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Editorial

# Psychedelics are Bringing a new wind to the Pharmacopoeia

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Hallucinogenic substances such as psilocybin, LSD or ecstasy are now the subject of several hundred clinical trials around the world to test their ability to restore our mental health.

Psilocybin (active ingredient in hallucinogenic mushrooms), LSD (derived from compounds from ergot), dimethyltryptamine (or DMT, part of the composition of ayahuasca), mescaline (derived from peyote), but also MDMA ( amphetamine better known under the name ecstasy) or even ketamine (1), this anesthetic long used in veterinary medicine (and misused in rave parties) before becoming the darling of the psychiatry labs… Praised to the skies by the thurifers of the Beat Generation and the counterculture of the 1950s and 1960s, then banned at the turn of the 1960s and 1970s - the United Nations classified them on the list of narcotics, dangerous and of no therapeutic benefit, in 1971 -, psychedelics have experienced a strong resurgence of interest from the scientific community over the past ten years.

The first study on the use of psilocybin to treat tobacco addiction dates back to 2014; Since then, this research has multiplied. “On the ClinicalTrials.gov website alone, which lists therapeutic trials carried out in the United States, there are 275 studies on the use of psychedelic molecules, half of which concern psilocybin, and the rest MDMA or LSD.

While conventional antidepressants take, in the best case, between 4 and 6 weeks to act, and a third of patients receiving these drugs do not benefit from them and continue to sink deeper and deeper into the meanders of depression, the “journey” induced by the controlled intake of certain hallucinogenic molecules can have a rapid and lasting beneficial effect, including against the most severe depressions. On condition, however, that this is done in the hospital environment, the only one able to offer guarantees on the composition of the molecule and where all precautions are taken to prevent the experience from turning into a “bad trip”.

In the spring of 2021, the “New England Journal of Medicine” revealed the more than encouraging results of a large-scale phase II clinical trial, carried out on 233 patients resistant to antidepressants; among them, 79 had been administered a single dose of 25 mg of psilocybin (the others having received lower doses), and the experimenters had noted a significant and lasting improvement in their symptoms, almost a third even being in remission three weeks after this single dose(2). More recently psilocybin was studied for use in treatment-resistant depression. In this trial of psilocybin administered in a single session with psychological support, a 25-mg dose but not a 10-mg dose resulted in a significantly greater reduction (improvement) in MADRS total scores than a 1-mg dose at 3 weeks in participants treatment-resistant depression but was associated with adverse events (3).

But how does the active ingredient of the “magic mushroom” succeed where antidepressants custom-synthesized by the world’s largest pharmaceutical laboratories fail? How and why does a “trip” that lasts only a few hours continue to block the discomfort induced by depression several weeks after this experience, as disconcerting as it is occasional? The drug as a medication presumably works on the brain (as a “catalyst”), but there is a separate psychotherapy that it facilitates (4).

Psilocybin, LSD, DMT or mescaline all have in common that they are serotonin “agonists”, molecules mimicking the action in the brain of this neurotransmitter, which is precisely lacking in depression (this is why conventional antidepressants strive to increase the quantity in circulation, by blocking its reuptake at the synapses).

More precisely, these four psychedelics activate a specific receptor (the 5-HT2A receptor) which also activates serotonin; they therefore boost the serotonergic system. (The action of ecstasy and ketamine is different; the first, an amphetamine, stimulates the dopaminergic system, while the second affects a third neurotransmitter, glutamate.)

But this observation only constitutes a preamble to a real explanation. This comes in a study published in July in “Nature”. It is the neural network constituting the “default mode” that this work is interested in.

This network is active when our brain is in a state of waking rest, in other words when our mind, not fixating on anything specific, begins to wander, from vague thoughts to uncertain daydreams - which, for a depressive, is the door wide open to ruminations, to the incessant rehashing of dark ideas. This network and this mode serve as support for three dimensions: the spatial dimension, the temporal dimension and the dimension of the self (the little voice that speaks to us in our head).

What did the authors of the “Nature” study discover? That psilocybin has the effect of desynchronizing, during the “trip”, the neurons weaving this network. No wonder our perceptions of space and time are profoundly altered when we “hover”, we tell ourselves. But that's not all (4).

The dimension of the self is itself affected: we are no longer “the same self” during the trip as before. And above all, when the effect of psilocybin ceases, and the default mode neurons resynchronize with each other and with those of other structures or cervical systems, this reconnection does not amount to a return to the status quo ante. In

particular, communication remains disrupted for several weeks between the default mode network and the hippocampus, this key structure, center of memory and spatial navigation (it's our little internal GPS), part of the limbic system. also called the emotional brain. Long after the "trip" has stopped, we are, literally, no longer the same as we were. The brain has undergone a "reset", a profound reset.

It is very likely that what has just been shown for psilocybin applies equally well to LSD, DMT or mescaline, which are from the same family. And it is positively certain that all this wonderfully illustrates one of the essential characteristics of the brain, which makes it such a fascinating organ: its plasticity.

In addition to anxiety-depressive disorders and depression itself, ongoing studies and clinical trials are exploring the therapeutic benefits that psychedelic molecules could provide in other mental pathologies. Addictions (to alcohol and tobacco, to narcotics), post-traumatic stress disorder (PTSD) and even existential anxieties caused by the end of life are particularly affected.

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