

Festina lente: Psychedelics

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Summary

Background: In the last few years, the use of psychedelics for therapeutic purposes has become an increasingly popular topic in psychiatric science as well as in society in general. Because of that, this paper aims to discuss the current trends surrounding psychedelics and their use for therapeutic purposes.

Method: We have made an overview of the available literature on psychedelics.

Results: Although some research on the use of psychedelics for therapeutic purposes gives promising results, they are still not solid. The social context in which the discoveries related to psychedelics are interpreted is dominantly optimistic. However, potential problems and pitfalls await us in the process of legalization and introduction of psychedelics into clinical practice.

Conclusion: Current knowledge about psychedelics still calls for caution. Maintaining a critical view and leading a wider social discussion is necessary.

Keywords: psychedelics, trend, personality disorders, legalization, criticism

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The perception of psychedelics in society has changed a lot in the last few years. They were once banned in most countries of the world, affected by the so-called “War on Drugs” in the United States of America (USA). Today, there is a call to respect the human rights of people who use psychedelics, especially if they are part of their cultural practices (Schwarz-Plaschg, 2022; Krebs, 2015). The USA is a good example of such a trend at the level of society. The change in the legislation that regulates the status and attitude towards psychedelics started in federal states with a liberal ruling majority, but today it is also present in “conservative” federal states. While 5 reform laws were passed in 2019, there were 36 in 2022. Most of them propose decriminalization, primarily of psilocybin. In the state of Oregon (USA), psilocybin should be available not only to those who seek psychiatric help, but also to those who want this form of support in personal and spiritual development (Siegel et al., 2023; Smith & Appelbaum, 2021; Marseille et al., 2022). In Australia, the use of certain psychedelics for therapeutic purposes has been approved, although a meta-analysis did not provide arguments for this (Kisely et al., 2023; Kisely, 2023).

„Festina lente“, the favorite saying of Emperor Augustus according to the records of Suetonius, is a Latin translation of the Greek original meaning hurry slowly, i.e. don't rush (Enciklopedija.hr, 2023). We plan to outline the reasons why there is a rush to use psychedelics for therapeutic purposes and their legalization, but also why we should not rush.

WHY THERE IS A RUSH

The use of psychedelics in the “West” was associated with the counterculture, but today it is part of the mainstream culture more than ever before. Steve Jobs described lysergic acid diethylamide (LSD) as “one of the most important things in life”. Large Silicon Valley companies strongly promote the benefits of psychedelics, microdosing as part of an attractive and prestigious lifestyle, a solution to personal and social problems, finance research, open institutes, and start workshops on psychedelics (Tvorun-Dunn, 2022). Searching for the term “psychedelics” in PubMed will yield 31,094 results. For 2015, the search offers 688 results, 2020 1073 results, 2022 1715 results (Nih.gov, 2023). Private equity investments in psychedelic research for 2020 and 2021 totaled \$31.2 million. In the period from 2015-2019, a total of 49.5 million dollars was invested. Public and non-profit investors have a hard time following such investment growth (Marseille et al., 2022). On the other hand, advocates of full legalization of psychedelics show concern that the medicalization and commercialization of psychedelics will limit their availability in various ways (Noorani, 2021). Certainly, the “Psychedelic Hype Bubble” is already being talked about. Traditional media, social networks, and medical online services regularly bring positive news about psychedelics, while the possibility of abuse is hardly mentioned. They are spoken of as a panacea, every research is groundbreaking, it represents a breakthrough, a turning point, and the field of indications is getting wider (Yaden et al., 2022; Sellers

& Romach, 2023). In addition to resistant depression and post-traumatic stress disorder (PTSD), psychedelics are now also mentioned as a therapy for various forms of addiction, behavioral and substance, various mood disorders, anxiety disorders, and disorders related to stress and trauma. They could also have their place in child psychiatry, psychotherapy, and palliative care. Psychedelics also fit nicely into the “nature” cult, according to which everything that comes from nature is a priori better than synthesized, for example, psychopharmaceuticals (Marseille et al., 2022; Yaden et al., 2022; Sellers & Romach, 2023; Zafar et al., 2023; Edelson & Sisti, 2023; Sicignano et al., 2023). Of course, in such social circumstances, in addition to existing economic interests, we can also expect bad science, i.e. the bias of scientists and scientific journals (which we will refer to later). If we add to this that for some patients suffering from depression and PTSD, the existing therapy is not effective, has no effect, or is minimal and slow to achieve, and side effects are also present, it is clear that psychedelics have “found their place” and offer hope. They have been presented as a relief of suffering for millions of patients. Not only do they achieve healing, usually with one dose, but they also cause a feeling of comfort, and satisfaction and increase sociability (Marseille et al., 2022; Sellers & Romach, 2023; Hall & Humphreys, 2022; Galvão-Coelho et al., 2021). But we have to ask ourselves if it is really so and how much we know about psychedelics.

WHY WE SHOULD NOT RUSH

Current knowledge about psychedelics, as well as the shortcomings of certain research, call for a more cautious approach to the process of legalization and entry of psychedelics into clinical practice. 2020 Luoma et al. published 1st meta-analysis of studies comparing psychedelic-assisted therapy with placebo. For the period from 1994 to 2020, they found 9 studies that met the criteria. Five studies examined 3,4-methylenedioxy-methamphetamine (MDMA), two psilocybin, one ayahuasca, and LSD. Indications were social anxiety, anxiety, depression, and PTSD. A total of 211 respondents were included. Three studies followed subjects for 7 weeks to 6 months. It concluded: “However, several weaknesses were identified and improvements are needed regarding the conduct and reporting of trials in the future. Despite these limitations, large effect sizes are rare in psychiatry and psychology and our findings suggest that psychedelic-assisted therapy presents a promising new direction in mental health treatment (Luoma et al., 2020).” New meta-analyses and systematic reviews followed, which also stated that the results were

promising, but also that there were numerous limitations of previous research and that additional research is needed before the introduction of psychedelics into clinical practice (Sicignano et al., 2023; Kisely et al., 2023; Hodge et al., 2023). Disadvantages of research on psychedelics so far include problems such as blinding and bias of subjects and examiners, a small sample of subjects, problem of selection of adequate subjects and generalization of conclusions, lack of monitoring of drug effect, inadequacy of measuring instruments, problem of safety of subjects. There are unknowns about pharmacokinetics, pharmacodynamics, interactions (eg. with antidepressants), doses, and expected effects of psychedelics. There is a possibility of hallucinations, delusions with disturbing content, and a hallucinogen persisting perceptual disorder (HPPD). Impulsive reactions, autoaggressive and heteroaggressive behavior are possible (Sellers & Romach, 2023). To illustrate, we can mention the controversial relationship between psychedelics and personality disorders. Personality disorders are usually cited as an exclusion criterion when investigating the therapeutic effects of psychedelics. On the other hand, there are old studies on the role of psychedelics in the treatment of personality disorders and new studies have only recently started to be conducted (Svrakic et al., 2019; Bender & Hellerstein, 2022; Oehen & Gasser, 2022; Iliff & Moslehi, 2022; Traynor et al., 2022; Weiss et al., 2023). It is estimated that the prevalence of personality disorders among psychiatric patients is between 40% and 60%, and among the hospital population is even higher (Beckwith et al., 2014; Tyrer et al., 2015). People with personality disorders have an increased risk for abuse, suicidality, and psychotic decompensation (Pascual et al., 2023; Leichsenring et al., 2023; Minarikova et al., 2022). It is known that personality disorders are often a comorbidity of resistant depression and PTSD, and these are currently the only approved indications for the use of psychedelics (Young, 2018; Bollinger et al., 2000; Ford & Courtois, 2021; Kisely, 2023). The question then arises as to who are adequate patients for the use of psychedelics, how to assess it, and how many there are.

In addition to examples of quality research, which offer hope but also call for caution, we also have examples of less quality research. In the already mentioned socioeconomic circumstances, such researches are easier to reach prestigious journals, once strict criteria, and to bombastic media covers (Hall & Humphreys, 2022). An example of such research is the 2021 study by Carhart-Harris et al., published in the *New England Journal of Medicine* (NEJM), comparing the effects of psilocybin and escitalopram in patients with a long-term moderate or severe episode of depression (Hall & Humphreys, 2022; Kisely et al., 2023; Kisely, 2023; Carhart-Harris et al., 2021). For

psychedelics to enter and take root in clinical practice, the most important thing is that they prove to be more efficient, in at least one aspect, and at least equally safe compared to existing antidepressants. The conclusion from the abstract of the study by Carhart-Harris et al. was: “On the basis of the change in depression scores on the QIDS-SR-16 at week 6, this trial did not show a significant difference in antidepressant effects between psilocybin and escitalopram in a selected group of patients. Secondary outcomes generally favored psilocybin over escitalopram, but the analyses of these outcomes lacked correction for multiple comparisons. Larger and longer trials are required to compare psilocybin with established antidepressants (Carhart-Harris et al., 2021).” Subsequently, a group of researchers, partly the same, performed a Bayesian reanalysis in the new paper and concluded: “The overall pattern of evidence provided by this Bayesian reanalysis supports the following inferences: (1) psilocybin did indeed outperform escitalopram in this trial, but not to an extent that was clinically meaningful and (2) psilocybin is almost certainly non-inferior to escitalopram. These results provide a more precise and nuanced interpretation to previously reported results from this trial and support the need for further research into the relative efficacy of psilocybin therapy for depression with respect to current leading treatments (Nayak et al., 2023).” In the third study, which is also a review of the first one, they asked about the adequacy of the Quick Inventory of Depressive Symptomatology Self-Report 16-item (QIDS-SR-16) as a method for measuring depression (Weiss et al., 2023). In the original study, psilocybin was provided by a mental health care company whose consulting fees were received by individual researchers, as noted at the end of the article (Carhart-Harris et al., 2021; COMPASS Pathways, 2023). But the problem, as Hall and Humphreys noted, is that research is published in NEJM, which states: “The peer review process works to improve research reports while preventing overstated results from reaching physicians and the public. Each published NEJM manuscript benefits from hundreds of hours of work by editors, statistical experts, manuscript editors, illustrators, proofreaders, and production personnel, who work to ensure that every paper meets exacting standards (Hall & Humphreys, 2022; Nejm.org, 2023).” How does the study by Carhart-Harris and colleagues in which a total of 59 subjects participated, of which 30 received psilocybin, 29 escitalopram, and their effect was monitored for 6 weeks, correspond to this statement? The authors themselves state in the research: “... no clinical conclusions can be drawn from these data (Hall & Humphreys, 2022; Carhart-Harris et al., 2021).” Another problem of this research is that it is described as a double-blind study and it is not stated whether the blinding

was successful, which is a known limitation in studies of psychedelics (Hall & Humphreys, 2022; Bender & Hellerstein, 2022). The 2021 study by Carhart-Harris et al. remains the only one, as far as we know, that compares a psychedelic (psilocybin) and an antidepressant (escitalopram). Is one such study, with all methodological flaws, sufficient to approve the use of psilocybin in the treatment of resistant depression? MDMA or ecstasy is approved in Australia for the treatment of PTSD. As far as we know, no such research exists for MDMA (Kisely, 2023; Prouzeau et al., 2022). A possible answer may go in the direction of the question: “Why would there be a need for research comparing psychedelics with antidepressants, if psychedelics have been shown to be effective in conditions where existing antidepressants have not been effective.” In addition to what researches and meta-analyses suggest, for various reasons, it is an integral part of modern science, necessary when testing the effectiveness of therapy, we will show on one example why logic alone is not enough in practice (Prouzeau et al., 2022; Zeiss et al., 2021; McLaughlin, 2013). It is a study by Goodwin and associates, similar to the aforementioned studies, “Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression” from 2022, which was published in the same journal and sponsored by the same company as the study of Carhart-Harris and associates from 2021. The subjects were divided into three groups, one of which received 25 mg of synthetic psilocybin, the second 10 mg, and the third 1 mg of psilocybin. A dose of 25 mg showed significantly better results on The Montgomery-Åsberg Depression Rating Scale (MADRS) after three weeks than a dose of 1 mg, which is subtherapeutic. After 12 weeks, the number of subjects with a favorable response decreased and there was no longer a significant difference between the high dose and the subtherapeutic dose. Although people with a clinically significant risk of suicide were excluded from the study, by the end of the third week, some of the subjects, especially in the groups of subjects who received a dose of 10 mg and 25 mg of psilocybin, had suicidal thoughts and non-suicidal self-harm. The authors report that the favorable response to the 25 mg dose of 37% after three weeks was lower than in studies of citalopram, nefazodone, escitalopram, sertraline, and venlafaxine. They also state that studies comparing psilocybin and existing depression therapy are needed to determine its effectiveness and safety (Kisely, 2023; Goodwin et al., 2022; Rush et al., 2006; Saveanu et al., 2015). As with the previously analyzed paper published in NEJM, we can ask the same questions. We have already mentioned that enthusiasm for psychedelics, apart from scientists and scientific journals, is also shared by various media, more or less (non)professional. A good example is the *Psychiatric Times*, which

writes about Goodwin et al. research in the article “A Single Dose of Psilocybin for Treatment-Resistant Depression (Psychiatric Times, 2022).” In it, they state the following: “Yet in this study, a substantial number of patients in the 25 mg group experienced improvement in their symptoms of depression, with the effects lasting for up to 3 months,” said Scott Aaronson, MD, Chief Science Officer of the Institute for Advanced Diagnostics and Therapeutics, Sheppard Pratt Health System, and a principal investigator on the trial.” Then: “COMP360 psilocybin was generally well-tolerated; on the day of administration, common adverse events included headache, nausea, and dizziness.” And finally: “We saw positive results in a particularly difficult to treat group of patients, and the highest dose of COMP360 psilocybin had the greatest impact on people’s depression. This suggests that COMP360 psilocybin has a true pharmacological effect, a finding that is critical for it to be recognized as a new treatment option in the future,” said Guy Goodwin, MD, DPhil, Chief Medical Officer at COMPASS Pathways. “We look forward to starting our phase 3 program later this year, moving us closer to providing COMP360 psilocybin with psychological support for patients who desperately need it.” An effect lasting up to 3 months sounds better than an effect ceasing after 3 months. Suicidality is not mentioned, but that is why we have “a discovery that is crucial” (Psychiatric Times, 2022). It is interesting that the BBC also reported on this research on its portal, but did not omit to mention suicidality and stated what kind of research are needed in the future (BBC, 2022).

CONCLUSION

Psychedelics have the potential for use in various areas of psychiatry. However, there is still not enough evidence for their use in clinical practice. Research shows shortcomings, but efforts are being made to correct them. For example, side effects are poorly defined and probably under-reported, and ways are proposed to solve the problem of blinding, i.e. placebo, etc. This should continue to be insisted on, which means adhering to strict scientific criteria, high criteria by top journals and critically looking at new and old findings (Sellers & Romach, 2023; Hall & Humphreys, 2022; Gomez-Busto & Ortiz, 2020; Earleywine & Herrmann, 2022; Butler et al., 2022; Brecksema et al., 2022; Nutt et al., 2023; Ona et al., 2022; Kaiserman et al., 2024).

As we have already explained, psychedelics are not a subject of interest only for scientists and mental health experts. This is also clear from the process of approval

of psychedelics for therapeutic use in Australia. There are similarities with the process of cannabis legalization in certain states, as recognized by Sellers and Romach (Sellers & Romach, 2023). Social changes, through the influence of social networks, strongly influenced the process of decriminalization and legalization of cannabis, although there is no solid evidence of its effectiveness, but it is known how harmful it is. The standard argumentation went in the direction of economic benefit and that only those who already use it will now do so legally. Of course, the data showed the opposite, the use and abuse increased, as well as all the resulting complications (Sellers & Romach, 2023; Bae & Kerr, 2020; Kerr et al., 2018; Koval et al., 2019; Myran et al., 2022a; Myran et al., 2022b; Gonçalves-Pinho et al., 2020; Forti et al., 2019). Until recently, the Australian Therapeutic Goods Administration (TGA) classified psilocybin and MDMA as prohibited substances. They claimed they had no therapeutic benefit. Mind Medicine Australia (MMA) is a charity and lobbying organization aiming to: “alleviate the suffering caused by mental illness in Australia through expanding the treatment options available to medical practitioners and their patients. We are focused on the development of safe and effective psychedelic-assisted therapies to cure a range of mental illnesses (Kisely, 2023; Mind Medicine Australia, 2023).” In February 2020, the TGA rejected the MMA’s proposal to authorize the use of psilocybin and MDMA for therapeutic purposes. Such a decision was made by a committee of experts (Advisory Committee on Medicines Scheduling) consisting of pharmacists, clinicians, political advisors, and community representatives. This sparked criticism and the TGA called for an investigation. Kisely et al. then conducted a meta-analysis which concluded: “... while MDMA and psilocybin(e) might show promise in highly selected populations in closely supervised settings, trial quality was variable with only small proportions of potential participants included in randomized comparisons. As a result, the certainty of evidence was rated as low or very low using the Cochrane Collaboration’s GRADE framework in a subsequently published peer-reviewed meta-analysis of the findings.” The TGA subsequently stood by its decision and rejected the MMA’s proposal. It wasn’t long before the TGA changed its decision and from July 2023 psilocybin and MDMA can be used in the treatment of resistant depression and PTSD. The decision was made by TGA delegates against the advice of their experts, based on approximately 3,500 submissions that were mostly the opinions of individuals rather than experts. Given the experience of marijuana legalization, it is assumed that psychedelics will be legalized in most US states

between 2034 and 2037 (Siegel et al., 2023; Kisely et al., 2023; Kisely, 2023).

In the end, from all of the above, it is clear that crucial things take place “outside” of science, in society, in the public, and in politics. In addition to insisting on scientific methodology, it will probably be necessary to engage independent experts and professional associations in public debates that are already taking place or will take place.

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