Research on psychedelics moves into the mainstream

The backlash against the recreational use of psychedelic drugs in the 1960s had a negative effect on research into their potential therapeutic benefit. But now attitudes are changing and work in this area is being revitalised, with several early-stage trials underway. Kelly Morris reports.

Some 50 years ago, substances called psychedelics were hailed as the new tools of psychiatry. After their use in diverse clinical contexts, not always with rigorous methods, and following widespread non-medical use, "research was quashed for misguided but understandable reasons", explains Rick Doblin, president of the US Multidisciplinary Association for Psychedelic Studies (MAPS). Now, that scenario is rapidly changing, with several phase II trials underway worldwide, and many more studies ongoing or planned. "It's amazing how much is going on", Doblin told *The Lancet* after the World Psychedelic Forum that took place in Basel, Switzerland at the end of March.

Part of this resurgence, say experts, is down to a more measured attitude of researchers towards the risks and the benefits of drugs like lysergide (LSD), psilocybin, and methylenedioxymethamfetamine (MDMA). "What we see now is the [US] FDA (Food and Drug Administration) making decisions based on data rather than politics, and major universities involved in research", notes Tom Roberts, a professor of educational psychology from Northern Illinois University, IL, USA, and co-editor of the book *Psychedelic Medicine*. Clinical studies are the most appropriate context to start re-exploring the use of psychedelics, says Roberts, because of rigorous review processes and the step-by-step development of studies. The "Timothy Leary era" of informal or illegal explorations "caused a lot of problems", he notes. Ben Sessa, a consultant psychiatrist based in the UK, agrees. "At the end of the 1960s these drugs were labelled as dangerous drugs of abuse in the wake of the explosion of recreational use by the general public. The resulting war on drugs has been only minimally effective at tackling recreational use but has been extremely damaging for any genuine medical research", he says.

What the experience of the 1960s has shown is pointers to many possible therapeutic and non-medical uses. "The evidence so far suggests that the anxiety (neurotic) disorders tend to do well with psychedelics—that includes anxiety, post-traumatic stress disorder, and obsessive-compulsive disorder. This is because these drugs are particularly good at allowing the user to access otherwise repressed and painful memories and do some meaningful psychotherapeutic work under the influence of the drug", says Sessa. Previous clinical experience, plus more recent informal use, has indicated other potential therapeutic uses for cluster headaches and addictions, among other conditions.

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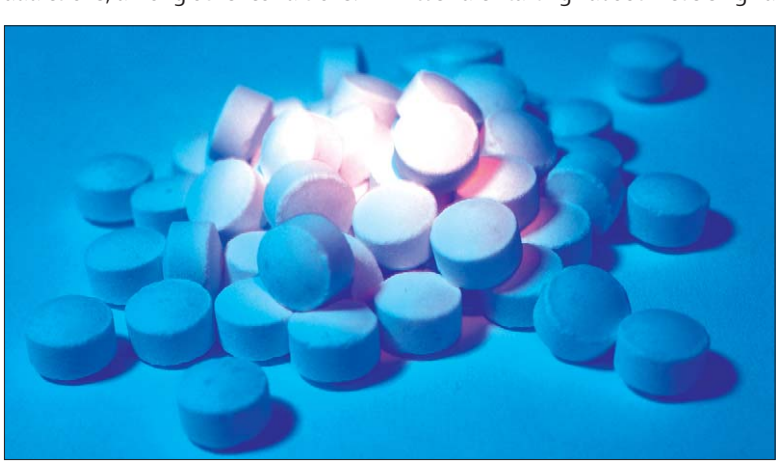
Some of the first clinical trials have focused on MDMA, which is not a classic hallucinogen. Doblin was keen to develop protocols for formal phase II studies given the drug's reported capacity "to enhance people's ability to feel, accept, and integrate difficult emotions" within a psychotherapeutic context. Of MAPS' three pilot studies for post-traumatic stress disorder worldwide, the US study ends first, in July. Three further phase II studies are in planning. "What we need to do is to replicate the US findings", says Doblin, who then hopes to see the development of phase III trials in Europe and the USA, which, if positive, could pave the way for MDMA to be available as a prescription medicine.

"We have shown that LSD [historically] and MDMA given in a psychotherapeutic context can be safe", notes Doblin, but he emphasises that the therapeutic outcome seems highly dependent on the therapeutic context. Thus, as Roberts explains, "in psychotherapeutic sessions, psychedelics are best thought of as adjuncts to psychotherapy, not as whole treatments themselves". Doblin concurs: "We are talking about reversing a



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The therapeutic benefit of MDMA is being tested in pilot studies for post-traumatic stress disorder

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Psychedelics might be of benefit in the treatment of cluster headaches

lifetime of patterns, in some cases, so the magic bullet or single-dose miracle cure theory is out the window. Multiple doses are needed in the context of long-term psychotherapy."

Now, the first clinical trial of psilocybin in terminal cancer patients led by Charles Grob at the University of California is nearing completion, and others are recruiting or about to start further investigating psilocybin, MDMA, or LSD in similar situations. For example, a study led by Stephen Ross and Anthony Bossis from the New York University School of Medicine, NY, USA, is about to commence using psilocybin with psychological support, with endpoints that include reductions in anxiety, depression, pain, and increased acceptance of death. "I am interested in novel ways to relieve suffering for end-of-life cancer patients", says Bossis. "We are looking to determine whether a mystical state can alleviate the psychosocial and existential anxiety associated with the end of life." Roland Griffiths from Johns Hopkins University School of Medicine, Baltimore, MD, USA, is also researching the effect of psilocybin on anxiety surrounding cancer diagnosis; this trial is unique in that patients with and without disease progression will be eligible.

Amanda Neidpath, director of the UK Beckley Foundation, has been working for years to initiate new research on LSD, by collaborating with various groups worldwide. In addition to therapeutic research, she believes "we need to understand the mechanisms by which we get these changes of perception that may be beneficial…how these substances work, how they are helpful, and for whom". Also, since psychedelics would not be efficacious in everyone, an understanding of mechanisms may point to non-psychedelic means to achieve the same therapeutic effects. Research on mechanisms might also help explore other potential uses for psychedelics. One such study about to commence will investigate the effects of LSD on brain connectivity and sensory processing, which might clarify previous suggestions about how psychedelics might enhance cognition and creativity.

"As our view of the human mind and nervous system expands, it is being recognised that different mind-body states, different from our waking state, are also useful", says Roberts. One such state, which has been anecdotally linked with enhanced wellbeing and anti-addictive properties, is the group use of ayahuasca. This ancient compound is not pure, but a mixture of plants used mainly by indigenous and spiritual groups. Traditional mixtures vary, but all contain a source of the psychedelic dimethyltryptamine plus a compound to prevent its gastrointestinal breakdown.

Jordi Riba and a team led by Manel Barbanoj from the Hospital de Sant Pau in Barcelona, Spain have been studying ayahuasca in healthy volunteers for about 10 years. Using a freeze-dried preparation, administered at standard doses of the active alkaloids, the team have done tolerability and pharmacokinetic studies in addition to collecting data on neuroendocrine, immune, and subjective parameters. "During the acute phase [3–4 h], volunteers reported having gone through a deeply introspective and emotional experience with thoughts usually revolving around personal concerns", notes Riba. "Most participants found this interesting and useful, and it is in this remarkable characteristic of ayahuasca where the potential for modifying self-destructive behaviours, such as drug abuse, could reside", he speculates. EEG and SPECT studies have confirmed changes in brain electrical activity and blood flow consistent with these subjective effects, and now the team plans to assess the effect on long-term healthy users.

In learning lessons from the 1950s and 1960s, researchers in general remain cautious about the potential for psychedelics and how they are investigated. Roberts notes that except for a study on cluster headaches (which reviewed informal use), all studies presented at the recent Basel forum specify that psychedelics are taken in the presence of a trained professional, and programmes for educating and training professionals are starting to be developed. MAPS is planning to seek FDA approval for a training programme for psychotherapists or nurses to become psychedelic psychotherapists. Ross, with Jeffrey Guss, has developed a course on psychedelic medicine, taught earlier this year to a group including medical students, psychiatry residents, and post-doctoral addiction fellows at Bellevue Hospital department of psychiatry in New York, USA. The course focuses on use of psychedelics for addiction.

The development of education in parallel with research is essential to ensure an academic focus towards psychedelic medicine, Ross and others believe. "Often people hold very passionate and pseudo-scientific opinions about these drugs on both sides of the debate. As clinicians, we need to remain dispassionate and hold true to the principles of evidence-based medicine…we owe it to those patients who may benefit from this approach", says Sessa.

Kelly Morris