

# Drugs of Potential Misuse for the Treatment of Depression and Other Psychiatric Disorders

## Part 2 – Psychedelics: Psilocybin, LSD

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Psychedelics are believed to exert their effect via serotonin receptors called 5-HT<sub>1A/2A</sub>. Common effects reported include alterations of sensory perception, ego loss, an increased awareness of the present- leading to sometimes profound personal insight and even mystical experience (Sherwood *et al.* 2018). Some other symptoms experienced include:

- Vivid imagery
- Visual alterations (such as hallucinations)
- A feeling of disembodiment (being separated from your body)
- Impaired thinking
- Anxiety
- Audio visual synesthesia (when a sound stimulus can elicit visual experiences)
- Changed meanings of perceptions
- Religious experience
- Experience of “unity” with nature and the surrounding world
- Blissful state

Abnormalities in neuroplasticity (the ability of the brain to form and recognise synaptic connections) contribute to the pathogenesis of mood disorders. Psychedelics are believed to enhance neuroplasticity and offer a novel approach to the treatment of mood disorders. Psychedelics modulate neural circuits (Vollenweider *et al.* 2010).

It appears that a mystical type experience has a key role in the therapeutic outcome in psychedelic therapy (Pahnke *et al.* 1970, Griffiths *et al.* 2006, Griffiths *et al.* 2008, Griffiths *et al.* 2011). Administered in a controlled environment with appropriate support, psychedelics have a favourable safety profile (Johnson *et al.* 2008).

Psychedelics can produce a wide range of effects depending on:

- The individual
- The individual’s expectations of what will happen
- Settings in which the drug is taken
- Drug dose

### **PSILOCYBIN (Magic mushrooms)**

This drug activates 5 HT<sub>2A</sub> receptors. It is a natural substance found in over 100 species of mushrooms. It has low physiological toxicity and low abuse liability.

Psilocybin can be administered as part of structured psychotherapy. Studies of the drug have usually excluded patients with psychosis (hallucinations or false beliefs) and the sessions are monitored with interpersonal support provided.

There is a moderate risk of elevated blood pressure - so patients with heart problems may be excluded. These substances produce a profound state of altered consciousness and there is a major risk of overwhelming anxiety, fear and confusion that may lead to dangerous behaviour in unmonitored settings (Johnson *et al.* 2017). As a result, they should not be prescribed for self-monitored use at home. Therapy sessions require supervision and patients receive support and guidance prior to drug administration.

A single dose of psilocybin has been found to be of use in treating depression and anxiety in patients with terminal cancer or another life threatening illness (Grob *et al.* 2011, Griffiths *et al.* 2016, Ross *et al.* 2016). In these studies, the majority of the patients had an immediate improvement in depression and anxiety and 60-80% had a clinically significant sustained reduction in depression and anxiety at 6 months follow-up.

Psilocybin with psychological support was also studied in a very small study by Carhart-Harris (Carhart-Harris *et al.* 2016) for treatment resistant depression. Depression was found to be reduced at week 1 and at 3 months post treatment, with 8 out of 12 patients meeting the threshold for complete remission. Similar to the situation in depression, Moreno (Moreno *et al.* 2006) showed that patients with treatment resistant obsessive compulsive disorder had a reduction in symptoms following psilocybin use. However, it should be noted that in this study, even very small doses of the drug had an effect suggesting that the effects seen could be a dummy/placebo effect.

Psilocybin has also been studied for effects in other situations, including help stopping smoking, and reducing alcohol use. Johnson (Johnson *et al.* 2014) carried out a study on 15 treatment resistant smokers using 2 treatments of psilocybin and cognitive behavioural therapy. At 6 months follow up 80% were abstinent from smoking and at 2.5 years 75% were abstinent from smoking. Bogenschutz (Bogenschutz *et al.* 2015) showed that 1-2 treatments of psilocybin, along with therapy, was effective in reducing the number of days that drinking alcohol occurred. There is very limited evidence that psychedelics cause dependence or addiction. Tolerance develops quickly. There is no known withdrawal syndrome and there is a low potential for abuse unlike other psychoactive substances (Fabregas *et al.* 2010) (Gable 2007). Long term benefits appear to be greater for those whose psilocybin session leads to a mystical type experience (Johnson *et al.* 2017). This may include feelings where there is a direct connection with the divine; a sense of timelessness; pure bliss, joy or gratitude; a sense of holiness or sacredness about the nature of reality and a sense that the experience cannot be fully or properly described in words.

By the end of the 1960's many papers described the use of psilocybin and LSD in clinical populations with non-psychotic mental health problems (Grinspoon *et al.* 1981). The recreational use of psychedelics increased as did the unethical and covert use of these drugs. A decision was made to classify these drugs as

Schedule 1 drugs. As a result, doctors were no longer permitted to prescribe psychedelics and their use quickly ceased. In the 21st century interest in these drugs has been renewed due to several promising studies.

It is usually suggested that commonly prescribed psychiatric medications should be carefully withdrawn prior to the use of psychedelics. **This is NEVER recommended without discussion with, and support of, a health care professional.** A psychiatrist with a schedule 1 licence is required to prescribe and administer psilocybin, to manage other medications and to provide assessment and management of the patient's mental state. A psychological session is essential to prepare the patient to the likely effects of psychedelics long forgotten, unknown or emotionally charged material may become apparent. Psilocybin has an onset of action of 30 mins and peaks at 90 mins, subsiding after 4-6 hours. This means that patient can potentially receive the treatment as 'day-case patients'.

Changes in mood, confusion, anxiety, agitation, panic and paranoia are all expected reactions although usually mild and respond to reassurance. If the symptoms are more significant a "rescue medication" such as lorazepam may be prescribed and the patient may need to stay in the hospital setting overnight.

There is a large study of psilocybin for treatment resistant depression being run in 2018/19 in the UK (including in Newcastle), Europe and North America. The results of this will hopefully confirm whether or not psilocybin is effective or not and what is the optimal dose to be used.

## **LSD**

LSD can cause perceptual distortions and hallucinations. It can enhance self-awareness and can facilitate the recollection and release from emotionally loaded memories (Sandison 1954, Schmiege 1963). This appealed to psychiatrists as a unique property that could facilitate the psychodynamic process during psychotherapy. This is when the primary focus is to reveal the unconscious content of the client's psyche in an effort to alleviate psychic tension. The client has an increased self-awareness of their inner world and understanding of the influence of the past on present behaviour. In 1970 LSD was widely popularised as a drug of abuse and highly dangerous and it was classified as a schedule 1 drug. Research was limited and funding restricted.

Neuroimaging and brain mapping increased the understanding of the molecular mechanisms of action of psychedelics and has renewed interest and research in humans. Gasser (Gasser *et al.* 2014) showed that LSD was affective for anxiety associated with terminal illness. Two thirds of cancer patients given LSD had reduced anxiety and reduced fear of death (Kast 1966, Pahnke *et al.* 1969). Lysergic Acid Diethylamide (LSD) has a relatively long duration of action. This is one reason why most of the current research into therapeutic effects of psychedelics is on psilocybin.

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