapists also envision practical applications for their use in therapy. Psychologists propose that these substances can help a patient confront traumatic events by inhibiting the "fear response," help the patient build intimate communication, and foster a strong relationship between the patient and therapist [4]. Thus, this literature review will discuss physical, emotional, and psychological responses brought about by LSD, Ayahuasca, and Peyote as suggested therapeutics.

LSD AND ADULT NEUROGENESIS

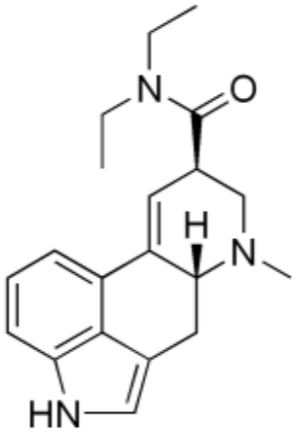

Figure 1: Common Name - Lysergic Acid Diethylamide (LSD), IUPAC Name - (6aR,9R)-N,N-diethyl-7-methyl-6,6a,8,9-tetrahydro-4H-indolo[4,3-fg]quinoline-9-carboxamide, Molecular Weight - 323.44 g/mol, Molecular Formula - $C_{20}H_{25}N_3O$

Lysergic acid diethylamide, LSD, is a hallucinogen that mediates excitatory and inhibitory input in structures of the cortex located along the midline. Although its synthesis is quite extensive, the starting product is always lysergic acid, which then gets activated and reacts with diethylamine or N,N-carbonyldiimidazole. LSD acts as an agonist on frontocortical 5-hydroxytryptamine 2A-serotonin (5-HT2A) receptors and as an agonist at D1 and D2 dopamine receptors. 5-HT2A helps regulate the production of Brain-Derived Neurotrophic Factor (BDNF), which in turn helps regulate neurogenesis and neuroplasticity. These serotonin receptors show nootropic benefits, especially within areas essential for learning and memory. Furthermore, the drug's serotonergic action is also implicated in anxiolytic and antidepressant cognition. Studies have shown that the 5-HT2A receptors specifically located in the fronto-parieto-occipital cortex play a role in invoking a positive mood [5]. Given this information, researchers have begun a closer examination of how the drug works employing electrophysiology, neuroimaging, and molecular analysis techniques to test its efficacy in therapeutics [6]. Functional clustering analysis has demonstrated that LSD enhances pathways involved in neurotransmission, energy metabolism, neuropeptide signaling, and, most importantly, synaptic plasticity [7].

However, with chronic LSD use, there has been an increase in tolerance, leading to decreased 5-HT2A receptor binding and increased pathways involved in the pathogenesis of schizophrenia and related psychotic illnesses, which is supported by a study of LSD in populations of children with autism and adults. The study showed that children with autism were less likely to develop tolerance and the associated schizophrenia-like adverse effects than adults.[6] Further clinical research has proven that when only two doses of LSD are used, patients suffering from anxiety report a significant reduction of symptoms for up to 2 months after exposure [7]. Numerous published case studies have found that therapeutic uses of LSD lead to an overall increase

in mental-health positivity. For example, Dr. Grob, a pediatric psychiatrist, has even administered psychedelics to treat anxiety during terminal-stage cancer treatments, aiming to address psychological, spiritual, and existential crises often encountered in patients facing terminal conditions. These patients go through psycho-spiritual revelations that lead to decreased usage of narcotic pain medications as well as sustained improvement in mood and anxiety [8].

Various studies have shown that LSD increases learning new conditioned behavior rates in rabbits, with increased doses of hallucinogens resulting in faster learning [9]. Researchers' results treating psychological conditions such as Major Depressive Disorder using therapeutic psychedelics are auspicious. In a randomized, placebo-controlled cross-over study, LSD was used twice a week for patients with life-threatening physical diseases; A high dose (200 µg) was compared with a very low dose (20 µg) as an active placebo. The two sessions were embedded in a psychotherapeutic process that lasted for several months. Two months after administration of the high dosage, reductions in the state-trait Anxiety Inventory (STAI) were found in the "trait anxiety" (d = 1.1; p = 0.033) and "state anxiety" (d = 1,2; P = 0.021). No complications were reported that persisted beyond one day after ingestion of the substance. The reduction of anxiety symptoms was still detectable after 12 months [10]. While studies have not been able to prove that BDNF directly causes increased learning capabilities, there is an increase in the expression of BDNF within the hippocampus during learning tasks. Comparatively, genetically modified mice that do not produce BDNF show behaviors similar to psychiatric illnesses such as eating disorders and OCD. Studies conducted on these mice "indicate that endogenous BDNF is critical for the normal development and function of central 5-HT neurons and for the elaboration of behaviors that depend on these nerve cells. Therefore, BDNF+/− mice may provide a useful model to study human psychiatric disorders attributed to dysfunction of serotonergic neurons [11]." Currently, no study has been conducted on the direct effects of psychedelics and increases of BDNF through 5-HT2A receptor activation within the hippocampus. If performed, this experiment should be designed to show that an animal could learn a new task faster after taking LSD with primary endpoints looking at the level of BDNF in the hippocampus.. There have been strict regulations on studies of LSD. However, there is much anecdotal evidence that microdosing in quantities less than that causes perceptual disturbances that can lead to increased productivity and positive changes in thought patterns. Dr. Fadiman's early results presented at the Psychedelic Science 2017 showed that people reported lowered depression and procrastination followed by increased energy and creative thinking. [12].

AYAHUASCA AND ADULT NEUROGENESIS

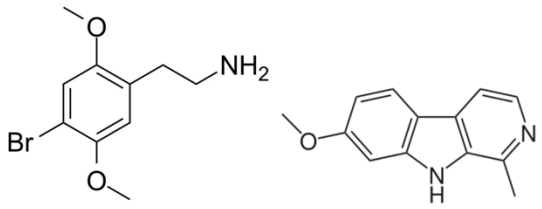

Figure 2: Left -Common Name - DMT, IUPAC Name - 2-(5-methoxy-1H-indol-3-yl)-N,N-dimethylethanamine, Molecular Weight - 218.3 g/mol, Molecular Formula-$C_{13}H_{18}N_2O$
Right -Common Name - Harmine, IUPAC Name - 7-methoxy-1-methyl-9H-pyrido[3,4-b]indole, Molecular Weight - 212.252 g/mol, Molecular Formula - $C_{13}H_{12}N_2O$

Ayahuasca is a vine with hallucinogenic properties found in the Amazon that can exert its effects for up to 4 to 8 hours after ingestion. Indigenous populations of the Amazon

have concocted a tea of Ayahuasca and leaves from the Psychotria virdis shrub. The shrub contains N,N-dimethyltryptamine (DMT), an agonist of the serotonergic 5-HT2A receptor. DMT is synthesized starting with L-tryptophan, which is decarboxylated to form tryptamine. This compound undergoes methylation to produce N-methyltryptamine, which again gets methylated to produce N,N-dimethyltryptamine [13]. Harmine, a beta-carboline alkaloid, is responsible for the brain remodeling effects of Ayahuasca and works through a mechanism that inhibits monoamine oxidase (MOA) and tyrosine-phosphorylation-regulated kinase (DYRK1A) [14]. Harmine is synthesized from tryptophan, which is then decarboxylated to produce tryptamine; upon the addition of an alpha-keto acid, this is converted to beta-carboline carboxylic acid, which is decarboxylated to produce 1-methyl beta carboline. This compound will finally be oxidized to yield harmaline, which will be dehydrated to produce harmine [14]. A study was done in which human neural progenitor cells (hNPCs) were cultured with harmine and the number of cells in the group of hNPCS increased by 71.5%. It was specifically the DYRK1A inhibition mechanism that was responsible for this neurogenesis, as it has been shown to have a major role in mediating cellular proliferation and development of the brain. This neurogenic finding has significant implications for Ayahuasca usage as a therapeutic drug as rodent models of Major Depressive Disorder show that classic antidepressants exert their effects by stimulating neuronal proliferation [14].

Neuroimaging has revealed increased blood perfusion to the fronto-medial and anterior cingulate cortices of the frontal lobe and medially located structures of the temporal lobe; this correlates with improvement in planning and inhibitory control following the administration of Ayahuasca. Additionally, “applying spectral analysis and source location techniques to cortical electrical signals showed changes in neuronal activity that predominated in more posterior sensory-selective areas of the brain [15].” This study established a connection between two contradictory findings “by simultaneously enhancing endogenous cortical excitability and reducing higher-order cognitive control, ayahuasca temporarily disrupts neural hierarchies allowing inner exploration and a new outlook on reality [16].” Other findings also report increased positive mood, amended visual sensations, and anti-depressant qualities without characteristics of addiction. Unlike LSD, both acute and chronic use of Ayahuasca did not lead to psychopathology or deficits in cognition. One study found that Ayahuasca can lead to cortical thinning of the posterior cingulate cortex, a part of the default mode network, which is more active during restful states than in task-performing states [17]. This brain area is also responsible for introspection. An fMRI study revealed that Ayahuasca leads to decreased activity throughout the network, mimicking altered brain states brought about by meditation and sleep. This alteration increases mindfulness, allowing one to think less emotionally and be better equipped to handle trauma and other highly emotional events, only increasing the therapeutic power of Ayahuasca [13].

PEYOTE AND ADULT NEUROGENESIS

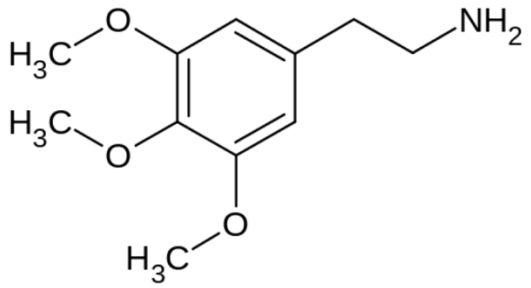

Figure 3: Common Name - Mescaline, IUPAC Name - 2-(3,4,5-trimethoxyphenyl)ethanamine, Molecular Weight - 211.161 g/mol, Molecular Formula - $C_{11}H_{17}NO_3$

Peyote is a cactus that grows close to the ground that produces euphoric and psychoactive effects. The succulent synthesizes a hallucinogenic compound known as mescaline which causes a wide range of effects from spiritual insight to hallucinations. The plant is consumed through chewing or made into tea. Tribes in regions of Mexico even use peyote buttons as an anesthetic or for pain relief. Today, Native American tribes continue to use it for its curative properties. Mescaline or 3,4,5 - trimethoxyphenethylamine is a naturally occurring alkaloid in the phenethylamine class comparable to LSD and psilocybin. The synthesis of Mescaline begins with dopamine in Lophophora williamsii (Peyote), using Catechol O-Methyl Transferase (COMT) and Guaiacol O-Methyl Transferase (GOMT) enzymes. Other biosynthetic pathways can also lead to the production of mescaline, using either Phenylalanine or Tyrosine as the starting amino acids. In vivo synthesis has been proposed as the following: oxidation of tyrosine to produce dopa, decarboxylation of dopa to yield dopamine, followed by oxidation of dopamine to produce 3,4,5-trihydroxy-phenyethylamine, which then gets methylated, resulting in mescaline. Synthetic synthesis of mescaline can occur through variousroutes, starting with acetal, nitro alkene, or chromium complex.

The stimulating compound, mescaline, is a non-selective serotonin receptor agonist. Like other hallucinogens, the drug's stimulatory actions are postulated to come from its interactions at the 5-HT2A serotonin receptors. Mescaline peaks in the brain 60 minutes after ingestion and remains constant for another hour. "Human subjects given C14-mescaline by mouth excrete an average of 87% of the dose during the first 24 hours and an average of 92% during the first 48 hours. Average half-life of mescaline in six hours [18]." Hallucinogenic effects due to increased blood flow to the frontal cortex induced by the drug include intense mental images, synesthesia, increased sensory stimulation, distortion of reality, fixation on thoughts, and deceptive sense of body weight. The G-coupled protein receptors and ligand-gated channels on which this drug acts are responsible for releasing hormones in addition to neurotransmitters. "These receptors play an important role in a variety of processes, such as anxiety, cognition, aggression, learning, memory, nausea, sleep and mood. As a result, they are the target of therapeutic agents, as well as illicit drugs, including hallucinogens [19]." Thus, the drug mimics physiological effects produced by norepinephrine and epinephrine, such as increased heart rate and temperature, nausea, dizziness, sweating, dilated pupils, and anxiety. Symptoms produced by toxic amounts of this drug can be alleviated with valium or chlorpromazine.

Decreased amounts of serotonin are seen as a biochemical model for Major Depression. Although there is not much information in the literature on mescaline use as a therapeutic tool, its positive action on serotonergic receptors could have significant implications for its ability to be utilized. However, research shows that drugs that cause less distortion of reality than mescaline or LSD can be used as supplements in treating such illnesses. These specific drugs belong to the phenylisopropylamine subgroup of phenylalkylamines and are called entactogens [4]. Entactogens promote a brain state of open mindedness, "interpersonal closeness, intimacy, and empathy." [21] Research postulates that entactogens would be a good addition to psychotherapy treatment plan, as they would help the patient feel more prone to opening up to the therapist about traumatic events [20].

CONCLUSION:

There is much to learn about adult neurogenesis. Neurogenesis and neuroplasticity are two interlocking concepts that are not fully understood. The substances mentioned in this

paper, alter the brain in ways that can increase our understanding of how the brain changes and adapts in both short and long term exposures and diseased states. These findings have massive implications in the understanding and treatment of diseases such as Alzheimers and Traumatic brain injury. More in depth, larger scale research trials are needed to fully understand the impact of these substances on adult neurogenesis and future treatment options.

AUTHOR INFORMATION

Mohan Muvala, DO (chinnumohan2000@gmail.com)

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Case Report

Cannabis-Induced Psychosis in a 32 year old male

Sami Ghozayel, BS, Joseph Pullara, MD

INTRODUCTION

Cannabis is the most widely used illicit drug in the United States. In 2002, 11% of those over the age of 12 reported using cannabis. The rate of cannabis use further rose to nearly 18% in 2019 [1]. This trend holds across much of the world. In 2019, an estimated 200 million people worldwide used cannabis, according to the United Nations Office on Drugs and Crime [2]. They also note that adolescents in the United States perceive cannabis use as less harmful than in past years.

The mechanism for intoxication is reasonably well established. There are hundreds of compounds within the cannabis plant. The notable compounds of interest are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC binds the cannabinoid-type receptor 1 (CB1) of the endocannabinoid system. The result is colloquially known as the "high" those who use cannabis seek [3]. As the prevalence of cannabis consumption has increased, so too has the potency of cannabis. The concentration of THC in a typical joint has increased by a factor of 10 over the last 50-60 years [4].

In diagnosing cannabis-induced psychosis (CIP), the DSM-V requires distressing delusions or hallucinations that occur after the consumption of cannabis, which cannot be ascribed to any other psychiatric illness[5]. Research into the possibility of cannabis-induced psychosis began in earnest in the 1980s and has continued in the decades following [6]. The pathogenesis of CIP remains elusive, but it is thought that environmental and genetic differences in intracellular signaling pathways may increase susceptibility [7].

CASE REPORT:

The patient is a 32-year-old African-American male with longstanding anxiety who was involuntarily admitted for self-mutilation. He reported smoking cannabis and experiencing auditory hallucinations, which he claims were telling him to "take himself out." The hallucinations were described as multiple voices coming from inside and outside his head, both male and female. They were goading him into harming himself, and eventually, he could not take it anymore, so he decided to barricade himself in the bathroom. He then lacerated his forearm and was brought to the emergency room by his family. After medical stabilization, he was transferred to another facility three days later. He was subsequently admitted to an inpatient psychiatric floor. His auditory hallucinations had resolved four to five days before his psychiatric admission date, and he reported preceding anxiety and insomnia in the days leading up to the episode of psychosis.

The patient postulated that he may have smoked synthetic marijuana because he was a daily cannabis user, and hallucinations had never happened to him before. As for his past psychiatric history, he reported longstanding anxiety for which he had trialed Wellbutrin. He also noted trials of Focalin, Ritalin, and Adderall for ADHD. He denied any history of psychosis, suicidal ideation, or suicide attempts. He reported no family history of psychiatric illness. For other substances, he reported consuming alcohol 1-2 times per month, smoking 1-2 cigars daily, and occasionally using MDMA. The patient was started on a trial of quetiapine, 50 mg QHS, and he agreed to seek outpatient care. He was discharged two days later.

DISCUSSION AND CONCLUSIONS

In a patient with no reported personal or family history of psychosis or recent use of any other hallucinogen, it appears his episode of psychosis was related to his use. It is fair to say that this was not a case of a patient simply being intoxicated due to cannabis use. The patient's habitual cannabis use without a similar episode supports this claim.

A limitation of this report is that it is unknown if the patient truly smoked cannabis alone or if there was synthetic marijuana (K2) instead. The patient did note that he smoked cannabis he did not personally inspect, which is not typical for him. K2 is known to cause similar psychotic effects to what the patient experienced [8]. It is also unknown what quantity the patient smoked that day of the incident.

The legalization of cannabis for medical and recreational use has become more prevalent at the state level in the United States and in many other jurisdictions worldwide. Societal condoning of cannabis use has grown, as well as its use. It is not a stretch to imagine that with increased use and strength of cannabis, there would be a rise in reported cases of CIP. However, that has not always been the case. A 4-year study in Canada found no association between cannabis legalization and increased ER visits for CIP, though they acknowledge limitations to their study [9]. A European study noted a significant association between the daily use of cannabis and psychosis [10].

The major implication of this case is to add another case of CIP to the literature. There are myriad case reports on CIP, and more extensive studies are needed to strengthen correlation and potentially find a causal link. More research may halt the tide of social acceptance and legalization throughout many nations.

AUTHOR INFORMATION

Send correspondence to Sami Ghozavel, BS (sg2310@mynsu.nova.edu)

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