

Small Pharma
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Psychedelic-assisted therapy: a new approach to treating depression

With clinical trials for its novel psychedelic drug underway, trailblazing neuropharma company Small Pharma is exploring a novel path to better mental health.

Psychedelics gained notoriety as recreational drugs, but they are now part of a new paradigm in treating mental health disorders, when used with psychotherapy. Small Pharma is the first company to conduct clinical trials to treat depression with the psychedelic *N,N*-dimethyltryptamine (DMT). "Combining pharmacological and psychological intervention is a departure from existing practices so we're treading on virgin territory," said Small Pharma chief executive officer, Peter Rands.

Based in London, Small Pharma was set up in 2015 to develop new drugs using known active ingredients, an area previously neglected by big pharma. The company operate a virtual model, contracting out its research and development and in May 2021 was listed on the Toronto stock exchange for venture stage companies.

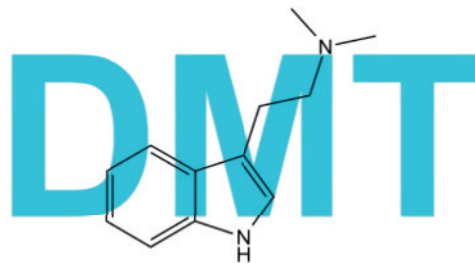
Small Pharma began to focus on mental health early on. "Very little progress was being made in treating depression, so we decided to start there," said Rands, a patent attorney with 15 years of experience in the pharmaceutical industry. Current treatments for depression are dominated by selective serotonin-reuptake inhibitors (SSRI) that work by blocking the reuptake of the neurotransmitter serotonin, but their efficacy is often limited. They typically take six to eight weeks to work, have unpleasant side effects, and more than a third of patients do not respond at all.

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Peter Rands, CEO,
Small Pharma

Therapeutic psychedelics

In the last few years, the research community has shown renewed interest in the therapeutic use of psychedelics when administered in highly controlled therapeutic environments and used in conjunction with psychotherapy. Much of the research has focused on psilocybin, a naturally occurring tryptamine compound found in the



psychoactive psilocybe genus of mushrooms. A recent small trial, conducted by researchers at Imperial College London suggested psilocybin compared favourably to the standard SSRI drug, escitalopram to treat major depressive disorders¹.

However, psilocybin has its drawbacks. It has one of the longest durations of action of all psychedelics, making it difficult for clinicians to deliver. So Small Pharma has focused on another psychedelic drug, DMT. This is one of the active ingredients of the traditional Amazonian herbal medicine ayahuasca and it is also found endogenously in plants and animals. DMT is a serotonergic psychedelic that affects a number of serotonin receptors in the brain. "We're very interested in its ability to change the brain's large-scale neuronal structure, known as the Default Mode Network. We believe that DMT follows the same mechanism as psilocybin, increasing 'entropy' in the brain and allowing neuronal connections to be remade in positive ways, but on a much shorter clinical time frame," explained Rands.

One goal of the company is to optimize the pharmacokinetics and bioavailability of DMT, as the molecule itself is quickly metabolized. Small Pharma is researching DMT analogues, replacing specific hydrogen atoms with deuterium, which extends the half-life of the molecule. These novel forms of DMT (deuterated DMT) have longer durations than DMT when delivered intravenously and may even make oral delivery possible. "We developed a library of deuterated forms and will be selecting two candidates, that could offer a short to medium acting orally-delivered psychedelic, that can be used during therapy sessions," said Rands.

Collaborating and trials

Given the novelty of its approach, Small Pharma is collaborating closely with David Erritzoe at the pioneering Centre for Psychedelic Research at Imperial College London, one of the pre-eminent global research centres in psychedelics. "They

have been closely involved in designing the trial protocols for the integration of the drugs and therapy," said Rands. The company has now initiated a combined phase 1/2a trial to evaluate the effects of an intravenous formulation of its first drug candidate, SPL026, in healthy volunteers and in patients with moderate to severe depression. As well as tolerability, the trial will look at certain well-being markers and will also evaluate the antidepressant efficacy of this treatment in patients. The company intends to follow participants over a 6-month period to monitor the longer-term impacts of the treatment.

Small Pharma acknowledges that the task of integrating both pharmaceutical and psychotherapeutic elements into its trial requires unique expertise, which it is developing. The company is however open to new collaborations and investment to further the clinical development of its drug candidates.

"I'm certain that psychedelics have some place in the future of psychiatry," said Rands. Whilst he suggests that psilocybin is likely to be the first psychedelic drug to be licensed for use, with its various shortcomings, he added, "it's not clear to me that psilocybin will be the best." Ultimately Rands expects that the 'best-in-class' therapeutics for treating depression will be based on DMT. With more than 300 million people suffering from depression worldwide, the company is looking to provide a rapid onset and long-lasting alternative treatment for the many patients who currently don't respond adequately to conventional anti-depressants.

1. Carhart-Harris, R. et al. *N. Engl. J. Med.* **384**, 1402-1411 (2021).

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