The need for publicly funded research on therapeutic use of psychedelic drugs

A psychedelic drug is one that "produces thought, mood and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis"[1]. It does so "without causing physical addiction, craving, major physiological disturbances, delirium, disorientation or amnesia"[1].

The "classic psychedelics" include mescaline, psilocybin, lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), and plant-based substances such as ibogaine and ayahuasca. Their chemical structures differ, but they all act on the 5-HT2A serotonin receptor[1]. 3,4-methylenedioxymethamphetamine (MDMA) is also included, although it does not produce the perceptual effects of the classic psychedelics[2].

Over the past two decades, there has been a revival of clinical research on the therapeutic use of psilocybin and MDMA[2,3]. This research has been encouraged by the US Food and Drug Administration (FDA) because in phase 2 trials these drugs have produced substantial benefits, respectively, in patients with treatment-resistant depression and post-traumatic stress disorder (PTSD)[3]. Funding for psychedelic research has largely been philanthropic, because the pharmaceutical industry is not interested in drugs that are off patent.

The new psychedelic research that is being done in leading universities in the US and Europe includes randomized controlled trials conducted to the standard required for FDA approval[3]. Psilocybin has been chosen rather than LSD, because it has a shorter period of action (4-6 hours vs. 8-12 hours), its pharmacology is better understood, it is less likely to produce "bad trips", and it does not carry the cultural baggage of LSD[3]. Clinical trials have also been done on MDMA-assisted psychotherapy in PTSD.

If phase 3 trials confirm the results of phase 1 and 2 studies, psilocybin is likely to be approved for treatment-resistant depression, and for depression and anxiety in patients with terminal cancer. MDMA-assisted psychotherapy may also be approved to treat PTSD.

A major challenge in conducting randomized placebo-controlled trials of psychedelics is that it is impossible for patients and therapists not to be aware of who has been given a psychedelic drug[4]. Recent trials have used an "active placebo", such as methylphenidate or dextroamphetamine, or used low, moderate and high doses of the psychedelic drug to see if treatment effects are related to dose[5].

It has been argued[6] that psilocybin has a low abuse potential, because it does not produce euphoria in humans or self-administration in animals, and there are much lower rates of regular use of this drug in population surveys than for cannabis, cocaine and opioids. Furthermore, users rapidly develop tolerance to its effects and so do not persist in using it.

Studerus et al[4] reported very few acute, subacute and long-term effects of psilocybin in 110 participants in laboratory studies followed up for 8-16 months. This was a select group in that persons with a family or personal history of psychiatric disorders were excluded and 40% had used a psychedelic drug at least once. The short-term adverse effects were minor: fatigue, headache, lack of energy, and difficulty concentrating the day after. Eleven individuals reported "negative changes in psychological well-being and/or mental functions" after the psilocybin session. One reported "persistent emotional instability, anxiety and depressive feelings" that he "attributed to suppressed memories" released by the drug. He recovered after receiving psychotherapy.

Psilocybin has been described as a "disruptive" treatment because a single dose produces an immediate clinical response – unlike selective serotonin reuptake inhibitors (SSRIs) that require two weeks of treatment – and its benefits are sustained for six months in a substantial proportion of patients[2,3]. It also appears to act by different mechanisms than SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs)[2].

The major limitations of the current evidence for psychedelic drugs are interconnected. In the absence of pharmaceutical industry interest, limited support from philanthropic sources has funded the research, restricting trials to relatively small samples of patients because of the cost of doing larger studies. The persons who have done the research believe in the therapeutic value of psychedelic drugs. This is to be expected, given the history of psychedelics and the reputational challenges in conducting clinical research on them.

If psychedelic drugs are introduced in clinical practice, there is a risk that their use will get ahead of the evidence on their safety and efficacy, in much the same way that "medical cannabis" has done[7]. If psilocybin is approved for treatment-resistant depression, patients and prescribers are likely to demand its use as a first-line treatment for severe depression rather than requiring that patients first fail to respond to SSRIs and other antidepressants. It is unclear whether the FDA and other drug regulators will require trials of psilocybin as a first-line treatment. There may also be demands to use psilocybin off-label to treat anxiety disorders. If MDMA-assisted psychotherapy is approved to treat PTSD, there may be demands to use MDMA off-label to treat other anxiety and depressive disorders. If the criteria for who is a qualified therapist are relaxed, MDMA may be used to treat unhappiness, anxiety and existential angst.

The evidence may be used to argue for compassionate access to other psychedelic drugs, such as LSD, mescaline and DMT. It is uncertain if the use of psychedelics will remain under medical supervision for approved disorders, or whether their use will be advocated for spiritual and other nonmedical purposes. A combination of libertarian and utilitarian arguments may be used to justify the legalization of adult use of these drugs for any purpose, because they cause little harm to users and have a low abuse potential[8].

There may also be demands for compassionate access to plant-based psychedelic drugs in advance of any research evidence. US

states may pass citizen-initiated referenda to legalize the medical use of psychedelic mushrooms and plants, such as ibogaine and ayahuasca, by appealing to the putative "entourage" effects of whole plants and the misconception that medicines derived from plants are safer than "synthetic" pharmaceuticals[9].

For all these reasons, we need public funding of independent evaluations of the efficacy of psychedelic drugs. Trials should involve larger numbers of patients who are representative of those clinical disorders for which these drugs may be used, and should include longer-term follow-up evaluations of safety and sustainability of favorable outcomes.

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DOI:10.1002/wps.20847

Rationale for and usefulness of the inclusion of gaming disorder in the ICD-11

Video games are among the most popular consumer electronic products in the world. They are having a growing mass appeal both as an interactive recreational activity, in which one can engage individually or with other players, and as a passive entertainment in the form of viewership of broadcasted gaming events, including e-sports and live-streamed games (e.g., twitch.tv). Modern games offer a diverse range of unique and highly immersive experiences. Portable consoles and smart devices have promoted the ubiquity of video games by making them easily accessible almost anywhere.

Gaming can produce numerous benefits for many players, including the fulfilment of psychological needs of social relatedness, autonomy and competence. However, over the last three decades, there has been increasing research interest in the phenomenon of problematic gaming. Survey studies and clinical case reports have highlighted that some individuals experience difficulties in regulating their engagement in gaming activities and play to an excessive degree, resulting in mental and physical symptoms as well as functional impairment[1,2]. A meta-analysis[3] reported that the worldwide prevalence of problematic gaming, as defined by standard addiction criteria, can be estimated to be 1-2%.

Internet gaming disorder was considered as a potential mental disorder for the DSM-5, but the decision was for it to be listed only as a condition for further study. The DSM-5 criteria were consistent with substance use and addictive disorders, including reference to loss of control, tolerance, and withdrawal. Gaming disorder is now included in the ICD-11 among "disorders due to addictive behaviours". Here we outline the approach taken in the ICD-11.

In the ICD-11, gaming disorder is defined as a dysfunctional pattern of gaming, characterized by: a) impaired control (e.g., failed attempts to cut or diminish gaming involvement; gaming performed in a more prolonged or intensive way than planned); b) an increasing priority given to gaming to the extent that it takes precedence over other life interests and daily activities; and c) a continued involvement in gaming despite negative consequences for the individual and his/her acquaintances. To meet the diagnosis, the maladaptive gaming pattern has to be either continuous or episodic and recurrent, be manifested over an extended period of time (typically 12 months), and cause psychological distress or significant impairment in personal, family, social, professional, and/or other important areas of functioning.

Several features are key to emphasize. First, the guidelines include only a few essential requirements, making them practical for use in multiple settings by different health care practitioners. Second, the guidelines do not include withdrawal and tolerance, as these are not relevant to gaming[4]. Third, the emphasis on functional impairment is key for differentiating between people with gaming disorder and the large proportion of individuals engaged in intense or persistent patterns of gaming (e.g., 20-30 hours per week) without experiencing associated negative consequences[5].

The decision to introduce gaming disorder in the ICD-11 was guided by epidemiological, clinical and neurobiological studies, as well as data obtained from treatment providers[1,2]. These lines of evidence have consistently shown that problematic gaming behaviours are associated with a range of negative outcomes (e.g., depressed mood, poorer work performance and school grades, worse sleep, interpersonal conflicts). In addition, there is a growing treatment demand internationally for gaming-related problems, particularly among adolescents and young adults, and an increasing number of clinical trials involving self-referred patients seeking help for these problems[6]. The treatment literature, while still developing, indicates that some therapies targeting the mechanisms underlying gaming disorder and promoting adaptive coping strategies can have positive long-term outcomes[7].

Although there is increasing agreement among researchers and practitioners, in the areas of psychiatry, clinical psychology and public health, that gaming-related harms constitute an im-