An evaluation of two classical hallucinogens, lysergic acid diethylamide (LSD) and psilocybin, for their use in therapeutic contexts

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After a several decade long hiatus of research following their ban in the 1970s, psychedelic drugs are once again receiving attention in the academic as well as the public sphere (Sessa, 2012). As of 2015, however, many of them remain scheduled as substances that have no medical use, prohibiting their possession, and in the United States even much of their research. However, in the relatively short window between the discovery of those substances and their prohibition, a new use has been found in psychiatric settings about which there has been a number of studies. In this paper, I am going to focus on the possible therapeutic application of two specific substances, lysergic acid diethylamide (LSD) and psilocybin, specifically using studies published no longer than five years ago.

Both substances share some important characteristics for which they have been chosen for this paper. They are both categorized as “classical” hallucinogens, meaning that they’re 5-HT (serotonin) agonists (Glennon, 1999). And although their mechanism is still not fully understood (Gasser, Holstein, et al., 2014), it can be inferred that their pharmacodynamics are to some extent similar as they also show cross-tolerance, meaning that administering one substance affects the subsequent response to the other (Isbell, Wolbach, Wikler, & Miner, 1961). Finally, they have also been proposed as an aid in similar circumstances, i.e. for anxiety reduction (Grob et al., 2011; Gasser, Kirchner, & Passie, 2014) and alcoholism treatment (Krebs & Johansen, 2012; Bogenschutz et al., 2015).

A brief excursion into history is necessary in order to satisfactorily explain the current state of psychedelic therapy. LSD was first synthesized in 1938 by Albert Hoffman. Its psychoactive properties were not known at the time, and were discovered only five years after its synthesis when Hoffman accidentally ingested the substance. On the other hand, psilocybin, being the active component in psilocybe mushrooms, occurs in nature, and it has been suggested that psychedelic mushrooms have been used as early as 9000 years ago (Samorini, 1992). It was first isolated and synthesized in 1958 (Bogenschutz & Johnson, 2015). There was a short-lived boom

in research into psychedelic substances, and they quickly found their use in psychotherapy due to the nature of the experience. Self-experimentation also happened during this period, for instance in Czechoslovakia (Winkler & Csémy, 2014). Despite good results (Sessa, 2012) and support from researchers, both were banned due to an increase in non-medical use. A United Nations treaty called the *Convention on Psychotropic Substances* of 1971 banned both LSD and psilocybin for all but medical and scientific uses under strict regulations (though curiously, only psilocybin itself is covered, not the mushrooms that contain it). In the United States, however, the *Controlled Substances Act* is even stricter in allowing medical research. These are the factors which had led into a severe hiatus of psychedelic research, which is only recently changing.

This, however, means that the majority of all research conducted on these substances was conducted in the 1960-1970s. Thus, most of psychedelic research has happened before the spread of modern technologies which would greatly aid such research. It also means that due to the practical and legal difficulties connected with experimenting with these substances, the amount of research is relatively scarce, and the sample sizes are mostly small. Many definite conclusions regarding the safety or mechanisms of psychoactive drugs therefore cannot be made as of yet, and even further research is needed if certainty is to be achieved.

During that early period of psychedelic research when the substances were legal, two main approaches to psychedelic therapy were devised, termed “psycholytic” and “psychedelic”. They were used at various times by various therapists, as there was no time for a standard procedure to form. The two approaches differ significantly in how the session proceeds and what is the patient’s role in it. In psycholytic therapy, the patient is given a low-to-moderate dose of the psychedelic drug in frequent sessions, which proceeds like a usual psychotherapeutic session would. It was named by Hanscarl Leuner who pioneered the method in 1961, who used amounts of LSD that were no higher than 250 micrograms (Eisner, 1997). One of the motivations for this kind of therapy, namely that psilocybin apparently lowers psychological defences and thus helps along the process of therapy, was recently confirmed by an fMRI study (Carhart-Harris et al., 2012). Psychedelic therapy, on the other hand, works by administering higher doses in less

sessions with the intention of inducing a mystical experience. (Kurland et al., 1967, as cited in Bogenschutz et al., 2015). During such sessions, the therapist only scarcely interacts with the patient, who is often advised to be introspective, wear eye-shades and/or to listen to music. Both methods also typically include a period of integration of the experience, during which the experience is discussed with the therapist.

One of the areas where LSD was thought to have a potential benefit was in treating alcohol addiction. A recent meta-analysis (Krebs & Johansen, 2012) has examined the results of six randomized double-blind trials that took place from 1966 to 1970. These would be considered "psychedelic therapy", as LSD was only administered once, and the dose ranged from 210 micrograms to 800 micrograms. The analysis has shown that in these studies, the single dose of LSD was effective for up to 6 months, but the effect was not statistically significant when following up after 12 months. Although there were in total eight reports of acute adverse reactions, no negative long-term effects were reported.

A recent original study (Bogenschutz et al., 2015) used psilocybin also in the form of psychedelic therapy. Ten[1] volunteers have undergone 14 sessions in 12 weeks, and psilocybin was administered in two of those sessions - first after 4 weeks (0.3 mg/kg), second after 8 weeks (0.4 mg/kg or 0.3 mg/kg, see study for details). The study found a significant decrease in alcohol consumption during weeks 5-12 (i.e. after psilocybin was administered) not only relative to baseline, but also to weeks 1-4 (i.e. when sessions consisted of counseling only). Those improvements lasted for the duration of the follow-up (36 weeks). No long-term adverse effects were found.

In another recent study (Grob et al., 2011), psilocybin was administered to twelve adults with advanced-stage cancer who were found to be suffering from anxiety. Out of those, four were hallucinogen-naive, and the rest reported having some prior experience. To provide an agreeable

[1] As was mentioned above, the sample size is usually rather small. The study started out with 70 volunteers, but only 10 passed through the screening procedure. The authors themselves acknowledge this and, motivated by their results, they propose trials with larger sample sizes.

environment even in the context of the hospital rooms in which the sessions took place, the rooms were decorated with fabrics and flowers. There were two sessions, one with an active placebo, and one with psilocybin (0.2 mg/kg) of which the subjects were informed, but only the research pharmacist had known the order in which the substances were administered. During the session itself, patients were advised to lie down with eye-shades and listen to music as in psychedelic therapy, although the dose itself was described by the researchers as "moderate" (p. 76). Even that dose however, produced some statistically significant result 1 month and 3 months after the treatment.[2]

A similarly oriented study (Gasser, Holstein, et al., 2014; Gasser, Kirchner, & Passie, 2014) administered LSD to twelve people with various life-threatening diseases. The subjects went through two full-day sessions two to three weeks apart in which they received 200 micrograms of LSD and were encouraged to be introspective and focus on their inner perception and cognition. For this purpose, music was played in two thirds of the sessions. These were followed by three drug-free sessions in order to properly integrate the experience and to proceed with the psychotherapy. As an active placebo, a low dose (20 micrograms) of LSD was used, as it is enough to be perceptible, but not enough to affect the therapeutic process significantly. The results showed a clear trend of reduction of anxiety for people in the treatment group as well as the cross-over group[3], with no drug-related severe adverse effects, e.g. panic attack, suicidal crisis, psychotic state, etc.

However, one must still be cautious about the potential unknown effects of psychedelic drugs. While no physiological toxicity has been shown (Johnson, Richards, & Griffiths, 2008), and they are not associated with a withdrawal syndrome (O'Brien, 2006 as cited in Johnson et al., 2008), there may be some potential psychological risks. Hallucinogen persisting perception

[2]The researchers marked an elevation of stress levels at the 6-month point; however, they note that it was not statistically significant and might be plausibly caused by the advancing cancer of the patients. Out of the 12 patients, only 2 were still alive at the time the study was published.

[3]Two months after the second session, the patients in the placebo group were debriefed and given a choice to transfer into the treatment group.

disorder (HPPD), or colloquially “flashbacks”, are a well-known phenomenon, being even categorized as a separate disorder in DSM-IV. They are described as re-experiencing visual or cognitive phenomena following the use of a psychedelic drug, but long after it has stopped being active in the body. Although likely[4] uncommon (Halpern & Pope, 2003), they are most likely a genuine phenomenon which must be taken into consideration when discussing the potential risks and benefits of psychedelics. Probably the most serious risk is that of triggering underlying mental conditions, which has been documented (Strassman, 1984), and it is why screenings for studies which deal with psychedelics must be very strict and thorough. On a more personal level, it has been suggested (McCabe, 1977; Grof, 1980 as cited in Johnson et al., 2008) that during psychedelic therapy sessions, unconscious conflicts that the patient has not had a chance to properly process yet might come to surface, causing prolonged distress. This only emphasizes the importance of a proper (clinical) environment for psychedelic experiences.

And lastly, probably the most common (Johnson et al., 2008) adverse effect associated with psychedelic drugs is acute psychological distress, also colloquially known as a “bad trip”. This is a state during which a person is overwhelmed with anxiety, fear, persecutory delusions or unpleasant physical experiences, and lasts for the duration of the psychedelic experience. van Amsterdam, Opperhuizen, and van den Brink (2011) even claims that it is “probably the main reason of users of magic mushroom to visit emergency care facilities.” (p. 425) However, as “bad trips” are a risk primarily for unprepared people in uncontrolled environment, an argument can be made that this risk can largely be mitigated by the use of proper “set and setting”. This is a phrase meaning the “mind-set” with which a person is undergoing a psychedelic experience, and the physical/social setting in which the drug is taken. Proper precautions need to be taken so that the person is well prepared for the experience, i.e. expects that some possibly distressing situations may arise and knows that the psychedelic experience takes up to several hours, at least in the case of classical psychedelics (van Amsterdam et al., 2011). There is additionally a number of adverse

[4]Due to the only recent definition in the DSM, it is hard to estimate the prevalence of HPPD as it was not classified as such before.

physiological effects, such as tachycardia or nausea in the case of psilocybe mushrooms. In a large number of recorded fatal cases however, the use of psychedelics is combined with other drugs like alcohol or cannabis; the compounded risk of drug combinations should not be underestimated.

In conclusion, there is still a lot of research needed to be conducted if there is to be a definite statement on the therapeutic potential of psychedelic drugs, specifically lysergic acid diethylamide and psilocybin. After several decades of hiatus, there has been a renewal of interest in the research of psychedelics, which is starting to show some interesting and promising results. One must nevertheless always keep in mind the potential risks involved inherent in altering the brain's chemistry. The fact that a lot is unknown means there is a lot of potential for positive effects as well as the negative. Psychedelic drugs are a powerful tool which should not be neglected but even less should they be taken lightly.

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