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Editorial

Natural Hallucinogens in Mental Health

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In the last two decades, an increasing trend has unfolded toward the possible beneficial uses of natural hallucinogenic substances for treating mental health disorders. The description of the fast-acting antidepressant effects of the dissociative drug ketamine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, in the early 2000s [1] opened the doors to new, innovative approaches to treat depression that produced profound subjective effects and modulated other neurotransmission systems (in this case, the glutamatergic system) that were not the classic monoamines. However, there is some concern about the abuse potential and possible bladder toxicity linked to ketamine [2]. Thus, renewed interest has emerged in other drugs with psychedelic subjective effects that may act as fast-acting antidepressants, such as lysergic acid diethylamide (LSD), psilocybin (present in several mushroom species), and ayahuasca (an *N*,*N*-dimethyltryptamine(DMT)- and *β*-carboline-containing concoction used in Amazonian medicine) [3,4].

Interest in these drugs in psychiatry (mainly LSD) dates to the 1950s to 1960s, when they showed promising preliminary results in patients with depression and anxiety [3,4]. However, due to increases in recreational use, an association of these drugs to the counterculture, and regulatory changes for performing clinical trials (demand for the use of control groups and/or placebo), human research with these drugs was abruptly stopped in the early 1970s, only to reactivate in the early 1990s [3,4]. Interestingly, different from the first wave of hallucinogen research in the 1950s to 1960s during which LSD was the main drug used, modern (post-2000s) studies are more focused on psilocybin and, to a lesser extent, ayahuasca. Moreover, except for the semi-synthetic drug LSD, psilocybin and ayahuasca have been used for centuries for religious and healing purposes by several cultures in the Americas, where they are still being used. Therefore, together with the atypical psychedelic/hallucinogen ibogaine, natural hallucinogens are deeply immersed in the history, culture, and healing practices of traditional communities and have been used for generations in ritualized, controlled settings.

Small modern trials have shown that ayahuasca and psilocybin have promising antidepressant and anxiolytic effects on patients with major depressive disorder [5–8] or on those showing depressive and anxious symptoms associated with cancer or other life-threatening diseases [9,10], as well as in substance use disorders [11]. Remarkably, these drugs induced significant reductions in depressive and anxiety symptoms within hours/days, and the beneficial effects were sustained for weeks to months. Additionally, contrary to ketamine's abuse potential and possible bladder toxicity, classic psychedelics are considered substances with low abuse potential and toxicity [3,4].

Nevertheless, despite these promising results, it is important to acknowledge that data are still preliminary, and much remains to be investigated in this field. Indeed, both the

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number of concluded trials and the sample sizes in these trials are small, most trials used a crossover design, the blinding was not efficient in some trials, and the safety and tolerability of the repeated doses of these compounds are unknown. Furthermore, it is still unknown if whole preparations (mushroom, ayahuasca) are more effective or better tolerated than isolated compounds, or what is the contributing role of different psychotherapies in the treatments. Thus, the objective of this Special Issue entitled "Natural Hallucinogens in Mental Health" is to present and discuss the possible uses of natural hallucinogens as therapeutics in psychiatric disorders and mental health in general.

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References

1. Berman, R.M.; Cappiello, A.; Anand, A.; Oren, D.A.; Heninger, G.R.; Charney, D.S.; Krystal, J.H. Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* **2000**, *47*, 351–354. [CrossRef] [PubMed]
2. Jauhar, S.; Morrison, P. Esketamine for treatment resistant depression. *BMJ* **2019**, *366*, l5572. [CrossRef] [PubMed]
3. dos Santos, R.G.; Hallak, J.E.C. Therapeutic use of serotoninergic hallucinogens: A review of the evidence and of the biological and psychological mechanisms. *Neurosci. Biobehav. Rev.* **2020**, *108*, 423–434. [CrossRef] [PubMed]
4. Nichols, D.E. Psychedelics. *Pharmacol. Rev.* **2016**, *68*, 264–355. [CrossRef] [PubMed]
5. Palhano-Fontes, F.; Barreto, D.; Onias, H.; Andrade, K.C.; Novaes, M.M.; Pessoa, J.A.; Mota-Rolim, S.A.; Osório, F.L.; Sanches, R.; Dos Santos, R.G.; et al. Rapid Antidepressant Effects of the Psychedelic Ayahuasca in Treatment-Resistant Depression: A Randomized Placebo-Controlled Trial. *Psychol. Med.* **2019**, *49*, 655–663. [CrossRef] [PubMed]
6. Carhart-Harris, R.; Giribaldi, B.; Watts, R.; Baker-Jones, M.; Murphy-Beiner, A.; Murphy, R.; Martell, J.; Blemings, A.; Erritzoe, D.; Nutt, D.J. Trial of Psilocybin versus Escitalopram for Depression. *N. Engl. J. Med.* **2021**, *384*, 1402–1411. [CrossRef] [PubMed]
7. Davis, A.K.; Barrett, F.S.; May, D.G.; Cosimano, M.P.; Sepeda, N.D.; Johnson, M.W.; Finan, P.H.; Griffiths, R.R. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder. *JAMA Psychiatry* **2021**, *78*, 481–489. [CrossRef] [PubMed]
8. Goodwin, G.M.; Aaronson, S.T.; Alvarez, O.; Arden, P.C.; Baker, A.; Bennett, J.C.; Bird, C.; Blom, R.E.; Brennan, C.; Brusch, D.; et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *N. Engl. J. Med.* **2022**, *387*, 1637–1648. [CrossRef] [PubMed]
9. Ross, S.; Bossis, A.; Guss, J.; Agin-Liebes, G.; Malone, T.; Cohen, B.; Mennenga, S.E.; Belser, A.; Kalliontzi, K.; Babb, J.; et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *J. Psychopharmacol.* **2016**, *30*, 1165–1180. [CrossRef] [PubMed]
10. Griffiths, R.R.; Johnson, M.W.; Carducci, M.A.; Umbricht, A.; Richards, W.A.; Richards, B.D.; Cosimano, M.P.; Klinedinst, M.A. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *J. Psychopharmacol.* **2016**, *30*, 1181–1197. [CrossRef] [PubMed]
11. Bogenschutz, M.P.; Ross, S.; Bhatt, S.; Baron, T.; Forcehimes, A.A.; Laska, E.; Mennenga, S.E.; O'Donnell, K.; Owens, L.T.; Podrebarac, S.; et al. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs. Placebo in the Treatment of Adult Patients with Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* **2022**, *79*, 953–962. [CrossRef] [PubMed]