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SCIENTIFIC CONTRIBUTION

Compassionate use of psychedelics

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Abstract
In the present paper, we discuss the ethics of compassionate psychedelic psychotherapy and argue that it can be morally permissible. When talking about psychedelics, we mean specifically two substances: psilocybin and MDMA. When administered under supportive conditions and in conjunction with psychotherapy, therapies assisted by these substances show promising results. However, given the publicly controversial nature of psychedelics, compassionate psychedelic psychotherapy calls for ethical justification. We thus review the safety and efficacy of psilocybin- and MDMA-assisted therapies and claim that it can be rational for some patients to try psychedelic therapy. We think it can be rational despite the uncertainty of outcomes associated with compassionate use as an unproven treatment regime, as the expected value of psychedelic psychotherapy can be assessed and can outweigh the expected value of routine care, palliative care, or no care at all. Furthermore, we respond to the objection that psychedelic psychotherapy is morally impermissible because it is epistemically harmful. We argue that given the current level of understanding of psychedelics, this objection is unsubstantiated for a number of reasons, but mainly because there is no experimental evidence to suggest that epistemic harm actually takes place.

Keywords Ethics · Compassionate use · Psychedelic · Uncertainty · Epistemic harm · Naturalism

Introduction

Psychedelics are psychoactive substances that induce profound changes in the perceptual, affective, and cognitive domains of subjective experience. Classical psychedelics, such as psilocybin, mescaline, and lysergic acid diethylamide (LSD), are serotonin 2A (5-HT_{2A}R) receptor agonists. A related substance, methylenedioxymethamphetamine (MDMA), is occasionally labelled as "psychedelic" as well. Although MDMA shares some effects with classical psychedelics, its mechanism of action and effects are distinct; as a result, it cannot be regarded as a classical psychedelic (Johnson et al. 2019). With the exception of synthetic substances like MDMA and LSD, psychedelics have been traditionally used by cultures around the world for centuries and millennia (Samorini 2019, p. 64).

During the 1950s and 1960s, these substances were objects of psychiatric and scientific interest, showing promise in the treatment of various psychiatric disorders as well as the advancement of cognitive sciences. After the political and cultural upheaval of the 1970s, they were scheduled as controlled substances, which effectively stopped further use and research for decades (Carhart-Harris and Goodwin 2017, p. 2106). Over the past 20 years, however, the situation has changed. Contemporary studies published in peer-reviewed journals have once again stirred interest in the therapeutic and scientific use of psychedelics.

Two substances are at the forefront of this psychedelic revival: psilocybin and MDMA. When administered in a controlled, guided setting and in conjunction with psychotherapy, psilocybin shows promise in the treatment of cancer-related psychological distress, depression, and possibly addiction and other disorders (Johnson et al. 2019). MDMA-assisted therapy is studied as a hopeful treatment for PTSD and possibly addiction (Sessa et al. 2019). Both substances were designated with breakthrough therapy status by the FDA and are currently undergoing phases II and III of clinical trials respectively (MAPS 2017; COMPASS 2018).

This means that, as of yet, psilocybin and MDMA are merely investigational drugs, not formally approved as

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medicines. They cannot be regularly prescribed to patients diagnosed with the aforementioned disorders. However, patients with terminal, serious or chronic diseases, who exhausted proven treatments options, can ask to be administered investigational drugs on the basis of the institution of unproven treatment. Unproven treatment is a way for seriously ill patients in dire circumstances to gain access to investigational drugs outside the context of clinical trials. The institution is known by several names ("compassionate use", "right-to-try", "expanded access") and falls under different regulatory frameworks in different countries (Borysowski and Górski 2019).[1] In the last years, compassionate MDMA therapy has been conducted in Switzerland, and, at the time of writing, FDA agreed to expanded access programme for MDMA-assisted therapy for PTSD (Sessa et al. 2019; MAPS 2020).

As requests for unproven treatment are, at least in the US, on the rise (Pace et al. 2018; Borysowski and Górski 2019), the need for compassionate psychedelic psychotherapy, especially in psychiatric and palliative care, may be substantial. It may be in the interest of terminally ill, profoundly depressed, and incurably or chronically ill patients suffering from psychological distress to try compassionate psychedelic therapy (Byock 2018, p. 418). To do so may also be in the interest of people considering euthanasia or suicide. However, given the publicly controversial nature of psychedelics, the novelty of psychedelic psychotherapy itself, and the inherent risks of unproven treatments, it seems that the therapy calls for ethical justification. Hence, this paper discusses the ethics of psilocybin- and MDMA-assisted therapy (labelled here together as psychedelic therapy or "PT").

There are some concerns related to the issue of how to conduct PT ethically. For instance, there may be difficulties in properly informing the patient about the hard-to-convey nature of psychedelic experience, in maintaining clear sexual boundaries between the therapist and the patient, or in understanding the role and influence of suggestion (Sisti 2018; MAPS 2019). If these concerns are substantiated, then ethically conducted PT has to account for them. In this paper, however, we limit ourselves to deal with a more fundamental issue. Rather than asking how could compassionate PT be conducted ethically, we ask: *Can compassionate PT be ethical at all*? We aim to contribute to the discussion on the ethics of PT by arguing for the affirmative.

In the next section, we review the available evidence on safety and efficacy of compassionate PT, while in the third, we make a case for its moral permissibility on the basis of beneficence. However, since psilocybin and MDMA are investigational drugs, there is considerable uncertainty with regard to their side-effects and efficacy. Consequently, compassionate PT may be too risky or useless. Hence, also in the third section, we respond to this objection and discuss several others. In the fourth section, we respond to a novel objection to PT, one that questions PT irrespectively of its psychological benefits and physical safety, and regardless of the treatment regime it is being employed in. It was proposed by Letheby (2016), who argued that psychedelics can be harmful to one's knowledge of the world.

Efficacy and safety

Psilocybin

The pharmacodynamic profile of psilocybin is similar to that of LSD, although the pharmacokinetics of psilocybin seems somewhat more suitable for clinical use, mainly because of its shorter duration of effect (approximately 6 h). Although the two substances differ in their pharmacokinetic properties, the pharmacodynamics and phenomenology of the psychedelic state is identical for both substances. Since psilocybin and LSD are also pharmacologically related, we will include the findings of LSD-related research in our discussion on psilocybin (Mithoefer et al. 2016).

The long-lasting therapeutic effect of a single dose of psilocybin and LSD can be better explained by changes at the level of dysfunctional neuronal circuits than through the theory of transmitters. Classical psychedelics seem to interfere with cortical connectivity and thereby increase global connectivity, opening up possibilities for correcting dysfunctional circuits (Carhart-Harris et al. 2016b; Scheidegger 2018). This appears to be the biological basis for the rapid antidepressant effect, which is less dependent on the duration of action of the substance and more on the nature or intensity of the experience itself.

Psilocybin and LSD show promise mainly in the treatment of end-of-life psychological distress, addiction, and depressive symptomatology in general. Between the 1950s and 1970s, both the therapeutic and negative effects of these drugs were widely researched (Johnson and Griffiths 2017).

Three studies have been conducted in the twenty-first century so far, confirming the positive therapeutic effect of LSD and corroborating the findings of prior research. The first study to investigate the therapeutic effect of psilocybin on cancer-related psychiatric disorders was carried out in 2011 (Grob et al. 2011). It monitored symptoms of depression and anxiety in twelve patients with advanced-stage cancer after the administration of a medium dose of psilocybin (0.2 mg/kg), comparing it with niacin. Following the ingestion of psilocybin, depression and anxiety symptoms continually and significantly decreased over a 6-month period.

[1] In this paper, we will use "compassionate use" and "unproven treatment", as well as "compassionate" and "unproven" interchangeably.

The second, 2016 study compared the effect of very low (0.01–0.004 mg/kg) and very high (0.31–0.43 mg/kg) doses of psilocybin in 51 cancer patients (Griffiths et al. 2016). High-dose psilocybin significantly and lastingly reduced depression and anxiety in patients, while 60% of participants lost these symptoms altogether.

In the third study, researchers focused on adjustment disorder and generalised anxiety disorder in cancer patients (Ross et al. 2016), comparing high-dose psilocybin with niacin. It confirmed the results of both previous studies, as 60% of participants also reported a complete disappearance of symptoms.

A Swiss study on LSD from 2014 also documented a significant improvement in the psychological wellbeing of cancer patients (Gasser et al. 2014).

Both the older and more recent studies suggest that psilocybin and LSD have a positive effect on depression and anxiety in cancer patients. A British study from 2016 (Carhart-Harris et al. 2016a) furthermore notes that psilocybin also has a significant antidepressant effect in treatment-resistant patients.

What is all the more encouraging about these findings is that to achieve these results, classical psychedelics only had to be administered once, which is preferable to the regular administration of conventional antidepressants.

Safety of psilocybin

Psilocybin is a substance of very low toxicity. So far, there is no record of human deaths directly attributable to its consumption. Studies usually administer doses of 0.4 mg/kg on average. The LD_{50} in mice is 285 mg/kg, in rabbits 12.5 mg/kg. Side-effects are related to psilocybin's psychophysical effect on humans. The effect of psilocybin is very similar to that of LSD. These are the most commonly reported physical symptoms: dilated pupils, slight change in blood pressure, vertigo, and nausea. The motor tension grows and a slight tremor may also appear. In addition, higher doses were observed to cause elevated heart and breath rate. Endocrine activity (cortisol, prolactin) is not significantly affected (Passie et al. 2002).

Where psychological symptoms are concerned, patients report changes in visual perception as well as an altered perception of time and space. Derealisation and depersonalisation were regarded by participants both positively and negatively. In addition, psilocybin can induce mood lability and altered self-perception. Concentration becomes temporarily impaired and unusual thoughts may appear. Acute effects are difficult to predict, but factors predictive of positive results include pleasant physical and social environment, spiritual intention, a feeling of preparedness, positive expectations, certain personality traits, and suitable music (Haijen et al. 2018; Kaelen et al. 2018). Acute effects do not normally last longer than 6 h (Jerome 2007).

During initial trials, where about 2,000 participants received psilocybin, no serious side-effects were documented (Metzner 2005). The most common side-effects include panic reactions and prolonged unpleasant experiences (so-called difficult or bad trips). These can last several hours and are characterised by feelings of fear, dysphoria, or paranoia (Johnson et al. 2008). Johnson and colleagues also warn that under improperly supervised conditions, these experiences can lead to risky and dangerous behaviour, namely aggression against self or others, and on rare occasions, self-harm.

Perhaps the most serious side-effect is a prolonged psychosis. Cohen and Malleson have examined this reaction during LSD-assisted psychotherapy in two studies (Cohen 1960; Malleson 1971). Data show that such reactions occurred in 5 cases out of 5000 (25,000 doses) in the general population and 37 cases out of 4300 (49,500 doses) in psychiatric patients. The incidence of psychotic reaction is similar to the incidence of schizophrenia in the population. According to these numbers, in psychiatric patients, a psychotic reaction is expected in 4 cases out of 1000, or one for every 1338th administration of LSD. This is why current studies exclude patients with a personal or immediate family history of psychotic disorder.

About 1% of participants may experience the so-called post-hallucinogen perception disorder (HPPD) (Jerome 2007), which is characterised by persistent alterations mostly in visual perception. According to Matefy and Krall (1974), in 45% of subjects, these perceptual experiences are usually or always unpleasant.

Among the studied effects of psilocybin is the possibility that it causes lasting changes in personality and values (Bouso et al. 2018; Johnson et al. 2019, pp. 93–95). Within the five-factor personality structure model, some studies have shown an increase in openness, a decrease in neuroticism, and some other effects after an experience with psilocybin (MacLean et al. 2011; Lebedev et al. 2015; Griffiths et al. 2018; Erritzoe et al. 2018). Other studies using different personality models and scales showed connection between psilocybin use and liberal political views, openness, nature relatedness and a decrease in authoritarian political views (Nour et al. 2017; Lyons and Carhart-Harris 2018).

MDMA

MDMA is a member of the phenylethylamine family, scientifically often called an empathogen or entactogen as a reference to its tendency to increase a sense of empathy towards others as well as oneself. However, unlike classical psychedelics, it does not induce a full psychedelic state.

MDMA affects several monoamine systems besides the serotonergic one, enhancing the release of serotonin, noradrenaline, and dopamine into the synaptic cleft. Importantly for therapy, it also increases oxytocin levels and regulates the connection between the amygdala and the hippocampus. Its therapeutic dose is normally around 60–125 mg (Sessa 2017a).

Several studies are underway to examine the effect of MDMA-assisted psychotherapy on various psychiatric diagnoses. The research on MDMA's impact on post-traumatic stress disorder is in phase III trial and could be potentially introduced to the US market in 2021 or 2022.

The analysis of six phase II studies (between 2004 and 2017) showed that after two months, as much as 54.2% of patients (compared with 22.6% of the control group) suffering from PTSD ceased to meet the criteria for this diagnosis (Mithoefer et al. 2019). One year after the therapy, 66.2% of patients were in remission (Yazar-Klosinski and Mithoefer 2017). In the course of therapy, MDMA was administered on one or two occasions.

The authors of this study furthermore state that therapy did not only ameliorate the participants' PTSD symptoms, but it also improved their sleep quality, emotional control, and coping mechanism. The authors propose expanding the indication spectrum of MDMA-assisted psychotherapy for depression, anxiety disorders, obsessive–compulsive disorders, suicidality, eating disorders, and addictions. These trials demonstrated the superiority of MDMA-assisted psychedelic therapy over classical psychotherapy (Yazar-Klosinski and Mithoefer 2017).

MDMA-assisted therapy is expected to be effective in addiction treatment because of its proven effect on psychological trauma, since in patients suffering from addiction, there is a high correlation with the trauma they experienced. At the time of writing this article, a study is carried out on MDMA-assisted psychotherapy for alcohol addiction (Sessa 2017a, b).

Safety of MDMA

In the late 1980s and afterwards, before clinical studies, MDMA was safely given to thousands of patients by some therapists exploring its potential (Sessa et al. 2019, p. 1). Although MDMA is significantly safer when used clinically, epidemiological and experimental data suggest that it is relatively safe even in recreational setting (Sessa et al. 2019, pp. 2–3).

In phase II clinical trials, participants often spontaneously described adverse effects related to slight discomfort. These symptoms included insomnia, nausea, bruxism, impaired concentration or balance, dry mouth, and thirst. Less frequent symptoms included psychomotor agitation, increased tension in various parts of the body, and rapid breathing. Anxiety, headache, insomnia, and loss of appetite were experienced by 40–60% of participants. Most of these reactions only lasted for the period of drug effect. Subacute reactions persisting for the next 24 h (insomnia, fatigue, increased sleepiness, weakness, irritability) were reported less frequently.

The most important side-effect is a temporary elevation in blood pressure during the period of drug effect (above 140/90 mmHg), even though no medical intervention was needed. This is why candidates suffering from hypertension or cardiovascular or cerebrovascular diseases were excluded from this study. During treatment sessions, blood pressure is regularly measured. MDMA ingestion is furthermore linked to a rise in body temperature (1–1.5 °C), which also requires monitoring.

Mild episodes of anxiety or depression were occasionally reported, which appeared about 3–5 h after the administration of the drug and whose duration ranged between 5 min and 5 h. These episodes usually arose when the subjects were faced with difficult and emotionally challenging themes. In some cases, benzodiazepines had to be administered. However, such reactions could be reduced with proper preparation for treatment sessions (Doblin and Mithoefer 2015).

A much-discussed side-effect of MDMA is neurotoxicity. Although it was corroborated by animal studies, these employed inappropriately high doses. Studies conducted on human volunteers only reported neurotoxicity when MDMA was combined with other substances. When administering MDMA during clinical trials, no neurotoxicity was observed, and its occurrence is considered minimal in medical setting. Although MDMA possesses moderate abuse potential, it is lower than that reported for other substances, such as methamphetamines or opiates, and participation in MDMA-assisted trials was not linked to subsequent MDMA abuse (Doblin and Mithoefer 2015).

During these six phase II studies, no unexpected side-effects occurred, although on one occasion, there was suicidal behaviour prior to MDMA exposure, and on another, a participant experienced supraventricular extrasystoles. The authors of the study concluded that MDMA-assisted psychotherapy is effective and well-tolerated (Mithoefer et al. 2019).

Beneficence defence of PT

The cardinal, and for many the only, reasons for determining the moral status of any therapy are related to facts about its safety and efficacy. Some would say that if a therapy is expected to do more harm than good, then it is not in the patient's interest and it is irrational for them to try it. And if it is not rational for them to try it, then, in the

context of physician's duty to not harm, it cannot be morally permissible for a physician to provide it. Conversely, if the expected benefits do outweigh the expected harms, and no therapy with more favourable risk/benefit ratio is available, then the therapy is in the patient's interest and it is rational for them to try it.

If this conception is correct, we only need to ask: Does compassionate PT have higher expected value than the available alternatives? On balance, given the successes of PT in alleviating symptoms of psychiatric disorders and the relatively low probability of harmful outcomes, as described in the previous chapter, it seems to us that the expected benefits of compassionate PT can well outweigh its risks. To elaborate, given the aforementioned evidence, it does not seem irrational for one to expect that PT will be efficacious and safe in one's own case. If one is severely or chronically ill and has exhausted all proven treatment options, as it should be true for patients eligible for compassionate use, then the potential gains are high. On the other hand, the main dangers of PT seem to be of psychological nature, revolving around the risks of having a difficult trip, psychotic reaction, or of experiencing anxiety and depression. But knowing that the occurrence of difficult trips and psychotic reactions can be reduced with proper safeguards and patient screening, the risks seem relatively low. Admittedly, there is also uncertainty with regard to the moral status of the personality changes that PT potentially evokes. However, changes in personality traits (mainly neuroticism) occur relatively commonly during classical psychotherapeutic interventions, including during the administration of antidepressants (Roberts et al. 2017). Thus, as long as the potential personality change is likely to be beneficial and desired, we do not, given the current understanding of psychedelics, see it as morally problematic.

Overall, it seems to us that these risks will be rationally well acceptable for some, if not most, unproven PT candidates.

To be clear, we are not suggesting that unproven PT reaches some pre-set and absolute measure of expected value. Rather, our claim is comparative; for some patients, the expected value of undergoing unproven PT can be significantly higher than the expected value of *not* undergoing unproven PT. That is, higher than the expected value of routine care, palliative care, or no care at all. We claim this because if we, the authors, being aware of the relevant facts, were to find ourselves in a situation of a typical compassionate PT candidate, we think we would be interested in trying compassionate PT ourselves and in recommending it to others. It does not seem to us that this is an irrational or outlandish statement. Thus, we think it is safe to say that there will be patients for whom it will be rational to try compassionate PT. If this is so, then the physician providing compassionate PT to such patients would not violate their duty to not harm them. On the contrary, they would fulfil their obligation to benefit them.

There is, however, a frequent objection to beneficence defence of any unproven treatment. Some think that these treatments are either too risky to try or useless and therefore psychologically and financially detrimental (Rubin 2015). Obviously, since these treatments have not passed all the clinical trials and procedures necessary for approval, they are not formally guaranteed to be safe and efficacious. Surely, formally approved drugs are not perfectly safe and efficacious either (Greenfield et al. 2007). But in cases of unproven interventions, the prospects are undeniably worse. The range of possible outcomes and their probabilities are less understood. Because the outcomes are less certain, unproven treatments are more likely to have unexpected harmful side-effects or lack efficacy. Hence, unproven treatments have by their very nature markedly lower expected value than proven ones.

Several authors have called attention to the concerning success rates of investigational drugs (Raus 2016; Borysowski et al. 2017; Pace et al. 2018). To be exact, it is estimated that drugs in clinical testing have only a 11.83% chance of being approved, while an earlier study showed that of all drug attritions, 20.5% were due to safety and 35.3% due to efficacy concerns (DiMasi et al. 2016; DiMasi 2001). The probability of a drug's eventual success also depends on the trial phase it is in. But according to some estimates, 54% of drugs in late-stage clinical trials fail, of which 57% for efficacy and 17% for safety reasons (Hwang et al. 2016).

The data show that the majority of drugs in clinical testing will not be fit for approval, with more than half of them for efficacy and safety reasons. This suggests that the risk of unexpected harmful side-effects or of frustrated hopes is relatively high. One could then argue that (1) given this uncertainty in outcomes, it is not rational for a patient to try unproven PT, and (2) since is not rational for them to try PT, it is morally impermissible, ceteris paribus, for a physician to provide it. Therefore, unproven PT is morally impermissible. Since we claim that unproven PT can be rational to try, we are committed to contest the argument's first premise, despite the uncertainty and the bleak chances of success.

Admittedly, uncertainty makes decisions about unproven treatments more difficult than decisions about proven ones, especially in less severe and borderline cases. In the light of these difficulties, it might seem better to be safe than sorry (Simianu et al. 2016). But uncertainty cannot make any treatment irrational by itself, since it is present in all forms of clinical decision-making, not just in the context of unproven treatments (West and West 2002). Alternatives to unproven treatment—routine care, palliative care, or no care—are also laden with some level of uncertainty. Nonetheless, uncertainty can in principle be accounted for in

mathematical models of decision-making (Edwards, 2006, p. 80). Thus, uncertainty is, in our view, an irremovable problem that manifests itself mainly in real-life decision-making with individual patients.

Our aim is not to discuss individual cases but to show that for a meaningful category of candidates it will be rational to try unproven PT. We think so because there is reason to believe that PT is unlike average unproven treatment for the better, and because the condition of some patients is so poor that even highly risky interventions may be expectedly beneficial for them.

As for the first reason, we already mentioned that research into psilocybin and other classical psychedelics has a favourable track record without any serious adverse events documented (Metzner 2005; Nichols 2016, p. 274). These substances also belong to "one of the safest classes of CNS drugs" (Nichols 2016, p. 275) and have been used for centuries and millennia by various cultures around the world (Nichols 2016, p. 268; Samorini 2019), which gives reason to doubt that altogether unexpected and serious harmful outcomes will be discovered. When it comes to MDMA-assisted therapy, similar arguments from historical use understandably cannot be used. However, we emphasise that according to the research and therapeutic sessions done so far, the substance is well-tolerated (Mithoefer et al. 2019).

As for the second reason, it seems to us likely that for some patients, perhaps many, PT is well worth the risk despite its uncertain outcomes, simply because the alternatives available to them are expectedly worse. These alternatives are the virtually certain devastating outcomes stemming from their condition, including long-term disability or death. In particular, we have in mind profoundly depressed patients, the severely addicted, the terminally ill, and people wishing to end their lives, all of whom exhausted proven treatment options. In their case, the potential risks seem to be low and the potential gains high, despite the aforementioned approval rates of investigational drugs. In agreement with Carhart-Harris and Goodwin (2017, p. 2109), we consider this intuition to be robust in cases of suicidal patients and people considering assisted death or euthanasia. To put the matter into perspective, noticeably worse odds are acceptable for cancer patients who consider enrolling in early trials. According to Agrawal et al., "[m]ore than 90% of patients said they would still participate in the study even if the experimental drug caused serious adverse effects, including a 10% chance of dying" (2006, p. 4479).

And finally, there are reasons to reject the argument because of its implications. Firstly, if unproven PT is not rational to try because psychedelics are only investigational drugs, then it is irrational for patients to try all or most typical unproven interventions, as these are also conducted with investigational drugs, with the very same success rates. This may seem radical, as most think unproven treatments have a place in health care systems.

Secondly and more importantly, if it is irrational to try unproven treatments because they are conducted with investigational drugs, then, for the same reason, it could be irrational to participate in clinical trials. One could, of course, defend the rationality of clinical trial participation by arguing that the standard of care in clinical trials is higher, and so is the expected value of clinical trial participation. But this may not do, as clinical trial participation has a substantial downside in the possibility of not receiving the investigational drug at all. Hence, the expected value of compassionate use may be in some cases higher than enrolling in clinical trials. But to say that in these cases clinical trial participation is not rational for participants would put the moral permissibility of clinical trials in serious doubt.

Thus, on the basis of these considerations, we think that PT can be morally permissible, despite the uncertainty of outcomes.

There is no shortage of further ethical objections against unproven treatments like compassionate PT and against our position. While some base their objections on considerations of justice, autonomy, consent, or economic realities, others question the beneficence defence of unproven treatment (see Walker et al. 2014; Darrow et al. 2015; Raus 2016; Borysowski et al. 2017). For instance, Walker et al. (2014) consider the possibility that although compassionate use could be justified from the point of view of the individual patient's interest, as we have argued, it may not be justified from a collective perspective that minds the good of the population as a whole. The widespread use of unproven treatments could hamper enrolment in clinical trials. That could undermine the generation of new medical knowledge and drugs from which the population at large benefits. It is therefore possible that although compassionate use is individually beneficial, it is collectively harmful.

This particular objection is regulation-dependent. By regulation-dependence we mean the fact that its plausibility or applicability depends significantly on the legal framework in which unproven treatment is being implemented. To explain it in connection to Walker et al.'s (2014) argument, in the European Union, for example, compassionate use is allowed only on the condition that the patient is not eligible to participate in a suitable clinical trial. Thus, the knowledge generation from clinical trials is not undermined. Alternatively, some countries regulate unproven treatments in line with the 37th paragraph of the Declaration of Helsinki and compensate for the loss in knowledge generation and drugs by obligatory data collection (Walker et al. 2014, pp. 7–8; WMA 2013, p. 2194).

Although it is important to address regulation-dependent objections in given contexts, we avoid them here, as we do not wish to discuss compassionate PT ethics only in the US,

or only in the EU, or elsewhere. We wish to consider the ethics of compassionate PT itself.

There remain several traditional moral arguments against psychoactive drug use, like the ones based on addiction or harmfulness. But these are arguably hard to apply to psilocybin and MDMA when used as medicines (see Smith 2008, pp. 1–13; Lovering 2015). Of the objections to psychedelic therapy that remain, we are not aware of any other explicit one except for Letheby's epistemic harm argument, which we will discuss below.

Epistemic harm

Psychedelics are classified under a broader category of hallucinogens, implying that the states of mind they induce are hallucinatory. But if one takes this classification seriously, one could question the authenticity of personal insights PT seems to provide. In that case, the value of the psychological benefits that these insights convey is in question as well. To put it bluntly, how could one have respect for these benefits if they are based on hallucinations?

It is somewhat traditional to suspect psychoactive substances of providing a fake picture of reality. In case of psychedelics, some wonder if they involve deception as well, albeit in a new guise. Reflecting on a psilocybin study with terminal cancer patients, Pollan wrote: "It's one thing to conclude that love is all that matters, but quite another to come away from a therapy convinced that 'there is another reality' awaiting us after death … or that there is more to the universe—and to consciousness—than a purely materialist worldview would have us believe" (Pollan 2015). Beliefs in afterlife and god are typical supernatural beliefs, while belief in the mental nature of reality seems inconsistent with physicalism and naturalism.[2] Since beliefs like these seem suspect to Pollan on metaphysical grounds, the concern is that psychedelics are philosophically deceptive.

Letheby elaborates on this concern by pointing to studies showing correlation between the therapeutic effect of psilocybin and the occurrence of mystical experiences (Garcia-Romeu et al. 2014; Letheby 2016; Griffiths et al. 2016; Ross et al. 2016; Roseman et al. 2018). These experiences of "immaterial ultimate reality", feelings of "unity, transcendence of time and space", and encounters with divine, seem to be experiences with non-natural reality, invoking supernaturalistic, or at least non-naturalistic, metaphysics (Letheby 2016). It is crucial to add that mystical experiences also exhibit a so-called noetic quality, which is meant to capture the measure of how certain one felt in encountering the ultimate reality, in the sense of "being able to know and see what is really real" (Johnson et al. 2019, p. 94). Given that the more fully mystical one's experience gets, the more likely it is to be felt as "real", it seems to support the idea that one is compelled to take the experience as veridical. Citing Pollan, Letheby then goes on to argue that "[i]f naturalism is true, and if mystical experience is the primary mechanism of psychedelic therapy, then it seems undeniable that psychedelic therapy is 'foisting a comforting delusion on the sick and dying'" (Letheby 2016, p. 32).

The objection is that PT is harmful to one's knowledge because it causes metaphysical delusions via compelling hallucinations. Letheby likens the effects of PT to so-called motivated delusions, which can function as a psychological defence mechanism (Letheby 2016, p. 31). For example, a man might firmly believe that his ex-partner, Jane, is still with him and even that they married. But in fact they never married and are no longer together. The delusion that *I am married to Jane* might then save the man from the psychologically devastating truth.

We agree with Letheby that the epistemic risks of PT are relevant to policy debates and, we might add, to ethics (Letheby 2016, p. 35). But the ethical implications of his argument's conclusion need to be fleshed out. Admittedly, any treatment that foists delusions is morally problematic because it is epistemically detrimental. So the natural way to take the conclusion is to add the principle that *if therapy foists delusions, it is morally impermissible*. We can then infer the second conclusion that PT is morally impermissible. The argument from epistemic harm then runs as follows:

P1 If mystical experience is the therapeutic mechanism of PT and if philosophical naturalism is true, then PT is foisting comforting delusions.

P2 Mystical experience is the therapeutic mechanism of PT.

P3 Philosophical naturalism is true.

C1 Therefore, PT is foisting comforting delusions.

And

P4 If therapy foists delusions, it is morally impermissible.

C2 Therefore, PT is morally impermissible.

Now to evaluate it. It should be noted first that the argument does not apply to MDMA-assisted therapy, as MDMA does not induce mystical experiences (Lyvers and Honours 2012). It does, however, apply to psilocybin and other classical psychedelics.

[2] By "physicalism" we mean the view that everything is physical. "Naturalism" is a notoriously ambiguous term, but at minimum, it refers to the view that supernatural entities like gods, spirits, and magical spells do not exist.

One could take a pragmatic approach to the problem and claim that as long as PT is beneficial, it is permissible even if it foists delusions. At least when severe cases are considered, the approach is appealing to several researches working with psychedelics (Pollan 2015; Letheby 2016). Returning back to the man's delusion that *I am married to Jane*. If we think that the delusion saved him from the devastating and potentially life-threatening truth, we might think it better for the man to harbour this delusion than to be psychologically devastated and potentially suicidal. In other words, the epistemic harm of a delusion may be outweighed by its psychological benefit. If this is the case, then (P4) ought to be rejected.

The pragmatic approach is arguably more appealing in severe cases or when psychedelics are used sparingly, which will likely cover compassionate use of PT as well. But according to this response, PT will not be morally justified in less severe cases or as a regular, proven treatment. Although we sympathise with this reasoning, we do not think it necessary to concede that PT actually is epistemically harmful. In what follows, we provide a different response to the argument and make way for PT being morally permissible in less severe cases or as a proven treatment.

In our view, the most problematic is not the fourth but the first premise (P1). It presumes that mystical experience compels one to accept some non-naturalistic beliefs, like the belief that *Afterlife exists*. But this claim is conjectural, as we are not aware of any evidence that mystical experiences actually do that. Although we do not think Pollan's concern is groundless, it is based on anecdotal evidence only. Letheby acknowledges that we do not know how mystical experiences influence one's beliefs. He also acknowledges that it seems genuinely possible for some psychedelic users to form, on the basis of their mystical experiences, beliefs that are consistent with naturalism (Letheby 2016, p. 32).

Second, if classical psychedelics had the power to compel one to accept non-naturalistic beliefs, it would not follow that they foist delusions. To clarify, let us presume that naturalism is true and that mystical experiences truly compel one to accept non-naturalistic beliefs. Why think that these would be delusions? There is a difference between being compelled to believe falsehood and being deluded, as delusion presumably requires irrationality. For example, one can be compelled to believe that *Afterlife exists* during and some time after PT, but be later able, on the basis of reason, to believe otherwise.[3]

The second premise (P2), namely that mystical beliefs are the therapeutic mechanism of PT, deserves two remarks. First, we do not doubt the claim that mystical-type experience is a strong predictive factor of positive outcomes in depressive symptomatology (Griffiths et al. 2006). It is not, however, the only predictive factor, and it does occur only occasionally. Other factors include a feeling of catharsis, the cognitive experience of sudden change of attitude towards personal problems, and the psychodynamic experience of becoming aware of an unconscious conflict (Passie and Gasser 2016). Simply put, mystical experiences may not be the therapeutic mechanism of PT. Johnson and colleagues suggest that it may be more suitable to focus on so-called quantum-change experiences, which are meant to encapsulate sudden and significant insights into one's own problems (Johnson et al. 2019, pp. 92–93).

Second, psychedelic mystical experiences are, at least in personal importance and phenomenology, identical to the naturally occurring mystical experiences of mystics and religious believers (Griffiths et al. 2006, 2019). Hence, if psychedelic mystical experiences foist metaphysical delusions, then natural mystical and religious experiences may do so as well. But, as we will discuss momentarily, to say that religious experiences may lead to delusions is problematic.

Our final criticism is directed at the third premise (P3), which states the truth of philosophical naturalism. The premise seems to us questionable in the context of the epistemic harm argument. In essence, the argument states that PT is morally impermissible because it is harmful to our knowledge of the world. This is true only if it is *known* that naturalism is true. But is it? Metaphysics is a controversial discipline even for philosophy's standards. In fact, it is historically so controversial that there is a well established tradition of rejecting the very possibility of metaphysical knowledge.

The trouble with metaphysical knowledge can be seen in the practice of psychiatry itself. According to ICD-11, *delusion* can be described as.

> A belief that is demonstrably untrue or not shared by others, usually based on incorrect inference about external reality. The belief is firmly held with conviction and is not, or is only briefly, susceptible to modification by experience or evidence that contradicts it. The belief is not ordinarily accepted by other members or the person's culture or subculture (i.e., it is not an article of religious faith). (WHO 2018, MB 26.0 Delusion).

If we accept this description of delusion, how should one diagnose metaphysical delusion? The truths of metaphysical beliefs, like the beliefs that *Reality is immaterial*, *God exists* and similar, are not likely to be contradicted by empirical evidence or refuted by the best natural science. One surely cannot demonstrate the falsity of belief in the immaterial nature of reality the way one can demonstrate the falsity of the man's belief that *I am married to Jane*. The criterion of

[3] We thank an anonymous reviewer of this journal for their clarifying remarks on this point.

delusion of not being "susceptible to modification by experience or evidence that contradicts it" seems to be trivially met for metaphysical beliefs. So the description is not applicable to metaphysical beliefs.

Notice also that a belief cannot be delusional if its truth is accepted by other members or the person's culture, subculture, or religion. But metaphysical beliefs like *Afterlife exists, Reality is immaterial,* and *Things outside time and space exist, namely god* are the ones that are typically accepted this way. The description excludes metaphysics ad hoc.

We are inclined to think that this is not a bug but a feature. Let us suppose that future research will show that PT compels one to accept some non-naturalistic beliefs and that we should care about philosophical naturalism in psychiatry. What would be the appropriate policy recommendations for PT? Consider the following two.

First, the therapists who are going to provide PT to seriously ill patients should not remain philosophically neutral with regard to the patients' comprehension of the experience. Whenever possible, the therapists should minimise the epistemic harm caused by PT. They should design and conduct the therapy in such a way as to steer the patient's understanding away from non-naturalism and towards naturalism.

Second, let us say that it is possible to reason PT patients out of their non-naturalistic beliefs with the best philosophical case for naturalism. If this is so, then it must be possible to undo the epistemic harm done via PT! Thus, PT patients could subsequently undergo "philosophical therapy" in which the best case for philosophical naturalism would be made.

Our point is not to refute naturalism. It is merely to show that it would be hard to take these recommendations seriously, as they would likely be met with a poorly concealed smile. It is difficult to believe that it would be appropriate or right to "correct" the patients' metaphysical views with "philosophical therapy" and to steer them towards any metaphysical conception unless they consent to it.

To drive the point even further, imagine *naturedelic therapy*. This therapy is identical to PT with but one difference; naturedelics compel one to believe in philosophical naturalism. Would it be permissible to subject, say, a deeply religious patient to naturedelic therapy, without him consenting to the effect of the therapy on their broader view of the world? It seems to us it would not. But if it is morally permissible to retain one's "false" metaphysical beliefs, should it not be permissible to acquire them?

These considerations suggest that (P3), the claim that philosophical naturalism is true, is actually not the kind of thing we generally think we *know*. We therefore suggest that metaphysical matters are sufficiently controversial and uncertain so that, regarding the question of therapies foisting metaphysical delusions, it is better to suspend judgement and perhaps ignore metaphysics in medicine as much as possible. In that case, PT would not be harmful to one's knowledge of the world.

Either way, one would expect that (P3), as a claim to knowledge, would receive substantial argumentative support. It would not be sufficient to successfully argue that *philosophical naturalism is true*. Since the argument works only if (P3) is a case of knowledge, its proponent has to engage in higher order argumentation and argue that *it is known that philosophical naturalism is true*. But Letheby does not attempt to do any of this, which suggests that his argument should not be taken as a serious attack on the morality of PT. Perhaps we should view it merely as a challenge to those who already accept philosophical naturalism, share Pollan's initial concern, and take interest in PT.

Conclusion

We reviewed the safety and efficacy of psilocybin- and MDMA-assisted therapies and argued that it can be rational for some patients to try compassionate psychedelic therapy. Since the therapy can be rational to try, it can be morally permissible on the basis of beneficence.

We provided responses to two regulation-independent objections against moral permissibility of compassionate PT. We first claimed that compassionate PT can be rational for patients despite the uncertainty of outcomes, as the expected value of PT can in principle be assessed and can well outweigh the expected value of routine care, palliative care, or no care at all. We then claimed that compassionate PT can be morally permissible despite its potential epistemic risks. We pointed out that this objection is applicable only to psilocybin and eventually to other classical psychedelics but not to MDMA. Nevertheless, even when limited to psilocybin, the objection is not substantiated because it is not known how classical psychedelics influence one's beliefs or whether they make one metaphysically irrational, and because metaphysics should be ignored in medicine as much as possible.

Therefore, based on the objections considered and given the current state of our understanding of psychedelics, we see no ethical barrier against compassionate PT.

Nonetheless, there are bound to exist suboptimal uses of psychedelics, regardless of the context of their use. Perhaps these problematic uses will be associated with changes in personality. Since personality changes are not necessarily beneficial, it is conceivable that one may be "too open" or "not neurotic enough" for one's own good. Whatever the case may be, we hope that advancements in the scientific understanding will shed more light on the issue and drive further ethical reflection of psychedelics.

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Compliance with ethcial standards

Conflict of interest The authors declare that they have no conflict of interest.

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