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# Efficacy of psilocybin in severe depression: what is the evidence?

In a world first, the Therapeutic Goods Administration (TGA) in Australia has scheduled psilocybin in the treatment of severe depression treated by registered psychiatrists, acting with approval of a human research ethics committee (from July 1 2023).[1] The decision has been controversial because risk of leakage to the streets is substantial and because it was made in the setting of extreme lobbying by outside organisations and individuals. Leaving these interesting aspects on one side, I summarise here the published evidence for the efficacy of psilocybin.

How do we "know" a therapeutic drug works? The listing of a drug as a medicine relies of scientific evidence of efficacy. The underlying epistemological question is how can that reliable evidence be obtained? The gold standard accepted globally is by a controlled clinical trial, which takes account of random or systematic sources of bias that might cause approval of agents that are either ineffective or toxic. However, interest groups often argue that the clinical trial criterion of effectiveness trial can be suspended in specific cases. The reasons vary and include the severity and poor prognosis of the disease to be treated, the absence of existing treatment, the expense of drugs that have not been funded by government subsidy, or a belief borne of observations in a few or individual patients who appear to benefit. These and similar arguments have been used by supporters of psylocybin for severe depression.

The history of the TGA listing of psilocybin and MDMA included an initial rejection followed within a few months by qualified approval, during which substantial lobbying took place. Thus these drugs can now be prescribed by duly recognised (and hence trained) psychiatrists. The approval does not relate to government funding under the Pharmaceutical Benefits Scheme. Also, no specific psilocybin product has been approved, leading to the unusual situation of a right to be prescribed in an empty market. The cost is uncertain but has been reported to be in the order of AU$35,000 - $40,000 per year,[2] which does not include the added cost of administration. These are likely to be high because of requirements for close supervision during and between doses.

## Evidence of efficacy (in order of publication)

Psilocybin (3-[2-(dimethylamino)ethyl]-1H-indol-4-yl dihydrogen phosphate) is an alkaloid pro-drug of the active agent (psilocin), formed quickly after ingestion by hepatic dephosphorylation. In nature it is found in over 200 species of mushrooms, notably of the genus *Psilocybe* ("magic mushrooms"). It has been known and used in societies since before written history. Psilocin has mind-altering effects such as euphoria, visual and mental hallucinations, changes in perception, a distorted sense of time, and spiritual experience, as well as nausea, anxiety and panic. These effects result from an agonist action on brain serotonin receptors. Both psilocybin and its active metabolite are listed by the UN as Schedule 1 drugs, that is, they have a high risk of abuse, and the drug remains prohibited in all other circumstances. Thus, leakage to the streets of medicinal psilocybin is a likely problem. Several clinical trials have been conducted for depression.

Before studies in advanced or severe depression, psilocybin was investigated for potential benefit in depression associated with life-threatening illness such as cancer. Benefit was noted by Grob *et al* (2011) in relation to anxiety

and depression, with no adverse reactions,with a dose of 0.2 mg.Kg in 12 patients, with placebo control.[3] The abstract states *"The State-Trait Anxiety Inventory trait anxiety subscale demonstrated a significant reduction in anxiety at 1 and 3 months after treatment. The Beck Depression Inventory revealed an improvement of mood that reached significance at 6 months; the Profile of Mood States identified mood improvement after treatment with psilocybin that approached but did not reach significance."* Note the long term effects, a feature of psilocybin that was to be confirmed in later studies.

Griffiths and colleagues (2016) carried out a double-blind cross-over study design using two different doses of psilocybin (initially, 30 mg/70 Kg but this was decreased to 22mg/70 Kg after 2 patients; and 3 mg/70 Kg reduced to 1 mg/70 Kg after a dose ranging study) given in random order 5 weeks apart to 56 patients with life-threatening cancers exhibiting depression or anxiety.[4] Data from several rating scales including GRID-HAMD were studied. The low dose group was considered as control. Beneficial effects are displayed in Fig 3 of their paper, available on-line, and showed marked score reductions.

In 2018 Cohart-Harris *et al* reported results from an open-label (uncontrolled) study of psilocybin in 20 patients with mainly severe treatment resistant depression.[5] Applying the QIDS-SR16 rating scale they noted longstanding "marked reductions" in symptoms across several domains of concern in severe depression,with a significant effect ($P = 0.0035$) remaining 6 months after 2 doses (10 and 25 mg) given 1 week apart.

Davis *et al* measured (2021) the efficacy of "psilocybin–assisted therapy" in a small (n = 27, aged 21 – 75 years) prospective trial in which 15 of the 24 were given "immediate treatment".[6] In 12 "waiting list controls", treatment was delayed by 8 weeks, achieved with additional support. Thus the delayed treatment group served as controls for the immediate treatment group for assessments that were performed at 5 and 8 weeks. All patients had moderate or severe depression, and other eligibility criteria on safety grounds. The primary outcome measure was the GRID-HAMD, a version of the Hamilton Depression Rating Scale. One and 4 weeks after dosing in the immediate treatment group, the GRID-HAMD scores were significantly less than in the "control" group (Immediate, 8.0 and 8.5; delayed, 23.8 and 23.5 respectively). In the overall sample, 17 patients (71%) had a ≥50% reduction in the GRID-HAMD score after 1 and 4 weeks, and at week 4, 13 (54%) were in remission. More recently, the same study authors report that the full effect can be observed after 12 months.[7] This astounding result is shown graphically as Fig 1 of their publication.

Carhart Harris and colleagues compared (2021) the efficacy of psilocybin and escitalopram in moderate to severe depression.[8] The trial was in 59 patients with about half being randomised to each agent. Two 25 mg doses of psilocybin were given 3 weeks apart to one group, and the other group received 1 mg psilocybin 3 weeks apart (assumed to have negligible activity) and daily escitalopram 10 mg. Reported data were collected after 6 weeks, and 6 month follow-up data are awaited. Both drugs demonstrated significant efficacy using multiple psychiatry scales, but the treatment effects were more pronounced with psilocybin. No serious adverse effects were noted in either group.

Goodwin and colleagues (2022) studied the effect of 3 doses (25, 10 and 1 mg) of psilocybin in treatment-resistant major depression (n = 253).[9] The 1 mg dose served as "control". The results using the MADRS scale applied at 2 days, and 1, 3, 6, 9 and 12 weeks after dosing showed a positive effect of the 25 mg dose after 3 weeks, but the difference between the 10 and 1 mg groups was not significant. In addition, adverse effects occurred in an unusual pattern: between 3 and 12 weeks, 23, 24 and 24 patients in each dose group had any effect. In 4, 3 and 4 patients the effect was "serious", and suicidal behaviour was noted in only the high dose group (3 cases).

Finally, Von Rotz *et al* undertook (2023) a double blind randomised trial in 52 patients with severe depression.[10] Randomisation was to a single dose of psilocybin (0.215 mg/Kg; 15 mg/70 Kg) or placebo. Symptom severity measured on the MADRS and BDI scores was decreased significantly more with active treatement, and after 2 weeks response rates were higher (15/26 vs 4/26 (MADRS) and 14/26 vs 3/26 (BDI)) About 50% of patients achieved remission at the same time point. Secondary end-points also showed significant treatment effects. Adverse events were minor.

**Comment**

Though most of the above papers lack the rigour of fully controlled prospective randomised trials, the treatment effect appears sufficiently large to conclude that psilocybin is effective in the treatment of severe depression. The therapeutic action appears greater than with traditional drugs, is immediate and may be long-lasting, possibly greater than 1 year. There are uncertainties over the optimum dose and whether it should be based on body weight; cost; practicability bearing in mind the high staff requirements; and potential street leakage. Its performance against electroconvulsive therapy (ECT) has not been measured, and there is only 1 head-to-head trial against traditional antidepressant drugs.[8]

We conclude that the TGA has issued justified recognition of the therapeutic effects of psilocybin. However problems arise from the decision. Further research is required to define the optimum dose and frequency of administration, the extent of supervision and frequency of follow-up required between doses, and how the drug compares clinically and economically with established treatment of severe depression. The absence of a proprietary preparation of psilocybin is a paradox. We note that the benefit has been measured in only clinical grading scales and that the effect on harder endpoints such as hospitalisations or suicides remains uncertain. Continuing occurrence of suicidal behaviour in *only* the high dose group was noted in the Goodwin study, the largest to date, though the numbers of patients involved was small. The TGA decision unleashes major practical problems, as use of psilocybin in the above clinical studies has required supplemental consultant staff during administration, and intensified follow-up. Thus it has the capacity to damage current (already stretched) mental health provision. The quoted costs are horrendous for a relatively common disease and the implied total cost to governments (if it is subsidised) will be high.

**J A Millar**
*Editor, Tasman Medical Journal*

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