A right to try psychedelics?

An ethical evaluation of compassionate use of psychedelics for psychiatric disorders

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SUMMARY

Psychedelics are increasingly studied as treatment options for psychiatric disorders, showing promising results. However, official approval of most psychedelic treatments is not expected in the near future. Given the significant prevalence and impact of psychiatric disorders, the question arises whether certain individuals should have access to psychedelic treatment before official approval. This is called compassionate use, which allows patients with unmet medical needs access to unauthorized drugs for their potential therapeutic benefits. Nevertheless, compassionate use raises ethical concerns regarding safety and effectiveness, autonomous decision-making, equal access and hindering of efficient research processes. These concerns are further amplified when considering the unique aspects of psychedelics and psychiatric disorders. Therefore, this thesis explores whether compassionate use of psychedelics for psychiatric disorders is ethically justified, and if so, under what conditions. Firstly, the ethical considerations associated with compassionate use in general are examined, resulting in a moral framework. Subsequently, relevant characteristics of psychedelics and psychiatric disorders are described. By combining the general moral framework with these specific characteristics, it is argued that the compassionate use of psychedelics for psychiatric disorders is ethically justified under nine conditions, including the pivotal role of an assessment committee. Since this thesis concerns an initial exploration, further inquiry and practical testing are necessary.

Keywords: Bioethics, Compassionate use, Expanded access, Psychedelics, Psychiatric Disorders

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CHAPTER 1: INTRODUCTION

> *"I have suffered from post-traumatic stress disorder for years, and have been in therapy for at least ten years. My patterns, thoughts and feelings torment me. My family is affected by my behaviour. I am losing friends. I have watched the Netflix series 'How to Change Your Mind' [documentary series about psychedelic use]. I desperately want to heal. Can you help me please?" (ZonMw, 2023, p.12)* [1]

> *"I suffer from a persistent obsessive-compulsive disorder, of which, after a few years of therapy, I had a severe relapse. I have already tried to take my own life twice. I have read promising results about the treatment for obsessive-compulsive disorder with psilocybin and ended up at [name medical center]. It would mean a lot to me because I just do not feel like I will ever get rid of it." (ZonMw, 2023, p. 12)* [1]

In recent years, many studies have researched the therapeutic potential of different psychedelics (e.g. ketamine, psilocybin, MDMA) for an expanding range of psychiatric disorders. Preliminary findings indicated promising results for their effectiveness in reducing symptoms and improving well-being of patients with various disorders (e.g. Mitchell et al., 2021; Van Amsterdam & Van den Brink, 2022). However, ketamine is currently the only psychedelic treatment officially approved by European and US drug authorities, for treatment-resistant depression (Grabski et al., 2020). Most psychedelics will not be officially approved for the treatment of psychiatric disorders in the foreseeable future. This is due to the recent nature of most studies in the field and the average duration of clinical trials of seven years from first testing to market approval (Kaitin, 2010).

At the same time, there is an urgent need for new therapies in psychiatry, driven by the high prevalence and burden of mental illnesses, which is associated with substantial healthcare costs (World Health Organization [WHO], 2022). Additionally, a considerable number of patients has limited or no response to currently available treatment options, commonly referred to as 'treatment-resistant' disorders (Howes et al., 2021). For these individuals, the need for new

[1] These quotes are extracted from e-mails that researchers in the psychedelic field received from patients, translated from a ZonMw research report about the therapeutic applications of psychedelics (ZonMw, 2023).

effective therapies is particularly urgent, as they have often suffered from mental illness for years and generally experience a reduced quality of life (Howes et al., 2021). Moreover, they have a shorter life expectancy, partly due to the risk of suicide, and sometimes even opt for euthanasia because of the hopelessness of their situation (Van Veen & Widdershoven, 2021; WHO, 2022). Therefore, the emergence of psychedelic treatment options gives hope to these patients with unmet needs, as illustrated by the introductory quotes, while also having potential benefits for society at large. However, a large proportion of these patients do not meet the eligibility criteria for participation in clinical trials and must therefore wait for official approval. Given the dire circumstances faced by these patients, this waiting time might be detrimental to them.

Thus, the question arises whether psychedelic treatment should be accessible to this group of individuals before official approval, when the safety and effectiveness of such treatments have not been definitively established yet. This practice is called compassionate use (or expanded access), defined as the therapeutic use of unauthorized drugs outside of clinical trials (Borysowski & Górski, 2019). In many countries, compassionate use regulations have been implemented, although their specific conditions and procedures vary (Borysowski et al., 2017). Generally, compassionate use is reserved for patients with severe or life-threatening illnesses who have no alternative treatment options and are ineligible for participation in clinical trials (Bunnik et al., 2018).

Although compassionate use offers potential benefits to patients in exceptional circumstances, this practice is not without risks (Raus, 2016). Within the ethical literature, concerns have been raised regarding the lack of established safety and effectiveness of treatment options, autonomous decision-making of patients in dire circumstances, fair patient selection, equal access and potential negative consequences for efficient research procedures (Borysowski et al., 2017; Hordijk et al., 2022; Walker et al., 2014). Therefore, compassionate use requires ethical justification. This includes addressing the concerns and developing strategies to effectively minimize them in practice. Several authors have already provided practical conditions for ethical compassionate use (e.g. Borysowski & Górski, 2020).

Although important ethical considerations have been identified for compassionate use in

general, these are insufficient for the specific ethical evaluation of compassionate use of psychedelics for psychiatric disorders. The unique characteristics of both psychedelics and psychiatric disorders introduce distinct and additional concerns that must also be taken into account. For example, the psychedelic experience is difficult to convey to patients, which can complicate the process of informed consent (Jacobs, 2023). Moreover, psychiatric disorders have a complex biopsychological nature, that makes it complicated to establish the irremediability or lethality of the disease, which are often requirements for compassionate use (Greif & Šurkala, 2020). These two examples highlight the need for ethical justification of this specific application of compassionate use. Therefore, this thesis aims to answer the following research question:

Is compassionate use of psychedelics for psychiatric disorders ethically justified, and if so, under what conditions?

To date, only two ethical articles have addressed the topic of compassionate use of psychedelics, both of which had a limited scope. Greif & Šurkala (2020) focus primarily on the question of whether the safety and effectiveness of psychedelics are sufficiently established to justify compassionate use. In the other article, Campbell & Williams (2021) argue for compassionate use based on the fair treatment of people with psychiatric disorders compared to other types of disorders. Although these articles both raised relevant points, they focused on only one ethical aspect, leaving other important ethical considerations out of their analysis. Furthermore, they did not provide any conditions for compassionate use of psychedelics in practice.

This thesis expands upon the existing literature by (1) explicitly evaluating the justifications for compassionate use, (2) addressing a broad range of ethical considerations, derived from various ethical principles, (3) analysing the normative implications of specific aspects of psychedelics and psychiatric disorders and (4) establishing conditions for ethically justified practice. These contributions are useful, as the demand for compassionate use of psychedelics is expected to increase in the future, coupled with the current lack of guidance on handling patient requests for such treatments. Therefore, this evaluation could help in the

development of decision-making guidelines and possibly serves as an example for the evaluation of other compassionate use treatments, particularly within the field of psychiatry.

Scope and definitions

Firstly, the term psychiatric disorders refers to the diagnostic categories as described by the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). The growing contested use of these psychiatric diagnostic categories is acknowledged (e.g. Werkhoven et al., 2022). However, these diagnostic categories are still used here, as they are the common language in current psychedelic research and provide a way to be clear and consistent throughout this thesis. As such, the term 'disorders' is used for these diagnostic categories and 'patients' for the individuals who are diagnosed with them. However, these are explicitly used in a non-derogatory sense.

Secondly, the definition of psychedelics by Greif & Šurkala (2020) is used: "psychoactive substances that induce profound changes in the perceptual, affective and cognitive domains of subjective experience" (p.485). A distinction is often made between classic psychedelics, such as lysergic acid diethylamide (LSD) and psilocybin, which affect the same serotonin receptor, and related substances, such as MDMA, that have distinct working mechanisms (Johnson et al., 2019). Nonetheless, both categories are included in this thesis because of their overlap in effects on the subjective experience and their similar applications in research.

Thirdly, the literature often distinguishes between group-based and individual compassionate use. Group-based compassionate use usually occurs after the successful completion of clinical trials, serving to bridge the gap between successful trial completion and actual market availability (Bunnik & Aarts, 2019). In these cases, the safety and effectiveness of a drug have already been established, and a treatment protocol is developed to facilitate widespread compassionate use for eligible patients (Darrow et al., 2015). However, this thesis focuses on individual compassionate use, in which individual requests are initiated by physicians and patients while clinical trials are still ongoing (Bunnik & Aarts, 2019). Considering that the research process for most psychedelic treatments is far from being completed, individual compassionate use was chosen as the primary focus of this thesis. Also, investigating individual compassionate use has more relevance, as the uncertainty regarding the safety and

effectiveness of the drug introduces additional ethical concerns, and because it is the most prevalent form of compassionate use (Bunnik et al., 2018; Darrow et al., 2015).

Outline

In Chapter 2, a moral framework is developed for compassionate use in general based on relevant ethical literature. Using the literature, four ethical themes are distinguished, largely based on the four principles of Beauchamp & Childress (2001). These themes are individual benefits and harms, respect for autonomy, justice and collective interests. Within each theme, the ethical justifications and concerns are addressed, resulting in central ethical questions. In Chapter 3, relevant characteristics of both psychedelics and psychiatric disorders are described. These medical and social aspects need to be taken into account for the ethical evaluation of compassionate use for psychedelics and psychiatric disorders. In Chapter 4, the case for compassionate use of psychedelics for psychiatric disorders is made. This is achieved by combining the moral framework for compassionate use in general with the specific aspects of psychedelics and psychiatric disorders. Firstly, the arguments supporting compassionate use of psychedelics are presented. Subsequently, the normative implications arising from the distinctive characteristics of psychedelics and psychiatric disorders are addressed. In Chapter 5, the conditions for ethically justified compassionate use of psychedelics for psychiatric disorders are established. The central ethical questions per moral theme, as identified in Chapter 2, are answered, resulting in nine conditions for ethical practice. These conditions relate to the patient, the drug, the costs and the establishment of an assessment committee. Chapter 6 concludes the thesis and presents the implications for practice and suggestions for future research.

CHAPTER 2: DEVELOPMENT OF A MORAL FRAMEWORK FOR COMPASSIONATE USE IN GENERAL

To answer the research question, identification of the main ethical considerations for compassionate use in general is necessary, since specific literature on compassionate use with psychedelics or in psychiatry is lacking. Firstly, the compassionate use process and regulations are explained as contextual information. Secondly, the identification of four moral themes as categories for ethical considerations is described, largely based on the four principles of biomedical ethics of Beauchamp & Childress (2001). Subsequently, for each of the moral themes, the ethical justifications and concerns are discussed, resulting in the identification of central ethical questions per theme. Lastly, the ethical considerations are summarized in a moral framework.

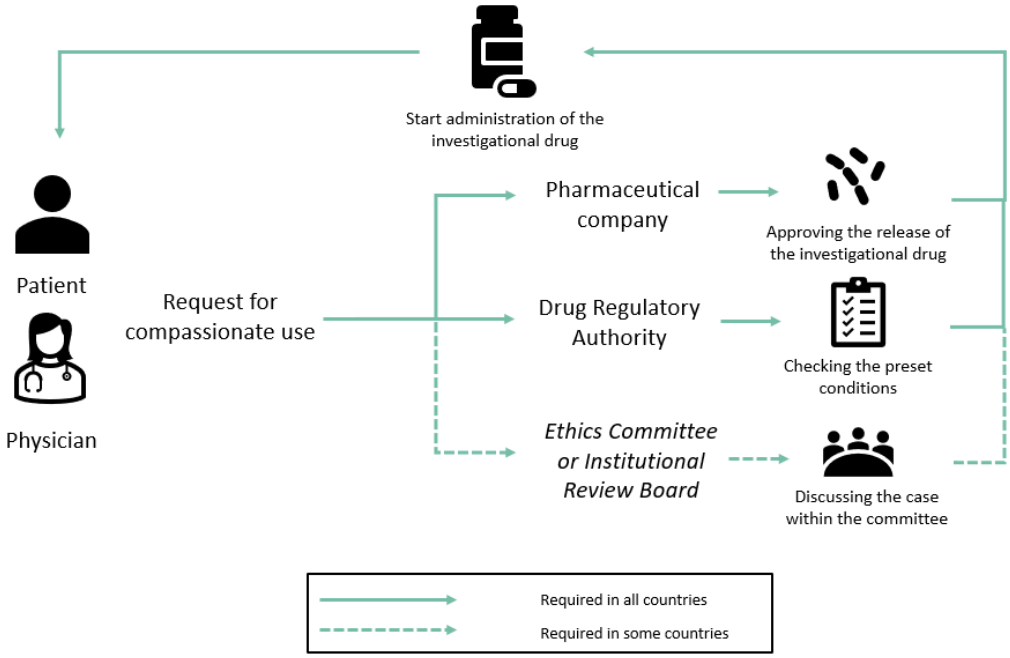
Compassionate use process and regulations

Compassionate use is the therapeutic use of unauthorized drugs outside of clinical trials (Borysowski & Górski, 2019). Due to exceptional circumstances, an individual patient is given access to a drug that is still being investigated in clinical trials. The patient does not participate in any study; the purpose of receiving the drug is for the patient to gain its therapeutic benefits (Borysowski et al., 2017).

The general pathway of compassionate use is illustrated in Figure 1. The process begins with the patient or physician initiating a conversation about compassionate use in the treatment context. Typically, compassionate use is considered by physicians when there are no other available treatment options (Bunnik & Aarts, 2019). In agreement with the patient, a request for compassionate use is drawn up. Subsequently, two steps are necessary to gain access to the drug: release of the investigational drug by the pharmaceutical company and approval from the drug regulatory authority (Bunnik & Aarts, 2019). Furthermore, a few countries additionally require the approval of an ethics committee (sometimes called an institutional review board) (Borysowski & Górski, 2019).

Figure 1

The general pathway for compassionate use



Most national regulations have set certain conditions for compassionate use. Both physicians and drug regulatory authorities have an important role in ensuring that these conditions are fulfilled. Although the specific conditions vary between countries, there are several common conditions shared by most regulations, which are summarized in Table 1. These conditions were identified using articles that reviewed regulations on compassionate use from the EU, Canada, the US and Australia (Borysoswki & Górski, 2019; Bunnik et al., 2018; Whitfield et al., 2010).

In addition to these conditions, the financial regulations surrounding compassionate use vary depending on the healthcare system in question. In a few countries, health insurance organisations or authorities automatically cover the costs of compassionate use (Bunnik et al., 2018). However, in most countries, the pharmaceutical company, the patient or the hospital are obliged to bear the costs, while reimbursement is rare and determined on an individual basis (Bunnik et al., 2018).

Table 1 *Common conditions for compassionate use from (inter)national regulations and guidelines*	
	**Drug-specific conditions** 1. The drug is undergoing clinical trials, with some evidence of its safety and effectiveness.[1]
	**Patient-specific conditions** 2. The patient suffers from a serious and/or life-threatening illness.[1-3] 3. The patient has exhausted standard authorized treatment options.[1,2] 4. The patient is ineligible for a clinical trial investigating the same drug.[1,3] 5. The patient must give informed consent.[1,3]
	**Physician-specific conditions** 6. The physician must report on serious adverse effects of the drug.[1,3]
[1] Borysowski & Górski, 2019: review of regulations from the EU, USA, Canada and Australia [2] Bunnik et al., 2018: summary of regulations of 'developed-world' healthcare systems [3] Whitfield et al., 2010: review of regulations of ten European countries	

Four moral themes of compassionate use

To identify the ethical considerations associated with compassionate use in general, a literature search was conducted in PubMed, searching for articles that included the terms 'compassionate use' or 'expanded access' and 'ethics' or 'ethical' in their titles or abstracts. Articles that were available in full-text that described ethical considerations for compassionate use in general, without focusing on any particular drug or disease, were read full-text. The ethical justifications and concerns mentioned in these articles formed the foundation of this chapter.

During the review of the literature, it became apparent that numerous articles referred to the four principles of biomedical ethics proposed by Beauchamp & Childress (2001), which are beneficence, non-maleficence, respect for autonomy and justice (e.g. Buckley & O'Neil, 2020; Bunnik et al., 2018; Walker et al., 2014). Beauchamp & Childress (2001) introduced these principles as central ethical principles for health care, which integrate aspects of both consequential and deontological theories. These principles are considered to align with a 'common morality', a set of universal basic normal norms shared by all persons committed to morality (Beauchamp & Childress, 2001). Indeed, with these four principles, they have identified

important ethical themes which align with the goals of medicine and more generally, with common ideas about good healthcare and a good society. Therefore, these principles were considered valid starting points for the ethical reflection of compassionate use.

However, rather than using the principles as decisive measures regarding whether or not compassionate use is justified, they serve as moral themes to clarify what is at stake in the specific context of compassionate use, which was an approach described by Verweij (2000). In this way, the principles are used as "chapter headings in reflections on ethical dimensions of concrete situations or practices" (Verweij, 2000, p.30). Nevertheless, reviewing the literature showed that relying solely on the four principles of biomedical ethics was insufficient to effectively capture the morally relevant aspects of compassionate use. Therefore, two adjustments were made. Firstly, the principles of beneficence and non-maleficence were integrated into one moral theme, named 'individual benefits and harms'. The primary characteristic distinguishing compassionate use from standard treatment options lies in the uncertainty surrounding the benefits and harms of the drug. Consequently, within this context, the majority of moral arguments revolved around weighing the potential benefits against the potential harms. Therefore, reviewing these closely linked aspects together was useful. Secondly, a moral theme was added, named 'collective interests'. The principles of Beauchamp & Childress (2001) mainly address the individual, considering benefits, harms and autonomy at an individual patient level. However, the effects of compassionate use can extend beyond individual cases, having implications for larger groups. By circumventing standard clinical research processes, compassionate use carries the risk of negatively affecting these processes, which aim to ensure the safety and effectiveness of interventions for larger groups of patients (Walker et al., 2014). Although this theme also concerns harms and benefits, it was deliberately separated from the theme of individual benefits and harms, to pay explicit attention to collective interests and to underscore the contrast between collective and individual interests within the context of compassionate use.

Concluding, the ethical reflection on compassionate use in general encompasses four moral themes: individual benefits and harms, respect for autonomy, justice and collective interests. Each of the following four sections evaluated one moral theme, with several

objectives: (1) to identify and evaluate the justifications, (2) to describe the ethical concerns, (3) to identify the central ethical question(s) and (4) to summarize propositions to answer this central question. Although the initial justifications and concerns originated from the literature, this evaluation critically examines these, and when necessary, adjusts them. The outcome of these four objectives is a moral framework for compassionate use in general.

Individual benefits and harms

This theme contains ethical considerations regarding the principles of beneficence, “to act for the benefit of others” (Beauchamp & Childress, 2001, p.166) and non-maleficence, “not to inflict harm to others” (Beauchamp & Childress, 2001, p. 113).

Throughout the literature, beneficence emerges as the primary justification for compassionate use. Physicians aim to offer patients access to the potential benefits of unproven medication, such as improvement of their quality of life or prognosis (Bunnik & Aarts, 2021; Raus, 2016). This goal of benefiting patients also underlies many other forms of clinical care (Polak & Lynch, 2023). Sometimes, this justification is described in terms of compassion, reflecting the physician’s sense of urgency to act empathetically towards patients in dire circumstances (Walker et al., 2014). Indeed, beneficence is a valid justification for compassionate use. Aiming to provide potential health benefits to patients aligns with the physician’s duty to act in the patient’s best interest and care for their well-being. Furthermore, compassionate use is often the only way to provide potential benefits to patients, as other viable options are usually not available. This strengthens the moral commitment of the physician to provide help to the patient in this way. In conclusion, beneficence serves as a legitimate justification and motivation for compassionate use.

Apart from beneficence, justifications for compassionate use based on non-maleficence are not explicitly given throughout the literature. However, Raus (2016) suggests that waiting for official drug approval could be harmful to patients in need, because they are likely to pass away in the meantime. A justification from the principle of non-maleficence could view compassionate use as a way to avoid this harm. However, this justification would be inadequate. Non-maleficence typically involves the obligation not to inflict evil or harm onto others (Beauchamp & Childress, 2001). Although waiting for official approval may result in

harmful consequences, such harm arises from the progression of the disease, rather than as a direct consequence of the physician's actions. As such, it is difficult to argue that a physician bears direct responsibility for this harm and therefore should prevent it by approving compassionate use. So, it is unconvincing to use non-maleficence as a justification for compassionate use.

Thus, the primary justification of compassionate use is beneficence, to provide the patients with potential benefits. Although this is widely accepted in the literature, there are doubts as to whether (1) the potential benefits of compassionate use are sufficiently proven to support this justification and if (2) the potential benefits can outweigh the potential harms of compassionate use.

The first concern (1) is that the effectiveness of the drug is not unambiguously established yet, and might never be. Because compassionate use concerns unproven treatment, there is less proof of effectiveness compared to regular treatments (Raus, 2016). Most drugs tested in clinical trials, even in advanced stages, are never officially approved due to a lack of effectiveness (Schüklenk & Lowry, 2008). It is therefore possible that the patient does not benefit from the medication and their condition may in fact deteriorate (Darrow et al., 2015). Thus, even though the physician aims to provide the patient with potential benefits, the chances of actually obtaining these benefits in practice can be small.

The second concern (2) draws attention to the potential harms associated with compassionate use. As discussed, physicians not only aim to provide benefits, but also have a duty not to inflict harm upon patients, on grounds of non-maleficence. There is a tension between these two goals within the context of compassionate use, due to the potential harms that arise. These harms consist mainly of unknown side effects of investigational drugs, because the safety has not been entirely established yet. Therefore, unknown severe side effects might arise, which might even be fatal in exceptional cases (Bunnik et al., 2018). Furthermore, patients requesting compassionate use are often in a frail state, which further increases their risk of side effects (Fountzilas et al., 2018). While it may seem rational for terminally ill patients to accept greater risks because they already have a high risk of death, that does not mean they have nothing to lose, as serious side effects could still negatively impact the important end-of-life

phase (Raus, 2016). Additionally, patients can suffer financial harm, because compassionate use is often not reimbursed and the costs can be exceptionally high (Raus, 2016).

Concluding, the main justification for compassionate use stems from beneficence, whereas non-maleficence is not a compelling justification. However, for beneficence to constitute a solid justification, the effectiveness of the medication must be proven to some degree and weighed against the potential harms associated with compassionate use. The central ethical question for compassionate use regarding individual benefits and harms is therefore the following:

Which conditions should be met to ensure an acceptable balance between harms and benefits for the individual patient?

Three common conditions for compassionate use currently aim to ensure an acceptable risk-benefit ratio (Table 1): there has to be some evidence of the effectiveness of the drug, the patient must have a serious and/or life-threatening illness and must have exhausted standard authorized treatment options. Within the literature, Borysowski & Górski (2020) state that there must be a reasonable chance of cure to compensate for the substantial risks that patients are exposed to. To ensure this, they propose that an independent review committee must review the available evidence in each patient case (Borysowski & Górski, 2020). Rosenblatt & Kuhlik (2015) argue for a general rule to mitigate the risks of uncertainty, namely limiting access to compassionate use, by only allowing it when drugs are tested in phase III trials.

Respect for autonomy

This theme contains ethical considerations that relate to the principle of respect for autonomy, "To acknowledge a person's right to hold views, to make choices, and to take actions based on personal values and beliefs" (Beauchamp & Childress, 2001, p. 63).

In the ethical literature, compassionate use is sometimes justified using the principle of respect for autonomy. For instance, Kearns et al. (2018) argue that patients should be able to decide for themselves if they are willing to take the risks associated with compassionate use. Darrow et al. (2015) argue similarly, claiming that as rational agents, patients are entitled to establish their own risk-benefit threshold and that this forms the "primary ethical argument for

expanded access" (p.283).

Although the patient's autonomous decision is an essential part of compassionate use, respect for autonomy cannot serve as its primary justification. Firstly, respecting autonomy does not entail that physicians are obligated to fulfil every well-considered wish of the patient requesting specific treatment options. The physician's active involvement in carrying out the treatment grants them the responsibility to independently assess the appropriateness of available options, regardless of patient preferences. Consequently, patients are not entitled to treatment options solely based on their wishes, particularly in compassionate use, which is an exception rather than a standard treatment option. Secondly, autonomy loses its meaning without considering the potential benefits of compassionate use first. If there are no potential benefits for the patient, granting their autonomous wish would be unreasonable for a physician, who should act in the patient's medical interest.

Of course, respect for autonomy is a necessary condition for providing compassionate use, just like for standard health care decisions. An autonomous choice requires that the patient decides intentionally, with substantial understanding and without controlling influences determining the decision (Beauchamp & Childress, 2001). For compassionate use, there are concerns whether the patients can actually make autonomous decisions. The first concern is that patients with no other treatment options have a bigger chance of therapeutic misconceptions: due to their circumstances, they can easily overestimate benefits and underestimate risks of the drugs (Borysowski & Górski, 2020; Hordijk et al., 2022). Secondly, cognitive capacities necessary for decision-making capacity can be diminished due to the physical effects of severe or terminal diseases (Hordijk et al., 2022). Thirdly, patients have limited information to base their decision on, since research data are limited in compassionate use (Kearns et al., 2018). Additionally, patients do not have the medical knowledge to adequately value the existing data on compassionate use presented to them (Borysowski et al., 2017; Darrow et al., 2015). Fourthly, patients might experience pressure from loved ones to try everything they can and keep "fighting" (Walker et al., 2014).

In conclusion, respect for autonomy is not a sufficient justification for compassionate use, but it is a necessary condition. There are many concerns surrounding the autonomous

decision-making of patients in compassionate use. So, the central ethical question regarding respect for autonomy is the following:

Which conditions should be met to ensure autonomous decision-making of patients?

Currently, most compassionate use regulations require that the patients give informed consent (Table 1). Most authors emphasize the importance of adequate informed consent procedures, with a special focus on correcting misconceptions and on shared decision-making between the patient and the physician (Borysowski & Gorski, 2020; Hordijk et al., 2022).

Justice

There are many theories about justice, using distinct definitions and ideas. Regarding the principle of justice, Beauchamp (2007) wrote that there is no specific definition, but it is rather "a group of principles requiring appropriate distribution of benefits, risks and costs fairly" (p.4). A fundamental idea of justice is that persons who are equal in relevant aspects should be treated equally (Beauchamp & Childress, 2001).

Raus (2016) argues for compassionate use by appeal to the principle of justice. This entails that "a great deal of patients will be denied access" (Raus, 2016, p.3) to clinical trials based on factors beyond their control, such as certain inclusion criteria or the limited number of participants included. This is considered an unfair distribution of the potential benefits of therapeutic research, which might be addressed by providing compassionate use to certain individuals (Kahn et al., 1998).

However, there are three counterarguments against this justification. Firstly, this justification assumes that research participants have equal access to the investigational drug, and its potential benefits. Yet, in most drug studies, half of the participants receive placebos instead of the actual medication. Secondly, it conflates the aims of research and clinical treatment. Even if the participant receives the investigational drug instead of a placebo, individual benefits are often not realized. The primary aim of research is to establish the effectiveness and safety of the drug, not necessarily to provide therapeutic benefits to individual patients. Thus, in clinical research, there is no entitlement to benefits as the argument based on justice implies. Thirdly, the justice-based argument assumes that equal

access can be achieved through compassionate use. In reality, however, compassionate use is associated with risks of unequal access, as discussed in the next section. Consequently, the principle of justice is generally not a sufficient justification for compassionate use.

However, justice could serve an important role in the specific situation when clinical trials have been successfully completed, but the drug is not yet approved by drug authorities. In such cases, it might be unfair to deny certain patients access to the drug, based on bureaucratic procedures, even though its safety and effectiveness have already been sufficiently established. Nevertheless, this consideration is only applicable to a limited number of drugs that have reached advanced stages of development.

In any case, the principle of justice still plays an important role for compassionate use in practice. Within the literature, two ethical concerns are frequently expressed regarding justice: equality of access and fair patient selection. Regarding equality of access, it is stated that certain individuals have easier access to compassionate use, based on three types of non-medical and thus irrelevant factors (Borysowski & Górski, 2020; Darrow et al., 2015). Firstly, the high costs associated with compassionate use can pose a barrier for patients, as many health insurance providers only reimburse officially approved drugs (Bunnik et al., 2017). Secondly, there is an uneven distribution of information about compassionate use. Patients and physicians often lack awareness that compassionate use exists, resulting in many patients not being able to pursue this option (Bunnik & Aarts, 2019; Bunnik & Aarts, 2021). Thirdly, some patients have gained access to compassionate use through social media campaigns in the past, resulting in well-connected individuals having easier access than others (Kearns et al., 2018). Hence, more affluent, informed and well-connected individuals have easier access to compassionate use, despite these factors being irrelevant in deciding whether compassionate use would benefit them. Regarding fair patient selection, there are also concerns. In line with the principle of justice, authorities examining requests for compassionate use should judge equal cases equally, based on relevant characteristics. However, due to the absence of general guidelines to judge patient requests, there is currently no guarantee that the drug is allocated in a fair and consistent way (Borysowski & Górski, 2019; Raus, 2016). Consequently, there is an inherent risk that the allocation of compassionate use is (unintentionally) influenced by irrelevant

characteristics, such as certain social characteristics of the patient (Borysowski & Górski, 2020).

In summary, the principle of justice is generally an inadequate justification for compassionate use, although it might be relevant in more advanced stages of clinical trials. The principle of justice is crucial to consider in the practical implementation of compassionate use, in which concerns arise regarding equal access and fair patient selection. Therefore, the two central ethical questions pertaining to the principle of justice for compassionate use are:

1. Which conditions should be met to ensure equal access?

2. Which conditions should be met to ensure fair patient selection?

There are no common conditions in regulations relating to justice as of yet (Table 1). Public campaigns have been proposed as a way to promote equal access of information about compassionate use (Bunnik et al., 2018). However, increased publicity might result in overly optimistic expectations of the treatment (Bunnik et al., 2018; Kearns et al., 2018). To establish fair patient selection, Borysowski & Górski (2020) propose that an independent ethics committee judges patient requests for compassionate use, working with clear guidelines.

Collective interests

This theme contains ethical considerations regarding collective interests, which are the benefits or harms for a group of individuals. The collective could be any group of individuals impacted by compassionate use, such as certain patient groups or society in general.

No justification for compassionate use in general was identified on the basis of collective interests within the literature, because compassionate use primarily focuses on individuals seeking personal health benefits. However, collective interests might justify compassionate use during population-level health emergencies such as the COVID-19 pandemic. In these cases, there might not be enough time to await results from trials, and compassionate use could slow the spread of the infectious disease in the meantime, thus benefiting a large group of people (Zuckerman et al., 2021). Nevertheless, this justification is only relevant when it concerns highly contagious and severe infectious diseases, as it is only in such cases that the impact extends beyond individual benefit. Theoretically, compassionate use could have additional collective benefits, such as reducing healthcare costs and relieving burdens on caregivers. However, these

effects could only be realized if compassionate use is widely accessed and predominantly produces positive outcomes, which is often highly uncertain. Therefore, a justification based on collective interests is only plausible in emergency pandemic situations.

Contrarily, compassionate use carries a risk of negatively affecting collective interests, by hindering efficient drug development (Schüklenk & Lowry, 2008). Compassionate use is generally a more appealing option for patients than participation in a clinical trial, which involves a fifty percent chance of receiving a placebo and imposes greater burdens in terms of procedures and time commitment (Borysowski & Górski, 2020; Schüklenk & Lowry, 2008). Consequently, patients may be less willing to participate in clinical trials, leading to insufficient numbers of research participants and potential delays in the research process. These delays prolong the time until official drug approval, resulting in lost life years for patients who could have benefited if the drug was approved earlier (Schüklenk & Lowry, 2008). Moreover, if the drug's effectiveness is never established, the delay could have harmed patients who opted for compassionate use during that period. Some argue that compassionate use in this way prioritizes the requests of current patients over the interests of many more future patients (Rosenblatt & Kuhlik, 2015; Schüklenk & Lowry, 2008). This concern highlights the fundamental tension between compassionate use, which prioritizes individual interests, and research, which emphasises collective interests. Therefore, the central ethical question regarding collective interests in compassionate use is the following:

Which conditions should be met to ensure an acceptable balance between individual and collective interests?

Three propositions have been made to address this question. The first is that patients requesting compassionate use must be ineligible for participation in a clinical trial investigating the same drug (Table 1). This condition prevents patients from choosing compassionate use as a more appealing option, thereby reducing the likelihood of decreased research participation and consequential delays in clinical trial progress (Schüklenk & Lowry, 2008). An alternative approach to safeguard collective interests involves collecting more data from compassionate use patients. Currently, only severe side effects must be reported (Table 1). Walker et al. (2014) argue for expanded data collection "to limit any negative social implications" (p.12) of

compassionate use. Expanded data collection could benefit collective interests in multiple ways. Firstly, real-world data could provide valuable insights into everyday practices and challenges, complementing data from controlled research settings (Polak & Lynch, 2023). Secondly, data collection could shed light on the effects of compassionate use, helpful for the identification of future individuals who would benefit from it (Caplan et al., 2018). Finally, safeguarding collective interests could also be achieved by generally restricting access to compassionate use, permitting it only in advanced clinical research stages. In this way, it could be ensured that compassionate use does not hinder the research that is necessary for establishing effectiveness and safety of the drug.

Moral framework for compassionate use

In this chapter, justifications for compassionate use on grounds of beneficence, non-maleficence, respect for autonomy, justice and collective interests were evaluated. Among these, beneficence was identified as the primary justification, to act in the benefit of the patient in dire circumstances. The others were evaluated as insufficient justifications in their own right, although justice and collective interests can be relevant grounds in specific circumstances. Nonetheless, all four moral themes are important in the practice of compassionate use, as ethical concerns arise in each of these categories. Table 2 provides a moral framework for compassionate use, presenting the ethical concerns and central ethical questions per moral theme. Five overarching conditions are established that must be met for ethically justified compassionate use: an acceptable balance between individual harms and benefits, autonomous decision-making of patients, equal access, fair patient selection and an acceptable balance between individual and collective interests. These conditions serve as a broad foundation for evaluating compassionate use for psychedelics in psychiatric disorders, specifically.

Table 2 *Moral framework for compassionate use in general, categorized using four moral themes*		
Moral theme	**Ethical concerns**	**Central ethical question(s):**
Individual benefits and harms	Unproven effectiveness Unproven safety Financial harm	Which conditions should be met to ensure an acceptable balance between harms and benefits for the individual patient?
Respect for autonomy	Therapeutic misconceptions Diminished cognitive abilities Limited research data External pressure	Which conditions should be met to ensure autonomous decision-making in patients?
Justice	Inequal access Unfair patient selection	Which conditions should be met to ensure equal access? Which conditions should be met to ensure fair patient selection?
Collective interests	Delays in clinical research processes	Which conditions should be met to ensure an acceptable balance between individual and collective interests?

CHAPTER 3: RELEVANT MEDICAL AND SOCIAL ASPECTS OF PSYCHEDELICS AND PSYCHIATRIC DISORDERS

Having established a moral framework for compassionate use in general, this chapter presents medical and social aspects of psychedelics and psychiatric disorders, that are relevant for the context of compassionate use. Firstly, different aspects of psychedelics are discussed: the current research, treatment context, media attention and illegal status. Secondly, three relevant characteristics of psychiatric disorders are described: the global mental health crisis, diminished competence and the lack of irremediability.

Relevant aspects of psychedelics

Psychedelics induce altered states of consciousness, characterized by mystical, dream-like, religious, visual or auditory experiences (Breeksema et al., 2020). These often meaningful experiences have shown to be essential for their therapeutic effects, as they can disrupt rigid thought processes and provide new perspectives (Yaden & Griffiths, 2020). This frequently leads to improved self-awareness, emotional accessibility and interpersonal connectedness (Breeksema et al., 2020). Although the biological mechanisms are not fully understood, it is hypothesized that psychedelics enhance the brain's adaptability (neuroplasticity), reduce activity in brain regions associated with worry and self-reflection and facilitate communication between previously non-communicating brain regions (De Vos et al., 2021).

Psychedelic research

Between the 1950s and 1970s, psychedelics were studied as treatment options for psychiatric disorders. However, due to safety concerns and societal tensions, they were classified as controlled substances, after which further research stopped for a long time (Greif & Šurkala, 2020). Yet, recent decades have witnessed a revival of psychedelic research. Ketamine has been studied for the treatment of depression, PTSD and substance use disorders and received official approval for treatment-resistant depression (Schenberg, 2018). MDMA is studied for the treatment of PTSD, anxiety and substance use disorders (Schenberg, 2018). For PTSD, MDMA is especially promising, as it showed significant symptom reduction in phase III trials (Mitchell et

al., 2021). Psilocybin, primarily studied for the treatment of depression, but also for anxiety and substance use disorders, has shown generally positive effects, although larger-scale studies are needed (Van Amsterdam & Van Den Brink, 2022). Lastly, LSD has demonstrated positive therapeutic effects for alcohol use disorder (Fuentes et al., 2020). Other psychedelics are only studied in small open-label studies at this moment (Johnson et al., 2019). So, MDMA, psilocybin and LSD would currently be the most likely candidates for compassionate use, as they are not officially approved yet but there is preliminary evidence for their effectiveness for some psychiatric disorders.

Although systematic reviews generally report positively on the preliminary effects of psychedelics, they also draw attention to certain research limitations (Fuentes et al., 2020; Van Amsterdam & Van Den Brink, 2022). Firstly, blinding in placebo-controlled trials is complex due to the acute and intense subjective experiences psychedelics induce (Barber & Dike, 2023). Secondly, many studies have small sample sizes and a lack of diversity in their study population, with Indigenous people and people of colour being underrepresented (Pilecki et al., 2021). Thus, these methodological challenges deserve attention.

Generally, the currently known side effects of psychedelics are mild, with increased blood pressure and headaches being the most commonly reported (Greif & Šurkala, 2020). However, the psychedelic experience itself can have harmful effects. Firstly, during the administration of psychedelics, feelings of fear, panic reactions or paranoia may arise, typically lasting a few hours (Greif & Šurkala, 2020). Secondly, patients undergoing psychedelic therapy are more suggestible, making them susceptible to manipulation, exploitation and possibly even abuse, as documented sporadically (Barber & Dike, 2023). Thirdly, the psychedelic experience is often personally transformative, meaning that there are lasting changes in one's personality, beliefs, values or behaviour, which might sometimes be unwanted (Anderson et al., 2020; Barber & Dike, 2023). For example, psilocybin was shown to decrease neuroticism and increase openness and extraversion (Smith & Sisti, 2020). Giving informed consent to such transformative experiences is complicated, as they can only be fully understood by personally experiencing them (Jacobs, 2023).

Treatment context

Due to the potentially harmful effects of psychedelics, they are always used in conjunction with psychotherapy delivered by trained therapists (Schenberg, 2018). As patient outcomes heavily depend on the context in which the drugs are administered, the aim is to create safe and effective treatment sessions while minimizing negative experiences (Breeksema et al., 2020). Initially, preparatory conversations aim to build trusting relationships and prepare patients for treatment sessions (Haijen et al., 2018). Subsequently, during six to eight-hour sessions, psychedelics are administered while therapists provide non-directive guidance and support, for example, when patients become overwhelmed by emotions (Pilecki et al., 2021). Afterwards, in integrative sessions, the experiences and insights from the therapeutic sessions are discussed, including strategies for incorporating them into the patient's life (Pilecki et al., 2021). Thus, treatment with psychedelics is embedded in extensive therapy sessions to maximize safety and effectiveness. However, it is important to note that the extensive nature of this treatment process results in high costs; for example, for MDMA treatment, the costs have been estimated at 15,000 dollars (Pilecki et al., 2021).

Media attention

Psychedelic treatment has received significant media attention, with coverage in talk shows, newspapers and podcasts (Pilecki et al., 2021). Newspapers report headlines such as "The psychedelic revolution is coming. Psychiatry may never be the same"(Jacobs, 2021). Positive study results are extensively discussed in the media, while the limitations and side effects generally receive less attention (Barber & Dike, 2023). Consequently, psychedelics have generated large public interest, leading to increased requests for psychedelic treatment and participation in psychedelic research (Barber & Dike, 2023; Pilecki et al., 2021). However, this media attention carries the risk of creating unrealistic expectations regarding psychedelics (Yaden et al., 2022). As a result, disappointment and possibly hopelessness can occur if the promising treatment options prove to be ineffective (Jacobs, 2023). Furthermore, this hype has the potential to influence research outcomes, as elevated expectations may inadvertently impact study outcomes (Barber & Dike, 2023).

Illegal status

Psychedelics are controlled substances in most countries, although they are among the least harmful drugs with a low risk of addiction (Nutt et al., 2010). Also, despite their illegal status, psychedelics are among the most used drugs worldwide, especially MDMA (United Nations Office on Drugs and Crime, 2022). Therefore, individuals suffering from psychiatric disorders might resort to illegal access to psychedelics to mitigate their symptoms, and it might be relatively easy for them to obtain psychedelics in this way. However, illegal access introduces several risks, such as an increased chance of negative experiences, due to less controlled circumstances than in the therapeutic context (Barber & Dike, 2023; Pilecki et al., 2021). Additionally, illegal access can come with questionable quality of the product, adulteration and inherent dangers associated with the procurement process (Barber & Dike, 2023).

Relevant aspects of psychiatric disorders

Psychedelics are mostly studied for PTSD, depressive, anxiety and substance use disorders, although the range of psychiatric disorders they are tested for is expanding (ZonMw, 2023). Most psychedelic research involves participants who have already tried several treatment options without satisfactory results, so-called treatment-resistant disorders. Therefore, the aspects discussed in this section concern general features of psychiatric disorders, with a focus on treatment-resistant disorders.

Global mental health crisis

Psychiatric disorders increasingly contribute to an enormous global burden of disease, with substantial costs (Campbell & Williams, 2021; Schenberg, 2018). Currently, approximately one in eight people worldwide have a mental health disorder, with anxiety and depressive disorders being the most prevalent (WHO, 2022). The increasing prevalence of psychiatric disorders is accompanied by increasing suicide rates and euthanasia requests (Van Veen & Widdershoven, 2021). For individuals with treatment-resistant disorders, the burdens are even more significant; healthcare burdens and costs are up to tenfold higher compared to the general patient population, they have a reduced life expectancy and more commonly attempt suicide (Howes et al., 2021; WHO, 2022).

Thus, there is an urgent need to address this increasing trend of psychiatric disorders. However, currently available pharmaceutical options are ineffective for a large group of patients, and research into new drugs for psychiatric disorders is scarce, especially for treatment-resistant disorders (Campbell & Williams, 2021; Howes et al., 2021). Moreover, governments spend on average only two percent of their healthcare budget on mental health (WHO, 2022). Consequently, many people with psychiatric disorders currently do not receive adequate care (Kuehn, 2022). The combination of the increased prevalence of psychiatric disorders and a lack of treatment options and funding is what Campbell & Williams (2021) call a "dire mental health emergency" (p.2). This global mental health crisis is likely to result in a large pool of potential and interested candidates for the compassionate use of psychedelics.

Diminished competence

Competence in healthcare refers to a patient's ability to make autonomous decisions, which is a required element of informed consent (Beauchamp & Childress, 2001). A person is generally considered competent when they understand the relevant facts, can deliberate on risks and benefits, apply them to their own situation and make a decision based on this deliberation (Doernberg et al., 2016). Higher standards of competence are generally required when more risks are involved in a certain decision (Beauchamp & Childress, 2001).

For psychiatric patients, concerns arise regarding their competence to make decisions, as psychiatric disorders can impair attention, understanding and reasoning, which are crucial components of decision-making (Gupta & Kharawala, 2012). For instance, it is challenging to determine the competence of a depressed patient with chronic suicidal thoughts requesting physician-assisted suicide. Although this is an extreme example, it is generally complex to reliably determine when a patient's decision is excessively influenced by the psychiatric disorder in question. Consequently, within the field of psychiatry, special attention is given to competence judgements. However, it is crucial to recognize that the majority of psychiatric patients are generally capable of making decisions within the context of their illness (Calcedo-Barba et al., 2020). Therefore, although caution is warranted, healthcare professionals should avoid stigmatizing individuals with psychiatric disorders by assuming they are generally incapable of making decisions because this is inaccurate and could be harmful.

Lack of irremediability

Two common conditions for compassionate use are the presence of a life-threatening illness and the absence of alternative treatment options, collectively referred to here as "irremediability". These conditions aim to ensure an acceptable risk-benefit ratio, as having a terminal illness and no other treatment options can change the relative weight of risks and benefits. For example, having no other treatment options generally increases the value of the possible benefits. Also, waiting for official approval of medication is not a viable option for terminally ill patients, who are likely to die in the meantime. However, applying these two conditions to psychiatric disorders presents several challenges.

Firstly, psychiatric disorders typically lack a direct association with mortality. Unlike diseases such as cancer, which have a clear biological basis and often a predictable course leading to death without effective treatment, psychiatric disorders rarely have such characteristics and often come with an expected lifespan of several decades, even without adequate treatment (Van Veen et al., 2020). However, psychiatric disorders can lead to death by suicide, which some view as worse than death from other causes (Van Veen et al., 2020). Nevertheless, predicting suicidality in psychiatric disorders is complex, making the concept of lethality unreliable within the psychiatric context.

Secondly, determining when all treatment options have been exhausted is complicated. The range of biomedical and psychotherapeutic treatment options within psychiatry is practically endless, including recovery-based care, supportive care and daytime activities (Van Veen et al., 2022). Consequently, establishing the complete absence of treatment options is often impossible. Furthermore, reviewing whether treatment options have tried adequately is challenging for many forms of psychotherapy, as its success heavily depends on factors that are difficult to evaluate, such as the patient's motivation and the relationship between the therapist and the patient (Van Veen et al., 2022).

CHAPTER 4: THE CASE FOR COMPASSIONATE USE OF PSYCHEDELICS FOR PSYCHIATRIC DISORDERS

In this chapter, the case is made for compassionate use of psychedelics for psychiatric disorders. To do so, the moral framework of compassionate use in general is combined with the characteristics of psychedelics and psychiatric disorders in two ways. Firstly, it is argued that there are valid arguments to grant compassionate use of psychedelics for psychiatric disorders. Secondly, the normative implications of the distinct characteristics of psychedelics and psychiatric disorders for compassionate use are discussed.

Arguments for its use

Chapter 2 evaluated the justifications for compassionate use in general, considering justifications based on beneficence, non-maleficence, respect for autonomy, justice and collective interests. It was determined that the primary rationale for compassionate use is rooted in beneficence, aiming to provide patients potential health benefits. As was discussed, this justification is reinforced when alternative treatment options are unavailable, which is the case for compassionate use, as it places physicians in a situation where the only potential means to alleviate the patient's symptoms is to grant them access to compassionate use.

For compassionate use of psychedelics specifically, the primary justification also relies on the principle of beneficence, as the underlying aspects are similar. Psychiatrists, like other physicians, aim to help patients by providing them the means to alleviate their psychiatric symptoms. When standard treatment options are exhausted, psychiatrists may turn to compassionate use as a last resort to potentially offer health benefits. Furthermore, although psychiatric patients may experience suffering in distinct ways from patients with somatic disorders, both groups are suffering and share the wish to alleviate their suffering. Because of these similarities, the primary justification of compassionate use of psychedelics also relies on beneficence, to provide the psychiatric patient with potential health benefits. Moreover, based on the unique characteristics described in Chapter 3, there are three additional arguments advocating for the compassionate use of psychedelics for psychiatric disorders: (1) the presence

of a large and urgent need, (2) the important expressive function and (3) its potential to prevent illegal use and its associated harms. These arguments are further elaborated below.

The first argument is the presence of a large and urgent need for compassionate use of psychedelics. Chapter 3 highlighted the significant and growing population of psychiatric patients, of which a substantial portion is inadequately served by the currently available treatment options. Compassionate use of psychedelics therefore emerges as one of the limited options available to potentially provide health benefits for this specific group. While the presence of a large group of possible candidates alone cannot justify compassionate use, it does emphasize the relevance and urgency of offering access to unproven treatment options.

The second argument is that the compassionate use of psychedelics has an important expressive function, because it communicates the importance of taking suffering caused by psychiatric disorders seriously. In Chapter 3, it was described that psychiatric disorders are currently less researched and underfunded compared to other types of diseases. Campbell & Williams (2021) describe that in this way "people with mental illnesses are left out" (p.2). They argue that even though the suffering of many psychiatric patients is evident, the level of attention given to these disorders falls short in comparison to somatic disorders (Campbell & Williams, 2021). Allowing compassionate use for psychiatric disorders may be way to partly address this problem, by reflecting that society genuinely recognizes the suffering caused by these disorders. This is both an expressive and communicative function, which Van der Burg (2001) has described as an important function of the law, expressing the common values of a certain community. In this case, the underlying value is equality, that the suffering of psychiatric disorders deserves to be recognized as equally serious as that of somatic disorders. This holds particular importance because psychiatric patients face stigma and discrimination not typically associated with somatic disorders (Campbell & Williams, 2021). This expressive function offers an additional rationale for compassionate use for psychiatric disorders.

The third argument is that compassionate use can prevent the illegal use of psychedelics and thereby mitigate the risks associated with it. Due to the limited availability of effective treatment options for many psychiatric patients and the positive media attention for psychedelic research, it is reasonable to anticipate that a group of psychiatric patients may

resort to illegal access to psychedelics for their therapeutic benefits. By doing so, they expose themselves to potential harms of using these drugs outside of controlled circumstances, as discussed in Chapter 3. Furthermore, increased illegal use of psychedelics could also have negative consequences on a collective level, as more individuals would become involved in illegal drug trade. Consequently, compassionate use of psychedelics would provide a way to prevent these individual and collective harms by granting a legal way to obtain psychedelics for health benefits. Of course, however, this does not implicate that every person interested in the therapeutical benefits of psychedelics would automatically gain access to compassionate use, as strict conditions must still be met. So, not all cases of illegal psychedelic use for therapeutic purposes would be prevented; however, the group of patients who need it the most, those with no other options, would not need to resort to illegal access. Thus, preventing illegal psychedelic use and associated harms is an additional advantage of compassionate use of psychedelics that extends beyond medical benefits only.

Concluding, the primary justification for the compassionate use of psychedelics lies in providing benefits to patients, similar to other forms of compassionate use. However, the large and urgent need of psychiatric patients, the expressive function and the potential to reduce illegal psychedelic use are additional arguments to allow this practice. These factors collectively reinforce the case for compassionate use of psychedelics.

Reviewing the normative implications of psychedelics and psychiatric disorders

This section examines the normative implications of the specific characteristics of psychedelics and psychiatric disorders that were outlined in Chapter 3 for the practice of compassionate use. These characteristics are analysed in relation to the overarching conditions established for compassionate use in general: an acceptable balance between individual benefits and harms, autonomous decision-making, equal access, fair patient selection and an acceptable balance between individual and collective interest. Potential strategies and approaches to address ethical concerns resulting from the characteristics are proposed.

Normative implications of psychedelics

Regarding psychedelics, Chapter 3 discussed the aspects of psychedelic research, treatment context, media attention and their illegal status. The moral implications of each of these aspects are discussed down below, relating them to the overarching conditions of the moral framework of compassionate use in general.

Firstly, psychedelics are still being researched, and their effectiveness and safety have not been unambiguously established, except for ketamine in treatment-resistant depression. The existing evidence varies significantly, depending on the specific psychedelic and psychiatric disorder being studied. Nevertheless, the lack of unproven effectiveness and safety is not unique to psychedelics, but a defining characteristic of compassionate use for any drug, which makes thorough review of the evidence an essential component of the compassionate use process. As the evidence of psychedelic research currently offers promising results with relatively few side effects, it seems that an acceptable balance between individual harms benefits could be obtained in practice. However, there needs to be specific attention for the methodological challenges of psychedelic research, such as the complexities of conducting blinded placebo-controlled trials due to the intense subjective experiences that occur. Nevertheless, this does not implicate that evidence of psychedelic research is by definition unreliable, as placebo-controlled trials are not the only way to adequately establish effectiveness (Jacobs, 2023). Thus, for the compassionate use of psychedelics, the specific evidence should be examined with extra caution and on a case-by-case basis. Also, efforts should be made to conduct larger and more diverse clinical trials, in general, as methodologically sound evidence forms the basis of compassionate use. It is crucial to address these challenges and maintain a critical view of the available evidence when the compassionate use of psychedelics is considered, in pursuit of an acceptable balance between harms and benefits for the individual patient.

Secondly, the psychedelic experience is fairly unique when compared to other types of medication, as it often involves intense and possibly transformative experiences. These unique experiences carry certain risks, including acute emotional reactions (‘bad trips’) and potentially long-lasting effects on the patient’s personality. However, the integration of psychedelic use

within psychotherapeutic sessions guided by trained therapists helps minimize and regulate the majority of acute emotional reactions (Greif & Šurkala, 2020). Furthermore, the long-lasting effects on a patient's personality or worldview are often perceived as positive by the patient, indicating that harm is not the primary concern here (Jacobs, 2023). Instead, the concern is that potential transformative personality changes are difficult to capture in standard informed consent procedures, as it would be difficult for the patient to grasp the meaning of this experience at the time of consenting to (Jacobs, 2023). It therefore directly relates to the overarching condition of autonomous decision-making of patients, identified for compassionate use in general, and necessitates an alternative and more extensive approach to informed consent, which is discussed in the next chapter.

Thirdly, the media attention surrounding psychedelics poses certain risks, as it can lead to misconceptions and overly optimistic expectations of the treatment. When patients would request compassionate use of psychedelics, having such misconceptions could interfere with autonomous decision-making. Consequently, these risks also relate to the overarching condition of autonomous decision-making. For compassionate use, it is essential that these misconceptions are actively searched for and corrected. More generally, physicians and researchers could also have a role in correcting the overly optimistic picture of psychedelic treatment that is currently sketched by the media, by openly disputing incorrect information, as Yaden et al. (2022) suggested. In this way, misconceptions would be prevented rather than corrected.

Fourthly, the current illegal status of psychedelics does not inherently have normative implications for compassionate use. However, the underlying reasons for their illegality are relevant, mainly that they are conceived to be harmful or dangerous. Yet, psychedelics are among the least harmful drugs in recreational circumstances (Nutt et al., 2010). For compassionate use, psychedelics will always be used in combination with psychotherapy, in which even fewer negative consequences occur (Greif & Šurkala, 2020). Additionally, compassionate use of psychedelics can actually prevent illegal use and the associated harms, as discussed in the previous section. Thus, their illegal status is a reason to encourage the compassionate use of psychedelics rather than a valid ethical concern.

In conclusion, the unique characteristics of psychedelics emphasize the importance of ensuring an acceptable balance between individual harms and benefits and adequate informed consent procedures to ensure autonomous decision-making. All highlighted aspects are expected to be effectively addressed through the formulation of specific conditions regarding their compassionate use, which will be addressed in the next chapter.

Normative implications of psychiatric disorders

Regarding psychiatric disorders, Chapter 3 highlighted three aspects: the global mental health crisis, diminished competence and the lack of irremediability, of which the normative implications for compassionate use are discussed here.

Firstly, the global mental health crisis, which refers to the increasing prevalence of psychiatric disorders with a lack of effective treatment options, outlines the importance of allowing compassionate use for these types of patients, as addressed in the beginning of this chapter. However, it is crucial to consider the potential effects of a large-scale implementation of compassionate use for psychiatric disorders. If compassionate use is accessed on a large scale, it may pose challenges for ongoing clinical research and consequently negatively affect collective interests. Nonetheless, current evidence suggests that the introduction of compassionate use of psychedelics is not anticipated to negatively impact research participation in a significant way, as many patients express their willingness to engage in clinical trials (Barber & Dike, 2023). Nonetheless, the global mental health crisis asks requires extra attention for the overarching condition of an acceptable balance between individual and collective interests. Therefore, specific conditions to safeguard collective interests are addressed in the next chapter.

Secondly, psychiatric patients have a greater risk of incompetence in decision-making, as psychiatric disorders can impair cognitive aspects necessary for adequate decision-making (Gupta & Kharawala, 2012). This potentially poses a risk for the overarching condition of autonomous decision-making of patients. However, the evidence indicating that the majority of psychiatric patients are usually considered competent for decision-making in the context of their healthcare showed that this group of patients are often capable of making decisions (Calcedo-Barba et al., 2020). Thus, this characteristic emphasizes the need for a thorough

evaluation of competence in such cases, preferably by someone who has expertise on this subject, such as an experienced psychiatrist.

Thirdly, the lack of irremediability for psychiatric disorders was discussed, leading to the conclusion that lethality is not a useful concept for psychiatric disorders. If terminal illness was a required condition for compassionate use, as regularly proposed, this would consequently mean that compassionate use for psychiatric conditions would not be an option. One could argue that compassionate use should be reserved to terminally ill patients, because these patients cannot await official drug approval, as they will likely pass away before it is granted, while non-terminal patients have the option to wait. Also, terminally ill patients will not suffer long-term side effects due to their imminent death. However, there are two counterarguments against this position.

Firstly, the concept of terminal illness is more nuanced than presented here. The argument fails to recognize that severe psychiatric disorders can actually lead to death through suicide, through physical diseases that associated with severe psychiatric disorders or, in rare cases, euthanasia (WHO, 2022). Moreover, accurately predicting the timing of death for somatic disorders is challenging, with evidence indicating that physicians tend to overestimate survival predictions and that there is variability among physicians (Glare et al., 2003). Consequently, psychiatric patients may die before official approval is granted, while some patients labelled as terminally ill may survive until the medication is actually approved.

Secondly, even if terminal illness would be a reliable criterion, this argument fails to provide a legitimate argument for excluding non-terminal patients. Although there are indeed valid reasons to grant compassionate use to terminally ill individuals, this does not automatically mean there are not equally valid reasons to provide compassionate use to severely suffering individuals who are not in the terminal phase. Considering the significant number of psychiatric patients who suffer severely and have limited effective treatment options, granting compassionate use to this group is reasonable as well. Waiting for official approval would require them to endure this suffering for years until approval, even though there is a promising alternative available. Although not all patients would experience an improvement in their quality of life through compassionate use, some individuals are likely to gain significant benefits.

In conclusion, the characteristics of psychiatric disorders that were discussed here necessitate extra caution regarding collective interests, autonomous decision-making and require new criteria for eligibility, not based on having a terminal illness. These implications are addressed in the next chapter regarding the conditions for practice.

CHAPTER 5: CONDITIONS FOR ETHICALLY JUSTIFIED PRACTICE

This chapter discusses under which conditions compassionate use of psychedelics for psychiatric disorders is ethically justified. The aim is to give practical conditions for future practice. Guided by the central ethical questions of the moral framework for compassionate use in general, nine conditions are formulated, which include patient-related, drug-related and costs-related conditions. Lastly, the oversight of an independent assessment committee is recommended.

Moral framework of compassionate use

Table 3 recapitulates the identified moral themes of compassionate use in general and the corresponding central ethical questions. These questions are answered in the following four paragraphs, categorized per theme and specified for psychedelics and psychiatric disorders. Lastly, the role of an independent assessment committee is discussed, which does not specifically relate to one moral theme but rather results from aspects from different themes.

Table 3
Overview of central ethical questions of compassionate use in general

Moral theme	Central ethical question(s):
Individual benefits and harms	Which conditions should be met to ensure an acceptable balance between harms and benefits for the individual patient?
Respect for autonomy	Which conditions should be met to ensure autonomous decision-making in patients?
Justice	Which conditions should be met to ensure equal access? Which conditions should be met to ensure fair patient selection?
Collective interests	Which conditions should be met to ensure an acceptable balance between individual and collective interests?

Individual harms and benefits

Condition 1: The patient has a severe and chronic psychiatric disorder.

In Chapter 4, it was argued that having a terminal illness should not be a necessary requirement for compassionate use, as the concept of terminal illness is not clear-cut, and it excludes patients who suffer severely, who could also benefit from compassionate use. However, to maximize the potential benefits and minimize the risks of compassionate psychedelic use, only patients with severe and chronic psychiatric disorders should be considered. These patients have already experienced significant suffering in their lives for a long period, which make the potential risks associated with unproven medication more acceptable. Severity in this context refers to the profound impact that a disorder has on an individual's quality of life. Patients with relatively mild disorders should reasonably be expected to wait for official approval, as there is no right to try psychedelics. As the distinction between severe and non-severe disorders will certainly not always be clear-cut in practice, further specification of this criterium is necessary. The assessment committee, with expertise in the field of psychiatry, could have an important role in judging what constitutes severe.

Condition 2: The patient has tried all acceptable authorized treatment options.

Ideally, if authorized treatment options are available, these should be preferred over compassionate use, due to the greater understanding of risk and benefits through more extensive research. However, in the field of psychiatry, it is unrealistic to expect that all possible treatment options have been exhausted, given the wide range of therapies available, as discussed in Chapter 3 (Van Veen et al., 2022). Therefore, the condition that all authorized treatment options should have been tried is overly demanding for psychiatric patients, particularly considering the long treatment period often required for psychotherapeutic interventions to work. Instead, it is proposed that only the acceptable treatment options should have been tried. The concept of acceptability consists of several factors, including the evaluation of benefits and harms of treatment options for specific patients and the number of treatment options that were tried. For instance, if a patient has already undergone various forms of psychotherapy without significant improvement, it may be deemed unacceptable to initiate another form of psychotherapy. Also, some patients might personally find certain risks unacceptable, for example, the risks of invasive procedures such as deep-brain stimulation. Thus, the acceptability of different treatment options depends on a combination of medical and

personal factors. Therefore, acceptability should preferably be determined in a shared decision-making process between the physician and the patient, combining the medical expertise and experience of the physician with the patient's assessment of acceptability given their personal circumstances. In cases where disagreement arises, the physician should be able to ask the assessment committee for advice as a second opinion. Although the patient's view on acceptability is essential, the final say regarding which treatment options should have been tried rests with the medical professionals who possess the necessary expertise. This precaution helps prevent patients from rejecting treatment options, solely due to a desire to explore psychedelic therapy, which may be largely influenced by the current psychedelic hype and media attention.

Condition 3: There is some credible evidence of the safety and effectiveness of the drug for the patient's condition.

An inherent characteristic of compassionate use is that safety and effectiveness have not yet been definitively established, as the drug is not officially approved. However, it would be unreasonable to provide a drug to a patient that has not been researched at all. Therefore, there must be at least some evidence of its safety and effectiveness to justify compassionate use. Furthermore, the evidence must be credible, meaning that trials have been conducted with sound methodology. In the context of psychedelic research, this thesis has highlighted several methodological challenges, such as the complexity of conducting placebo-controlled trials and the lack of diversity in study populations. Therefore, for psychedelic research, it is especially important to critically evaluate the methodology of the evidence when compassionate use is requested. Additionally, there should be evidence specific for the disorder affecting the patient who requests compassionate use. Although psychedelics may have similar mechanisms of action across different disorders, it is necessary to establish that there is some evidence that they work for the specific diagnosis that the patient has.

This condition intentionally remains broad, as it is challenging to draw a definitive line between trial stages when the scientific evidence would or would not be sufficient to justify compassionate use. For instance, even the phase I trials could provide credible evidence, if they are conducted in a methodologically sound manner and show exceptional results. Hence, the assessment of the evidence must be made on a case-by-case basis.

Respect for autonomy

Condition 4: The patient has given enhanced informed consent.

Compassionate use, psychiatric disorders and psychedelics each come with concerns regarding autonomous decision-making. Therefore, a standard informed consent procedure is insufficient. A more extensive informed consent procedure is required, named 'enhanced' informed consent, a term used by Smith & Sisti (2021) in the context of psychedelic research. The foundation of standard informed consent procedures remains intact, including establishing competence and voluntariness, disclosure of relevant information, recommendation of a plan, understanding of the information and recommendation and making the decision (Beauchamp & Childress, 2001). However, the enhanced procedure requires extra attention to several aspects, which can be addressed during standard preparatory sessions that take place before the actual psychedelic treatment sessions, as described in Chapter 3.

Firstly, it is crucial to address and correct any misconceptions or unrealistic expectations that can arise from the hype surrounding psychedelics or the desperate situation patients find themselves in. Open discussions should be initiated to understand patient's expectations, followed by clear and comprehensive information about the current understanding of the drug's effectiveness and safety. Secondly, patients need to be informed about the limitations of research, as compassionate use comes with uncertainty and unknown side effects may occur. Thirdly, comprehending the psychedelic experience and its potential impact on the patient's personality may be challenging at the time of consenting (Jacobs, 2023). Nevertheless, efforts should be made to provide the most accurate information regarding these aspects. Patients should be made aware that the psychedelic experience could be very meaningful, but also carries the possibility of unwanted effects (Jacobs, 2023). Smith & Sisti (2021) have identified essential areas for discussion in the consent process of psychedelics: information about the experience, potential long-term changes, underlying mechanisms and reflective questions. They have developed templates to facilitate meaningful conversations with patients, suggesting statements such as "You may become more open to new experiences and different points of view" and "You may feel profound connections that would have seemed odd to you prior to this experience" (Smith & Sisti, 2021, p.811). Utilizing these templates can provide starting points for

addressing the unique aspects of psychedelic experiences and their long-lasting effects. Additionally, experiences from patients who have previously undergone psychedelic therapy can offer valuable perspectives to help patients better understand what to expect.

While these specific points of attention provide initial guidance for the enhanced informed consent procedure, further elaboration and specification are necessary for practice. It is essential to ensure that the consent process facilitates an open and transparent dialogue between the physician and the patient, allowing for the exploration of individual concerns, preferences and values, as a fundamental basis for respect for autonomy.

Justice

Condition 5: Patient requests are judged using consistent and transparent criteria, based on medical factors.

Ensuring fair patient selection requires consistent and transparent evaluation of patient requests, using the same criteria in each case. The establishment of an assessment committee, which evaluates requests in a standardized manner, largely contribute to this goal (Condition 8). Furthermore, it is essential to consider only relevant medical factors when assessing patient requests, as these factors determine the likelihood of benefitting from compassionate use. This can minimize the influence of implicit biases regarding certain social characteristics on the judgement of patient requests. To do so, blinding the assessment committee to social characteristics should be considered, which has been done in a pilot of compassionate use allocation for oncology agents (Caplan et al., 2018). This condition also prevent individuals gaining access to compassionate use through social media campaigns, where social characteristics have a significant influence. In the context of psychiatric disorders, there can be a fine line between medical and social characteristics, as social factors can have an important impact on the patient's symptoms. However, efforts should still be made to minimize the influence of social characteristics. Only relevant information directly related to the criteria for patient eligibility should be taken into account.

Condition 6: The patient does not bear the costs of compassionate use.

Requiring severely ill patients to bear the financial burden of compassionate use is

unreasonable, as it creates unnecessary barriers for accessing this treatment option. It is unfair that individuals with greater financial resources would have easier access to compassionate use, while others may be deprived of the same opportunity. Although this conditions is not specific for compassionate use of psychedelics but applies to all forms of compassionate use, it is particularly relevant here, because psychedelic treatment is anticipated to be costly and having financial difficulties can exacerbate mental health problems (Ljungqvist et al., 2016). Ideally, the costs of compassionate use would be reimbursed by health insurances, which is done in a few countries, such as Turkey (Bunnik et al., 2018). However, in many countries, health insurance companies require adequate scientific evidence as a condition for reimbursement, so compassionate use does not qualify. In such cases, the costs of compassionate use should be paid by either the pharmaceutical company or the hospital. This approach may come with challenges in practice, as some pharmaceutical companies or hospitals might lack the financial resources to do so. These practical issues require further attention, and some authors have already addressed this problem (Buckley & O'Neil, 2020; Bunnik et al., 2017; Darrow et al., 2015). Solving these practical issues will be challenging and need to be further addressed. However, these feasibility issues do not change the condition that patients should not bear the costs for compassionate use, as this leads to unequal access and can reinforce existing health disparities.

Collective interests

Condition 7: The patient is ineligible for a clinical trial investigating the same drug.

To ensure the progress of clinical trials is not hindered by a significant uptake of compassionate use, this condition is necessary. Given the current widespread interest in psychedelics and the global mental health crisis, there is substantial expected demand for compassionate use. Therefore, it is crucial to avoid a scenario in which a high number of patients accessing compassionate use negatively impact clinical trial participation. By reserving compassionate use to those who are unable to participate in clinical trials, it is ensured that sufficient numbers of participants are still recruited for trial participation, preventing unnecessary delays.

An alternative proposition to further safeguard the research progress is to categorically prohibit access to compassionate use while clinical trials are still ongoing. In this way,

compassionate use would only be possible after the clinical trials have been completed, to ensure that interference with this research is not possible. However, this condition would be overly demanding, as it ignores that there are patients who urgently have a need for new treatment options and suffer severely in the time that they have to wait until the completion of clinical trials. Thus, reserving compassionate use only for the time period between the completion of trials and official approval is not justified.

Condition 8: Data on safety and effectiveness of the drug are systematically collected.
When patients have access to compassionate use, data should be systematically collected on the effectiveness and the side effects. This data collection serves multiple collective interests, as were shortly highlighted in Chapter 2. Firstly, it enables the gathering of real-world data, which can complement the existing research data. This can enhance the understanding of the drug outside of controlled research settings, benefiting future patients. Secondly, systematic data collection in compassionate use settings can provide valuable insights into the effects of compassionate use itself. This is particularly valuable for patients who are considering compassionate use, as it allows them to make more informed decisions based on empirical evidence. Additionally, this data can help identify specific patient groups for whom compassionate use is the most effective or has the least side effects. So, data collection promotes interests of several larger groups, in this way contributing to the acceptable balance between individual and collective interests.

To ensure the ethical use of collected data, the assessment committee should be entrusted with the task of gathering and evaluating the data. Furthermore, patients should be informed about the goals and storage procedures of the data collection process and explicitly give their informed consent for this.

Assessment committee

Condition 9: An independent assessment committee judges patient requests.
To ensure consistent and thorough evaluation of patient requests for compassionate use of psychedelics, an independent assessment committee should be established. This committee should ideally include psychiatrists, bioethicists and epidemiologists who possess knowledge

about psychedelics and psychedelic research. Together, they review each patient request on a case-by-case basis and make the final decision on whether compassionate use is allowed. Several arguments support the establishment of such a committee.

Firstly, an assessment committee can ensure fair and consistent evaluation of patient requests, based on medical factors. Their main task is determining which patients fulfil the medical conditions for compassionate use, such as having a severe psychiatric disorder. By using pre-established criteria and being transparent about the decision-making process, the assessment committee mitigates the risk of unfair patient selection and ensures that equal cases are treated equally (Borysowski et al., 2017). Secondly, an assessment committee for compassionate use of psychedelics will develop expertise over time in the field of psychedelic treatments and research. In this way, they build a foundation of knowledge that is useful to judge the scientific evidence on psychedelics. In this way, the committee is in a better position to judge psychedelic research evidence than individual physicians, who may find it time-consuming and complicated to review preliminary research (Borysowski & Górski, 2020). In this regard, including an epidemiologist in the committee is crucial. Thirdly, an assessment committee serves as an additional safeguard for ensuring informed consent, which can be challenging in the compassionate use of psychedelics due to many previously discussed reasons. The committee's involvement provides an extra layer of caution to verify that the appropriate informed consent has been obtained, thereby minimizing the lack of autonomous decisions of patients. Lastly, the assessment committee has an essential role in monitoring and evaluating the implementation of compassionate use of psychedelics on a national level. By collecting and analysing data from patients undergoing compassionate use, the committee contributes to the ongoing assessment of the treatment's effectiveness and safety. This systematic data collection and evaluation enable the committee to continuously improve the compassionate use process, identifying emerging concerns or issues, and guide evidence-based decision-making for future patients.

Regular committee meetings provide a platform for critical evaluation and adaptation of compassionate use conditions in response to doubts or concerns that arise. This process ensures that the compassionate use of psychedelics can develop and respond to emerging

scientific and ethical considerations. It is important to note that the assessment committee does not replace the valuable role of the physician, as the patient and physician still prepare a request for compassionate use together.

Overview and concluding remarks

Table 4 presents an overview of all conditions for ethically justified practice of compassionate use of psychedelics for psychiatric disorders, categorized in conditions relating to the patient, the drug, the costs and the assessment committee. Some conditions overlap with the general common conditions for compassionate use, which were previously shown in Table 1. Also, most of the conditions are formulated in a general way, making them applicable to a wide range of psychedelics and psychiatric disorders. However, the specific implementation and relevance of each condition can vary depending on the specific drug or psychiatric disorder. While the previous sections have provided some specifications and explanations of these conditions, their implementation in practice will require further refinement and adaptation.

Table 4

Overview of conditions for ethically justified compassionate use of psychedelics for psychiatric disorders

	**Patient** 1. The patient has a severe and chronic psychiatric disorder. 2. The patient has tried all acceptable authorized treatment options. 3. The patient is ineligible for a clinical trial investigating the same drug. 4. The patient has given enhanced informed consent.
	**Drug** 5. There is some credible evidence of the safety and effectiveness of the drug for the patient's condition. 6. Data on safety and effectiveness of the drug are systematically collected.

	**Costs** 7. The patient does not bear the costs of compassionate use.
	**Assessment committee** 8. An independent assessment committee judges patient requests. 9. Patient requests are judged using consistent and transparent criteria, based on medical factors.

CHAPTER 6: CONCLUSION

In this thesis, the question was addressed whether compassionate use of psychedelics for psychiatric disorders is ethically justified, and if so, under which conditions. Although two articles briefly addressed the topic of compassionate use of psychedelics, this thesis adds to this existing literature by evaluating a wide range of ethical considerations, based on various ethical principles. Also, the normative implications of specific aspects of psychedelics and psychiatric disorders for the practice of compassionate use were explicitly discussed. Lastly, this thesis is the first to establish the necessary conditions for ethically justified practice.

Initially, a moral framework for compassionate use in general was established from the ethical literature, based on the four moral themes of individual benefits and harms, respect for autonomy, justice and collective interests. Justifications from each of these themes were evaluated, and beneficence was identified as the primary and sufficient justification for compassionate use. Reviewing ethical concerns for these moral themes resulted in five overarching conditions for compassionate use in general: an acceptable balance between individual harms and benefits, autonomous decision-making, equal access, fair patient selection and an acceptable balance between individual and collective interests. Subsequently, relevant characteristics of psychedelics and psychiatric disorders were examined, resulting in unique aspects that deserve attention in the practice of compassionate use of psychedelics.

Hereafter, the general moral framework of compassionate use was combined with specific aspects of psychedelics and psychiatric disorders. Firstly, the arguments for compassionate use of psychedelics were given, relying mainly on the justification of beneficence, but with the additional benefits of preventing illegal psychedelic use and expressing the importance of taking suffering by psychiatric disorders seriously. Secondly, the normative implications of each of the unique characteristics of psychedelics and psychiatric disorders were addressed, resulting in a need for extra caution on the identified themes of individual benefits and harms, autonomous decision-making and collective interests.

Lastly, using these normative implications, nine practical conditions were formulated for ethically justified practice of compassionate use of psychedelics for psychiatric disorders: the

patient has a severe and chronic psychiatric disorder (1), has tried all acceptable authorized treatment options (2), is ineligible for a clinical trial investigating the same drug (3) and has given enhanced informed consent (4). Furthermore, there is some credible evidence for the safety and effectiveness of the drug for the patient's condition (5), and data on its safety and effectiveness are systematically collected during compassionate use (6). Moreover, the patient does not bear the costs of compassionate use (7). Lastly, an independent assessment committee judges patient requests (8), using consistent and transparent criteria, based on medical factors (9).

Although many ethical considerations were taken into account in this thesis, an important limitation arises from conducting such a broad evaluation. As each subject – compassionate use, psychedelics and psychiatric disorders – had its own relevant ethical considerations, it was challenging to address all these ethical considerations sufficiently and in-depth. Certain topics, such as giving informed consent for the psychedelic experience, definitively require further exploration in future research. Nevertheless, by formulating the conditions in a broad manner, this allows for flexibility and adjustment in practice as certain topics are further investigated. While this limitation highlights the need for future research, it does not diminish the value of the results presented in this thesis.

Furthermore, this thesis provides a foundation for both further research of compassionate use in psychiatry and practical testing of the conditions. Firstly, an important finding from this thesis is that compassionate use for psychiatric disorders is strikingly similar to compassionate use for other types of disorders. This is partly reflected by the overlap in conditions for compassionate use. This observation is particularly noteworthy considering the lack of compassionate use in the field of psychiatry, and the limited ethical literature available on the topic. Also, given the current global mental health crisis, the lack of attention for compassionate use in psychiatry becomes even more remarkable. This suggests that the similarities between psychiatric and somatic disorders are not adequately addressed in the context of compassionate use. Therefore, it is crucial for future research to delve into the underlying reasons behind the scarcity of compassionate use in psychiatry, to address these differences.

Moving forward, the feasibility and acceptability of the practical conditions should be tested in practice. A possible way to do this would be to conduct a pilot study for compassionate use of a specific psychedelic, using the established conditions. In this way, the actual impacts can be reviewed and conditions may be adjusted accordingly. With regards to feasibility, the establishment of and procedures surrounding an assessment committee might pose significant challenges due to their expected financial burdens.

In conclusion, this thesis was the first to conduct an ethical evaluation of compassionate use of psychedelics for psychiatric disorders by offering a framework of conditions for ethically justified practice. It serves as the beginning of ethical inquiry on this topic, with further research and practical testing being needed.

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