Signaling

Therapeutic uses of psychedelics

Opportunities, challenges and care innovation for treatment-resistant psychiatric disorders

ZonMw

ZonMw report

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March 2023

Colophon

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Accountability

This ZonMw report has been drawn up on the basis of an extensive literature search, a stakeholder analysis and many other discussions with the parties involved. This includes individuals and organizations currently involved in TTP research and/or treatment, as well as stakeholders who are expected to play an important role in this in the future. Discussions were held with experts and representatives from: - Dutch universities, university medical centers and specialist mental health institutions - Patients and their relatives - Professionals who have experience with TTP as a practitioner - Health insurers - Policymakers and representatives of various political parties - Professional organizations - Pharmaceutical companies and Contract Research Organizations - Science funds, other grant providers and private investors - Center for Future Affordable Sustainable Therapy Development (FAST)

- Enforcement agencies - National and international registration authorities - National and international experts and organizations in the field of TTP

The monitoring report also contains a number of short case descriptions, and excerpts from messages from patients and relatives sent to clinical researchers who are conducting research in this area. Possible traceable details in these expressions taken from real life have been adjusted to guarantee anonymity.

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Photo cover: ARQ Centrum '45. Impression of an MDMA treatment for patients with PTSD

Resume

An estimated 200,000 people in the Netherlands with a psychiatric disorder continue to have serious psychological complaints despite regular treatment. These chronic and difficult to treat psychiatric disorders have a major impact on the quality of life and functioning of patients, their relatives and other close relatives. It is precisely these treatment-resistant disorders that make a major contribution to the social burden of disease, high healthcare costs and long waiting times in mental health care. These disorders are responsible for a significant reduction in lifespan, poorer physical health and suicide.
Unfortunately, few therapeutic innovations or new drugs have been developed in psychiatry in recent decades that have been able to break this impasse.

In recent years, an increasing number of studies have indicated that therapeutic applications of psychedelics (TTP) can provide significant improvements for patients with treatment-resistant psychiatric disorders and (neurological) pain disorders. This report describes the state of affairs in the field of TTP, the possible target groups and proponents and opponents, the knowledge gaps and the barriers that stand in the way of research and implementation. Solutions are also identified, in particular the establishment of an extensive national research and implementation programme.

TTP: drugs and therapeutic context In

therapeutic applications of psychedelics, drugs such as psilocybin, ketamine or MDMA are used in the treatment of patients with psychiatric disorders such as depression or post-traumatic stress disorder. The results in a majority of patients with treatment-resistant psychiatric conditions are promising.
There are often longer lasting positive effects that make a real difference to the quality of life of the patient and those around him.

To use psychedelics safely and effectively in a therapeutic context, careful preparation, guidance and aftercare are essential. Without this therapeutic context, administration of psychedelics to people with psychiatric problems is unsafe and therefore contraindicated.
Pharmacotherapy is usually used in psychiatry in combination with other forms of therapy.
This is especially true for the use of psychedelics. This report therefore consistently refers to TTP, to emphasize that this therapeutic innovation requires an integrated approach in which pharmacotherapy and psychotherapy are combined for an optimal effect. This has consequences for how care is offered, but also for the assessment by regulatory authorities and health insurers.

A variety of psychedelic drugs have been investigated in the context of TTP. For a considerable part, this concerns substances that currently fall under the Opium Act, such as psilocybin, MDMA and LSD.
An exception is the drug ketamine, which was already registered for use in anaesthesiology and has now also been registered for the treatment of treatment-resistant depression.

Psychiatric and Other Indications

TTP has been studied to varying degrees for the treatment of a variety of psychiatric conditions. It primarily concerns patients in whom several regular treatments have failed (therapy resistance). Examples of TTP for which there is already some scientific support are: ketamine and psilocybin in depression, MDMA in post-traumatic stress disorder (PTSD), ketamine and psilocybin in substance-related disorders ('addiction'), LSD and lysergine derivatives in cluster headaches.

The strength of the scientific evidence varies widely and is not yet sufficiently representative of the large group of treatment-resistant patients in the Netherlands who are looking for better treatment and a better life perspective. In addition, there are several methodological challenges inherent in TTP research, including the complexity of treatment. Moreover, due to the strong direct effects of psychedelics, it is not easy to conduct double-blind placebo-controlled research

(where both the patient and the practitioner cannot guess whether the active substance or a placebo has been administered).

Knowledge gaps and points for attention To use TTP as regular treatments in mental health care and pain treatment, more knowledge is needed in various areas. It concerns methodological and substantive questions in the field of clinical scientific research, research into cost-effectiveness and questions in the field of *health technology assessment* (HTA), ethical, legal and social aspects. It is also important that practical issues are tackled, such as training therapists and setting up TTP within mental health care institutions.

An overarching problem that stands in the way of answering these knowledge questions and tackling bottlenecks is the fact that research into TTP has so far been too fragmented.
Although the preconditions and support for research into TTP are present within the current mental health care system (such as the registration of treatment outcomes, for example), there is still no adequate infrastructure for the necessary large-scale clinical studies. There is an urgent need for more volume and coherence to address the knowledge gaps in a systematic, coordinated manner and to achieve responsible implementation within a time frame that does justice to the burden of disease and the needs of patients. In the shorter term, expansion of *off-label* treatment and *compassionate use* programs may offer a solution for distressing cases. Safe and careful implementation of TTP requires early involvement of participating institutions and staff and timely investment in the development of high-quality training, treatment protocols, guidelines for professional conduct and supervision.

Risks and social context The media pays a lot of attention to the possible positive effects of psychedelics, which leads to hope among patients and those around them who have been looking for ways to alleviate their suffering for years. However, important questions remain unanswered, and research so far is too small-scale, uncoordinated and progressing in small steps. It is sometimes forgotten that the use of psychedelics also entails risks. In the short term, side effects may include dizziness, nausea, and feelings of fear, confusion, paranoia, or panic.
Especially in people with psychiatric problems, these side effects can be overwhelming.
Some people also experience such negative consequences and re-experiences for some time after a psychedelic session. The frequency, seriousness and impact of these undesirable effects have so far not been systematically mapped out sufficiently.

The tension between the desperation of patients and the (too) rosy picture that is being painted here and there entails the risk that patients, outside the regular care circuit, will look for ways to improve their condition with psychedelics. All this increases the chance of incidents and makes it more difficult to make a careful social assessment of the use of TTP. To be able to use treatment with psychedelics in a safe, efficient and effective manner in larger groups of patients within the foreseeable future, an extensive national research and implementation program is of great importance.

Conclusion and recommendations As this monitoring report shows, TTP is a hopeful development that can be of great significance to patients with treatment-resistant psychiatric disorders. At the same time, important knowledge gaps and risks are identified in the field of effect and side effects, and (cost) effectiveness, and there are important points for attention in the field of regulation, ethical and social aspects.

In order to capitalize on the opportunities that TTP offers for patients with treatment-resistant psychiatric disorders and to offer TTP safely, responsibly and cost-effectively, the government should set up a coherent research and implementation programme. Such a programme, to be carried out by a broad-based national consortium, could consist of the following components: 1) high-quality applied scientific research, 2) stepwise implementation of new treatments, 3) quality assurance and systematic monitoring of outcomes and side effects , 4) availability, affordability and efficiency and 5) education, training and accreditation. With such a program, the Netherlands can play an important role in this area

of high-quality, multidisciplinary clinical research into TTP and thus strengthen its international position in the field of therapy development and innovation in mental health care. For Dutch patients and their peers worldwide, it is to be hoped that these efforts will lead to new applicable insights and to safe, effective treatments.

Reading

guide The purpose of this report is to provide an overview of the current state of affairs regarding therapeutic applications of psychedelics (TTP). What are the possibilities, obstacles and opportunities for research and subsequent implementation of TTP in Dutch mental health care, and which stakeholders and perspectives should be involved in a coordinated and careful approach?

Chapter 2 first explains what TTP entails and what risks are associated with it.
Chapter 3 then discusses what is already known about treatment effects in various psychiatric and neurological disorders. Chapter 4 discusses the most important knowledge gaps and points for attention that need to be addressed before a broader implementation of TTP in mental health care can be started. Chapter 5 explores a number of solutions for this. This report concludes with the most important conclusions, recommendations and follow-up actions.

Case 1: MDMA helps policewoman recover from trauma Layla

Demir is 46 years old and has been working for the National Police for over 20 years. In 2016, as a police officer on duty, she had to investigate a fatal collision at the scene. The seriously injured victim turned out to be her brother. Since that day she had almost daily relives and nightmares about her brother and other victims, which meant that she hardly slept. She began to avoid anything that reminded her of the incident, and became so anxious that she was afraid to go out, and even grocery shopping became a challenge. Layla had a work-related post-traumatic stress disorder (PTSD), presumably due to the combination of high work pressure, many serious incidents in a relatively short time and little space to process these events. Her case is by no means unique. Unfortunately, PTSD is more common in police officers.

After a trajectory within specialized mental health care, Layla underwent various trauma treatments for years. These treatments did provide some relief and insight, but did not bring her the desired recovery that would have allowed her to resume her work. As an out-of-treatment patient, she was eligible for a 2019 trial of MDMA therapy for severe PTSD. Layla was the first participant in this innovative study.

During two sessions that lasted eight hours, which she herself describes as intense and emotional, Layla was able to relive her traumas, say goodbye to her brother and come to peace with her situation with the help of experienced therapists. The careful guidance and good relationship of trust with the two therapists made her feel understood and dared to be vulnerable. A year and a half later, she is still free of complaints and has largely regained her life; she is working again and has been trained as an experience expert to support other colleagues with PTSD.

1 Introduction: the social question

Psychiatric disorders are common and have a major impact on the quality of life of patients and those around them. This impact is significantly greater than that of common physical illnesses. This is also because conditions such as depression, anxiety disorder, psychosis, post-traumatic stress disorder, or substance-related disorder arise relatively early in life; the peak is between the ages of 15 and 25. Often the condition returns or the same person develops psychiatric problems again later in life. The impact on patients' lives is therefore large and long-lasting: psychiatric disorders are the largest cause of disease burden for people between 20 and 50 years old (figure 1).

Treatment resistance

Psychiatric disorders are generally treatable. Yet there is also a group of patients for whom the current arsenal of treatments has no or insufficient effect. 1 Such a treatment-resistant psychiatric disorder is associated with considerable individual suffering for both the individual and those close to him. An estimate based on prevalence figures and percentages of treatment resistance suggests that more than 200,000 people in the Netherlands often suffer for years without hope of a cure. [2]

Treatment-resistant psychiatric disorders entail high healthcare and social costs, and are associated with significantly (up to 50%) higher direct and indirect healthcare costs than non-treatment resistant disorders. [3] Carrying long-standing psychiatric conditions strongly contribute to the individual and social burden of disease and long waiting times in mental health care. with additional because of the increased physical and/or psychological illnesses. Partly because of this, but also suicide risk, the life expectancy of patients with a treatment-resistant disorder is significantly shorter. 5–7

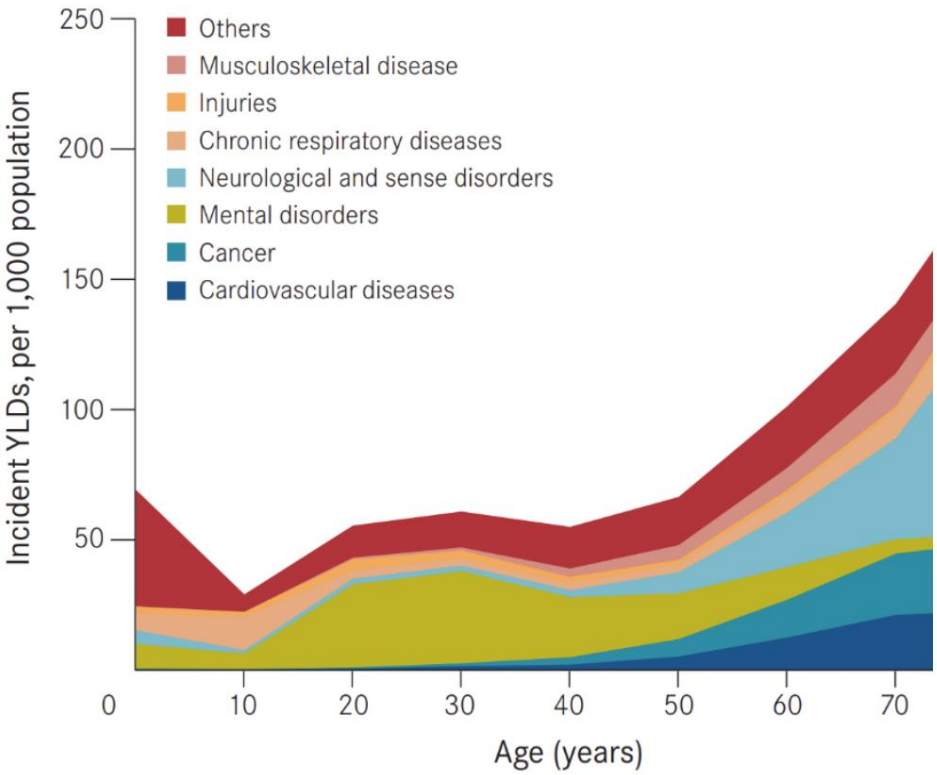

Figure 1 Disease burden of different groups of disorders, by age. Psychiatric disorders, or *mental disorders* (green), are by far the largest cause of disease burden for people aged 20-50. Burden of disease is expressed in incidence YLDs *(Years Lived with Disability),* calculated by multiplying the incidence (annual number of new cases) of a condition by its disability weight. Source: *Victoria Burden of Disease Study* (2001)

A lot of personal suffering is hidden behind the more or less neutral term 'treatment resistance'. Patients and their loved ones find themselves in a desperate and hopeless situation when treatments fail to achieve the desired result time after time. To illustrate this suffering, some fragments of the messages sent to researchers have been included anonymously below. Mails and requests to this effect come in almost daily. For some people, the situation is so intolerable that they see euthanasia as the only way out: euthanasia for unbearable and untreatable psychological suffering is now performed more than a hundred times a year. [8] In addition to the waiting lists for mental health care, the waiting list at the Euthanasia Expertise Center is also growing steadily.

'I've been battling depression and OCD since my teens. I have been fully on disability benefits for years because 'normal' functioning in society does not want to work. I'm ashamed to say it but I often envy people who have only a short time to live. Last night I saw a Netflix documentary in which someone got rid of his compulsive complaints after research with psilocybin. Please, please, please.
Invite me.'

'I suffer from a persistent obsessive-compulsive disorder that has completely relapsed after a few years of therapy. I've already tried twice to take my own life. I read promising results on treating OCD with psilocybin and came across the [medical center] *. It would mean a lot to me because I just don't feel like I'll ever get rid of it.'*

'I have suffered from PTSD for years, and have been in therapy for at least 10 years. My patterns, thoughts and feelings torment me. My family is affected by my behavior. I'm losing friends. I've seen the Netflix series How to Change Your Mind. I so want to heal. Can you please help me?'

From stagnation to hope

There is therefore an urgent need to develop new, more effective treatment methods, especially for the most ill patients. Unfortunately, this has not proved easy in recent decades. Psychiatric diseases are complex and research is expensive. Pharmaceutical companies have therefore often limited or even discontinued the development of new psychiatric drugs. The limited progress is in stark contrast to the increase in the demand for care from patients with persistent psychiatric disorders.

This gloomy picture has recently changed. There is increasing evidence that therapeutic applications of psychedelics – substances such as psilocybin, ketamine and MDMA – can have major effects in serious, often treatment-resistant, psychiatric disorders. This offers hope.

Scientific embedding However,

there are still many questions that need to be answered in order to be able to use these therapeutic applications safely and effectively within Dutch mental health care. There is understandably a lot of pressure from patients and from society to explore this theme. When that is not possible within the existing institutes, in a scientific setting, the risk of incidents and undesirable outcomes increases.

At the same time, there is also social resistance to psychedelics, also in a therapeutic context. To be able to conduct the public debate in a balanced way and with rational arguments, more knowledge and objective communication is needed about the desired and undesired effects of these substances. This also argues for a scientific embedding of TTP in the Netherlands.

Case 2: After 20 years of depression, finally improvement thanks to esketamine

Mr. Meijer (56) has been living with depression for more than 20 years. In addition, he has been diagnosed with obsessive-compulsive disorder (OCD) and suffers from psychotic symptoms: he sometimes hears voices that are not there. His illness makes it difficult for him to find work and sometimes he is unable to take care of himself. Since the onset of his depression, he has been treated with multiple medications, various forms of psychotherapy, and electroconvulsive therapy. However, these treatments have not yet led to significant improvement. An experimental treatment of an implant for deep brain stimulation (DBS) was also unsuccessful. After several attempts and a year of follow-up, DBS had not improved his complaints either. As a result, Mr. Meijer has become desperate, and he is increasingly suffering from suicidal thoughts.

Mr Meijer has now started an off-label treatment with esketamine. In addition to his regular medication, he was administered an esketamine drink twice a week in the hospital. This made him temporarily dizzy, but otherwise no side effects occurred. Soon his practitioners and he himself began to notice improvement. Remarkably, the treatment not only reduced his depressive symptoms, but also improved his OCD and psychotic symptoms. Mr. Meijer also managed to keep up with daily life again, and his functioning improved in various areas of life that are very meaningful to him. He is now still taking the esketamine drink at home, reducing the frequency in small steps in consultation with his practitioner. The improvements have now lasted for 17 months.

2 TTP: Therapeutic Uses of Psychedelics

This chapter describes what psychedelics are, what the therapeutic application of psychedelics can look like, how this therapeutic effect may come about and what risks are associated with the use of psychedelics.

2.1 What are psychedelics

Psychedelics are substances that bring about a transient radical change in perception, thinking and feeling. The term 'psychedelic' was coined in the 1950s by British psychiatrist Humphrey Osmond. By referring to the Greek words *psyche* (mind) and *delein* (to make visible), he wanted to make it clear that these substances could bring about special experiences and insights.9

Nowadays, a distinction is made between classic and atypical psychedelics. Classic psychedelics, such as LSD, psilocybin, mescaline and DMT are (semi) natural substances that are extracted from different types of plants and fungi. They have a long history of use in ceremonial and religious contexts, particularly in North and South America. Classic psychedelics have the common characteristic that the active substance is structurally similar to serotonin; a signal substance (neurotransmitter) in the brain. The structural similarity allows the classic psychedelics to bind to certain serotonin receptors, causing the psychedelic effect.

The atypical psychedelics differ in chemical structure and pharmacology from the classical psychedelics. This group includes ketamine, MDMA and ibogaine. Ketamine is a so-called NMDA antagonist. The drug temporarily inhibits the signal transmission of the neurotransmitter glutamate. Perhaps the most characteristic subjective effect of ketamine is dissociation. This can vary from a slight emotional distance from the immediate environment to a strong disconnection from one's own thoughts, emotions or feelings of identity and the blockage of signals between body and mind. The latter effect makes ketamine a particularly effective anesthetic and pain reliever, which has been used successfully in medicine for years. Compared to other anesthetics, ketamine has the advantage of not depressing breathing, making it known as a safe anaesthetic.

A completely different kind of atypical psychedelics are so-called entactogens, of which MDMA is the best known. Among other things, MDMA increases the release of serotonin, which leads to feelings of openness, trust and empathy. In addition, it enables people to open up, feel connected, and make contact with others more easily (entactogen).10 In a therapeutic context, it also helps to reduce feelings of fear, guilt, or shame and makes it patients easier to face emotionally charged subjects.

A final atypical psychedelic is ibogaine, which occurs naturally in the bark of the *Tabernanthe iboga* shrub. Ibogaine is used ceremonially in Central Africa; in the West, ibogaine is offered in some places, usually without medical supervision, for addiction treatment.

In this report, psychedelics are understood to mean classical psychedelics, MDMA and ketamine; due to the relatively unfavorable safety profile of ibogaine, this agent is not discussed.

2.2 Guidance and therapy Applications

of psychedelics for therapeutic purposes are not new. Cultures in which natural psychedelics have a ritual application also often use these resources to provide insights and healing. Psychiatric uses of psychedelics emerged in the 1940s and 1950s, following the discovery of the psychedelic properties of LSD by Swiss pharmacologist Albert Hofmann in 1943 and the successful identification and synthesis of psilocybin in 1959.

A fruitful period of scientific research began. Psychiatrists and psychologists have extensively experimented with various psychedelics as an aid to psychotherapy. Psychodynamically oriented psychiatrists and therapists saw psychedelics as a powerful tool to expose unconscious processes and feelings in patients and to make unprocessed psychological material available. Others gave high doses of psychedelics to induce intense 'peak experiences' to give patients a new perspective on their lives and their psychiatric problems. The research in this pioneering phase showed that psychedelics can be effective for several common psychiatric conditions; fears and depressions, addiction, traumatic experiences in prison and concentration camps and psychological problems in patients in palliative care/death phase.

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This first phase of research into TTP came to an end with the global ban on psychedelics in the 1970s. Its increasing popularity and political concerns about its widespread use led to social unrest. With the *'war on drugs'* came a worldwide ban on psychedelics, bringing research to a near complete standstill. Since the beginning of the 21st century, there has been renewed interest in TTP research.

Guidance before, during and after a psychedelic session The contemporary forms of TTP start with one or more preparatory conversations. In this way we work on building a relationship of trust between the patient and the accompanying therapist(s). Patients are also prepared in these conversations for the intense or challenging experiences they may have during the session with the psychedelic substance. During the introduction, attention is often also paid to the life story and the story of the psychiatric disorder from the perspective of the patient.

These preparatory talks are followed by the session in which the drug is administered. In some patients, a single session with substances such as LSD, psilocybin or MDMA seems to be sufficient; it seems that for the majority of patients, a few sessions, flanked by talk therapy sessions before and after, spread over several months, are most effective.
With ketamine, repeated administration may be more effective.

During a session with the psychedelic substance, the patient is largely in charge. For example, patients can choose whether or not to talk, listen to music or close their eyes.
The counselors adopt a non-directive attitude, and their main task is to guarantee a safe setting and to offer support and trust when the patient needs it. For example, support can be helpful when the patient has difficulty relaxing, cannot fully surrender to the experience, or is in danger of being overwhelmed by emotions, fear or panic. Grounding or breathing techniques practiced during the preparations can be very helpful in handling the experience.

Finally, after the treatment session, one or more integration interviews take place in which the patient and the counselor reflect on the experience. Together they investigate which thoughts or perceptions came up and how the experience can take on meaning in the personal context of the patient. The patient is also encouraged to use the insights and motivation gained to shape changes in their lives and in dealing with problems. The use of psychedelics in psychiatry represents an integration of pharmacotherapy and psychotherapy, focusing on the psychological significance of the patient's pharmacologically induced experience.

Set and setting

Already in the early years of therapeutic research into psychedelics, it became clear that the treatment context was important for a safe and effective session with psychedelics. Anyone under the influence of these substances is extra sensitive to sensory stimuli and emotional associations. For example, the first studies with psychedelics, in a clinical setting with doctors in white coats who completed questionnaires in a strict tone, often produced unpleasant reactions. Administration of psychedelics to test subjects who did not know what they were receiving also often led to problems.
That is why systematic attention is paid to the context, or the 'set and setting'.

'Set' refers to personal, internal factors, such as the degree of preparation for the experience, expectations, one's state of mind and the relationship of trust with other attendees.
The term 'setting' refers to the external environment during the session, such as the presence of music and the atmosphere in the room and the aforementioned non-directive supportive behavior of the facilitators. The setting also includes the broader social, cultural or clinical context within which the experience is integrated and made meaningful by the patient and the practitioner.

2.3 How do psychedelics work?

The (therapeutic) effect of psychedelics can be investigated and understood at different levels: at the level of brain cells and brain networks (neurobiological) or at the level of experience and mental processes (psychological). The most important insights are briefly discussed here, with the caveat that there is still a lot that is still unknown and that there are differences at every level between the various substances, especially between the classic and atypical psychedelics.

Pharmacology and neuroplasticity

At the cellular level, psychedelics affect signal transmission between brain cells and promote the production of *brain-derived neurotrophic factor* (BDNF). This substance protects brain cells and stimulates their growth and repair. BDNF is one of the factors responsible for the brain's ability to adapt to a changing environment or changes in the brain itself (neuroplasticity). and for recovery after damage to the [12] Neuroplasticity is essential for cognitive functions, such as learning and memory brain.

In the context of TTP, increased neuroplasticity makes it possible to see new connections, retrieve repressed memories and break out of the vicious circle of repetitive distressing thoughts and feelings that patients are often trapped in. The latter is also referred to as cognitive rigidity. For example, someone with depression may worry endlessly, dealing with the same self-criticism and negative conclusions and suicidal thoughts. Breaking through such a tormenting mindset makes a big difference for patients, and makes them more open to other perspectives and possibilities and also, for example, to talk therapy.

Brain networks

Thanks in part to imaging techniques, it has become clear that brain cells communicate with each other in networks. Psychedelics have been shown to inhibit activity in areas of the brain involved in self-reflection and worry, and to stimulate communication between other areas of the brain that are normally less closely connected.12 Brain scans have been made of people under the influence of psychedelics, which have shown increased activity. becomes of brain networks that are actually less active in a psychiatric disorder.13 Change also takes place at this level: new connections are made and rigid patterns are shaken up. It is quite conceivable that space is created in this way to look at things in different ways, to break through stubborn patterns and to develop new ones.

Meaningful experiences

On a psychological level, it appears that psychedelics (in the right set and setting) can evoke experiences of unity, insight and loss of self. There are feelings of increased connection with oneself, with others and with nature. The ultimate sense of belonging that people sometimes experience is also described as 'mystical', 'religious' or 'nondual'. 14 These experiences turn out to be very meaningful and can put patients' lives in a new perspective. They can even lead to significant shifts in worldview, values, relationships with others, or behavior.15 When properly managed, such experiences can be accompanied by therapeutically and personally meaningful growth. They can also lead to serious doubts about previously held beliefs or assumptions, which can be confusing and unpleasant.16

During a psychedelic session, patients can also gain new insights into themselves, into their own functioning, the causes of their disorder or into relationships with others. Such insights are often accompanied by changes in how they view themselves. They are also better able to get in touch with their own feelings, creating more compassion and a decrease in the often agonizing

present self-criticism. These increased feelings of connection, with oneself, with others, but also with nature, probably also contribute to the therapeutic effects.

Psychological Trauma

Psychological trauma is a common element in the life story of many people with a psychiatric condition. Psychological trauma occurs when someone is unable to accommodate a disruptive event. Exposure to extremely negative childhood experiences, such as neglect, maltreatment or sexual abuse, is one of the most important predictors of developing a variety of psychiatric disorders later in life. 17 Shocking events later in life can also have a major psychological impact, which, if insufficiently processed, can lead to the development of post-traumatic stress disorder (PTSD) or other psychiatric disorders. A characteristic phenomenon of PTSD is that the memories of the traumatic experience are difficult to suppress. This leads to insomnia, nightmares, jumpiness and intense re-experiences. The psychotherapeutic treatment of PTSD and related disorders is often based on retrieving traumatic memories, with the aim of viewing, discussing and eventually giving a place to the trauma. MDMA, and possibly other psychedelics, can facilitate this process by providing access to difficult experiences or memories while reducing the intensity of additional negative emotions. In this way, the origin of emotions or patterns can be explored, without patients being overwhelmed by negative emotions such as fear or shame. These experiences can then be reflected on in integrative sessions. For example, psychedelics can act as a catalyst for a (stalled) therapeutic process.

Other neurobiological effects In as

yet unknown ways, psychedelics also have direct effects on various functions in the brain, such as mood, motivation, substance cravings, sleep and the response to stress and emotion.18 These functions are disrupted in various psychiatric disorders. It is likely that the aforementioned changes at the level of neurotransmitters, cells and brain networks also play a role in the effect of psychedelics on these brain processes.

2.4 Risks of psychedelics There are

risks associated with the use of psychedelics. In the short term, psychedelics can induce effects such as dizziness, nausea and feelings of fear, confusion, paranoia or panic.19 These side effects are often transient, but when these effects occur in the absence of competent supervision, there is a risk that people will put themselves in unsafe situations. bring situations. With good guidance and preparation, unsafe situations can be avoided and people can usually be reassured. However, even in the presence of good guidance, people can have intense or negative experiences and become emotionally and psychologically disrupted. A recent review study shows that this does not occur often, but it also appears that these effects are not recorded consistently and that it is not always clear whether increased anxiety or suicidal thoughts or behavior were directly related to TTP.20 Undesirable effects on the longer term have so far been insufficiently investigated systematically.

Another risk is the occurrence of serotonin syndrome, a poisoning due to excessive amounts of serotonin that occurs when drugs that increase serotonin levels, such as MDMA and selective serotonin reuptake inhibitors (SSRIs), are combined with drugs that inhibit the breakdown of serotonin , such as MAO inhibitors.21 Thorough screening and proper preparation can prevent psychedelics from being combined with substances with MAO activity, and the risk of serotonin syndrome in a treatment setting is very small. Other potentially risky drug interactions can also be prevented through thorough screening.

It is still unclear whether psychedelics can be safely used by people who have difficulty letting go of control, such as people with severe personality disorders, and there is a risk that psychedelics can induce such episodes in people with a susceptibility to psychosis or mania. These possible contraindications for TTP are further explained in chapter 3.6 of this report. Finally, classical psychedelics do not seem to induce dependence.22 17

This may be different with repeated use of ketamine, which is potentially addictive, and MDMA, but the risk of this occurring in the context of TTP seems to be limited for the time being. 23,24 However, this risk, like other potential risks, should be closely monitored in follow-up studies.

2.5 In summary: treatments with psychedelics The use of psychedelics in psychiatry gives a completely new meaning to the combination of talk therapy and pharmacological treatment. The subjective experience induced by psychedelics is central to the treatment, for example by serving as a catalyst for a stalled therapeutic process and providing new information that can be addressed during further treatment. Psychedelics can also help break through rigid thinking and behavior patterns and stimulate psychological flexibility, so that it becomes possible to develop a different perspective and new habits. In addition to this strong interaction with psychotherapeutic interventions, psychedelics also have direct beneficial effects on the brain, stimulating neuroplasticity and normalizing various brain functions, among other things. With (therapeutic) use of psychedelics, undesirable effects and side effects can occur. With good guidance, these risks can be limited, but never completely excluded.

The following chapter describes which patients and which psychiatric disorders are eligible for TTP, and for which patients TTP does not appear to be a suitable treatment option.
An overview is also given of the available clinical research on TTP for these disorders.

Case 3: Experimenting with psychedelics helps reduce chronic cluster headaches

Menno Boerema is a 30-year-old man who has been suffering from cluster headaches since he was 22 years old. He gets six to eight bouts of severe, unbearable headaches every day, often every two hours, both during the day and at night. High doses of strong espressos, pure oxygen, or sumatriptan injections relieved his pain somewhat, but failed to prevent or reduce the attacks. As a result, he hardly slept and was very limited in his social life and work productivity. He was unable to maintain romantic relationships or friendships due to the pain attacks. Paid work was not possible, so he was completely dependent on benefits at a young age. He became isolated and felt increasingly lonely and desperate. Fearing the next attack, he lived in a constant state of stress and panic. Not much later he was diagnosed with social anxiety disorder and PTSD.
Menno had lost all prospect of improvement and attempted suicide out of desperation.

He finally got the idea to try psilocybin through the website Clusterbusters.org. In a smart shop he bought psilocybin-containing truffles, which he took alone at home. After a difficult psychedelic experience, he was pain free for the first time in years for a few days. He experienced that as nothing short of a miracle. Unfortunately, the pain returned after a few days, but after months of experimenting with different doses and means, Menno managed to find a psychedelic mixture that allows him to function (somewhat) and minimize the pain. He has never received such information from practitioners. Besides, they couldn't prescribe him psilocybin, LSD or DMT. Menno now advises fellow sufferers on obtaining and preparing these resources, which are largely not available through legal channels.

3 In which conditions can psychedelics make a difference?

With the current state of science, the following conditions are most likely to be treated for TTP: depression, post-traumatic stress disorder, substance-related disorders (addictions), neuropathic pain and cluster headache. These are relatively common disorders for which there are now strong indications of a beneficial effect. In addition, a significant proportion of patients with these disorders show treatment resistance and a chronic course.
TTP can also be effective in other indications, such as eating disorders, compulsive disorders and existential suffering in the presence of an untreatable physical condition. This chapter also discusses some conditions and problems for which TTP has so far been contraindicated, because psychedelics can worsen and/or have serious side effects in these patients.

3.1 Depression

Of all the conditions in which TTP shows promise, most research is devoted to the treatment of depression. The antidepressant effects of ketamine and psilocybin are the best studied, but LSD, ayahuasca and DMT may also play a role in the treatment of depression.

Nearly 1.5 million people in the Netherlands suffer from depression, of which an estimated 500,000 use mental health care.25,26 In approximately 20% of all patients, the depression persists for more than 2 years, and the disease often recurs. Up to 30% of patients with depression are treatment-resistant.7 In other words, there are 150,000 patients with depression in the Netherlands for whom regular therapies do not provide sufficient improvement. People with depression often suffer from persistent negative thought patterns such as prolonged fixation on negative emotions and thoughts, and persistent feelings of worthlessness and hopelessness. The condition has profound effects on physical health and quality of life and is a major cause of suicidality. Patients with depression have an increased risk of dying by suicide.27 In addition, depression causes serious limitations in social and personal functioning. It is the largest cause of absenteeism and disability in the Netherlands.28 In 2019, healthcare expenditure for depression in the Netherlands is estimated to be over 1 billion euros.29 The indirect costs of absenteeism and reduced productivity make the total social costs many times greater.

Depending on the severity of the condition, the treatment of depression consists of psychoeducation, psychotherapy or pharmacological treatment with antidepressants. When multiple drug and psychotherapeutic treatments have insufficient effect, more drastic treatments such as electroconvulsive therapy (ECT) can be used.

TTP in the treatment of depression

Ketamine was introduced to anesthesiology in the 1970s. Soon it was also investigated whether this dissociative agent can contribute to the treatment of psychiatric disorders. Ketamine consists of a mixture of levorotatory S-ketamine (esketamine) and dextrorotary R-ketamine (arketamine). Research mainly focuses on esketamine or the mixture of both forms. Meta-analyses and review studies show that ketamine can have a rapid and robust beneficial effect on both depressive symptoms and suicidality in patients with (treatment-resistant) depression. The beneficial effect, however, only lasts for a limited time. 30 A maintenance treatment in which ketamine is continued over a number longer period of time seems to be able to of days, up to a week. administered regularly over a prolong the therapeutic effect.31 As far as is known, the side effects of maintenance treatment appear to be mild and transient.
Cognitive problems and dependence are rarely observed, and kidney and liver damage also seem to be uncommon.31 This is different for non-medical users of ketamine, who are probably more likely to use higher doses than the dose of esketamine that patients receive. Urologists have recently expressed concern about the increasing number of young bladder patients as a result of long-term non-medical use of ketamine.32 This emphasizes the importance of research into side effects of maintenance treatment. Based on several large-scale studies, an esketamine nasal spray under the brand name Spravato® has now been registered as a medicine for the treatment of treatment-resistant depression.33

Psilocybin also seems to play a role in the treatment of depression. The US Food and Drug Administration (FDA) has awarded so-called *'breakthrough therapy' status* to psilocybin for the treatment of (treatment-resistant) depression.
This recognizes that treatment with psilocybin appears to offer a meaningful advantage over existing treatment options and supports manufacturers in accelerated clinical research and eventual market approval. Four studies have found evidence for a fast-acting antidepressant effect of psilocybin in combination with therapeutic support. In some patients, this effect lasts for up to several months. 34–37 An important caveat to these studies is that they were conducted with a small number of patients and that no placebo control group was used. In the past two years, methodologically stronger studies have been published, which also show that psilocybin has a significant antidepressant effect that lasts at least several weeks. 38.39

The effects of other psychedelics on depression are less well researched, but seem to point in the same direction as psilocybin and ketamine. Therapeutic applications of LSD40,41 ayahuasca42 , or 5-Meo-DMT43,44 also appear to be able to rapidly and significantly reduce symptoms of depression. However, research into the therapeutic use of these substances to treat depression is still in its early stages. Methodological limitations such as small group sizes, ineffective blinding, the lack of control groups or absence of long-term effects mean that firm conclusions cannot be drawn from the currently available data.

3.2 Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) can occur after someone has been the victim of a shocking event or very drastic situation, such as exposure to imminent death, serious injury or (sexual) violence, and has not been able to process this event sufficiently.
The risk of PTSD is greater in some professions, for example if you work for the police, defense, fire brigade or in the hospital. Some people have an increased vulnerability to PTSD, for example due to an unsafe childhood (neglect, abuse, abuse). In the Netherlands, more than 400,000 people suffer from PTSD, of which about 90,000 are being treated by mental health care.45 People with PTSD experience severe suffering from unwanted re-experiences, bad dreams, avoidance of thoughts or feelings that recall the trauma, negative changes in mood and emotional flattening and continued wakefulness and irritability. PTSD often coexists with one or more other disorders; it is estimated that one third to half of people with PTSD also have depression or problems with alcohol or drug use.46 In addition, there may be complex PTSD, in which patients also experience severe dissociative symptoms or personality problems. The National Health Care Institute has calculated that the healthcare costs for people with PTSD amount to 11,000 euros per year.45

The treatment of choice for PTSD consists of psychoeducation and trauma-focused psychotherapies, such as cognitive behavioral therapy, EMDR or exposure therapy, in which patients are repeatedly exposed to a traumatic stimulus. The aim of the treatment is to start processing and to regain balance as a person. Two drugs are registered for the treatment of PTSD, both of which show limited efficacy.47 Although research shows that trauma-focused therapies are effective, PTSD is a chronic disorder for a significant proportion of patients, even after multiple interventions.47

TTP in the treatment of PTSD

Research into TTP in the treatment of PTSD focuses mainly on the therapeutic application of MDMA. Because MDMA creates space to allow intense emotions and memories to enter and it can make people look at themselves with more empathy, this drug seems extremely suitable as a catalyst in the psychotherapeutic treatment of PTSD. Based on the promising research results, the FDA awarded *'breakthrough therapy status'* in 2017 to therapeutic applications of MDMA for the treatment of PTSD.
A pooled analysis of six small phase II studies showed that patients who received MDMA showed greater reductions in PTSD symptoms than placebo groups who received the same psychotherapy.48 After two treatment sessions, more than half of people in the

MDMA groups no longer meet the criteria for a PTSD diagnosis. In the control group this was about 20%. Following the success of these phase II studies, the first phase III study will be completed in 2021 in a large group of PTSD patients.49 Three sessions of MDMA therapy proved effective in the treatment of PTSD: 67% of the participants who received MDMA, did not meet the criteria for PTSD two months later, compared to 32% in the group receiving regular psychotherapy. The second phase III has recently been submitted to the FDA; at the time of writing, the results had not yet been published.

Based on a number of small-scale randomized studies, ketamine seems to have a rapid and beneficial effect on PTSD symptoms.50 The effect of ketamine lasts less than that of MDMA therapy, but can be prolonged by repeated administration and by combination with a mindfulness-based trauma treatment. However, the methodological quality of these studies is limited. There is less evidence for the effectiveness of other psychedelics in the treatment of PTSD51 .

3.3 Substance-Related and Addiction Disorders The so-called substance use disorders (the DSM-5 term for 'addiction') are chronic disorders with a strongly recurrent character. They are characterized by a strong desire for and regular use of a substance (such as alcohol, cocaine, tobacco, opiates or other substances) and having withdrawal symptoms when not using. In the Netherlands, more than 190,000 people experience problems with the use of alcohol or other substances, especially young adults.52 People who suffer from a substance-related disorder often experience social and interpersonal problems and function worse in various areas, such as fulfilling obligations at school and work and functioning as a partner or parent. In addition, these disorders are associated with social problems such as domestic violence, nuisance, crime and traffic accidents.53 Excessive alcohol consumption also causes disorders such as cirrhosis of the liver, inflammation of the pancreas, Korsakoff's syndrome and leads to an increased risk of cancer.54 Other substance-related disorders are, depending on the drug in question, associated with, among other things, heart problems, fatigue, weight loss or overdoses. Substance-related disorders account for a significant proportion of all years of life lost to psychiatric disorders worldwide.55 Alcohol or other substance use disorders often co-occur with other psychiatric problems such as anxiety disorders, depression and PTSD. For example, a quarter of people with depression also have a substance use disorder.56

In the Netherlands, more than 60,000 people are being treated in mental health care for problems resulting from alcohol or drug use. The healthcare costs for this group amount to more than 1 billion euros annually.56 The total social costs of alcohol consumption are many times this.57 Treatment of substance-related disorders is complex and mainly takes place through various forms of psychotherapy, but the relapse rates are high. Depending on the type of therapy, 40 to 80% of patients relapse into substance use disorder after one year. There is no convincing pharmacological treatment for many substance-related disorders.58

TTP in the treatment of substance-related disorders Research into TTP for the treatment of substance-related disorders dates back to the 1950s and 1960s, as well as in recent years. Older and more recent studies have been summarized in two review studies.10,59 These have shown that various psychedelics have a beneficial therapeutic effect on the treatment of disorders in the use of alcohol, opioids, cocaine and tobacco, among others. Psychedelics improve patient motivation and adherence, reduce substance use and increase the duration of abstinence. Moreover, the therapeutic effect of single or short treatment with psychedelics seems to last for a long time (3-24 months).10

Ketamine also appears to be effective in alcohol use disorders, withdrawal in opiate dependence and in reducing cocaine cravings. Psilocybin may be effective for alcohol and tobacco use disorders. Ibogaine shows promise for problem opioid and cocaine use, but there are concerns about safety: administration of the drug can lead to serious cardiac arrhythmias, which have even led to death in a non-medical context.60 The results for the use of LSD, DMT, mescaline and MDMA in substance use disorders

are not yet convincing, partly due to limitations in the methodological quality of the (often old) studies.59 They were often carried out with small groups of patients, it is not always clear whether the intended blinding (also when using active placebos) is effective and objective outcome measures are sometimes missing. In addition, there may be publication bias and negative results may be underrepresented. The authors of these review studies emphasize that the combination of psychedelics and therapy in particular appears to be effective and that the effect of psychedelics without a therapeutic framework is less strong. In some studies, psychedelics seem to have a rapid and long-lasting beneficial effect even at low to medium doses. However, other studies suggest that a higher dosage, which induces a peak experience, is necessary to achieve the desired effect. For ketamine, too, it is not yet clear to what extent combination with psychotherapy is necessary for optimal efficacy. Further research with different doses will have to show which dose is optimal for each agent to achieve the desired therapeutic effect.

3.4 Neuropathic pain and cluster headache Patients with neuropathic pain (also known as nerve pain or neuralgia) experience chronic pain caused by damage to nerve cells. These include phantom pain, pain caused by cancer, neuropathy in diabetes, complex regional pain syndrome (CRPS) and facial pain. For the entire population, the annual prevalence of pain with a neuropathic character is estimated to be between 6.9-10%.61 There are several drugs for the treatment of neuropathic pain, but the response to medication is often limited and side effects almost always occur. In addition, the risk of dependence on strong analgesic medication has proven to be considerable. The role of pharmacotherapy in treatment is therefore limited. The emphasis is therefore on psychotherapeutic treatment.62 Little is known about the healthcare costs and disease burden of neuropathic pain, partly because large-scale epidemiological studies often fail to distinguish between chronic pain due to back and neck complaints. In the United States, the total health costs of patients with neuropathic pain disorders are three times higher than those of peers without these disorders.63

People with cluster headaches experience attacks of intense, stabbing pain around the eyes or throughout the rest of the head, which can last up to three hours. The pain is often so severe that people cannot sit still and experience problems in their daily functioning. Cluster headaches occur in 1 in 1400 people, an estimated 12,500 people in the Netherlands.64 Although the headache attacks stop in many patients after a few weeks or months, ten to fifteen percent of patients suffer from chronic cluster headaches. In them, attacks occur almost daily, without disease-free periods. Because the attacks also occur at night, these patients have severe fatigue and cognitive problems in addition to pain. This combination of symptoms drives patients to despair and sometimes even suicidality.64,65 There are medicines that can reduce or prevent the pain attacks. Unfortunately, these often have serious side effects and can take weeks to achieve a therapeutic effect. Moreover, these drugs are not effective for everyone.66

TTP in the treatment of neuropathic pain and cluster headache

Research on TTP for the treatment of pain disorders is in its early stages.
A few case reports report beneficial effects of psilocybin and ketamine, but larger clinical studies on the efficacy of these agents are still lacking. Castellanos *et al.* (2020) have summarized the existing literature in a review article: some publications from the 1960s report favorable results of an LSD session in the treatment of phantom limb pain and cancer pain.67 These studies showed that LSD not only had a similar or better effect than other analgesics, but that this analgesic effect lasted up to three weeks after treatment. More recent retrospective questionnaire research in patients with cluster headaches suggests that the use of LSD and psilocybin is associated with a reduction in the severity and frequency of pain attacks.
A recent qualitative review of posts on an online forum on psychedelic self-medication shows that psychedelics are effective in reducing the frequency and severity of cluster headache attacks.67

A series of case reports have described the treatment of cluster headaches with a non-psychedelic form of LSD (BOL-148).68 Three doses of BOL-148 administered over ten days resulted in a significant and long-lasting reduction in the frequency and severity of attacks

in four out of five patients. Because BOL-148 has no psychedelic effects, this may indicate that the psychedelic effects of LSD and psilocybin may not be necessary for their therapeutic effect in cluster headaches.

The analgesic effects of ketamine are well documented. A literature review of a total of 36 studies with 685 patients analyzed the effect of different modes of administration of ketamine in patients with chronic or neuropathic pain.69 In these studies, ketamine was administered for an average of between 20 and 80 days, and appeared to be effective in the majority of the studies described. to reduce pain, even at low doses. Additional beneficial effects on depression or anxiety were also observed in some of these studies. However, six studies into intravenous administration of ketamine showed no reduction in pain symptoms.69 In addition, some studies showed that patients with chronic pain eventually needed a higher dose to achieve the same analgesic effect. An observational pilot study in six people with chronic migraine found that a metabolite of ketamine had an analgesic effect up to a week after administration.70 A case report of a patient with terminal cancer also states that repeated low doses of ketamine reduced the severity of pain and also contributed to to reduced use of opiates.71

3.5 Other possible indications

The effect of TTP has also been investigated for eating disorders, compulsive disorders and existential suffering. However, this research is in its early stages and the *evidence base* for the efficacy of TTP in these disorders is still small. However, (pilot) studies are already underway into TTP for these indications. These disorders are discussed here because there is a serious possibility that TTP may also play a significant role in these disorders in the future.

Eating disorders

In the Netherlands, nearly 200,000 people suffer from eating disorders such as anorexia nervosa, bulimia nervosa or binge eating disorder.72 In addition to physical complaints such as weight gain or loss, low blood pressure, cardiac arrhythmias and fatigue, many people experience feelings of shame and guilt and experience problems in their social or professional life.73
Eating disorders lead to a significant loss of quality of life and place a heavy burden on those close to them. Anorexia nervosa is the most fatal of all psychiatric disorders. One in five patients dies by suicide, somatic complications such as heart disorders or infections, and lack of nutrition are other important causes of death.74,75 Psychiatric comorbidity is common: more than half to almost 100% of the adults with an eating disorder also experience depression, substance abuse, suicidality or PTSD.76

With psychotherapy and other treatments, about half of patients can make a full recovery. Unfortunately, a significant proportion of people with an eating disorder do not recover sufficiently after treatment according to current guidelines, and chronicity is common. Given the regular occurrence of additional psychiatric disorders (comorbidities), antidepressants or mood stabilizers are often used in the treatment of eating disorders.
The antidepressant fluoxetine (Prozac) is used to treat bulimia nervosa, but no approved medications are available for anorexia nervosa. The annual health costs of people with eating disorders are 48% higher than the general population, and 3.3 million healthy life years are lost worldwide each year due to eating disorders.74

Compulsive disorders

Obsessive-compulsive disorder (OCD) affects at least 100,000 people in the Netherlands. OCD is characterized by disruptive obsessions and compulsive actions. The anxiety and fear created by obsessive thoughts can only be temporarily relieved by performing a compulsive act. Patients are severely limited in their daily functioning due to their disorder, can no longer concentrate on work, no longer have time for friends or family and are ashamed of their complaints. OCD often co-occurs with depression and/or an anxiety disorder. Cognitive behavioral therapy and treatment with medication can lead to improvement in 50-70% of patients. At least 10% of patients have very severe symptoms that cannot be treated.77

Existential suffering in the case of untreatable physical

illness The confrontation with imminent death in the case of an untreatable life-threatening illness such as cancer leads many patients to a range of palpable emotions and existential questions. Some of the patients with a terminal diagnosis develop psychiatric complaints such as depression, anxiety, demoralization, despair or existential distress.78,79 This is also referred to as existential suffering. Existential suffering has profound consequences on a physical, emotional, mental, social and spiritual level. Patients often lose meaning and dignity and experience hopelessness, suicidality, a reduced quality of life and well-being and fear of death.80 Existential suffering makes it difficult to deal with the disease as well as to conclude the last phase of life in a meaningful and dignified manner. It is therefore often poignant for relatives and caregivers.

Existential suffering is not a narrowly defined diagnosis category. There is a strong overlap in symptoms with anxiety, depression and adjustment disorders.81 Depending on the operationalization of the concept, existential suffering occurs in 3 to 29 percent of people with a terminal illness.82

TTP in the treatment of eating disorders, compulsive disorders and existential suffering

Eating disorders

In two qualitative studies, people with eating disorders were interviewed about their experiences with ayahuasca ceremonies.83,84 Recurring themes were the rapid reduction of thoughts and symptoms related to their disorder. People also mentioned that the experience contributed to the processing of painful emotions and memories and that they gained deeper insight into the underlying cause of their eating disorder, as a result of which they feel more self-acceptance and self-love after the ayahuasca ceremony.83 Changes in self-image were also experienced, and that symptoms of eating disorders improved or disappeared completely.84 In a randomized study of 90 people with severe PTSD, it was found that the influence of MDMA-assisted therapy (as opposed to placebo) led to a significant reduction in eating disorder symptoms.85

Obsessive-

compulsive disorders Two small uncontrolled studies and one small *randomized control trials* (RCTs) have been conducted on the treatment of patients with OCD with ketamine. The results of the two uncontrolled studies are mixed; the first found no effect of ketamine, while a second study saw a response in 5 of 8 patients when ketamine treatment was combined with ten therapy sessions86,87 . In the first placebo-controlled RCT with ketamine, there was a significant reduction in OCD symptoms in the ketamine group and 50% of the patients responded one week after the ketamine injection, while none of the patients responded in the placebo condition was.88 One crossover study looked at the effect of psilocybin on OCD. In all nine patients, a reduction in OCD symptoms was seen after administration of psilocybin (23-100%), which persisted at least up to 24 hours after administration.89

Existential

suffering The first study of LSD in critically ill patients was conducted in 1964 and focused primarily on pain management. After LSD treatment, patients not only experienced less pain, but also had more open and positive attitudes towards their disease.90 In follow-up research on patients with terminal cancer, it was found that 89% of the participants had gained 'valuable insights'. Patients also experienced an improved mood and a more positive attitude to life after the treatment. In addition, they were less concerned about their illness and death.91,92 Subsequent studies with LSD and other psychedelics showed significant improvements in anxiety, depression and social isolation.93,94 Some patients experienced side effects such as nausea during the session , vomiting, headache, tremors and difficulty breathing. The almost twelve-hour LSD sessions in particular were experienced as very tiring.95 Three recent RCTs into psilocybin or LSD were conducted in patients with existential suffering from advanced cancer.96,97 After TTP, anxiety and depressive symptoms decreased. Participants reported improved social interactions, new insights into how their illness affects their lives, and a more positive attitude towards their limited life expectancy. In qualitative studies, patients appeared to have had difficult, but often also transformative experiences. Afterwards they experienced less fear of the

dead and spent more time on things that were valuable to them, such as meaningful contact with loved ones.98

3.6 Contraindications for TTP TTP is not

suitable for all people with a psychiatric disorder. For example, caution is advised in patients with an increased risk of psychosis or mania, in people with a diagnosis or (family) history of schizophrenia spectrum disorder (SSD), bipolar disorder (BD), or depression with psychotic features. They run an increased risk of disruption when using psychedelics. The risk of this seems small in healthy people.99 The overwhelming nature of the psychedelic
experience can be experienced (very) negatively by people who have difficulty surrendering to it. Extra caution is therefore necessary in patients for whom loss of control causes great anxiety and distress, for example as a result of traumatic experiences and affective neglect early in life. This may be the case in patients with severe (borderline) personality problems.

A third group of patients in whom TTP may be problematic are people who are less able to express feelings in words, for example due to a low level of education and/or low intelligence. These features are frequently present in patients with various psychiatric disorders. This group of patients requires extra attention in the supervision.
Further research will have to show which specific characteristics constitute a contraindication for TTP.

3.7 In summary: for which conditions can psychedelics make a difference?

In this chapter, eight psychiatric or neurological disorders are described for which research indicates a beneficial effect of TTP. These are disorders with a significant impact on quality of life, with a large unmet demand for care due to therapy resistance and suboptimal treatment outcomes. As a result, there is a high level of suffering for patients and their environment. For a growing number of indications, the use of TTP is supported by the development of an *evidence base* and larger-scale, randomized and placebo-controlled studies have been or are being conducted. This includes depression, PTSD, substance use disorders, and (to some extent) existential suffering. For neuropathic pain and cluster headache, eating and obsessive-compulsive disorders the evidence is less strong and large-scale RCTs have yet to take place. However, all indications described here have in common that, despite the limited quality of the available research, TTP is so promising that further research is warranted.

Before TTP can play a significant role in the treatment of the indications discussed above, a number of important clinical-scientific and economic issues still need to be answered. In addition, research into and the possible implementation of TTP raises questions about financing, legislation and regulations and training of practitioners. This report therefore now focuses on the Problem Outline, in which the most important knowledge gaps and points for attention regarding TTP are identified and described.

Case 4: Psilocybin session enhances feelings of loneliness and abandonment

Claartje is a young woman of 25 who has been struggling with depression since childhood. She also suffers from various other psychological problems, including anxiety. Suspects are expressed of an autism spectrum disorder and/or attention deficit disorder, but a clear diagnosis in this area is not made. Due to her various complaints, Claartje is unable to find a treatment offer within the mental health care that suits her.

Claartje is eligible for a psilocybin study for people with a treatment-resistant major depressive episode. After the preparation sessions, which she experiences positively, she receives a high dose of psilocybin. She experiences this session as incredibly intense and overwhelming. She describes: “I was a baby bird that fell out of the nest, my wing broken, alone on the ground. That was me, I was so incredibly vulnerable at that moment. I couldn't save myself, I couldn't do it alone. I was that little bird, but I was also myself and finally I picked up that little bird and held it against myself. I knew I would die if no one helped me. I was incredibly vulnerable, someone has to help you and take care of you.”

The feelings of loneliness and deep sadness dominate the psychedelic session. Claartje cries almost all the time. In the days following the psilocybin session, she feels worse than before the treatment. The three planned counseling sessions are not enough for Claartje to even start discussing her overwhelming experience of loneliness during the psychedelic session. Her depression scores are deteriorating, and her therapists are trying to get her treatment elsewhere. Nevertheless, she feels as if she has been abandoned (again). She says: “It was as if I had a new trauma, purely from that treatment because I had been so unhappy and so lonely and sad. It had been so intense.”

4 Knowledge gaps and points for attention in the implementation of TTP

What we now know about TTP gives hope for patients with severe treatment-resistant conditions. TTP offers opportunities to significantly improve care for people with high levels of suffering and thus have a major impact on the lives of these patients and their loved ones.
They open the perspective of more cost-effective healthcare for these patients and a reduction of the social and economic damage caused by these disorders. However, we are at the beginning of a development and many questions still need to be answered. In addition to clinical-scientific questions, there are also important legal, societal and organizational challenges that need to be addressed. The tension between the desperation of patients, hopeful media coverage, the risks of psychedelics and the availability of some psychedelics outside healthcare also deserves attention. This chapter describes these diverse knowledge gaps and points of attention that require scientifically substantiated answers and targeted actions.

4.1 Clinical-scientific questions

In the clinical-scientific field, there are still important knowledge gaps in the field of the optimal research methodology, the representativeness of included patients and the optimal implementation and duration of treatments. The answer to these questions is of great importance in order to determine which resources can best be used in which patients, in what way, and for how long, in order to achieve an optimal result.

Insufficient generalizability of results Many of the current studies have been conducted in relatively small groups of patients. Moreover, there is little diversity when it comes to ethnicity, level of education, socio-economic status and other important demographic characteristics. The participants in these studies are often above average highly educated and largely white. An additional problem is that these participants sometimes already had previous experience with psychedelics. Their experiences are therefore not representative of the vast majority of patients, who have no experience whatsoever with psychedelics. Moreover, it is possible that people who did not have a positive experience or, on the contrary, had an unpleasant experience with psychedelics, therefore did not sign up for these studies. Due to these limitations, the question is to what extent the results obtained so far can be generalized to the entire population.

Replication and pooling of data A single study is not sufficient to draw reliable conclusions from research data. A solid *evidence base* is created by pooling data from different studies conducted at different research centers, comparing studies with each other and replicating study findings. This has not yet been done sufficiently in research into psychedelic therapy. It is difficult to pool data and compare research results because studies vary in design. There is an urgent need for a more standardized approach to study design, measurement instruments used and study outcomes, so that results of studies are comparable and can be used more efficiently to answer important overarching research questions.

Outcome measures

When formulating standardized outcome measures, it is important to look at different aspects of symptom reduction and recovery. It must be determined whether the symptoms consistent with a specific diagnosis have been reduced. From the perspective of patients and their families, a broader restorative approach is also very important. This means that we need to look systematically at how patients function, participate and experience their quality of life. In other words, whether the patient can get on with his life and participate to the best of his ability.

Expectations and blinding

The expectations of the patient and researcher about the outcome of an intervention can influence the effect. That is why comparative effectiveness research into (new) interventions is usually carried out double-blind and (placebo) controlled. That means that participants are randomly assigned to a group that receives the active intervention and a group that receives placebo and

that participants, therapists and researchers don't know who gets placebo and who doesn't. Due to the usually clearly noticeable direct effects of psychedelics, it is difficult to achieve successful blinding. It is often clear to both participants and researchers during the session who received the placebo or the active substance. This can affect the study results.
Psychedelic researchers are having a lively discussion about ways to solve or mitigate this problem. For example, supervisors and participants can be systematically asked whether they think that the participant has received the active ingredient or the placebo. Some studies work with an 'active placebo', a substance that does cause some changes in perception or experience, but has no psychedelic effect.

Psychotherapeutic framework As described in Chapter 2, psychedelics are usually used in the context of psychotherapy. Various therapeutic frames of reference are used for this. The choice of a form of therapy is partly determined by the individual needs of the patient, the nature of the psychiatric problem and by the training and frame of reference of the practitioner.
The emphasis of the different psychotherapeutic models differs: for example, cognitive behavioral therapy (CBT) focuses on behavior and persistent thoughts that perpetuate complaints.
A different approach is followed in the insightful therapies, which explore and discuss in a more associative way the underlying themes that are experienced by patients.
Existing models such as *Acceptance & Commitment* therapy (ACT) are in line with these objectives and are already being used as a basis for TTP. In addition, new models are being developed that pay attention to the social, physical, existential and emotional environment of 100 for a patient. However, it has not yet been systematically investigated which form of therapy is best works as a starting point for TTP.

Set and setting There are also questions about the role of non-pharmacological factors (such as music, atmosphere, attitude of the therapist during the sessions) on the outcomes of TTP. Although experts agree that set and setting play a major role in the subjective experience and therapeutic effectiveness of psychedelic drugs, these factors are often only briefly or barely described in the existing scientific literature.101 The quality of research into TTP would benefit from better description and standardization of these non-pharmacological factors during treatment sessions, including patient expectation, physical environment, and patient-practitioner trust. To begin with, it is very important that these variables are described in detail. It would also be interesting to vary these factors, to investigate which set and setting have a beneficial effect on the subjective and objective safety of patients, minimizing short- and long-term risks, and increasing the likelihood of long-term positive outcomes. treatment outcomes. On this point, research into TTP differs from traditional drug research, in which all non-pharmacological factors are kept as equal as possible. In TTP, non-pharmacological factors such as the treatment relationship will also be of decisive importance for the treatment outcomes.

Dosage and Duration of Treatment Approaches to the dosing of psychedelics vary from microdoses (a very small dose with no observable subjective effects) to psycholytic doses (a medium dose that acts as a catalyst for psychological or emotional breakthroughs) and psychedelic doses (a high dose intended to produce mystical or peak experiences). In addition, some psychedelics, such as LSD, psilocybin and MDMA appear to provide therapeutic benefits after just one or a few sessions, and ketamine may be more effective when offered as a longer-term maintenance treatment.31 However, with the exception of ketamine, systematic research into the optimal frequency of treatment did not or hardly occur.
An important objective for research in the coming years is to expand knowledge about the choice of a high or lower dose and optimal treatment frequency.

Systematic reporting of side effects To be able to register psychedelics as medicines and to make a balanced assessment of whether a patient is eligible for TTP, it is important to map out the full spectrum of side effects in addition to the therapeutic benefits. A recent systematic analysis of 44 clinical trials of MDMA and classic psychedelics shows that these drugs are among 29

other (transient) headaches, nausea and anxiety.20 Serious side effects are not commonly reported. Suicidal thoughts and behavior appear to be rare, but they do occur. However, the interpretation of the results from previous research is greatly complicated by the fact that side effects are inconsistently defined and are often not systematically recorded.
The extent and duration of follow-up also differs. Moreover, it is sometimes difficult to distinguish 'side effects' from 'effect' (therapeutically relevant experiences). Experiencing fear within a safe, therapeutic setting can be challenging, but also therapeutically valuable. However, anxiety can also last too long, be stressful and have undesirable consequences, for example if someone does not benefit from the treatment.

Especially now that research into TTP is increasing, including among vulnerable patients, the need for standardized and systematic monitoring of side effects is growing. To better understand the nature of side effects and negative experiences, specialized questionnaires (such as *Challenging Experience Questionnaire,* CEQ) and qualitative research methods can be used. Honest information about the side effects is essential for careful consideration in the context of *shared decision making* (deciding together) and for future therapists and patients to be able to do well.

Long-Term Effects In

the scientific literature on TTP, the long-term efficacy of psychedelic therapy is often cited as one of its greatest therapeutic benefits.102 Unlike existing drugs, the effect of a single TTP treatment could last for weeks to months, which could have significant implications. may affect (among other things) the cost-effectiveness of these treatments. The knowledge on which this assumption is based largely comes from studies in which effects are measured up to a few weeks after treatment.

It is particularly important for patients with chronic, persistent psychiatric problems to determine whether their suffering and functioning actually improve over a longer period of time.
Partly due to the chronic nature of psychiatric disorders and the high rate of relapse after regular treatments, the question is whether a study duration of a few weeks is sufficient to adequately assess long-term efficacy. It is still an open question how long the effects of TTP last, to what extent different types of psychedelics differ from each other, and how often a treatment session should take place to maximize the therapeutic effect.

'Real world evidence'

Longer follow-up requires larger studies with more resources and staff, ideally set up in the mainstream treatment setting. The importance of data from regular patients in clinical practice, or *real world evidence,* is increasingly emphasized. This is also an important question in the approval of new medicines and in phase 4 research, studies that take place after market authorisation. Ultimately, the added value of new treatments should not take shape in a study context, but 'in the real world'. Within Dutch psychiatry, many mental health care institutions already make active use of *Routine Outcome Monitoring* (ROM), or systematic measurement of treatment outcomes in practice. However, these data are currently not sufficiently accessible for research.

Indication and personalized treatment It is still

unknown which resources, which forms of therapy and which degree of intensity are most suitable for the treatment of which disorders in which patients. Based on current research, some drugs appear to be preferable for certain conditions over other psychedelics. For example, MDMA is being researched par excellence for the treatment of PTSD, and ketamine and increasingly psilocybin are the most commonly used drugs in the treatment of treatment-resistant depression. However, this does not in any way exclude the possibility that other psychedelics are also effective for these disorders. This has not yet been sufficiently investigated. In addition, it is necessary to investigate which patients can benefit most from TTP and on the basis of which individual characteristics.
In addition to diagnosis, this also applies to, for example, sensitivity to psychosis, trauma experienced, attachment problems and personality traits. There is therefore still an important knowledge gap in the field of personalized treatment.

Finally, the question arises of what place TTP occupy in the treatment process of an individual patient. At the moment, the emphasis is on patients who have gone through the entire regular treatment process and who respond insufficiently to it. It is clear that they are in the greatest need, and when all else has failed, *off-label* and *compassionate use* applications are more likely. However, it is conceivable that in the long term, TTP could also be an option for some patients at an earlier stage in the course of the disorder or the treatment process, without necessarily having to go through all regular treatment options. It is therefore important to determine over time which patients benefit from TTP, and at which step in their treatment TTP achieves the greatest effect.

4.2 Financial-economic questions

Funding of research

Conducting sound clinical research into innovative therapies generally takes a lot of time and is associated with high costs. The necessary funds are raised by the government and other grant providers, by academic centers (often in kind by funding researchers) and by the business community. For pharmaceuticals and advanced treatments, the pharmaceutical industry is the most important lender, especially in the clinical phase of the development process. The way in which this process is currently proceeding in TTP research is not very efficient and means that it takes a very long time before innovations in healthcare can actually be implemented.

Public funding: in the Netherlands, pilot research and *off-label* treatment have been initiated within a few academic centers and highly specialized healthcare institutions with their own funding, sometimes followed by a research project with public funding (ZonMw). A nationwide study of the effectiveness of *off-label* esketamine compared to electroconvulsive therapy in major depression and a study of ketamine in suicidality is currently underway . Several Dutch centers are also participating in international studies on psilocybin in depression financed by the industry, and a study on the treatment of PTSD with MDMA, financed by the American non-profit organization MAPS. However, the funding opportunities for research into TTP are currently very limited.

Private/ commercial funding: research initiated by market parties also focuses on improving the treatment of disease. In addition, a market party wants to register patents and intellectual property and ultimately create shareholder value with (preferably large-scale) application in healthcare. That standard drug development model does not apply to TTP. For starters, many psychedelics are natural substances that are difficult to patent or synthetic substances such as LSD that have long since expired. It is only possible to obtain a patent through chemical modifications or new routes of administration. A possible solution is that the medicines authority (EMA) grants a company exclusive rights *(data exclusivity)* to the results of clinical research with a drug that is not (or no longer) patented. These regulations are intended to encourage pharmaceutical companies to carry out research into these medicines. After a period of eight years, the collected information must be released so that other companies can develop generic variants. The advantage of this regulation is that it creates an incentive to conduct research into non-patentable resources. A disadvantage may be that other developers cannot carry out research into a promising substance for a number of years.

A more fundamental problem is the fact that the effect of TTP rests only partly on the pharmacological effect of a substance and largely on non-pharmacological factors that cannot be patented (psychotherapy, preparation, set and setting, integration afterwards).
There is also no incentive for companies to pay attention to the longer-term (cost) effectiveness in improving the prognosis of patients. Mutual comparisons between different resources and a more programmatic design of research into TTP are not in the interests of market parties and will therefore not be financed by them.
Several companies are currently researching and developing psychedelics and TTP.
However, the research is fragmentary. Moreover, history has shown that psychiatry is an uncertain therapeutic area for pharmaceutical companies, so that they are reluctant to make large investments.

All in all, obtaining scarce research grants for individual projects is a time-consuming and labour-intensive process with a high risk of rejection. In the current situation, a separate research infrastructure is often set up for each project (such as setting up a consortium, training staff, recruitment, screening, selecting measuring instruments and setting up data management systems), which often disappears after the study has ended because there is no means to maintain it. All this means that the time between formulating one clinically relevant research question and publishing the result is in the order of 8 to 10 years. In addition, a lot of energy is put into the set-up and organization for each study, which is not retained for other projects. A major disadvantage of all this is that there is no programmatic connection with other applications and projects, which means that efforts are not bundled. This means that it can take an extraordinarily long time to answer the minimum knowledge questions required for wider implementation of a potentially highly relevant innovation such as TTP. An important aspect of TTP research and implementation therefore concerns the question of how financing for TTP can be organized. Does this responsibility lie exclusively with governments, (also) with private parties, or should new ways of public-private collaboration be sought within a broader shared research and implementation agenda?

Cost effectiveness and HTA

Economic research and *Health Technology Assessment* (HTA) on TTP have so far been conducted to a limited extent. In light of the rapid development in clinical research into TTP, the cost-effectiveness of these new treatments is becoming increasingly relevant.103 Determining the cost-effectiveness of TTP requires thorough research for each group of patients. After all, both the costs and the potential benefits are large. TTP is associated with significant healthcare costs during the intensive treatment phase. As can be seen from the descriptions in chapter 2, TTP requires a substantial commitment of clinical personnel and availability of treatment rooms.104 However, if TTP fulfills the promises made in previous studies, a structural improvement can be achieved in patients with treatment-resistant conditions, whose healthcare costs are notoriously high. In the longer term, investing in a treatment with psychedelics can therefore yield large savings. The social and economic 'return' can also be great through improved functioning in relationships/families, in social relationships and in the field of labor participation and quality of life. In research into efficiency and cost-effectiveness, it is therefore recommended to look at both the direct benefits within healthcare and the social costs and benefits.103 Ultimately, the National Health Care Institute will need to have sufficient data for any application of psychedelics in a therapeutic context. to decide whether this treatment can be reimbursed as regular treatment (in the 'basic package').

The results of HTA and cost-effectiveness studies are an important factor in this.

Research into cost-effectiveness has not yet been carried out for most forms of TTP. The two exceptions are the treatment of treatment-resistant depression with esketamine nasal spray and MDMA therapy for PTSD.105 It appears that intranasal esketamine treatment in combination with standard care is cost-effective compared to standard care alone, and that the substantial costs of intranasal esketamine treatment outweigh the quality of life which is won by this.
However, the National Institute for Health and Care Excellence (NICE) in the United Kingdom recently rejected the inclusion of the Spravato® nasal spray in the National Health Service (NHS) 'basic package'.106 This rejection is mainly based on the ' clinical uncertainties' in the evidence provided of the efficacy of the drug, which feed through into the economic models and prevent a reliable cost-effectiveness analysis. In addition, NICE argued that the costs of implementation were insufficiently substantiated by the pharmaceutical company.

According to recent cost-effectiveness analyzes based on a phase 3 study in the United States, MDMA treatment of (profound) severe PTSD would yield significant cost savings compared to standard care, as well as health benefits and reduced mortality.107,108 These are patients with severe symptoms , which are not representative of the average patient with PTSD. In the total population, the cost savings from MDMA therapy could therefore be lower. Such analyzes may also be different due to differences between healthcare costs in the Netherlands and the United States.

4.3 Patients: between hype and hope

The favorable results of research into TTP have not only aroused the interest of scientists and clinicians. There is great interest in psychedelics in the press, on social media and in the form of Netflix series and documentaries. The growing social attention may have implications for patient safety and the context in which TTP is given.
After all, psychedelic substances can also be obtained outside a healthcare context, in the Netherlands even partly legally. Certainly as long as there is little or no regular supply of TTP within the healthcare sector, there is a possibility that patients themselves will start experimenting in a context that entails extra risks. The media hype surrounding TTP can also lead to patients having too high expectations of treatment. If a treatment does not have the desired effect in an individual case, the disappointment can be all the greater, especially for patients who have already tried many therapeutic options in vain. The popularity of the subject in the media also means that there will be a lot of attention when unwanted outcomes occur in the mainstream and alternative therapeutic uses of psychedelics. For example, a suicide attempt or suicide after a psychedelic session will quickly be attributed to the substance, whether rightly so or not.
Since there is still social resistance to psychedelics, such publicity can harm research. In short, researchers in this field should be aware of the social context and, where possible, contribute to realistic and fair imaging. An active media policy is an important part of the efforts in this area.

Psychedelic use outside healthcare

Media coverage of TTP is not always balanced and usually not very critical. For example, it is usually not mentioned that these are small-scale studies and risk factors are often disregarded.109 Due to overly positive reporting, patients with treatment-resistant psychiatric conditions who experience a great deal of suffering may be tempted to start experimenting with psychedelics themselves, as shown by below quotes from email messages. However, the use of psychedelics without support or guidance by people with complex psychiatric problems is undesirable. There is a real risk of psychological and/or physical harm.
This also applies to the growing commercial offer of psychedelic therapy by private parties, commercial institutions and individual therapists. This offer is more or less in line with the commercial offer of, for example, ayahuasca rituals for people who do not have psychiatric problems. Commercialization therefore threatens to anticipate evidence-based, safe implementation of TTP in psychiatry.
Incidentally, serious situations have been reported in which patients with a psychiatric disorder developed serious complications when using classical psychedelics in a gray circuit.

'I've been considering experimenting with psilocybin myself for some time, because I've been walking around with a persistent depression for years. Medication has never had sufficient effect with unpleasant side effects. I've been trying to achieve a few things with psychotherapy for years, and while I keep learning from it, it's never really had an effect on my mood'.

"I have suffered from depression since childhood. I take antidepressants, have gone through various therapies, but am now on the [medical center] waiting list again *because the complaints are increasing again. Three years ago I tried a 6-week microdose of psilocybin. I was able to stop taking antidepressants and after four weeks it was like the color came back into my life. After a few years I feel myself falling back into my depression. Can you please help me?'*

"I suffer from PTSD, panic attacks and insomnia. I have had 25 EMDR sessions and cognitive behavioral therapy. Nothing works. I read that MDMA is revolutionary therapy for this problem. I would 'like' to try MDMA or something else but in a safe setting.'

For ketamine, a registered drug, an extensive practice has developed in the United States in which private clinics offer ketamine sessions for a substantial fee. There is also great variation in the degree of care involved in diagnosis, treatment and monitoring in these clinics, which sometimes do not even have a psychiatrist attached.110 Healthcare professionals in the United Kingdom also warn about the high costs of ketamine treatments in private clinics and the lack of supervision on the screening and selection of patients.111

This development is now also taking place in the Netherlands and psychedelic retreats are being offered for high prices. These retreats do not seem to have an explicit therapeutic purpose for the time being, and mainly emphasize meditation and exploration of one's own mind. These retreats are not supervised and it is not always clear whether careful screening is done for indicators of an increased risk of, for example, psychosis or mania, and whether medical support is available when complications arise. Even if such sessions are offered with the best intentions, the lack of laws and regulations regarding the registration of institutions and persons who are allowed to work with TTP leads to a legal gray area in which quality of care is not guaranteed and the risk of abuses and serious incidents is greater is.

4.4 Treatments with non-registered medicines: off-label and compassionate use

In the Netherlands, TTP within regular mental health care is currently only performed in the context of scientific research, with the exception of intranasal esketamine for depression. This means that many patients currently do not have access to TTP. There are two options for prescribing promising, non-registered drugs to patients in distressing situations. These are also referred to as *expanded access* .

Off label

The *off-label* prescription of medicines means that a doctor prescribes a medicine to an *individual patient* that is not registered for the relevant indication (diagnosis, age group, etc.). *Off-label* use is only permitted under clear, defined conditions, formulated by the KNMG and the Zorginstituut Nederland.112,113 In the Netherlands, esketamine is registered as an anesthetic (used for general anesthesia during operations) and as an analgesic (for the treatment of certain types of pain). It is also prescribed *off-label* by some academic centers for patients with severe, intractable depression; in oral or intravenous form. Although an esketamine nasal spray is now available on the Dutch market for this indication, some practitioners prefer the *off-label* application of oral or intravenous ketamine preparations. The nasal spray is disproportionately more expensive and practitioners are concerned about the limited availability of this treatment for patients for whom it could potentially be effective.

Compassionate use

There is a second option for patients for whom alternative treatments no longer exist, who cannot participate in clinical trials and who urgently need treatment. Patients who may benefit from a medicine that has not yet been approved/registered can gain access to it in two ways: firstly for individual patients via 'delivery on doctor's note'.
114 To this end, a prescribing doctor must submit a request to the Health and Youth Care Inspectorate (IGJ), stating the reasons for the desired treatment with an unregistered medicine.

The other option applies to certain patient groups. When it comes to 'compassionate cases' – patients with a serious condition for which there is no alternative medicine on the market – and a medicine could be registered in the future, a medicine manufacturer can submit a request for a compassionate use program (CUP) . Granting permission for this is a national matter. In the Netherlands, the Medicines Evaluation Board (MEB) has the authority to approve such a CUP. Conditions are often attached to this: suspected side effects must be registered through a so-called pharmacovigilance system, and a CUP must not impede the inclusion of patients in ongoing clinical trials. In 2019, the esketamine nasal spray Spravato was briefly approved for people with a treatment-resistant

depression; at the end of 2019, the drug was registered for the treatment of TRD. As far as is known, applications for other psychedelics have not been requested in the Netherlands for individual patients or in the context of a CUP.

Internationally, there are some examples of countries with *expanded access* programs for psychedelics. In **Switzerland,** a select group of experienced psychiatrists are licensed by the Ministry of Health to prescribe LSD, psilocybin or MDMA in the context of CUP and self-use authorization in the context of learning therapy.115 A detailed application must be submitted for each individual patient . Since 2019, patients with severe PTSD in the **United States** and **Israel** are eligible for MDMA-assisted therapy if they are unable to participate in clinical trials.116,117 Participating treatment centers are pre-selected and treatments must follow the appropriate treatment protocol.118 In **Canada,** a a handful of patients with a terminal illness were given permission to be treated with mushrooms containing psilocybin.119 Six months later, permission was also granted to 16 practitioners to use psilocybin themselves as part of their TTP training. In **Australia ,** *licensed* psychiatrists may provide MDMA to patients with PTSD and psilocybin to TRD patients from July 2023.120 Which practitioners are authorized, what qualifications apply and how the quality of the treatment can be guaranteed is still unclear.

Before patients in **the Netherlands** can claim *expanded access,* important questions must be answered and choices must be made. The safety and effectiveness of TTP depends on their embedding in a therapeutic context. Administration should be supervised by TTP-trained healthcare professionals within a multidisciplinary team. Finally, clarity should be provided about reimbursement: there are no existing payment titles for the costs of medication, and there is no guarantee that the treatment hours of therapists will be reimbursed by insurers. An additional challenge is that there are only a limited number of manufacturers that produce psychedelics according to *Good Manufacturing Practice* (GMP; a quality assurance for the production of medicines) guidelines. In addition, it is conceivable that manufacturers are reluctant to supply the products, for fear of the occurrence of complications (which are conceivable in seriously ill patients) that are registered as a side effect and can make it difficult to obtain a marketing authorisation.

4.5 Training and organization of the health care

system Working with patients in an altered state of consciousness requires specific therapeutic skills. With current developments, there will be an increasing need for well-trained clinical specialists. In addition to the need to set up scalable training programs, wider implementation of TTP makes demands on integration in mental health care, accreditation, certification and positioning within the mental health care landscape.

Training of professionals

Since TTP is used for patients with serious disorders, and can bring about major changes in them, these should be offered by BIG-registered professionals, such as psychiatrists, healthcare psychologists, psychotherapists and (psychiatric) nurses. They have the desired experience with serious psychopathology and are bound by clearly defined professional codes. In addition to being 'qualified', they will also have to become 'competent' for these treatments through additional training in TTP.

Although several training courses for TTP have been set up worldwide in recent years, these have not yet been formally recognized and there are no guidelines or quality marks endorsed by the relevant professional groups that a training must meet. Nevertheless, there are several organizations worldwide, such as the Swiss medical association SÄPT and the American non-profit MAPS, that have developed years of knowledge and expertise about the curriculum and entry requirements. Core competencies for TTP practitioners have also been described in detail.121 The practical and theoretical knowledge acquired elsewhere can form a good basis for a thorough training programme. In addition to theoretical knowledge (such as knowledge about mechanisms of action, indications and contraindications, risks, etc.), training courses must also be able to offer practical experience. This includes hands-on experience in counseling people in altered states of consciousness, as well as insights into how these affect the therapeutic relationship and what this requires in terms of attitude and professional boundaries. Due to the small supply of TTP in the Netherlands and abroad

the possibilities for therapists to gain clinical experience in guiding patients are still limited. A third domain of knowledge concerns learning therapy: the possibility to gain personal experience with altered states of consciousness, in order to guide patients more adequately. Exploring this provides an opportunity for future therapists to gain hands-on experience and learn from it under the guidance of experienced therapists. Training and monitoring of therapists are also important conditions for *compassionate use* applications of TTP.

Integration within mental health care Good guarantees of safety and quality can be achieved by working with professionals who work in teams within mental health care institutions. In order to generate sufficient treatment capacity, it is necessary – in addition to the availability of sufficiently trained healthcare personnel – that mental health institutions furnish or adapt treatment rooms to the quality requirements of TTP. With current knowledge, it is clear that they must in any case be stimulus-free, restful treatment rooms, with quickly available emergency medication (in case of incidents) and the possibility of overnight accommodation if necessary. Due to the special nature of the states of consciousness and the importance of the patient-therapist relationship, it is recommended that patients can remain in care with the same institution and/or therapists (for longer periods where necessary) after the session(s).

Recognition of professionals and institutions

The lack of regulations and competence requirements regarding which institutions and professionals are allowed to work with TTP leads to a lack of clarity. To guarantee the quality of care and prevent abuses, patients and care providers benefit from clear professional criteria for the recognition of practitioners and institutions, preferably at both national and European level. Such guidelines can, for example, specify which professional groups are allowed to work with TTP, which requirements training as a TTP therapist must meet, which institutions are allowed to offer TTP, how compliance with professional guidelines is supervised and where patients and therapists can go with complaints or concerns. reports of abuses.

4.6 Legislation and regulations

The importance of a national infrastructure for accreditation and monitoring of institutions and treatment providers has already been outlined above. All relevant legislative and regulatory issues must be closely aligned with European and international developments in this area. TTP involves the administration of (largely still prohibited) pharmacologically active substances combined with psychotherapy, which means that many different authorities are responsible for safeguarding the legal and regulatory frameworks. Some of these challenges are briefly outlined below.

Rapid and careful development of TTP treatments In the United States, psilocybin and MDMA-assisted therapy have been granted *breakthrough therapy* status because of the expected benefit over existing therapies. The European Medicines Agency (EMA) has a similar scheme, PRIME *(priority medicines),* which has not yet been awarded for TTP. These arrangements provide support at an early stage in the development of promising therapies. They aim to accelerate the development and evaluation process, so that treatments reach patients with a high unmet need for better treatments sooner. In the Netherlands, government organizations such as the *Center for Future Affordable Sustainable Therapy Development* (FAST) could support the development of these complex innovative therapies, while taking into account affordability and sustainability, by connecting all parties in the healthcare and regulatory landscape.

The guiding principles in the development of TTP should be that it leads to better treatments, without unnecessary delays and with optimal care and sufficient attention to quality and safety.

Approval, market authorization and reimbursement of TTP Medicines may only be marketed after assessment and approval by a registration authority. In Europe, the European Medicines Agency (EMA) is responsible for the scientific assessment of medicines, in the Netherlands this is the Medicines Evaluation Board (MEB). These authorities are primarily set up to assess the safety, efficacy and quality of *pharmacologically active substances.* However, with TTP the security and

effectiveness of the administered substances are highly dependent on the *context:* careful administration by qualified, skilled healthcare professionals, with due regard for careful set and setting. Since it is precisely the combination of therapy and drugs that is essential for TTP, all conditions and restrictions regarding the safe use of TTP must be established at the time of approval.

The National Health Care Institute (ZIN) and the organization of Health Insurers of the Netherlands (ZN) play an important role in the reimbursement of interventions. ZIN assesses most medicines for inclusion in the basic health insurance package, while psychological treatments are initially assessed by ZN's knowledge center for mental health care. ZN advises the individual health insurers, who can each choose whether or not to adopt this advice. Finally, professional associations play a role in drawing up professional standards: which reserved actions and competence requirements are set for healthcare professionals.

Due to the combination of pharmacotherapy and psychotherapy, several organizations are involved in the process of approval, recognition and reimbursement. This can lead to (apparent) arbitrariness and uncertainty about the way in which health insurers contract institutions and reimburse TTP. A year after the esketamine nasal spray was included in the basic package in the Netherlands, some healthcare professionals sounded the alarm: only a few dozen of the estimated two thousand patients who would qualify for the treatment each year were actually treated.122 Health insurers point to the limited treatment capacity of institutions and are reluctant to contract healthcare providers, which means that national coverage is not guaranteed. In addition, the price of Spravato® may play a role. This example shows that widespread implementation of TTP requires more than solving knowledge gaps.

Legal status of psychedelics

With the exception of ketamine (which falls under the Medicines Act), virtually all psychedelics are on list 1 of the Opium Act.123 Following the main international treaties (such as the 1961 Single Convention or the 1971 Psychotropic Substances Convention of the United nations) psychedelics are classified in *Schedule 1* as having a high risk of abuse and no therapeutic value. This classification is inconsistent with the therapeutic potential of psychedelics and the minimal risk of dependence. The classification of MDMA and other serotonergic psychedelics in *Schedule 1* or List I of the Opium Act also complicates (pre)clinical research. To conduct scientific research into these substances, organizations need an opium exemption. This exemption can be granted by Farmatec (an implementing organization that falls under the Ministry of Health, Welfare and Sport). Organizations must then meet various conditions, including those relating to the preparation, processing, provision and stocking of psychedelics. These make it more complicated and costly to conduct clinical scientific research and produce these drugs. Additional permits are required for import and export.

Affordability and accessibility As the example of Spravato® illustrates, approval and admission to the market do not automatically mean that treatments also become (widely) available or are included in basic insurance. The initial healthcare costs of TTP are relatively high due to the length of treatment sessions and the involvement of multiple practitioners. *Real world data* on the long-term cost-effectiveness of TTP are not yet available. In addition, with other psychedelics it is not inconceivable that pharmaceutical companies charge high prices for patented variants.
Gaining *data exclusivity* can be a barrier to innovation by other companies, such as applications for other disorders. To guarantee affordability and accessibility, the National Health Care Institute (ZIN), health insurers and regulatory authorities must be involved at an early stage. It takes a concerted effort to ensure that treatments that can really help patients become available in a way that is affordable and meets professional quality standards.

4.7 Ethical issues in the treatment room At TTP, there are a number of ethical issues that partly resemble ethical issues in other treatments and are partly unique to this special form of treatment.

A real risk with TTP is that patients become seriously emotionally and psychologically disrupted. A recent review study seems to show that this does not occur often, but also shows that dysregulation is not consistently recorded.20 Moreover, it is certainly not always clear whether increased anxiety or suicidal thoughts or behavior were directly related to TTP. Particularly when patients are not followed for a long time, there is a risk that unpleasant experiences during TTP sessions will worsen rather than improve complaints. In short, TTP has side effects in the short and longer term, somewhat comparable to other radical treatments in healthcare.

Another ethical problem is that the intense psychedelic experience causes some patients to experience a dramatic shift in their worldview or religious beliefs. Such experiences, referred to as 'ontological shock', can on the one hand give rise to therapeutically meaningful growth, but can also cause serious doubts about previously held beliefs or assumptions.16 Ethically, this raises questions about the role and responsibility of the practitioner, and whether such an 'ontological shock' should and can be avoided, or whether it might be a desirable part of the treatment. The nature and intensity of such intense subjective experiences (including mystical, spiritual, or transpersonal experiences, or the loss of a sense of self)14 also raise questions about the ability to properly prepare patients for this and whether *informed consent* – the giving informed consent to participate in a treatment – is possible.124

Finally, the altered state of consciousness makes patients more vulnerable and susceptible to suggestion. As a result, they may be less able to assertively set boundaries and express their own wishes.125 Mutually approved 'therapeutic touch', such as holding someone's hand, can be calming and comforting during a psychedelic session. Some therapists argue that remembering this can even be counterproductive.126 Unfortunately, incidents involving sexually transgressive behavior have also been reported in TTP, as is the case with other care contacts. The specific aspects of a psychedelic session, but also the fact that these treatments were sometimes given by providers without formal training, BIG registration and professional codes, may have contributed to this.127,128 It is clear that it is extremely important to have unambiguous guidelines for this. and to test and enforce them in practice, and to adjust them where necessary. It is also essential that practitioners can be held (and if necessary sanctioned) to their professional professional code.

4.8 Social acceptance While many new medicines are relatively unknown at the time of their introduction to the market, psychedelics have been the subject of social debate for some time. Psychedelics not only have a place in medical treatments, but are also used in recreational, religious or other non-medical settings, and underground (illegal) psychedelic therapies are also offered here and there. The publication of the book *How to* change your mind and the Netflix documentary of the same name by journalist Michael Pollan have caused a huge revival of attention for psychedelics. This enthusiasm is further fueled by *believers:* researchers who believe in this research and are motivated to prove the efficacy of TTP, and scientists who seek out the media after the publication of positive results (without mentioning any caveats or limitations on the interpretation of findings) . This creates an unbalanced picture and leads to exaggerated expectations.

This TTP hype is further fueled by new small pharmaceutical companies that need to raise millions in investments to fund their costly clinical studies. When the first results of an RCT into psilocybin for the treatment of TRD were published in November 2021, they fell short of expectations. The occurrence of some cases of suicidal ideation also caused a huge drop in psychedelic stocks, a crash that has not since recovered. In addition, industry-sponsored studies may create conflicts of interest; sponsored studies are more likely to have significant positive results. 129 So there is a hype with exaggerated expectations in the field of TTP. As has also been seen with other hopeful new forms of therapy and technologies, such a hype often follows a phase of disappointment, after which a more realistic phase sets in. It is important to look beyond the hype by looking closely at which patients can benefit from TTP and how treatment with psychedelics can complement existing forms of therapy as closely as possible.

Incidentally, there are certainly not only proponents of TTP. Psychedelics have been controversial for decades. The intense experiences that arise from the use of these substances and the religious and philosophical questions they sometimes raise can also be experienced as threatening by people who would never use such substances themselves. There are also very different views on psychedelics among professionals. These range from taboo, concern, fear of deterioration of psychiatric well-being or dependence, to indifference, curiosity or adulation.
Some professionals are rightly concerned that the aforementioned hype leads to injudicious use and abuse of psychedelics by vulnerable patients, and are therefore turning away from TTP. Some opponents of TTP worry that the non-medical use of psychedelics will be stimulated by attention to TTP. A salient problem arises in the treatment of police officers, for example in the context of the treatment of PTSD with MDMA. In their daily lives, they are focused on combating the illegal production and sale of this drug, which means that it can be harsh to be self-administered in a treatment context.
Recent questionnaire research in the United States suggests that patients with mental health problems are generally positive about therapy and research with psychedelics. 130,131 Such research among patients has not yet been carried out in the Netherlands. It is clear that good, objective information is of great importance, not only to patients and professionals, but also to the wider public.

Points for attention formulated by stakeholders

Many of the themes discussed in this chapter originate (in part) from the discussions the authors had with various stakeholders (see also the justification at the beginning of this report). All stakeholders were explicitly asked to state what, in their opinion, are the main barriers, main points of criticism and points for attention regarding research into and implementation of TTP in the Netherlands. A wide range of important suggestions and considerations emerge from these conversations. Many see TTP as potentially valuable, but there are also criticisms and concerns. Below is an overview of the points for attention that emerged during these discussions. Here we specifically mention the most important domains in which knowledge gaps, barriers and objections to TTP were identified:

- The **political** context: the subject of psychedelics has evoked mixed reactions for decades. Conservative parties are concerned about the impact of these substances and of drugs in general. Relaxing the tight restrictions on psychedelics is not high on the political agenda for many. It is very important to take these concerns and sensitivities into account in the design of a program (see Chapter 5) and certainly also in communication.

- The **social** context: the attention paid to psychedelics and TTP in the media often focuses on the extremes of exaggerated optimism on the one hand and the risk of incidents on the other. This is not conducive to a balanced assessment of the pros and cons of TTP and can lead to injudicious use by patients who are not (yet) eligible for regular mental health care for this form of treatment. Several interlocutors expressed concern that acceptance of TTP will lead to an increase in the (non-medical) use of psychedelics in society.

- The **scientific** context: the scientific evidence for the effectiveness of many forms of TTP does not yet meet the applicable requirements, partly because very little comparative clinical research has been carried out in large representative groups of patients. This means that the inclusion must be broader than hitherto in the published studies, and that a network of institutions is necessary to realize the ambition. Considerable methodological challenges are associated with such research due to the complexity of TTP.

- The **legal** context: most psychedelics are prohibited under the Opium Act and international agreements. Moreover, there is no certification for practitioners who are allowed to apply TTP. The path of therapy development and final assessment by regulatory authorities is complex and requires timely coordination with various parties.

- The **practical** context: for large-scale research into TTP as well as for possible ones
  There are various practical barriers to its implementation in healthcare practice. The production of psychedelics under conditions is Good Manufacturing Practice current legal status of these substances. Pharmaceutical companies have little incentive to focus on this market, partly because most drugs can no longer be patented. Arrangements that give a company exclusive access to data carry the risk of monopolization. Partly due to the lack of sufficient clinical scientific data and cost-effectiveness studies, regular reimbursement of TTP by health insurers is not yet possible. The training of practitioners is (partly) limited by the fact that there is hardly any opportunity to gain practical experience.

4.9 In summary: knowledge gaps and points for attention

This problem outline describes the most important bottlenecks, knowledge gaps, concerns and issues per domain (clinical-scientific, financial-economic, patient interest, training and care organization, legal, ethical and social). TTP represent a promising innovation in the treatment offer for a variety of psychiatric and neurological disorders, but the quality and quantity of evidence varies widely. In addition to strengthening the scientific *evidence base,* essential clinical, methodological, financial and economic issues must also be answered before TTP can be implemented on a large scale in Dutch mental health care practice.

At the same time, there is a great deal of attention for psychedelics, also outside the medical and scientific world, with an imbalance between the positive image in the media about these substances and the very limited availability of TTP in regular care. As a result, it is conceivable that desperate patients will start experimenting themselves and that non-care professionals will tailor their offer to this target group. Although there are currently no clear indications in this regard, there is a risk that a situation will arise in which patients fall between two stools, in which there is a lack of supervision and quality of care is not guaranteed. If a commercial alternative circuit were to form for TTP, clinical research risks becoming incomplete and implementation is driven by interests other than safety, effectiveness and efficiency.

In order to continue to safeguard the interests of patients and to meet urgent care needs, it is therefore necessary to conduct clinical research into TTP efficiently and without undue delay, while also immediately looking at possibilities for responsible wider implementation. The objections and barriers that have been identified by various stakeholders must be taken into account. A nationwide, large-scale and well-coordinated program can meet this need. In the following chapter, the contours of possible solutions are outlined on the basis of the points mentioned in the problem sketch.

Case 5: Relapse into depression after initial recovery

Mrs. Sanchez (66) has regularly suffered from a long-lasting gloomy mood since a young age. Eight years ago she suffered a deep depression for the first time, which then returned several times. She doesn't feel like anything, becomes anxious in social situations, hates herself and feels that the world is better off without her. Multiple psychotherapies fail to bring relief and the various antidepressants she has tried have had many side effects, including unexplained aggressiveness, inability to sleep, sweating and a dulled emotional life.

In 2020, Ms. Sanchez is eligible to participate in a double-blind treatment study (RCT) with psilocybin. After a few introductory talks with her therapists, she receives a six-hour session with psilocybin under supervision, supervised by two therapists. In the session she experiences intense loneliness, followed by the feeling of being very connected, with nature and with others. In the days that follow, she is more open to her surroundings, suffers less from negative thoughts and is happier in life.
Ms. Sanchez has two more conversations with the therapists after the session, but then the guidance provided in the study protocol ends. A month after the session, her gloom gradually returns. She misses people around her who really understand her and has difficulty finding meaning in life. Three months later, she feels as bad as before her participation, and feels abandoned by her therapists.
According to her, more intensive psychotherapy shortly after her psilocybin session and longer follow-up contact with therapists could have prevented relapse.

5 Solution directions TTP offer

prospects for better treatment of disorders that are currently accompanied by a great deal of individual suffering, high healthcare costs and serious social and economic consequences. However, to realize this potentially effective innovation, many questions still need to be answered, both clinically and in various other areas. The limited current research efforts in this area are underfunded and fragmented. This chapter therefore outlines the contours of a coherent program of knowledge development aimed at rapid and careful implementation of TTP in Dutch mental health care. An ambitious government research and implementation program could provide an essential impulse for this. Such a program can also be the starting signal for related public-private partnerships with a wide range of parties from healthcare, industry, patients and science.

5.1 A coherent research program for fast, efficient and coordinated knowledge development

Clinical research program The aim of the proposed

research program is to generate generalizable and replicable outcomes that are essential to address the clinical and scientific knowledge gaps identified in Chapter 4. Obtaining this missing evidence base is crucial for broader, responsible implementation of TTP in Dutch highly specialized mental health care.

On the basis of the arguments discussed in chapter 3, such a program can first focus on five groups of indications; depression, post-traumatic stress disorder (PTSD), substance-related disorders, pain disorders, and a group of three promising but still under-researched indications (eating disorders, compulsive disorders, existential suffering). In all cases, these are patients with treatment-resistant disorders.

Such a program will have to be aimed at filling knowledge gaps in the areas of:

- Effectiveness and side effects of specific psychedelics, tailored to the different diagnoses, taking into account methodological limitations of existing research;
- Dosage, dosage form and frequency of administration for an optimal result;
- Optimal (psycho)therapeutic embedding;
- Course (long-term effects, need for continued treatment, possibly longer term side effects);
- Cost effectiveness;
- Predictive factors of treatment outcome of different drugs, looking in particular at individual patient characteristics (what works for whom?) related to the different drugs;
- Collection of additional data required for compiling dossiers on the basis of which the European and Dutch medicines authorities can proceed with registration, as well as for authorization within the Netherlands on the basis of the 'state of research and practice'.

Action plan per diagnosis group A

number of related investigations will have to be designed for each diagnosis, prioritized on the basis of current knowledge (gaps). This means that the studies will differ per diagnosis group and that the choice of research design depends on the primary research question.
For example, the evidence for TTP in the treatment of eating disorders is still at an early stage. The main research questions will primarily be about demonstrating effectiveness and safety in smaller (pilot) and possibly *off-label* or *compassionate use* treatments, to be followed up by clinical trials. In depression, where evidence for the short-term effectiveness of ketamine and psilocybin is now available, larger-scale clinical research can focus more on longer-term aspects, such as the optimal therapeutic approach and good matching between the patient and one of these treatments. In these studies, the methodological limitations of existing research identified in Chapter 4, such as ineffective blinding and homogeneous study populations, must also be taken into account. In addition to pilot studies and RCTs, this is also possible

other research methods are used, such as qualitative research, cohort research, *mixed methods* designs, pre-post studies and *stepped-wedge* designs. For example, research into optimization of the (psycho)therapeutic framework, the influence of non-pharmacological factors, dosage, frequency of treatment and personalization of treatment will not always have to be carried out in an RCT to obtain answers to important questions.

Overarching questions In order to be able to compare studies with each other, it makes sense to use the same measuring instruments, measuring moments and outcome measures everywhere. This applies not only to the primary outcomes per diagnosis, but also to important cross-diagnosis knowledge questions, including the rate of recovery and quality of life, which can be answered by pooling results from studies for the various diagnoses. In such a matrix, all diagnosis-surpassing questions (for example, regarding the form of psychotherapy, dosage, frequency, indication and personalized treatment) can be captured. In addition, such a matrix structure offers the opportunity to look in an innovative way at possible mechanisms of action of TTP, such as psychological changes (eg rigidity, self-insight, acceptance and sense of purpose); changes in physiological or neurobiological parameters and changes in functioning (e.g. quality of life, recovery, social, societal, economic). The same also applies to the registration of side effects, which can be registered in the same way in all studies, using valid instruments. This lays a solid foundation for better information provision to patients and informed clinical considerations about the possible risks and benefits of TTP for both individual patients and specific patient groups.

Data infrastructure

A shared data infrastructure is indispensable for the careful and systematic registration of such data. As described in Chapter 4, the Routine Outcome Monitoring (ROM) infrastructure already present at many institutions can be used to record treatment outcomes. Collected data can be retrieved using new technical possibilities such as *federated learning* . This means that algorithms are used to answer scientific questions from large data sets without exchanging this (privacy-sensitive) data themselves, so that the privacy of patients is guaranteed. A data collection in which study data, long-term effectiveness and side effects are recorded according to FAIR principles132 (findable, accessible, exchangeable and reusable) not only increases the scientific impact, but also improves the translation to clinical practice. In the future, such a data structure can therefore serve as a platform to compare *real-world* data and data from prospective cohort studies of regular treatments with results of short-term and longer-term clinical studies.

Network

A research program such as the above has the greatest chance of success if it is set up in a national collaboration of specialist healthcare institutions and university medical centers (umcs). Such a network encompasses both the clinical expertise in the treatment of patients with the aforementioned diagnoses and the scale required to organize a project of this size. For each diagnosis, a group of several specialized institutions can be formed, consisting of UMCs and specialized (top) mental health departments with a national distribution. Examples of such partnerships include the National Network for Persistent Depression, in which the UMCG, LUMC, Amsterdam UMC, Parnassia and Pro Persona work together. Other examples are academic workplaces, a knowledge infrastructure in which practice, research, policy and education work together, and the Network Psychotrauma Netherlands, a care chain in which care institutions and professional associations exchange knowledge and also build knowledge through joint research. In addition to healthcare and knowledge institutions, it is very important to work together with other relevant stakeholders, such as government agencies, insurers, registration authorities and industrial partners.

Patient involvement and setting up a support and follow-up trajectory

Patient organizations and other stakeholder organizations should play an important role in all phases of setting up and implementing a national TTP research and implementation programme. The perspective and expertise of patients is of great importance when it comes to ethical, legal and social issues, but also when it comes to prioritizing

knowledge questions and thinking along about the design of specific studies and broader implementation. An important aspect is setting up a process for the guidance and aftercare of patients, which should also pay attention to the impact on next of kin. This is important for the broader social embedding, but also when it comes to giving meaning and signaling possible problems, in the short and longer term. Fellow sufferers/experience experts with TTP can play a role in this. Their efforts can also be given a place in the preliminary phase, to prepare and support patients who have not previously experienced a psychedelic session.
Patient advocacy organizations can play an active role in establishing and maintaining such support pathways.

Financing of clinical scientific research and cost-effectiveness research There is a great need for more cohesion and for building a sustainable research infrastructure with regard to TTP research (in the Netherlands, but also internationally) with which important knowledge questions can be addressed more quickly and much more efficiently than is currently the case (see chapter 4.2 for an outline of the current situation). In this way, several knowledge questions can be examined in conjunction and the implementation and monitoring of *real-world* outcomes can also be considered. With financial guarantees for a multi-year (public-private) research program, research protocols can be standardized and the application and assessment of project applications becomes much more efficient. In addition, once set up, such a research infrastructure (screening, measuring instruments, data management systems, trained employees, collaborations between the parties involved) will continue to exist. The knowledge and experience gained will be retained within the organizations that implement the programme.
Funding in the context of public-private partnerships makes it possible to combine both the more pharmacologically oriented research questions of the industry with attention to non-pharmacological factors and aspects of care such as long-term (cost) effectiveness and improving the prognosis and quality of life of patients. patients.

The research and implementation program outlined in this report is complementary to, but does not coincide with, the National Main Affairs Plan; this is aimed at a much broader knowledge and innovation program in the treatment of brain disorders and psychological complaints. The research agenda described above focuses specifically on the treatment of the most treatment-resistant group of patients with TTP. In setting up and developing these initiatives, there is as much cooperation as possible, including with initiatives such as Hoofdzaken, in order to achieve maximum synergy.
For example, the research infrastructure described here can fulfill an extremely useful role for projects from the Main Affairs programme, and the aim is also to look for opportunities for standardization when elaborating the proposed research programme. for example, of outcome measurements across both programs.

It is essential, both for market approval and for the future reimbursement of TTP by health insurers, that hard figures become available with which costs, savings and health benefits can be realistically estimated.103 Research into economic considerations has yet to be carried out for many forms of TTP. Marseille *et al.* (2022) describe in an economic research agenda for psychedelics research various types of economic research that are also relevant in the Dutch context in policy-making and implementation of TTP.103 Based on cost-effectiveness analysis (KEA) and cost-benefit analyzes (KBA), the costs of TTP are weighed against the benefits, such as changes in quality of life, health care expenditure, improved labor force participation or reduced crime. In addition to KEA and CBA, which mainly provide insight into the effectiveness of an intervention, Budget Impact Analysis (BIA) can be performed to map out the total impact of implementing TTP.133 BIA can be used to gain insight into the expected shifts in required material and personnel resources and in the financial consequences of implementing TTP. A BIA also outlines at a national level the impact of the implementation of TTP on public health and the economy.103

Expanded access

As described, there are many patients in the Netherlands with a treatment-resistant psychiatric disorder for whom treatment options have been exhausted. For compassionate cases that are not eligible for participation in clinical trials, *off-label* treatment and

compassionate use programs in principle make it possible to prescribe promising, unregistered drugs. In order to make TTP possible via *expanded access* programs despite previously described obstacles, there is a need for:

- The short-term development of training opportunities for mental health professionals, accreditation, treatment guidelines as described under 4.5 'training and organization of the health care system';
- Willingness of mental health institutions, with already trained care providers, to free up capacity for the treatment of such harrowing cases;
- Removing ambiguities about the reimbursement of TTP: drawing up payment documents and guaranteeing reimbursement of treatment hours by health insurers;
- Collaboration with marketing authorization holders or manufacturers who are able and willing to provide medication to make available for this purpose; In
- special cases, production and distribution according to GMP guidelines can also involve other parties (such as pharmacy A15, a partnership of three UMCs with the aim of nationally supplying commercially unavailable but rationally necessary medicines). For example, the Office for Medicinal Cannabis could serve as an example.

Training and organization of the

healthcare system A crucial factor in enabling large-scale research, *expanded access* and eventual implementation of TTP is timely investment in the development of high-quality training, treatment protocols, accreditation and guidelines for professional conduct. Safe and careful implementation of TTP requires participating institutions and staff to be involved at an early stage. The experiences gained from participation in clinical research can be used in the design of *expanded access* treatments and eventual implementation of TTP. Findings from clinical research and practical experience can be used to train and supervise healthcare professionals. Due to short lines between research and training, the results of research projects can be quickly implemented in practice. A specialized and accredited training offer for all professionals involved in TTP must be developed as quickly as possible. It is essential to make use of the knowledge and experience that has already been gained by practitioners involved in (international) *compassionate use* programs and clinical studies at Dutch institutions. Comparable professional associations, training courses and treatment protocols in countries such as Switzerland, the United States or Canada can also be taken as a guideline.

To enable the training of healthcare professionals, there is a specific need for:

- Detailed description of required competencies and professional groups that work with TTP allowed to work
- Development of training programs and certification
- Setting up a professional association for monitoring training standards and certification
- Formulation of treatment guidelines based on existing treatment protocols
- Formulating quality requirements for furnishing and/or adapting TTP treatment rooms
- Accreditation of institutions and practitioners to work with TTP
- Legislation and regulations at national and European level that make accreditation possible and the removes ambiguities surrounding expanded access

Legal framework and adapted regulations For

registration authorities (EMA and MEB) TTP pose a challenge, because the safety and effectiveness of the treatment must be assessed as a whole, and the treatment consists of more than just the use of the pharmacologically active substance. In a recent publication in Lancet, the EMA underlined that regulating psychotherapy is not easy, and that standardization of the psychotherapeutic framework of TTP can contribute to effective regulation.134 This is therefore a task for a research programme. Conditions for the safe use of TTP must be established at the time of approval: how and by whom resources may be administered and what monitoring requirements there are.

It is therefore wise that the organizations involved enter into dialogue at an early stage, so that the professional groups involved, such as the Dutch Association for Psychiatry (NVvP), consult proactively with registration authorities, the National Health Care Institute and the Dutch health insurers about assessment processes, quality criteria and requirements for monitoring.
That is, *for whom, how, under what circumstances* and *by whom* the drug may be administered.
Existing regulatory instruments may already provide scope for this, for example by explicitly mentioning them in the summary of product characteristics (SPC), the Risk Management Plan (RMP) and the additional risk mitigation measures.134 These may include mandatory agreements on information material , training requirements and controlled access programs.

Support from FAST Since this is a new therapeutic approach, with a potentially large societal impact, it is very important to involve other stakeholders in addition to regulatory authorities such as MEB, EMA and ZIN, in particular professional associations, patient organizations and other interest groups . Support can perhaps be provided by FAST, an expertise center set up by the Ministry of Health, Welfare and Sport with support from Economic Affairs and Climate Policy (EZK) to make the chain of therapy development run more smoothly.
FAST aims to build bridges between different public and private parties and to solve problems related to legislation and regulations and to stimulate expertise in therapy development. A broad view, which also includes economic, HTA and social aspects, can promote that TTP are assessed on their actual merits by the regulatory authorities.

Research into ethical, legal and social implications Partly in view of the different opinions that exist in society and the role of the media in the communication about psychedelics, it is very important to pay special attention to ethical, legal and social aspects, also known as ELSI *(Ethical, Legal, Social Implications).* There is now a national ELSI service desk, which serves as a source of information for these types of issues.135 As discussed in Chapter 4, TTP raises various ethical issues that require further exploration. It concerns the use of substances that are still partly prohibited in a group of patients who are extremely vulnerable and in whom previous therapeutic interventions have failed. The psychedelic setting brings with it special challenges, which can only partly be overcome with the usual frameworks of regulations and guidelines.

It is inherent in the psychedelic experience that boundaries can become blurred. Specific attention should be paid to this within training, certification and supervision. With *informed consent,* the core principle of medical ethics, extra attention should be paid to the fact that it is not easy to sketch an adequate picture of the psychedelic experience for a patient who has never had it. This applies all the more to the inclusion of patients who are low literate, who do not fully master the Dutch language or who have communication limitations.

Targeted quantitative and qualitative research into these aspects by ethicists and other experts can address this. Various groups of stakeholders should be involved (patients, relatives, practitioners, social, religious and political groups, companies, etc.).
Such ethical research and the network of stakeholders that has been built up can then form the basis for a consultation structure that is involved in the development of guidelines, protocols, complaints procedures, incident reporting and information materials.

Chapter 4 described how uncritical communication about the benefits of psychedelics can lead to unrealistic expectations. In combination with the availability of these resources outside of regular care, this leads to potential risks for patients. Because injudicious use of psychedelics by patients and alternative providers cannot be prevented, it is of great importance to limit these risks as much as possible. Clear and nuanced communication about the current scientific knowledge, emphasizing that it concerns means that enhance psychotherapy, where a positive result is not guaranteed and dependent on careful therapeutic embedding, is of great importance. Given the urgency felt by patients and practitioners, it is of course very important to simultaneously focus on developing the evidence required for responsible implementation. A procedure can be initiated for distressing cases that cannot be included in one of the studies to be set up

of *expanded access* by healthcare providers participating in the national network. In this way, these treatments are offered with maximum care, and treatment outcomes can be added to the national *evidence base.*

5.2 Pioneering role of the Netherlands

The Netherlands has the ambition to play a pioneering role in the field of innovative therapy development. The university medical centers and other knowledge institutions in mental and neurological health care are among the world's best in medical research. An increasingly attractive climate is also developing for innovative companies in the biotechnology and pharmaceutical industries. The arrival of the EMA in the Netherlands has further sharpened the ambitions of politicians and the business community in this area.

Against this background, the aforementioned *Center for Future Affordable Sustainable Therapy Development* (FAST) was established and joint initiatives are being developed by the Ministries of Health, Welfare and Sport and Economic Affairs and Climate and the Top Sector Life Sciences & Health. These government initiatives are widely supported by the UMCs and universities, patient and family interest groups, the innovative business community and healthcare institutions, including mental health care. An innovative development such as TTP, which undeniably involves 'unmet medical needs' (FAST), is an excellent theme in which the Netherlands can lead the way. FAST and others are already paying attention in other areas to the kinds of challenges that also play a role in TTP: methodology of clinical scientific research, ethics, legislation and regulations, cooperation with stakeholders, training and embedding in healthcare.

Excellent starting position
The Netherlands has an excellent starting position in the field of TTP. Our GGZ has highly trained professionals who are experts in the field of pharmacotherapy and psychotherapy and are used to offering these forms of therapy in an integrated way in well-recorded care programmes. Outcome data are systematically collected and recorded through *routine outcome monitoring (ROM).* Certainly at the institutional level, there is a solid ICT infrastructure to evaluate progress per patient and to evaluate ROM data at an overall level. Dutch initiatives such as Health-RI136 are working hard to unlock such data for federated analyses. Thanks in part to these efforts, the Netherlands has an infrastructure that is increasingly suitable for multicentre clinical research, including in the field of TTP.

New developments, such as the use of *machine learning* and other AI applications, will also benefit from this infrastructure.

Cores of innovative research into TTP have already emerged in various UMCs, universities and mental health care institutions, which can serve as the basis for a network in which such a research and implementation infrastructure around TTP can land. Contours are beginning to emerge for a consortium of more than 20 institutions. If this set-up succeeds and if the associated infrastructure for research implementation can be financed, the Netherlands can play a pioneering role in the field of TTP, not only by coordinating the most important research questions, but (above all) also by creating the most important frameworks. around implementation. Dutch mental health care, which has been among the global top 5 for many years, can then further strengthen its strong international position in scientific research. The Netherlands will then also become even more attractive for partners from the business community and international organisations.

Social and cultural factors also contribute to the favorable starting position of the Netherlands in the field of TTP. The Netherlands has a rich tradition in the field of medical ethics and research into ethical, legal and social aspects of medical innovations. These important aspects of TTP can thus be well embedded in research and implementation. The Dutch consultation culture makes it easier to involve patients, family members and other relevant parties.

In recent decades, the Netherlands has played a pioneering role in a rational, public health-based approach to psychoactive substances. The Netherlands also led the way in the provision of heroin to people with a treatment-resistant dependence on this drug. Limiting harm *(harm reduction)* is paramount in the policy on substance use. This sober

attitudes to 'drugs', in which policies were based on protecting public health rather than prejudice, have had beneficial effects on public health and have not led to an increase in the number of people with substance dependence.

In short, it would be very valuable not only for Dutch patients, but also for their peers worldwide if the Netherlands takes the lead in this field and forms a global reference point for research, development and implementation of therapeutic applications of psychedelics in healthcare.

International perspective

Psychedelics and their therapeutic applications are a socially and legally complex field, also in the light of international agreements and obligations. Researchers, entrepreneurs, interest groups, practitioners and policymakers in other countries are also involved in this complex matter. A TTP research and implementation program would therefore benefit from close contacts with experts in Europe and beyond. Indeed, the EU institutions and WHO Europe are perfectly placed to develop and lead such efforts and the success rate will depend heavily on proactive action by the EU institutions and Member States before the eventual approval of TTP by the European Medicines Agency (EMA).).

In Australia, psychiatrists can register with the national registration authority TGA for the provision of MDMA and psilocybin. In the United States, an inter-institutional *task force* has now been set up at federal level to monitor and regulate TTP in the coming years. A similar initiative at European level could be instrumental in identifying and jointly solving the complex policy and regulatory issues in a timely manner. After all, it is very important that a wide range of stakeholders are closely involved in the process from the outset. If the Netherlands opts for an ambitious and widely supported TTP research and implementation programme, a significant contribution can also be made to the quality of the process at this level.
This collective effort will help build a strong and secure foundation for the implementation of TTP. By establishing European guidelines that EU member states could follow when setting up frameworks and structures to enable the medical use of psychedelics.

5.3 Phasing of research and implementation Although there is a clear urgency for patients with various treatment-resistant disorders, building an infrastructure for answering knowledge questions and implementing TTP in the Netherlands requires a phased approach.
In recent years there has been a pioneering phase in which inspired researchers at various knowledge institutions have once again paid attention to therapeutic applications of psychedelics after years of inactivity. Both within the Netherlands and abroad, these were small-scale studies in which experience was gained and valuable information was collected.

It is now time for a phase in which we work on more cohesion and volume. Given the required investments in infrastructure and large-scale studies, a joint research and implementation program is an essential precondition (see also section 5.4). Incidentally, this phase will not only involve large-scale clinical studies, but also explorations in the field of ethics, legal and social aspects, small-scale pilot studies on specific indications and context factors and the development of options for compassionate use and off - label *prescription* . The development of the infrastructure also includes training practitioners who have adequate knowledge and skills in the field of TTP. Another aspect that should receive a lot of attention in this phase is increasing social support and correctly informing the general public and specific target groups about the possibilities and impossibilities of TTP.

The ultimate goal of all these efforts is to develop a healthcare infrastructure in the field of TTP. The concrete implementation of this ideal depends strongly on the outcomes of the previous phase.
The exact place of TTP in the landscape of Dutch mental health care cannot yet be determined exactly. It is clear that there are important opportunities that need to be explored and assessed on their merits, both in terms of therapeutic effectiveness and in terms of costs and social benefits.

5.4 Recommendations

In order to fill the knowledge gaps and implement existing and newly developed knowledge in the field of TTP, it is desirable that a broadly supported cohesive research and implementation program is set up. The backbone of this program can be formed by a network of academic centers of expertise and their partners in mental health care and the innovative pharmaceutical industry. The program can also work on building and strengthening the infrastructure in the field of research, protocol development, implementation and training. The role of patients and other stakeholders must be safeguarded in this rega

Some important parties that should be involved (e.g. facilitated by FAST) in setting up and implementing a TTP research and implementation program are:

- Mental health care institutions: in the context of large-scale research projects, the necessary infrastructure is developed and the practitioners are trained that are necessary for possible implementation in healthcare;
- Professional associations: they develop care and quality standards and treatment protocols, as well as knowledge about training requirements and market approval of new treatments in which pharmacotherapy and psychotherapy are combined;
- Patient organisations: they are also involved in developing standards and ensuring quality of care; they represent the interests of patients and their loved ones;

- Regulatory authorities: can inform and support with licensing and certification of organizations and individuals, -
Government: can create the right conditions (and adapt laws and regulations) in a timely manner to integrate safe, cost-effective, accessible and scalable innovative treatments into the healthcare system.
- Health insurers: guarantees of high quality, affordable, accessible, insured care.
- Pharmaceutical industry: can play an important role in the production of psychedelics according to GMP guidelines and the funding of clinical trials

The main goals of this consortium and the research and implementation program are:

- Improving the health and well-being of patients with psychiatric disorders by ensuring optimal, patient-centred integration of psychedelic treatments in the Dutch healthcare system

- A mental health sector that is fully equipped to apply TTP *evidence-based,* regulated and on a large scale, together with the fully realized scientific, legal, financial, organizational and (other) social conditions for this.
- The availability of cost-effective and scalable treatments that contribute to reduction of the (financial) care burden, protection of the sustainability of the health care system and in particular mental health care, a structurally lower burden of disease among patients with treatment-resistant, chronic psychiatric disorders and increased labor participation and an increase in labor productivity in the Netherlands.

Secondary outcomes are:

- The visibility of the Netherlands as an innovative knowledge country, at the forefront of developments in stagnated mental health care;
- An internationally recognized knowledge institute that serves as a global reference point for clinical research into and implementation of TTP in mental health care;
- Partly temporary, partly structural new activity, including an important part where income is not collectively financed.

6 Literature review

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Appendix A Overview of knowledge gaps, challenges and solutions

	Knowledge gaps and points for attention	Solution directions
Clinical scientific	- Methodological limitations of existing research, such as homogeneous study populations and ineffective blinding hinder the generalizability of research. Replication and pooling of data hardly happens. - The outcome measures used vary and take insufficient account of a restorative approach that is relevant to patients. - Systematic research into questions transcending diagnosis (including which form of (psycho)therapy works best as a starting point for TTP; the effect of non-pharmacological factors; optimal dosage and duration of treatment) is not or hardly ever carried out. - Adverse reactions are described and tracked inconsistently. - Long-term effects of TTP are insufficiently known due to short follow-up periods, *real world evidence* is limited. - More knowledge is needed for better assessment and personalized treatments. -	- A coordinated research program with standardized research design can generate generalizable and replicable outcomes. - By using the same measuring instruments and outcome measures (taking into account quality of life and recovery) and a shared data infrastructure, knowledge questions that go beyond diagnosis can be answered. Side effects, long-term effectiveness and RWE can also be mapped systematically and consistently in this way. - Such a research program can be set up through a national collaboration of specialist healthcare institutions and UMCs. - Patient organizations should play an important role in all phases of a research and implementation programme.
Financial economic	- Subsidy possibilities for research and implementation of TTP are limited. - Investments in research infrastructure are lost and there is a lack of cohesion between research and projects, which means that overarching research questions can hardly be answered, if at all. - Research into cost-effectiveness and HTA has not yet been carried out sufficiently.	- Financial guarantees for a multi-year research program make it possible to standardize research protocols, maintain research infrastructure and answer broad, overarching research questions. - Economic analyzes such as KEA, KBA and BIA, and HTA are necessary for an informed assessment of compensation for TTP.
Patients: between hype and hope	- Increased visibility, uncritical communication and unrealistic expectations about TTP may contribute to higher psychedelic use and supply of TTP outside healthcare.	- Awareness among researchers or practitioners and an asset media policy can contribute to a fair image of TTP.

expanded access	- The provision of *off-label* treatment and CUP is hampered by the lack of training opportunities and the limited supply of trained mental health professionals; uncertainty about the reimbursement of treatments and limited availability and GMP production of psychedelics.	- Expanded access can be enabled by develop training opportunities for therapists; to free up capacity in mental health care institutions; remove ambiguity about compensation and enter into cooperation with producers.
Training and organization of the health care system	- Recognized training courses for TTP, guidelines endorsed by professional groups and quality requirements for training courses do not yet exist in the Netherlands. Opportunities to gain practical experience are very limited. - Integration in mental health care requires setting up or adapting treatment rooms to the quality requirements of TTP. - Recognition of institutions and professionals that are allowed to offer TTP requires clear regulations and competence requirements.	- To enable the training of healthcare professionals, there is a need for detailed descriptions of competencies, the development of certification and training programs, the establishment of professional associations, the formulation of treatment guidelines and quality requirements for TTP and the accreditation of institutions and practitioners.
Laws and regulations	- Available schemes to accelerate the development of complex TTP treatments are not yet implemented. - Different organizations are responsible for approval, market authorization and reimbursement of TTP, which can lead to ambiguity. - Legal List-1 status makes research into TTP more complicated and more precious.	- Centers of expertise such as FAST can play a role in the timely and coordinated development of TTP. - Standardization of the psychotherapeutic framework can contribute registration of TTP by the EMA and MEB. - Involved professional groups can consult proactively with registration authorities about assessment processes, quality requirements and monitoring requirements.
Ethical issues and social acceptance	- TTP is associated with short- and long-term side effects, and raises ethical questions about 'ontological shock' and *informed consent.* - Altered state of consciousness, therapeutic touch and the risk of transgressive behavior require the establishment and enforcement of professional guidelines. - There are concerns among various opponents of TTP about political and social acceptance, scientific evidence, and legal and practical obstacles.	- The national ELSI service desk can play a role in careful taking into account ethical and social issues and the objections of opponents of TTP. - Quantitative and qualitative research among various stakeholders and critics can contribute to the (further) development of guidelines and information material, among other things.

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