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Editorial

Everything old is new again: are psychedelic medicines poised to take mental health by storm?

Three years ago, when I accepted a position as Director of Clinical and Translational Research at Usona Institute, a non-profit medical research organization pursuing a new drug indication for the psychedelic medicine psilocybin, many of my colleagues in mental health research looked at me like I had two heads. A year later, many of these same colleagues were beginning to ask me how they could become involved in 'this exciting new field.' Fast forward to the present and psychedelics are everywhere in the popular press, multiple entities are pursuing therapeutic indications for these agents and the world's top psychiatric research institutions are beginning to talk about 'centers for the study of psychedelic medicines.' In three short years, I have had a front row seat to this amazing transformation, watching psychedelics go from the hippie fringe to the center of psychiatry, from being viewed with suspicion to potentially being over-sold. How is such a thing even possible?

The first and deepest answer to this question derives, I believe, from the fact that we are desperate for new and better treatments in psychiatry and have been desperate for a long time. For example, although everyone who does clinical work has seen currently available antidepressants save lives, both literally and figuratively, they leave much to be desired in terms of both efficacy and tolerability; with a shadow side rarely discussed, which is that up to 25% of depressed patients who take these agents may have done better if they'd been given a placebo instead (1).

Countering these dark musings is another, and brighter, reason for this explosion of interest in psychedelics. Over the last 3 years, studies have been published suggesting that these medicines have biological and behavioural effects that might make them uniquely valuable therapeutic agents for a range of mood and anxiety disorders. Like ketamine before them, psychedelic agents appear to do things that no one in mental health would have believed in advance, and would not believe now were it not for an increasingly consistent and hopeful database speaking to their efficacy.

Psychedelics snuck into modern medicine in the mid-1990s with the pioneering work of Rick Strassman and colleagues, who reported on the biological and behavioural effects of the rapidly acting agent N,N-dimethyltryptamine (DMT) (2, 3) and with the multiple basic science studies conducted by Franz Vollenweider and colleagues at the University of Zurich (4). At the time for many of us this work seemed to come out of nowhere, a testimony to our profound amnesia regarding the central role that psychedelics had played in the development of biological psychiatry decades earlier, before they were made illegal and removed from research (5). Indeed, upwards of a thousand papers were published on classic psychedelics in the 1950s and 1960s. Although none of these studies come close to meeting modern norms for rigor, many of them suggested therapeutic benefits for two conditions in particular: alcoholism and end-of-life depression/anxiety in patients with terminal cancer.

Based on these latter findings, as well as on a promising randomized trial in patients with cancer conducted by Charles Grob and colleagues at UCLA (6), when the door of possibilities opened a bit wider at the start of the 21st Century, researchers at Johns Hopkins and New York University (NYU) chose to use modern randomized, placebo-controlled, double-blind designs to examine whether the psychedelic agent psilocybin (the active ingredient in 'magic mushrooms') might really help depressed and anxious cancer patients. These studies were done on financial shoe-strings, funded mostly by the Heffter Research Institute. They were conducted against an impressive range of obstacles, and they took a long time to complete. When asked why psilocybin was the chosen agent, several of the researchers ruefully told me, 'Because it didn't contain the letters "L, S, D".' This honest confession spoke volumes about the

bias against these medications in those times. Both studies have limitations. But when they were published and the results were striking and consistent across the two trials, the tide of public opinion began to turn.

In the larger of these two studies, conducted by Roland Griffiths and colleagues at Johns Hopkins, 51 patients with cancer and clinically-significant depression/anxiety were randomized to a single treatment with either a high-dose or a low, non-psychedelic, dose of psilocybin, which served as the placebo condition. Approximately 5 weeks later, a double-blind cross-over was conducted. All patients were followed for an additional 6 months. Compared to the low dose, a single high dose of psilocybin produced very large effect size reductions in both depression and anxiety. At 6 months follow-up and with no further treatment, more than 50% of participants remained in clinical remission (7).

Concurrent with the Hopkins study, Steve Ross and colleagues at NYU were utilizing a similar, double-blind, placebo-controlled cross-over design to examine the effects of a single dose of psilocybin in patients with cancer and a clinical picture more dominated by anxiety than depression, but otherwise similar to the Hopkins population (8). However, whereas the Hopkins study used low dose psilocybin as the placebo control, the NYU study employed niacin, in the hopes that the flushing experience it induced would lend credibility to the sham condition. Despite these minor differences, the results were entirely concordant with those from Hopkins. Large effect size benefits of psilocybin were seen vs. placebo prior to cross-over for both depression and anxiety, and at 6.5 months post-cross-over rates of clinical response remained high (i.e. 60% to 80%). Moreover, this study examined the impact of psilocybin 1-day post-treatment and found that most of the antidepressant/anti-anxiety effects were already apparent, suggesting that psilocybin may have the same type of immediate effect seen with other new, rapidly-acting, antidepressants, such as ketamine (9), scopolamine, and whole body hyperthermia.

If these trials are one major source of our renewed interest in the clinical potential of psychedelics, another is a series of translational and clinical studies conducted by Robin Carhart-Harris, David Nutt and colleagues at Imperial College London (see Carhart-Harris 2018 for an overview of this work) (10), One of the most recent of these studies, *Effects of psilocybin therapy on personality structure*, is published in this edition of Acta Psychiatrica Scandinavica (11).

This study is a secondary analysis of an open trial of two doses of psilocybin separated by a week in 20 patients with rigorously defined treatment-resistant depression (TRD). Although the antidepressant effect of psilocybin in this chronically-depressed population was not as robust or as sustained as the effect seen in the depressed/anxious cancer patients, it was still considerable. Forty-seven per cent of participants achieved a clinical response, and of these, 66% maintained their response at 6 months post-treatment. No patient received any other treatment for the first 3 months following psilocybin dosing. However, after this a number of patients resumed their antidepressants or entered psychotherapy.

The current study reports that 3 months following psilocybin treatment these same patients had undergone changes in personality variables typically considered to be stable across adulthood. Specifically, neuroticism decreased, whereas extraversion and openness increased, and a trend-level increase was observed for conscientiousness. These findings replicate and extend an earlier study by Roland Griffiths and colleagues at Hopkins which found that psilocybin increased openness in normal volunteers 15 months post-treatment (12).

Carhart-Harris and the Imperial College researchers are quick to emphasize that psychedelics are not unique in their ability to impact therapeutically-relevant personality domains. Indeed, a robust dataset demonstrates that traditional antidepressants induce similar personality changes. However, whereas these changes typically require ongoing medication exposure to be maintained, psilocybin seems to set in motion personality changes that become self-sustaining.

Prior publications from this open study of psilocybin in TRD observed other differences between psychedelics and traditional antidepressants. Whereas antidepressants dampen amygdala responses to negative images following treatment (with this effect associating with therapeutic benefit), psilocybin actually enhanced these amygdala responses, which correlated with the medication's later antidepressant effects (13). Interestingly, these findings, although paradoxical, do not exist in a void. We and others have shown that compassion meditation induces similar stimulatory effects on amygdala function (14, 15) and that these effects are associated with reduced depression (15).

While the findings I have discussed in this editorial are both fascinating and promising, I would be remiss if I didn't invoke a note of caution into all this enthusiasm. It is undeniable that classic psychedelics like psilocybin have profound acute effects on brain function, one does not need a brain scan to

see this in the behavioural responses that patients experience during the 'trips' that are carefully orchestrated in all the recent studies. But the very obviousness of these effects makes blinding psychedelic treatments difficult in the extreme, at least in terms of patient perception. Moreover, all clinical studies to date of psilocybin have been small, and only two have used a randomized, placebo-controlled design. Many other potential antidepressant treatments that looked promising in the calm waters of small, single-site phase 2 studies floundered out on the wild and wide open seas of large, multi-site phase 3 trials. And while most data to date do not indicate that psychedelics have a high abuse liability, the question remains open as to whether, having tried the medicine once in a study, patients with depression will be at risk for increased future use, whether for recreation or self-treatment.

With these caveats in place, however, I am hopeful that the larger and more rigorous clinical trials to come, conducted by Usona Institute and others, will deliver on all the early promise I have highlighted in this editorial.

Conflict of Interest

Dr. Raison reports that in the prior 12 months he has served as a consultant for Usona Institute, Emory Healthcare, Alkermes, Shire and North American Center for Continuing Medical Education.

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