Considerations For Psychedelic Research

By Charlesice Hawkins

Abstract

Research on psychedelic substances is re-emerging. Here we review chemical and physiological effects in addition to medical uses for psychedelic substances. The most common substances included here as psychedelics are lysergic acid diethylamide (LSD), psilocybin, and peyote. Safety is the priority underlying the majority of the following studies.

The onset of mental illness and/or cognitive impairment as possible harmful user side effects of psychedelic drug use is a concern for researchers. Halpern *et al*[1] and Krebs and Johansen[2] addressed this directly by examining lifetime psychedelic use, whereas Johnson *et al* did so by exploring the history of such research and by providing physiological and psychological safety guidelines. Krebs and Johansen analyzed a large body data from the National Survey on Drug Use and Health[2]. They did not observe any positive correlation between lifetime use of LSD, psilocybin, mescaline, or peyote individually and an increased risk or rate of mental illness[2]. This study was limited by the use of self-reported data and lacked psychological testing. The Halpern *et al* analysis is less generalizable than that of both Johnson *et al* and Krebs and Johansen, but they were able to control for the use of other drugs. Such a control is rare in psychedelic research[1]. This study focused on lifetime use of peyote by Native

Americans specifically and included 1) a group of people who regularly ingested peyote throughout their life for religious purposes, 2) a group of currently sober individuals with past alcoholism, and 3) a control group who reported minimal use of any substance, including peyote and alcohol[1]. Halpern *et al* did not observe a significant correlation between the peyote group and increased neuropsychological issues, but did see an increase in cognitive impairment for the alcohol group[1]. It was also reported that the peyote group scored slightly higher on some aspects of the quality-of-life (QQL) tests they were given. The researchers mentioned that the results of lower significance, such as the QQL results, may be due to chance because they were unable to complete the multiple comparisons statistical analysis needed when comparing more than two groups[1]. The results that displayed a large significance value are more likely to be accurate; however, they are still generally unreliable without a complete statistical analysis.

Johnson and fellow researchers provided the most extensive account of potential risks in their review article[3]. They addressed the methodological flaws in previous research studies which accounts for a large portion of the descriptive reports on the negative effects of psychedelic drug use; however, Johnson et al did not exclude negative reports in their review[3]. They incorporated risks, variability, suggestions, as well as specific examples, both positive and negative, to support their arguments[3]. Unlike the previous two articles, Johnson *et al* addressed both the acute and long term effects of psychedelic drug use and also provided concrete information that is directly relevant to future clinical research.

Understanding the properties of psychedelic substances is also important for clinical research and the development of medical treatments. Passie *et al* examined the pharmacology of LSD, whereas Catlow *et al* and Carhart-Harris *et al* examined the influence of psilocybin on the brain through neurogenesis and blood flow respectively. To my knowledge, the Passie *et al*

report of LSD is one of the most comprehensive accounts of the pharmacological nature of any psychedelic substance. It included information about the chemical structure, toxicology, metabolism, neurophysiological affects, as well as psychiatric complications, tolerance, and drug interactions reported of LSD[4]. More importantly, they identified areas of LSD research that are lacking and concluded by describing their paper as being a potential "road map" for future research[4(p. 307)].

Carhart-Harris *et al* investigated the physiological effects that psilocybin has on the brain by observing changes in blood flow using functional magnetic imaging (fMRI)[6]. They hypothesized that the experience of psilocybin users is the result of over-activation in the brain; however, they observed a consistent decrease in blood flow to regions such as the anterior cingulate cortex, which is related to reward anticipation, empathy, and depression, as well as the medial prefrontal cortex, which is related to decision making[6]. This experiment is unique because of the use of fMRI and because the results conflict with previously established hypotheses and will thus need to be replicated. Likewise, techniques such as electroencephalography (EEG) could be used to examine activation patterns near the scalp to help reinforce the results. In a summary-like report of this experiment, Lee and Roth discuss how the observed results are "provocative" because they challenge the previously hypothesized excitatory mechanisms[7]. This is a strong argument that may motivate researchers to explore these mechanisms; however, the argument would have been more convincing had they provided evidence for both the excitatory and inhibitory mechanisms.

An inhibitory mechanism may explain why various researchers suggest using psychedelics as treatment for severe anxiety disorders such as PTSD. Catlow *et al* provide evidence for such a treatment[5]. Using a mouse model, they demonstrated that low doses of

psilocybin can increase neurogenesis and increase the rate of extinction of a conditioned fear response[5]. The mice were injected with a solution of psilocybin or saline, and then 24 hours later they were habituated to the testing chamber[5]. The following day the mice underwent shock fear conditioning[5]. On the third day after the drug administration, the mice were assessed to determine if they had retained the fear conditioning at all. Afterward researchers measured the rate at which that conditioning was extinguished[5]. Although the researchers confirmed that all of the mice had developed the fear response[5], their results may not be directly translatable to PTSD patients because, unlike PTSD patients, the mice were administered psilocybin before they developed the response. To increase the clinical relevance of this experiment, the researchers could use a longer lasting fear conditioning method that would allow them to treat the mice with psilocybin after the fear response had been established.

Psychedelic substances have also been considered as treatment for cluster headaches (CH), end-of-life anxiety, and mood disorders. Thus far, one of the most explored medical uses for psychedelics is in the treatment of CH. Tepper and Stillman provide a comprehensive collection of research on "when all else fails" CH treatments[8]. They acknowledge the severity of the condition and understand that conventional treatments are not always successful. Here it was reported that the "minimally hallucinogenic" [(p. 1184)] form of LSD (2-Bromo LSD or BOL-148) was a safe and relatively successful treatment compared to other more invasive options such as deep brain stimulation that although effective, often results in complications such as infection and discomfort[8]. By devoting equal space to each treatment the authors gave the impression that because treatment success varies drastically patient-by-patient, all possible treatments should be explored.

Karst *et al* carried out the BOL-148 studies referenced by Tepper and Stillman[9]. In one

study 5 patients, one with episodic CH and four with chronic CH, were treated with BOL-148[9]. All of the patients experienced significant improvement either in the period of remission, frequency, or intensity of attacks, with only one patient experiencing considerably less improvement[9]. This patient had continued to drink alcohol despite being advised not to do so[9]. The sample size of this study is small; however, the authors did acknowledge this as well as their un-blinded and un-controlled protocol. They described their results as preliminary and encourage further research[9]. The report itself is short (5 pages including the references) and is lacking a detailed explanation of the chemical nature of BOL-148. Of all of the articles reviewed here, this article contains the least amount of information on possible mechanisms of action despite their heightened importance in the absence of hallucinogenic experiences.

In a 2010 *Nature* opinion article, Vollenweider and Kometer discuss the history and current state of therapeutic research on psychedelic substances in addition to proposing mechanisms of action[10]. Ketamine was included in their paper along with LSD and psilocybin, but it will be excluded in this review as it is a dissociative anesthetic rather than a psychedelic. This article cited a large number of studies, but they were presented with little background information. The language used in the introduction was informal; however, the bulk of the paper, which discussed possible neurological mechanisms, was highly technical. Vollenweider and Kometer presented a novel hypothesis about neural circuit modulation that provides the foundation for developing less-hallucinogenic forms of current psychedelic substances that would have the same therapeutic benefits while also contributing to the understanding of the pathways involved in different psychological mood disorders.

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