Psilocybin: psychotherapy or drug?

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This edition of the Journal of Psychopharmacology highlights two very similarly designed studies of the effects of the serotonergic agonist psilocybin on the psychological distress of cancer patients. In each case, the study was a cross-over design which compared, respectively, low dose/high dose psilocybin and niacin (placebo)/high dose psilocybin. The results were very comparable and suggest a clinically important effect: a single high dose of psilocybin reduced symptoms of anxiety and depression both acutely and approximately after 6 months [Griffiths et al 2016; Ross et al 2016].

Psilocybin produced an acute increase in blood pressure and a variety of immediate and obvious subjective effects. The subjective effects were transient and did not lead to persisting abnormal perceptions. Nevertheless, patients experienced heightened states of consciousness with marked emotional accompaniments (anxiety, tearfulness and in a few cases, paranoid ideation). None of these effects were unexpected, given the previous literature.

In total, the trials add experience from a further 80 patients to a more substantial number (about 2000) who have been reported to have received psilocybin under highly supervised clinical conditions in the last two decades (Studerus et al., 2011). There has been no observed enduring mental illness reported in this population as a consequence of exposure to hallucinogens, which is consistent with data from the general population in the US (2001-2004 National Survey on Drug Use and Health) (Krebs and Johansen, 2013).

Safety is a major concern because of the history of hallucinogens like psilocybin as 'illegal drugs'. The experience to date gives reassurance that careful administration in highly supportive environments to selected clinical populations does no obvious harm. The more interesting question is whether this use of psilocybin does important good, how it does it and how many people would really benefit.

The outcome measures of both trials are entirely subjective, comprising self, community and clinician reports, just as most studies of antidepressants and anxiolytics have been. While this is understandable, it is a particular weakness of any study where blinding is inadequate. Any cue that makes participants in an experimental study aware of what the experimenter expects to find or how participants are expected to behave is called a demand characteristic. These studies have demand characteristics in spades. Just as for other studies, symptoms alone are also a limited way of assessing the value of treatment: more objective measures of activity, simply motor or economic, the costs of their cancer care etc., should also be part of the future picture for research in this area. For the moment, we cannot accept unvarnished subjective change as an outcome without qualification.

In addition, it may be helpful if studies of hallucinogens are not thought of as drug studies at all, but as psychological treatment studies. Psychotherapists believe that it is the experience or learning within therapy sessions that mediates relief of anxiety or depression by cognitive behavior therapy, for example. It is clear that the investigators of psilocybin equally believe that the mediating mechanism is the explicit patient experience during psilocybin exposure. The authors consider this mediating effect as 'mystical' and show that treatment effects correlate with a subjective scale to measure such experience. The Oxford English Dictionary defines

mysticism as 'belief that union with or absorption into the Deity or the absolute, or the spiritual apprehension of knowledge inaccessible to the intellect, may be attained through contemplation and self-surrender'. Perhaps a scale really can measure a relevant kind of experience, but it raises the caution that the investigation of hallucinogens as treatments may be endangered by grandiose descriptions of their effects and unquestioning acceptance of their value. Timothy Leary was a research psychologist before he decided the whole world should 'Turn on, tune in, and drop out'; it is best if some steps are not retraced.

If patients experience lasting improvement because of insights or re-framing of their view of life lived with terminal illness, the approach really does represent psychotherapy, albeit drug assisted. Accordingly the content of the psychological structure of the intervention is of paramount interest. Both groups were clearly very committed to helping their patients and provided a complex package of therapist input. However, the resulting pot pourri was inspired by the traditional view that it is a mystical experience that is being facilitated. Such psychotherapy practice tends to assume it has the answers without really posing the questions that might falsify their assumptions. For example, in relation to the psilocybin experience, there was a considerable emphasis on remembering and reconstructing a narrative of the day. This may indeed be what is required, but we don't know that to be the case. Psychotherapy research now has the potential to be much more concerned with mechanism and informed by neuroscience (Holmes et al., 2014). To formulate mystical experience in terms of neuroscience will be an interesting project, but not radically removed from experimental studies of moral sense, which are now mainstream (Siegel and Crockett, 2013).

There is an alternative possibility, however. 5-HT2 receptors are now known to be members of a large and complex family of proteins (McCorvy and Roth, 2015). Agonists at these receptor types (psilocybin is one example) may produce long lasting conformational changes, which may, in turn, directly underlie antidepressant and anxiolytic actions. Psychedelic experience could then simply be the automatic read out of acute agonist actions. Such experience might appear to mediate drug action, but it could be an irrelevant side effect. This possibility will be a challenge for future mechanistic studies to disprove.

Finally, the patient population entered into both studies is perhaps unusual and limits generalizability. In the NYU study, for example, about half the patients had used hallucinogens previously: that may be down to the demographics of baby boomers but it seems high. Patients were described as having a life-threatening cancer diagnosis and an associated psychiatric disorder (usually an adjustment disorder). The latter may be a pretty low bar and in one of the studies, patients without a terminal diagnosis were also included as the trial went on. If the desire is to improve cancer care, then future studies will need to provide treatment integrated into a normal care pathway rather than recruiting ad hoc. It will be fascinating to see whether the various existing legal and regulatory hurdles to the use of psilocybin can be surmounted. The first requirement will be irrefutable evidence from excellent clinical trial data.

How useful might psilocybin be in facilitating psychological treatment for a range of psychiatric disorders? There is probably little unique about the emotional disturbance

that so commonly accompanies a cancer diagnosis. Hence, the treatment for adjustment disorders related to cancer is unlikely to be very different from the treatment of adjustment disorders or mood disorder generally. Unfortunately, it is also obvious that legalization 'for medical use' could be a route that works, as it has for cannabis, as a gateway to wider access for recreational use. It is good that the cancer context protects the present initiatives from the reflex condemnation this will invite. Moreover, it seems prudent to get psilocybin's value really well understood in this patient group before seeking other indications. Hallucinogens are arguably among the most interesting drugs ever discovered, so it is good to have them back in the hands of clinical scientists. It is also an opportunity to move the clinical evidence to another level in deciding whether they work, as we must hope they will, for the benefit of many patients with unaddressed clinical need.

Declaration of conflicting interests

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