Potential Therapeutic Effects of Psilocybin/Psilocin are Minimized While Possible Adverse Reactions are Overrated

To the Editors:

The review article by Dr. Stebelska[1] is a comprehensive and welcome article, especially regarding the pharmacology of psilocybin/psilocin. These compounds present therapeutic potentials in several psychiatric conditions, including obsessive–compulsive disorder,[2] anxiety associated with advanced-stage cancer,[3] and drug dependence.[4] In the case of obsessive–compulsive disorder and anxiety associated with advanced-stage cancer, pilot clinical trials have been conducted reporting promising results.[2,3] Although these pilot studies present limitations, like the small sample size, it should be noted that these are just the first proof-of-concept, exploratory studies.

Nevertheless, even considering these potentials, it seems that they have been minimized in the review by Dr. Stebelska, which, however, seems to emphasize the psychotic potentials of psilocybin and overestimates its potentials for serious adverse reactions.

Regarding the psychotic-like effects, it should be noted that drugs like psilocybin are used to model only some aspects of schizophrenia, and that although there is some degree of resemblance between the early manifestations of schizophrenia or acute schizophrenic episodes and the acute effects of hallucinogenic drugs like psilocybin, a growing consensus has emerged affirming that the dissimilarities between the 2 states are too clear.[5] The gradual progression of a symptom complex that includes disturbed thought process, depersonalization, and auditory hallucinations, in many cases evolving into a generalized functional incapacitation, is characteristic of schizophrenia.[6] However, the effects of hallucinogens are marked by visual alterations and are limited to some hours.[7]

Moreover, prolonged psychotic episodes, as well as psychiatric disorders in general, are rare in ritual and controlled settings where hallucinogens are consumed or administered. Regarding psilocybin, a pooled analysis from 8 double-blind placebo-controlled experimental studies with this compound, conducted between 1999 and 2008, with follow-up between 8 and 16 months and including 110 healthy subjects,[7] reported that "acute adverse drug reactions occurred only in a relatively small proportion of subjects," "were all successfully managed by providing interpersonal support," and "did not need psychopharmacological intervention." Moreover, "follow-up questionnaires indicated no subsequent drug abuse, persisting perception disorders, prolonged psychosis, or other long-term impairment of functioning in any of the subjects."

Regarding ayahuasca, an Amazonian botanical hallucinogen rich in dimethyltryptamine, which is an alkaloid chemically and pharmacologically related to psilocybin, several double-blind placebo-controlled clinical trials investigating its acute pharmacology have been safely conducted in healthy volunteers in the last decade.[8] Moreover, the long-term (ie, years or decades) ritual use of ayahuasca by adolescents and adults presents a low level of adverse reactions.[8] The regular use of the mescaline-containing cactus peyote by Native Americans also presents a good safety profile with no evidence of cognitive or mental health deficits among this population; rather, total lifetime peyote use was associated with overall better mental health.[9]

Furthermore, controversies still persist regarding the potential causal relationship between the use of hallucinogens and psychotic disorders,[10] and LSD and psilocybin are consistently ranked in expert assessments as causing less harm to both individual users and society than alcohol, tobacco, and most other common recreational drugs.[11] Specifically in the case of psilocybin-containing mushrooms, a recent report affirmed that the use of these mushrooms is relatively safe, as only few and relatively mild adverse effects have been reported.[12]

Finally, a recent study evaluated the association between lifetime use of hallucinogens and current mental health.[13] No association was found between lifetime use of hallucinogens and any undesirable past year mental health outcomes, including serious psychological distress, mental health treatment, or symptoms of panic disorder, major depressive episode, mania, social phobia, generalized anxiety disorder, agoraphobia, posttraumatic stress disorder, or non-affective psychosis.

Regarding therapeutic potentials, the review by Dr. Stebelska[1] underestimates the potential therapeutic effects of psilocybin/psilocin, suggesting that results from previous human research indicating positive effects could be questioned because volunteers could be prompted by "dishonest" suggestions, that positive effects are "simply ingenuousness," that research for new treatment options with these compounds are "possibly nonethical," and that prolonged personality changes "may reflect serious and dangerous ego disorders."

The original studies criticized by Dr. Stebelska had good methodological rigor, and "dishonest" suggestions are not in line with the quality of the articles. Moreover, clinical trials with psilocybin were all performed in accordance with international declarations concerning experimentation on humans, and all were previously approved by ethics committees. Furthermore, there are abundant past and current animal and human data showing therapeutic potentials of hallucinogens,[14] including for health conditions with limited treatment options, what seems "possibly nonethical" is that law controls placed on these drugs make research into their potential therapeutic uses very difficult.[15]

Finally, the opinion that prolonged personality changes "may reflect serious and dangerous ego disorders" is simply not in line with the scientific literature on hallucinogens. Despite the overall excellent quality of the review, the potential therapeutic effects of psilocybin/psilocin are minimized, while possible adverse reactions are overrated.

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