PSY & ASd SGPP SSPP SSPP Schweizerische Gesellschaft für Psychiatrie und Psychotherapie Société Suisse de Psychiatrie et Psychothérapie Società Svizzera di Psichiatria e Psicoterapia		
Treatment guidelines		
Name of the guideline: Swiss Treatment Recommendations for Psychedelic Therapy (English Version)		
Approved by: SGPP	**Date:** 05.27.2024	**Last updated:** 09.18.2024

Treatment recommendations of the SGPP for the medical treatment of mental illnesses with psychedelics

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Lead

The Swiss treatment recommendations for psychedelic therapy mark an innovative step in psychiatric care. They provide a framework for the use of psychedelics in therapeutic contexts. With clear guidelines for patient selection, indication, implementation and safety measures, these recommendations set a high standard in the field of psychedelic therapy. As the use of psychedelics is an active clinical research environment, these treatment recommendations will be adapted in the future in line with new relevant findings. The range of indications for psychedelic therapy is constantly expanding, even beyond the field of psychiatry. For example, there is now also evidence of its effectiveness in the treatment of chronic pain syndromes, and indications from other medical specialties such as neurology and anesthesia are expected.

Introduction

For the first time, these treatment recommendations contain scientifically supported recommendations and framework conditions for the therapeutic use of psychedelics in a clinical-psychiatric context. As none of the classic psychedelics or MDMA have been approved as medication in Switzerland to date, there has been a lack of comprehensive information on side effects, contraindications and corresponding precautions prepared for clinical orientation. The present treatment recommendations are primarily based on a consensus reached under the auspices of the Swiss Society of Psychiatry and Psychotherapy (SGPP) among the relevant psychiatric and SGPP-affiliated specialist societies in Switzerland. In addition to the many years of clinical experience in the therapeutic use of psychedelics for mental disorders, the current state of scientific evidence has been integrated. These treatment recommendations will be revised as soon as new relevant findings become available. In addition, international position papers, including the guidelines of the American Psychiatric Association (Alpert et al., 2022; Barber and Dike, 2022) and the Royal Australian and New Zealand College of Psychiatrists (RANZCP, 2023) included.

Psychedelics are now regarded as an important future treatment option for various mental illnesses. They are increasingly being used in individual psychiatric institutions and specialized practices worldwide. In Switzerland, this has been made possible by the Federal Office of Public Health (FOPH) issuing special permits for restricted

medical use on a case-by-case basis in accordance with Article 8, paragraph 5 of the Narcotics Act (compassionate use) since 2014 (Saraga, 2023).[1] As psychedelic therapy differs from previously available pharmacological treatment methods in psychiatry **(Table 1)**, it places particularly high demands on doctors in terms of indication, information, implementation and documentation, as well as dealing with regulatory and ethical issues.

Table 1: Differences between psychedelic therapy and psychopharmacotherapy using the example of antidepressants (Vollenweider and Preller, 2020; Yehuda and Lehrner, 2023).

Criterion	Psychopharmacotherapy (antidepressants)	Psychedelic therapy
Regulatory status	Approved drugs based on phase I-III studies and a standardized approval process	Anesthetic, experimental therapeutic procedure, phase I-II studies, partly phase III, not yet approved
Primary indication	Depression, anxiety disorders, obsessive-compulsive disorders, etc.	No approved indication to date, used for treatment resistance in the context of depression, anxiety disorders, alcohol dependency, post-traumatic stress disorder
Onset of action	Delayed, approx. 2-4 weeks	Often rapid, <24 hours
Duration of action	While taking, possibility of discontinuation varies from person to person	Immediately altered consciousness (acute effect), clinically (target symptoms) days to months after one to two doses
Ingestion	Daily for months to years	Mostly single to few to repeated single doses, intake under supervision
Psychotherapeutic support	Not usually necessary during acute intake, recommended as part of overall treatment	Before, during and after ingestion as a safety measure, as part of the overall treatment
Subjective experience	Usually slow development of effects, generally not massively changed while taking medication	While substance intake usually changes significantly, clinical effects differ from acute effects
Main clinical effect	Slow reduction of symptoms, for example increased drive or improved sleep	Rapid reduction of symptoms, promotion of emotional-cognitive processes
Primary mechanism of action	Substance-dependent mechanisms, mostly favoring monoaminergic neurotransmission (serotonin, norepinephrine, dopamine) in the brain (monoamine hypothesis), sometimes other receptor effects and neuroplasticity	Classic psychedelics: activation of the serotonin 2A receptor in the brain, rapid neuroplasticity MDMA: release of serotonin, interaction with dopamine and noradrenaline system Nitrous oxide: NMDA receptor antagonism, effect on opioid receptor

[1] In 2023, there were around 60 doctors throughout Switzerland with an exceptional license from the FOPH; the number of licenses doubles from year to year and is around 100 individual licenses for psilocybin, which was the most commonly used psychedelic in 2023.

Side effects	Somatic (weight gain, sexual dysfunction, etc.) and psychopathological risks (e.g. restlessness, fatigue, temporary increase in suicidal tendencies)	Mainly acute psychological side effects (e.g. intensification of symptoms, temporary increase in suicidal tendencies), occasionally delayed psychological side effects (hallucinatory reverberation effects) Acute somatic side effects (headache, nausea, increase in blood pressure) Possible vitamin B12 deficiency with regular use of nitrous oxide Severe physical side effects may also be possible with MDMA (e.g. cardiovascular decompensation, hyperthermia) Long-term effects of serotonin 2B receptor agonism with effect on heart valves with very frequent use still to be determined (currently only single to few single doses are recommended)
Dependency potential	Not present, but risk of discontinuation symptoms/rebound phenomenon	Generally, no physical dependence, psychological dependence or misuse of MDMA in particular cannot be ruled out, potential for abuse and dependence in the case of nitrous oxide

Reason and objectives for these recommendations

Psychedelics have been used clinically and therapeutically since the middle of the last century (Herwig, 2024). Their use came to a virtual standstill in the early 1970s following the general ban on the use of drugs. The topic continued to be studied in Swiss psychiatry, both in basic science and clinically (Gasser, 1996; Kyzar et al., 2017; Vollenweider and Kometer, 2010). Since the 2000s, new scientific studies have confirmed the therapeutic potential of psychedelics. Since then, their clinical use has experienced a "revival" in medicine (Vollenweider and Preller, 2020). As a result, scientifically sound and clearly regulated framework conditions are becoming more relevant. As psychedelics continue to belong to the group of narcotics in Switzerland and there are no standards for their medical use, therapists take on a considerable liability risk when using them. This situation, with a lack of scientific standards, leads to unforeseeable and potentially critical consequences for those affected and those treating them (Goodwin et al., 2024; McNamee et al., 2023).

These Swiss treatment recommendations were therefore drawn up with the aim of providing a safe and standardized framework for treatment with psychedelics and establishing them in the psychiatric treatment spectrum. The SGPP therefore published a broadly supported position paper in October 2023 (Krähenmann et al., 2023) and recommended that the present treatment recommendations be drawn up by a commission of experts.

Treatment guidelines

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The substance class of psychedelics

Psychedelics are psychoactive substances that can cause acute, temporary, profound changes in thinking, emotions and perception. The term psychedelics (sometimes also called hallucinogens in classification systems) is made up of the two Greek words ψυχή (psyche, soul) and δῆλος (delos, revealed) and literally refers to a state in which "the soul is revealed". Classic psychedelics are primarily psilocybin, lysergic acid diethylamide (LSD), dimethyltryptamine (DMT, a component of ayahuasca) and mescaline. Atypical representatives are methylenedioxymethyl-amphetamine (MDMA), which is more of an entactogen[2] (Hysek et al., 2014) and ketamine/esketamine, which should rather be assigned to the class of dissociatives (Herwig et al., 2023; Reiff et al., 2020). Compared to classic psychedelics, MDMA has a more circumscribed effect profile, as it mainly affects emotional experience (Holze et al., 2020). Compared to MDMA, the classic psychedelics show a significantly greater variance in acute effects (dose-dependent and individually variable) and also a greater potential for negatively colored experiences (Holze et al., 2020). Psilocybin, MDMA and LSD are currently available for limited medical use in Switzerland. These treatment recommendations therefore focus primarily on these substances. The following overview provides an in-depth insight into the substance class of psychedelics, including the various substances and their characteristic features **(Table 2)**.

Table 2: Most important psychedelic substances (excluding ketamine/esketamine; for review, see also (Barksdale et al., 2024))

Substance	Pharmacological properties	Approximate number of randomized clinical trials since 2000
Psilocybin	Active substance contained in hallucinogenic mushrooms; is converted to psilocin after ingestion; acts on the serotonin 2A receptor	30 (Fang et al., 2024; Guo et al., 2024; Perez et al., 2023; Wong et al., 2024)
MDMA (3,4-methylenedioxy-N-methylamphetamine)	Rather classified as an entactogen; acts on serotonin, noradrenaline and dopamine	23 (Green et al., 2023; Smith et al., 2022; Yang et al., 2024)
LSD (lysergic acid diethylamide)	Synthetic psychedelic, discovered by Albert Hofmann; acts on the serotonin 2A receptor	18 (Holze et al., 2023; Ko et al., 2023; Liechti et al., 2017; Passie et al., 2008; Yao et al., 2024)
DMT (dimethyltryptamine)	Psychedelic substance, found naturally in many plants; only effective orally in combination with a monoamine oxidase inhibitor (cf. ayahuasca); alternatively IV administration or inhalation. With bolus administration or inhalation, strong, short duration of effect due to rapid metabolization	10 (Bosch et al., 2022; Falchi-Carvalho et al., 2024; Riba et al., 2001; Timmermann et al., 2024; Vogt et al., 2023)

Mechanisms of action of classic psychedelics

Although the mechanisms of action of psychedelics are the subject of intensive research, they are not yet fully understood. The most important hypotheses on the mechanisms of action are discussed below:

[2] Entactogens ("touching the inside", from the Greek en, "inside", Latin tactus "touched") are psychoactive substances under whose influence one's own emotions are perceived more intensely

Agonism at 5-HT2A receptors, 5-HT-, DA-, NA-releasing, or antagonism at the glutamate system

The so-called serotonergic psychedelics mainly act as agonists via serotonin 2A (5-HT2A) receptors. The serotonergic system is relevant for the regulation of mood, sleep, appetite and cognitive functions. 5-HT2A receptors are particularly important as they are involved in the processing of sensory stimuli and the regulation of emotions. It is assumed that psychedelics reduce the inhibitory control of sensory inputs, which can lead to more intense perceptions (Avram et al., 2024). MDMA acts via a release of serotonin, noradrenaline and dopamine (Nichols, 2016; Nichols et al., 2017). Similar to ketamine, nitrous oxide acts as a glutamate antagonist via NMDA receptors (Jevtović-Todorović et al., 1998; Kohtala and Rantamäki, 2021) and to a lesser extent via opioid receptors (Gillman, 1986).

Emotion processing, amygdala and cognitive processes

Research suggests that classic psychedelics influence general emotion processing and affect specific regions of the brain, such as the amygdala. Under the influence of psychedelics, it has been observed that the amygdala can change its normal way of reacting to emotional stimuli. Mechanistic studies in healthy individuals using imaging techniques such as functional magnetic resonance imaging show a dampened activity of the amygdala under psychedelic effects (Barrett et al., 2020; Bershad et al., 2020; Kraehenmann et al., 2015; Mertens et al., 2020; Mueller et al., 2017). This change could contribute to patients being able to have more intense emotional experiences under psychedelic influence because the fear response to fearful memory content may be downregulated (Mertens et al., 2020).

Psychedelics can lead to a qualitatively altered state of waking consciousness and manifest themselves in patterns of unusual thinking and sensations (Kraehenmann, 2017; Kraehenmann et al., 2017a, 2017b). This could be partly due to their interaction with different brain regions, including the cortical association areas (Tagliazucchi et al., 2014). Studies have shown that psychedelic substances can alter connectivity between different brain regions, leading to more divergent thinking and increased creativity (Petri et al., 2014). This phenomenon of cognitive alteration has sometimes been described as "dream-like cognition", as it has certain similarities to the unusual thought patterns during dreaming (Kraehenmann et al., 2017a, 2017b, 2017b).

Default Mode Network (DMN) and change of consciousness

Psychedelics alter activity in the DMN - a network of brain regions that becomes active in resting mode and is associated with self-reflection, identity and the processing of personal experiences. There is a close relationship between functional brain connectivity in the DMN and negative cognitions in people with depression (Borserio et al., 2021). Psychedelics can temporarily alter connectivity between regions of the DMN, which can lead to increased communication between otherwise less collaborative brain regions. This increased neuronal connectivity is associated with an altered state of consciousness - including a change in ego experience, sensory perception and cognition (Soares et al., 2023; Stoliker et al., 2023; Tagliazucchi et al., 2014).

Neuroplasticity and long-term changes

The long-term effects of psychedelics may be due in part to changes in the neuroplastic adaptation of the brain. It is hypothesized that psychedelics may stimulate neuronal growth factors and promote the formation of new synaptic connections (Calder and Hasler, 2023; Vargas et al., 2023). These neuroplastic effects could contribute to long-term changes in brain function and possibly to desired therapeutic outcomes.

Evidence of clinical efficacy and safety

A large number of randomized, controlled trials (RCTs) on the efficacy and safety of psychedelic therapy for various psychiatric disorders are now available. Due to some peculiarities of psychedelics, the bias effects (e.g., due to difficult blinding, expectation effects, environmental factors, small case numbers, etc.) are insufficiently controlled in the RCTs to date (Hovmand et al., 2023), which is why further RCTs with higher case numbers and control of influencing factors are necessary before any approval as medication. However, the efficacy of psychedelics is very

closely linked to the subjective effects in the context of altered consciousness, which is why the conventional gold standard of blinding for psychedelics is methodologically almost impossible to achieve (Goodwin et al., 2022). This in turn should not mean that a potentially effective method should not become available for this reason alone. Alternative designs, such as dose-response studies, are sometimes recommended by the regulatory authorities (FDA, 2023). It is currently unclear whether and which standard will be established here.

The best evidence of efficacy currently exists for the use of psilocybin in **depression**, particularly in treatment-resistant depression (Carhart-Harris et al, 2018; Carhart-Harris et al, 2016; Goodwin et al, 2022; Ko et al, 2023; Raison et al, 2023; von Rotz et al., 2023) as well as for LSD and psilocybin for depression and existential anxiety in connection with severe physical illnesses (e.g. terminal cancer) (Gasser et al., 2014; Holze et al., 2023; Ross et al., 2022, 2016; Schimmers et al., 2022). The meta-analysis by Guo et al. (2024) examined 72 randomized controlled trials of treatments for treatment-resistant depression. The analysis, which included 12,105 participants, highlighted electroconvulsive therapy, ketamine/esketamine and psilocybin as the preferred treatments for treatment-resistant depression due to their optimal balance between efficacy and tolerability. With effect sizes of over 1.0 in RCTs, it can be concluded that psychedelics are highly effective for depressive episodes (Luoma et al., 2020). However, the effect size is most likely inflated by functional unblinding and high expectations. Accordingly, it is to be expected that the effect sizes in larger RCTs will decrease compared to the initial studies, a phenomenon that is already known from RCTs in other areas.

It is worth mentioning that in a larger study (Carhart-Harris et al., 2021) psilocybin had comparable antidepressant effects compared to a "common" antidepressant, a selective serotonin reuptake inhibitor (SSRI), and in a re-analysis (Weiss et al., 2023) showed slightly superior effects. However, it should be noted that this study was not placebo-controlled, making it unclear whether the SSRI achieved efficacy above the placebo level. Clinical studies on dimethyltryptamine (DMT) are currently limited, but there is preliminary evidence that DMT is effective in treatment-resistant depression (D'Souza et al., 2022; Falchi-Carvalho et al., 2024; Reckweg et al., 2023). The efficacy and safety of nitrous oxide (laughing gas) in the treatment of treatment-resistant depression have been investigated in several RCTs and case series (Guimarães et al., 2021; Kronenberg et al., 2024; Nagele et al., 2015). The studies indicated that one to two one-hour nitrous oxide treatments can lead to a rapid improvement in symptoms that lasts for several weeks. The NMDA receptor antagonist esketamine is not discussed separately in these treatment recommendations, as esketamine is already approved in Switzerland for the treatment of treatment-resistant depression.

Further evidence for psychedelics at the RCT level exists for **alcohol dependence** (Bogenschutz et al., 2022; Krebs and Johansen, 2012; van der Meer et al., 2023) and for MDMA for **post-traumatic stress disorder** (Henner et al., 2022; Krediet et al., 2020; Mitchell et al., 2023).

Overall, the **safety and side effect profile** of psychedelics is favorable in the studies to date and the experience gained from their use in the context of individual case treatments (Carhart-Harris et al., 2021). They are generally well tolerated, and possible side effects occur mainly during or immediately after the substance session (e.g. headaches within 24 - 48 hours after administration). However, long-term effects have been little studied and need to be monitored in the longer term through pharmacovigilance measures (Belouin et al., 2022; Rouaud et al., 2024). It is also important to consider critical aspects and potential risks (see **Table 3**). For example, during the approval process for MDMA, concerns were repeatedly expressed that side effects such as suicidality were not sufficiently reported (Marks, 2024; Reardon, 2024). This incomplete documentation could lead to an underestimation of the risks associated with the use of such substances. In addition, postpsychedelic reverberation effects, for example, are often not sufficiently addressed (Breeksema et al., 2022; Evans et al., 2023).[3] Another critical point is the fact

[3] One prominent case is that of a pilot who, two or three days after taking psilocybin during a flight as a passenger, attempted to open the doors of the plane and turn off the engines to free himself from a persistent altered state of consciousness (Piercey et al., 2024). Such incidents illustrate that psychedelic substances can trigger unexpected and potentially dangerous behaviors even days after ingestion.

that previous clinical studies on psychedelics were conducted on patients who were selected much more rigorously and screened more intensively than those in studies on classic antidepressants. For example, a more detailed family history was taken in these patients, which means that the results of these studies may not be readily transferable to the general patient population (Hovmand et al., 2023). This selection could distort the safety and efficacy of psychedelics in a more realistic clinical setting, and is therefore a significant factor to consider when evaluating these substances.

Time course and dose dependence of the clinical effects

A distinction must be made between the acute effects of the substances and the clinical effects. The acute effects of MDMA, psilocybin and LSD last for approx. 5 to 12 hours, depending on the substance (Holze et al., 2022, 2020). The clinical effects of psychedelics also often occur during this period. They can last for several days, weeks or months with a certain variance. Thus, even with only one or two doses of a substance, clinical improvements can be observed over several weeks and sometimes even months (Agin-Liebes et al., 2020; Carhart-Harris et al., 2018; Gukasyan et al., 2022; Holze et al., 2024). The clinical efficacy of psychedelics shows a dose-dependent effect (Perez et al., 2023) with medium and higher doses (e.g. 25 mg psilocybin per os) showing greater efficacy compared to lower doses (e.g. 1-10 mg psilocybin per os). Especially for treatment-resistant depression, lower doses are probably not effective enough (Goodwin et al., 2022). For LSD and psilocybin in depressive symptoms and anxiety, there is evidence that repeated administration is more effective compared to a single dose (Leger and Unterwald, 2022).

Therapeutic response and remission rates

The response and remission rates have varied in previous studies (Goodwin et al., 2022; Guo et al., 2024; Raison et al., 2023; von Rotz et al., 2023). In the phase 2 RCT by Goodwin et al. (2022), in which 79 treatment-resistant depressive patients were treated once with 25 mg, 10 mg or 1 mg psilocybin, the response rate after three weeks was 37% in the 25 mg group, 19% in the 10 mg group, and 18% in the 1 mg control group. The remission rate was 29% in the 25 mg group, 9% in the 10 mg group, and 8% in the 1 mg control group. In the phase 2 RCT by Raison et al. (2023), in which 104 patients with major depression were treated once with 25 mg psilocybin or niacin control, the response rate after 43 days was 42% in the 25 mg group and 11% in the niacin control group. The remission rate was 25% in the 25 mg group and 9% in the niacin control group. In the RCT study by Von Rotz et al. (2023), in which 52 patients with major depression were treated once with a medium dose of psilocybin (0.215 mg/kg) or placebo, the response rate after 14 days was 54-58% in the psilocybin group and 12-16% in the placebo group. The remission rate was 46-54% in the psilocybin group and 12% in the placebo group.

Data on the long-term clinical effects of psychedelics in psychiatric disorders

Investigating the long-term effects of psychedelics in psychiatric treatment is crucial. It is not only about understanding the short-term effects, but also about understanding long-lasting changes and the potential therapeutic benefits. Data from studies covering a period of several months to several years will be considered.

Several studies have shown long-term positive effects of psilocybin in various psychiatric disorders. Griffiths et al. (2016) reported long-lasting improvements in quality of life and mental health in cancer patients after two psilocybin doses, which persisted even after six months. Ross et al. (2016) found that psilocybin showed long-term anxiety-relieving and antidepressant effects in patients with anxiety and depression due to advanced cancer that persisted one year after treatment. Holze et al. (2024a) showed a sustained reduction in anxiety and depression for up to two years after two doses of LSD. A single dose of LSD also produced long-lasting positive changes in personality and life satisfaction (MacLean et al., 2011). The combination of MDMA with specific psychotherapy shows promising results in the treatment of post-traumatic stress disorder. Long-term data from Mithoefer et al. (2013) show that the therapeutic effects after MDMA sessions can also remain stable over a longer period of time, with positive changes being detectable up to four years after treatment. However, it is not scientifically clear what role the pharmacodynamic properties of MDMA per se play in these therapeutic effects (Hashimoto, 2024; Mitchell et al., 2023).

Indications

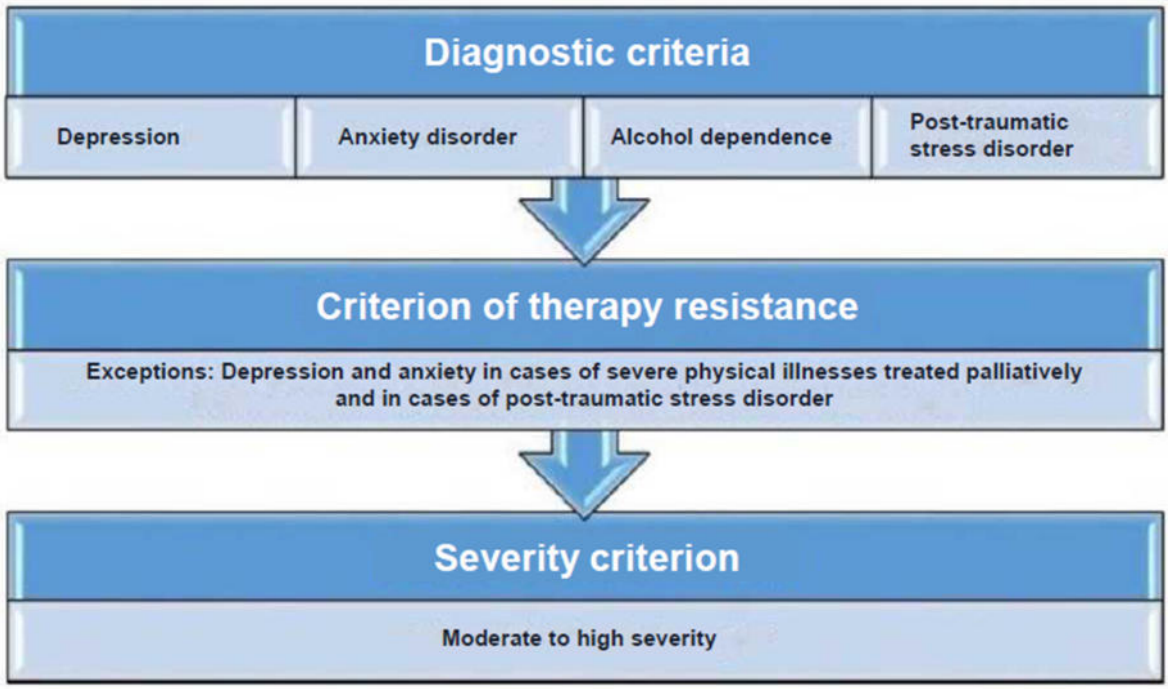
In principle, the FOPH can grant exemptions if the quality of life is severely impaired by the disease in question and there has been an inadequate response to previous therapies. According to the FOPH, there is no fundamental restriction on a specific disease pattern. However, based on the current scientific data, the SGPP recommends the use of psychedelics only in the following cases: the current evidence, given the still limited state of research, for a rapid onset and sustained efficacy on average, combined with good tolerability, initially positions psychedelic therapy as an **off-label third-line therapy for selected treatment-resistant, moderate-to-severe mental illnesses.** With further establishment and corresponding research results, it may also be conceivable in the future to use it earlier in the course of the illness for non-therapy-resistant illnesses. The criterion of treatment resistance currently applies to depression and anxiety in the context of severe, palliative treatment of physical illnesses[4] and to post-traumatic stress disorder[5]. Other indications (e.g., obsessive-compulsive disorder, eating disorders, etc.) are only justifiable in a scientific setting or in life-threatening cases due to the still inadequate evidence base.

Psychedelic therapy is therefore indicated if the following three criteria are met cumulatively: Diagnosis, resistance to therapy and severity **(Figure 1)**.

[4] The argument for the use of an experimental therapy such as psychedelic therapy in patients with life-threatening illnesses is that in this patient group the expected benefits (high therapeutic potential, improvement in quality of life, rapid and sustained efficacy, etc.) outweigh the potential risks, including the risks of not providing treatment (see also (Greif and Šurkala, 2020))

[5] **Based on several studies, including two randomized, double-blind, placebo-controlled phase 3 studies (Mitchell et al., 2023), which demonstrated the efficacy and safety of MDMA in patients with moderate to severe PTSD, the US Food and Drug Administration (FDA) accepted the marketing application for MDMA under the name midomafatemin (Lykos Therapeutics) for the treatment of PTSD and granted the application priority review status. However, on June 4, 2024, the FDA's Central Advisory Committee recommended that the requested approval of MDMA be denied for various reasons, including the unclear role of psychotherapy (Marks, 2024). On 11.08.2024, the FDA followed the advisory committee's recommendation of rejection and rejected the MDMA application for approval (Reardon, 2024). In addition, three studies (Feduccia et al., 2021; Jerome et al., 2024; Mithoefer et al., 2024) in connection with MDMA psychotherapy were withdrawn due to violations of the study protocol and unethical behavior during the conduct of the study.**

Figure 1: Algorithm for determining the indications for psychedelic therapy



Definition of a third-line treatment strategy

Third-line treatment strategy refers to the third, evidence-based treatment level in accordance with international treatment recommendations, in particular the German S3 guidelines (awmf.org/guidelines), the NICE guidelines (nice.org.uk/guidance) and the American Psychiatric Association Practice Guidelines (psychiatry.org/guidelines). The following treatment levels exist for the evidence-based treatment of depression (BÄK et al., 2022; Hättenschwiler et al., 2024):

First stage: Antidepressant monotherapy with a modern antidepressant (e.g., SSRI) or psychotherapy over a sufficiently long period and at a sufficiently high dosage (according to treatment recommendations for the respective disease group).

Second stage: Combination of an antidepressant with psychotherapy, (one-off) switch to an antidepressant of a different class (e.g., selective serotonin-norepinephrine reuptake inhibitor [SNRI]), combination of two antidepressants of different classes (e.g. mirtazapine with SSRI) or augmentation of an antidepressant (e.g. with lithium or an atypical antipsychotic) over a sufficiently long period and at a sufficiently high dosage.

Third stage: add-on therapy methods (high evidence for esketamine, electroconvulsive therapy, repetitive transcranial magnetic stimulation; experimental: psychedelic therapy)

In addition to patient preference, the strength of the evidence for the individual methods must also be taken into account for add-on therapies. For example, electroconvulsive therapy, repetitive transcranial magnetic stimulation and esketamine have a high strength of evidence in terms of efficacy, safety and feasibility, whereas psychedelic therapy as an add-on therapy method currently has a lower strength of evidence and is not yet included in the official treatment algorithms (BÄK et al., 2022; Hättenschwiler et al., 2024).

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Definition of treatment resistance

Treatment resistance is generally assumed to occur when there is an inadequate response to graduated treatment in accordance with the usual treatment recommendations. However, treatment resistance is not uniformly defined for all mental illnesses (Conway et al., 2017).

Treatment-resistant depression is referred to internationally and in the Swiss treatment recommendations for the treatment of unipolar depressive disorders (Hättenschwiler et al., 2024) if the depressive symptoms persist despite two treatment attempts with (different) antidepressants in adequate doses and over a sufficiently long period (>4 weeks). Specific psychotherapy should be considered or offered for mild-to-moderate depressive episodes. The same applies to severe depression in combination with psychopharmacotherapy. Psychotherapy in combination with an antidepressant is more effective than pharmacotherapy alone (Cuijpers et al., 2020) - and vice versa. For psychedelic therapy of treatment-resistant depression, therefore, in addition to a lack of response to two antidepressants, a lack of response to specific psychotherapy of sufficient duration must also be demonstrated (Conway et al., 2017).

Treatment-resistant anxiety disorders are not clearly defined (Seifritz et al., 2024). Analogous to treatment-resistant depression, psychedelic therapy for treatment-resistant anxiety disorder requires a lack of adequate response to pharmacotherapy and psychotherapy of sufficient duration (at least eight weeks) (Domschke et al., 2024).

Treatment-resistant alcohol dependence is not operationalized. Analogous to treatment-resistant depression, psychedelic therapy for treatment-resistant alcohol dependence requires an inadequate response or failure to achieve agreed treatment goals for several evidence-based pharmacological and psychotherapeutic treatment methods (DGPPN and DG-SUCHT, 2020).

Definition of severity

Severity levels are defined for the individual indications for psychedelic therapy in line with the studies used. For moderate **depression**, there must be at least 20 points on the Montgomery-Åsberg Depression Rating Scale (MADRS), at least 17 points on the Hamilton Depression Rating Scale (HAMD-D-21) or at least 20 points on the Beck Depression Inventory II (BDI-II) (Goodwin et al., 2022); for moderate **anxiety disorders** at least 40 points on the State-Trait Anxiety Inventory (STAI) (Holze et al., 2023); for moderate **alcohol dependence**, at least four days of heavy drinking in the 30 days prior to screening (defined as five or more drinks in one day for a man and four or more drinks in one day for a woman) (Bogenschutz et al., 2022)and for moderate **post-traumatic stress disorder** at least 28 points on the Clinician-administered PTSD Scale (CAPS-5) and a symptom duration of at least six months (Mitchell et al., 2023).

Summarized list of possible future indications for psychedelic therapy (as of summer 2024)

- Treatment-resistant moderate to severe depression (without psychotic symptoms)
- Therapy-resistant moderate-to-severe anxiety disorders
- Moderate to severe depression and anxiety in connection with severe, palliative treated physical illnesses (e.g. terminal cancer)
- Treatment-resistant moderate-to-severe alcohol dependence
- Moderate to severe post-traumatic stress disorder

Psychedelic therapy

In psychiatry, psychedelic therapy embodies a new category of treatment (Nichols et al., 2017). It should be used as a modular add-on within the available range of treatments. As a treatment module, psychedelic therapy comprises the three components: (A) preparation, (B) implementation ("substance session"), and (C) debriefing ("integration session").

The role of psychotherapy

The vast majority of studies on classical psychedelics combine psychedelic therapy with some form of (usually supportive) psychotherapy. Therefore, the strongest scientific evidence for safety and efficacy currently exists in the context of this combined application. However, there is currently no evidence base for the assumption that psychedelic therapy should be combined with psychotherapy in order to be effective, as this has not yet been scientifically investigated (Goodwin et al., 2024; Heifets and Olson, 2024). For example, the effect in the placebo-with-psychotherapy arm in the MDMA RCT study by Mitchell et al. (2023) points to the independent value of manualized psychotherapy, which was developed for use with MDMA. A similar argument was made by the US Food and Drug Administration (FDA) Central Advisory Committee regarding the approval of MDMA for the treatment of PTSD (Marks, 2024; O'Brien et al., 2024) and the American Psychiatric Association (Levin, 2024) in their statement: MDMA has only been studied in combination with psychotherapy; the specific role of psychotherapy in this context remains unclear and must first be investigated before approval can be granted. Also, based on the experience reports from clinical use (Aicher et al., 2024; Passie et al., 2022), embedding psychedelic therapy in specific psychotherapy can have an augmenting effect on psychotherapy as such.

Overall, it can be stated that psychotherapeutic support before, during and after the substance session is currently a relevant part of the usual psychiatric-psychotherapeutic competence - both with regard to safety aspects and due to the altered state of consciousness induced by the psychedelics and the corresponding emotional-cognitive changes. The aim of this psychotherapeutic support is primarily to provide psychological support and ensure safety.

Number of substance sessions

In the clinical studies to date (Carhart-Harris et al., 2018; Goodwin et al., 2022; Holze et al., 2024; Mitchell et al., 2023; von Rotz et al., 2023), single and sometimes double substance sessions were used for treatment-resistant diseases. These showed rapid and 6-12 months lasting clinical effects. A single RCT (Rosenblat et al., 2024) showed that a third substance session in the event of a relapse of depressive symptoms within 6 months of the first substance session brought an advantage over single or double dosing. Repeated substance sessions in the sense of maintenance therapy have not yet been investigated. From a current perspective, we therefore recommend a sequence of up to 3 substance sessions within 6 months, weighing up the costs, benefits and risks and taking into account the evidence. After this period, the indication should be reviewed. A second cycle of up to 3 substance sessions can then take place if necessary. The substance is usually administered at intervals of a few weeks. Once psychedelic therapy has been completed, patients can return to regular outpatient aftercare.

Dosage

The individual reaction to psychedelics can vary greatly. In addition, the psychotropic effects of psychedelics are not only dependent on the dose, but also on extrapharmacological factors such as set and setting (Studerus et al., 2021, 2012). The "set" comprises the psychological and emotional factors that influence a person's mental state during psychedelic therapy. These include the patient's expectations, beliefs, emotions and experiences before and during the session. The "setting" refers to the physical and social environment in which psychedelic therapy takes place. This includes the therapy room, the atmosphere, the presence of the therapy staff, and other external influences. The setting influences the effect of psychotropic substances in general and the effect of psychedelics in particular (Liechti et al., 2017).

Microdosing in psychedelic therapy refers to the use of subperceptual doses of psychedelics that do not lead to any noticeable impairment of cognition but are thought to offer potential therapeutic effects. However, the evidence on the actual effects of microdosing is currently insufficient and inconsistent, which calls for further research (Lo et al., 2024; Murphy et al., 2024).

Psilocybin: In clinical trials for the treatment of depression, the dosage typically ranged from 20 to 30 mg p.o. per session. In cases of treatment resistance, experience has shown that clinically relevant efficacy can only be expected

from the medium dose range (e.g. 25 mg) (Goodwin et al., 2022). Increasing the dose in the second session compared to the first session can be considered, for example, in order to increase efficacy.

LSD: Doses of 75 to 200 µg p.o. have been used in clinical studies, with the typical dose being 100-150 µg p.o. (Holze et al., 2023).

MDMA: The dosage of MDMA varies considerably. In clinical studies on the treatment of post-traumatic stress disorder, a dose of 75 to 180 mg was generally administered, although effects have been described for rather low doses (Mithoefer et al., 2018). In contrast to psilocybin and LSD, MDMA is moderately related to body weight, so dose adjustment can be considered. Limited data suggest that at doses above 140 mg, side effects increase disproportionately on average, while the target effects actually decrease (Brunt et al., 2012). A staggered dosing regimen (120 mg plus 60 mg after two hours) was used in the phase 3 studies. In Switzerland, 100 mg for women and 125 mg for men are the usual starting doses. Overall, it should be noted with MDMA that possible toxic effects cannot be ruled out, especially at high doses and repeated administration at close intervals (Hall and Henry, 2006). The therapeutic range is significantly smaller than that of classic psychedelics. This should be taken into account during administration.

DMT: The substance was investigated in the latest clinical studies on depression. The relevant therapeutic dose and repetition rate of DMT cannot yet be definitively estimated due to the small number of clinical studies. In the patient studies to date, doses between 15 mg and 60 mg p.o., or 0.3 mg/kg body weight parenterally, have been used (D'Souza et al., 2022; Falchi-Carvalho et al., 2024).

Nitrous oxide (N_2O/nitrous oxide): This substance has been investigated in a few clinical studies on depression. For inhalation therapy, a mixture of nitrous oxide and pure oxygen is used in a ratio of 1:3 (i.e. 25% N_2O with 75% O_2) or 1:1 (i.e. 50% N_2O with 50% O_2) over a period of 30 to 45 minutes. Compared to other psychedelics, a fundamentally different setting is used here. In previous clinical studies, two treatments per week were carried out over several weeks (Nagele et al., 2015). Further studies to investigate the effectiveness and safety of psychiatry are required for the recommendation for clinical use (Kronenberg et al., 2024).

Interactions and medication changes

The simultaneous use of psychedelics with psychotropic drugs can lead to drug interactions. It is therefore important for safe use to check interactions with existing medications. If no interactions/interferences are to be expected, the existing medication is generally continued. If there are relevant interaction risks, the existing medication should be adjusted (paused). In these cases, a break of at least 5 half-lives of the respective medication is recommended. A list of the most important interactions is provided and regularly updated by the Department of Clinical Pharmacology at the University Hospital Basel (Prof. Matthias Liechti, PD, Dr. med. Yasmin Schmid).[6] In the following, individual specific interactions are mentioned specifically and mechanistically.

Monoamine oxidase inhibitors (e.g. moclobemide) can trigger a potentially life-threatening serotonin syndrome in combination with MDMA (Gillman, 2005). This substance class must therefore be urgently discontinued in advance (in the case of tranylcypromine, for at least 14 days). Cases of epileptic seizures have been described for lithium when taken simultaneously with LSD and psilocybin (Nayak et al., 2021). This combination should, therefore, be avoided. For MDMA, one study (Cohen et al., 2021) reported lethal courses when MDMA and the potentially proarrhythmogenic metoclopramide (Paspertin® and others) were taken at the same time. Avoidance of metoclopramide is therefore recommended for MDMA, but also prophylactically for psilocybin and LSD.

All antipsychotics presumably reduce the acute effect of classic psychedelics and MDMA due to antagonism of the serotonin 2A receptor, and should therefore be discontinued seven days before treatment. Benzodiazepines probably also reduce the acute effect and should be discontinued if possible. Mirtazapine should be paused for 5-

[6] The list can be viewed online (https://saept.ch/begrenzte-medizinische-anwendung)

7 days and trazodone 1-2 days beforehand, as these antidepressants inhibit the serotonin 2A receptor (Bonson et al., 1996; Halman et al., 2024; Rucker et al., 2018). Antidepressants from the class of SSRIs or SNRIs do not need to be paused before using psilocybin or LSD, as they presumably have little influence on their antidepressant effect (Barbut Siva et al., 2024; Goodwin et al., 2022; Halman et al., 2024). SSRIs and SNRIs should be paused for 3-7 days (fluoxetine 14 days) before MDMA use, depending on the half-life, as otherwise the desired acute subjective effect of MDMA is blocked (Hysek et al., 2014; Liechti et al., 2000).

Side effects, risks, contraindications and precautions

The classic psychedelics and MDMA were generally well tolerated in previous clinical studies. All substances can cause acute and subacute non-specific side effects such as headaches, nausea, altered temperature sensation and sleep disturbances (Vizeli and Liechti, 2017). Psychedelic treatment can increase suicidality, which requires careful clinical assessment and monitoring (Goodwin et al., 2022). Further risks are of a psychological nature (e.g. emotional stress from the substance session) as well as risks associated with the behavior of the accompanying therapists (e.g. handling of touch or suggestibility) (McNamee et al., 2023). Clinically quite relevant are negatively experienced acute effects and a possible destabilization in the time after ingestion. In studies, around 20-30% of people experience significant negative effects such as anxiety and, less frequently, paranoia (Holze et al., 2022) and delayed reverberation phenomena (e.g. hallucinogen persisting perception disorder) (Martinotti et al., 2018).

The classic psychedelics' psilocybin, LSD, DMT and mescaline are generally well tolerated by the body, are medically safe and have a wide therapeutic range (Nichols, 2016). All substances lead to a moderate increase in blood pressure, although this is rarely clinically relevant (Holze et al., 2022). The side effects generally decrease quickly and, with a few exceptions, are temporary based on previous experience and the available studies. MDMA has also been well-tolerated in clinical studies to date. In recreational use, however, there have been isolated reports of serious, even fatal incidents, such as cases of malignant hyperthermia (Hall and Henry, 2006). With MDMA, it should also be noted that there are indications that a genetic predisposition to malignant hyperthermia could also favor MDMA-induced malignant hyperthermia, so caution is advised in persons with a known corresponding predisposition (Fiege et al., 2003). It is currently unclear at what dosages and administration frequencies MDMA can be expected to cause more serious side effects. Overall, however, the therapeutic range appears to be much narrower than in the case of classic psychedelics.

Overall, a careful risk-benefit assessment is important for psychedelic therapy. For example, patients with a history of psychosis and in some cases a family history of psychosis are excluded from psychedelic therapy due to the increased risk of psychosis. The same applies in the case of bipolar disorders, particularly with pronounced psychotic symptoms, although the use of psychedelics for depression in the context of a bipolar II disorder has already been investigated (Aaronson et al., 2024). People with borderline disorders, current acute suicidal tendencies and psychotic symptoms in the context of a depressive illness were also not included in most studies due to safety concerns. However, this deprives many patients who might have benefited from psychedelic therapy of a potentially effective treatment from the outset (La Torre et al., 2024; Schlag et al., 2022). Further studies are needed on these issues to evaluate the risks and possible measures to manage them. The contraindications mentioned, taking into account the main indication, therefore require careful evaluation and a well-informed decision by practitioners and patients, whereby it should be noted that the possible risks are currently difficult to assess **(Table 3)**.

Table 3: Overview of the most important side effects, contraindications and corresponding precautionary measures (authors' consensus recommendations; see also (Breeksema et al., 2022; Martinotti et al., 2018; Rouaud et al., 2024; Schlag et al., 2022; Simonsson et al., 2023))

Category	Side effects	Contraindications	Precautionary measures
Cardiovascular	Increased heart rate (MDMA with 10-15% strong increase) and increased blood pressure, dizziness, headaches (approx. 30%), with chronic use of classic psychedelics risk of cardiac fibrosis and heart valve disease, with chronic use of MDMA toxic effects on the nervous system, liver and other organs possible	uncontrolled high blood pressure, coronary heart disease, cerebral or aneurysmal vascular disease	Consider cardiologic clarification, monitor blood pressure and heart rate before, during and after substance administration (immediately before use, then every 30-60 min)
Mental	Anxious-paranoid syndrome (20-30%), confusion, mood swings (5-15%, depending on substance and setting), acute psychosis (<1% in people with no previous history)	History of psychotic disorders (e.g. schizophrenia), severe personality disorders (e.g. borderline personality disorder), bipolar disorder, dissociative disorder, severe anxiety or panic disorders, dementia, acute suicidal tendencies	Comprehensive psychiatric assessment prior to treatment, tend to exclude persons with a personal or family history of psychotic disorders in close relatives, immediate therapeutic intervention in the event of signs of psychosis
HPPD (Hallucinogen Persisting Perception Disorder)	Persistent flashbacks / visual disturbances (< 5%), especially in heavy users in a non-therapeutic context and predominantly with classic psychedelics		Informing patients about the risk
Neurological	Lowering the cramp threshold Neuropathy, vitamin B12 deficiency (nitrous oxide)	Epilepsy or a history of seizures For long-term use or pre-existing deficiency	Neurological assessment, drug-based seizure prophylaxis Prophylactic vitamin B12 administration and administration after

			nitrous oxide inhalation
Systemic	Malignant hyperthermia (especially MDMA)	Predisposition to malignant hyperthermia	Exclude treatment if necessary. Observe physical symptoms
Abuse/dependence **Additional substance use**	Psychological dependence (more common with MDMA, nitrous oxide and very rare with psilocybin and LSD), very low risk of physical dependence		Screening for substance disorders (incl. alcohol) in the past: for the duration of psychedelic therapy, there should be no co-use of psychotropic substances, drug urine checks before substance sessions, but no withdrawal from benzodiazepines or opioids
Pregnancy and breastfeeding		Lack of safety and efficacy data	Not recommended
Persons under the age of 18		Lack of safety and efficacy data	Not recommended

Driving ability

Psychedelics impair the ability to drive. In Switzerland, they are therefore considered to be fundamentally incompatible with participation in road traffic.

Screening and informed consent

Medical-psychiatric screening, diagnostics and severity assessment

Screening includes medical and psychiatric diagnosis, assessment of somatic and psychiatric risks, and risk-benefit assessment (Feduccia et al., 2023). The indication is primarily based on the psychiatric diagnosis and the previous course of treatment (treatment resistance or palliative indication), contraindications (e.g. exclusion of patients with acute psychosis or acute suicidality), but also takes into account factors that enable an individual risk-benefit assessment (e.g. comorbidities, personality traits, treatment motivation and expectations, social aspects, etc.). Particular attention is paid to medication adjustments, which are often necessary due to interaction risks. The screening includes a comprehensive catamnesis to determine previous treatment attempts and ensure a diagnosis. To rule out somatic causes of the psychiatric syndromes, an appropriate and thorough internal and neurological examination, laboratory chemical and hematological tests, possibly drug urine screening, an electrocardiogram (ECG) and, if necessary, cranial imaging or an electroencephalogram (EEG) are carried out. In addition, a psychometric assessment of the severity of the psychiatric illness should be carried out to determine the indication (self-rating and external rating) in order to enable a later assessment of the course of the illness.

Informed consent

Patients should be capable of judgment at the time of informed consent. This means that they should be able to understand the risks and benefits of the treatment in the context of their illness, the duration of the current episode and previous treatment history, and they should be able to give valid consent. In principle, the use of psychedelics is an off-label treatment. The ethical principle of autonomy of choice guides the process of informed consent (Lee et al., 2024). Largely due to media reports, many patients have high expectations of the treatment. Expectations

should be discussed and, if necessary, corrected to enable patients to make a more realistic assessment of effectiveness. The process essentially consists of informing patients about the procedure, risks, benefits, probable consequences and alternatives of psychedelic therapy. It should be noted that patients must be able to understand the decision, assess the consequences of the decision, and have the opportunity to decide against treatment at any time.

Substance session

Preparation

Preparing for a session with psychedelic substances is an important part of psychedelic therapy. It requires careful planning to ensure the safety and well-being of patients. On the one hand, it consists of preparing them comprehensively for the procedures, experiences and rules of conduct during the substance session. Detailed psychoeducation regarding the psychotropic effects of psychedelics is central to this. On the other hand, it is important to create a basis of trust in order to provide support during the usually emotionally and cognitively challenging experiences of altered states of consciousness in a therapeutically meaningful way. This basis of trust is often seen as a decisive factor in psychedelic therapy. Agreeing on the framework and rules for behavior during the substance session supports safe implementation and provides a safe framework (Jungaberle et al., 2018). "Dry runs" in the form of music-guided imagination or mindfulness exercises (e.g. body scan) can be helpful for preparation. Expectations for the treatment should be discussed. For example, a concise thought support or a pictorial metaphor can express a therapeutically meaningful and realistic approach goal without creating too much pressure to succeed (Evens and Wolff, 2024).

Implementation

The therapy session should take place in a relaxed, safe atmosphere in a quiet, aesthetically pleasing room that is adequately equipped for the medication requirements. Rooms in psychiatric clinics and outpatient clinics or in specific practices that are easily accessible in emergency situations and yet are away from the sometimes noisy rooms of a ward have proven to be suitable. At least one accompanying person (doctor, psychologist, nurse) should be present during the entire use of the psychedelic. For safety reasons, it has proven to be best for two people to accompany the patient, whereby the combination of a doctor or psychologist with a nurse is ideal in clinics. During the entire session, a doctor must be available on call at all times, i.e., be able to be in the therapy room within a very short time (minutes). In outpatient clinics or practices that are appropriately staffed and equipped, the treatment setting can be organized in a similar way. Group treatments are also possible, but for safety reasons (for example, if individual patients require intensive care and need to be separated from the group), there must be a sufficient ratio of therapists to patients. Based on previous experience with psychedelic therapy in a group setting (Agrawal et al., 2024; Ross et al., 2022), also in Switzerland from 1988 to 1993 and since 2016 (Oehen and Gasser, 2022), we recommend limiting the group size to a maximum of 4-6 patients and ensuring supervision by at least 2-3 therapists. For larger groups, a similar care ratio should be ensured.

The course of the substance session can be individually designed, whereby supportive accompaniment during the altered state of consciousness and the minimization of somatic and psychiatric safety risks are a central task. Patients should be accompanied throughout the entire treatment process so that intervention can be made if necessary in the event of emerging anxiety or other psychological symptoms. As the effects of the substance wear off, patients usually feel the need for a relieving, sometimes therapeutic conversation.

In the evening after administration, the patient's condition should be evaluated in the form of brief (e.g. nursing) contacts. Sufficient reserve medication (e.g. sleep reserve, analgesics for headaches) should be ensured. The patient should be discharged home on the day of the substance session once the substance effects have completely subsided (usually after 6 to 8 hours in the case of psilocybin and after 12 to 16 hours in the case of LSD) (Ley et al., 2023) and after careful assessment of the psychological and somatic risks. If a patient goes home after the session, it must be ensured that a reliable accompanying person takes the patient home and is available for the following

24 hours. The patient should be instructed to rest and not to undertake any physically or mentally demanding activities. It should also be discussed that no far-reaching decisions (e.g. resignation, ending a relationship, etc.) should be made in the next few weeks. Patients should also be given clear instructions on what to do in the event of any side effects or psychological distress, including emergency contact information. Telephone or electronic check-ins are scheduled for the next day and the following days to monitor the patient's condition and ensure that no complications occur. An initial follow-up visit to the clinic should take place within two to three days in order to carry out a comprehensive assessment of the patient's physical and mental condition and to initiate any necessary therapeutic measures. These follow-up visits are crucial in order to monitor therapeutic progress and adjust further treatment if necessary.

Physical touch

All therapists should be trained in ethical boundaries and the specific risks associated with physical touch. Physical touch during substance use sessions is associated with high ethical risks due to altered states of consciousness. Touching during substance use sessions can lead to boundary violations due to the increased suggestibility and vulnerability of patients. Historical abuses in the context of psychedelic therapies emphasize the urgency of strict boundaries to prevent touching that is clearly inappropriate and unethical (Villeneuve and Prescott, 2022). In contrast, the potential benefits of touch in specific situations must be weighed against this. Furthermore, certain types of touch are culturally accepted (e.g. social gestures such as handshakes) and are even necessary in certain situations to ensure patient safety (e.g. blood pressure checks, holding hands during acute anxiety). Touching that is potentially inappropriate and unexpected (e.g. hugging or stroking) is problematic and should therefore be rejected. We recommend that non-touch methods of calming are generally preferred during psychedelic therapy. The threshold for the use of touch should be set high. Prior to the substance sessions, a careful risk-benefit assessment should be carried out together with the patient and in the context of inter- and supervision sessions (Devenot et al., 2022; McNamee et al., 2023).

As the altered state of consciousness during the substance session affects the patient's cognitive ability to consent to or refuse touching, prior, written and fully informed consent should always be obtained regarding any necessary touching (e.g. for safety or medical reasons) during the substance session (Marks et al., 2024; McGuire et al., 2024). In particular, therapists should ensure that patients fully understand the location (e.g. hand) and duration (as brief and one-off as possible) of touching that may occur during sessions, the reasons for it (e.g. acute, verbally inaccessible anxiety) and their right to refuse touching at any time, including during the session. In addition, if mutually agreed upon, sessions can be videotaped to ensure accountability and transparency. In individual sessions, 2 people of different genders should usually be present, at least intermittently, to observe interactions and prevent inappropriate behavior.

Safety measures and emergency medication

Regular, intermittent, or continuous monitoring of vital functions and mental state should be carried out during use. With MDMA in particular, attention should be paid to possible physical side effects. Care should be taken to ensure adequate fluid intake, small snacks (e.g. cereal bars) and accompanied visits to the toilet. The intake of other medications should be avoided as much as possible during psychedelic treatment. On the other hand, emergency medication for the treatment of acute anxiety, psychotic exacerbations or increases in blood pressure that cannot be controlled with psychological measures must be available quickly **(Table 4)**.

Table 4: Recommended emergency and reserve medication during and after substance use sessions

Indication	Drug	Dosage
Blood pressure ≥ 180/110 mm Hg	Nifedipine (retard)	20 mg
Nausea	Domperidone	10 mg
Fear, panic, excitement	Lorazepam	1-2 mg

	Ketanserin (serotonin 2A receptor antagonist) (Holze et al., 2024b; Schmid and Klaiber, 2024)	40 mg
Psychosis	Olanzapine Ketanserin (Holze et al., 2024b; Schmid and Klaiber, 2024)	5-10 mg 40 mg
Headache	Paracetamol	500-1000 mg

Follow-up

Similar to the final discussion on the day of therapy, a therapeutic debriefing takes place in the following days. The early detection and treatment of side effects or psychological deterioration is an important task here (Evens and Wolff, 2024). As a result of the generally emotionally activating and challenging substance use, some patients may experience a temporary crisis-like intensification and worsening of symptoms, which can last for a few days, but in some cases even longer. In these cases, close monitoring and, if necessary, concomitant symptomatic drug therapy are necessary for at least the following days. This requires appropriate therapeutic availability in the future and good consultation and coordination with any other practitioners. The condition often improves significantly within a few days. However, non-response and deterioration can also be observed. It should also be borne in mind that psychedelic treatment appears to be the "last option" for many patients and that disappointment can lead to crises. Patients are then transferred back to regular care in a timely manner (e.g. continuation of outpatient psychotherapy and corresponding transfer of information to those providing follow-up treatment within days or a maximum of one week).

Quality assurance

Psychedelic therapy is a supplement to the existing state-of-the-art therapies in psychiatry and psychotherapy. For this reason, particularly high-quality requirements are placed on the training, further education and training of the doctors who use it. The quality of these specific competencies in psychedelic therapy should be ensured through transparent, evidence-based and certified basic, further and advanced training.

SIWF certificate of proficiency in psychedelic therapy

The certificates of competence recognized by the Swiss Institute for Continuing Education and Training (SIWF) are, according to Article 50 of the SIWF Continuing Education Regulations, "valid as confirmation of structured and controlled continuing education and training courses in the field of clinical and non-clinical medicine that, in terms of their scope or significance, do not meet the requirements of a specialist title. Certificates of competence can also be used to confirm the completion of further or advanced training courses for certain examination or treatment methods and for other, primarily technical skills".

As psychedelic therapy is a specific, circumscribed psychiatric treatment method, the creation of a SIWF-certified psychiatric certificate of competence in psychedelic therapy is intended to create a gold standard for further training in psychedelic therapy. Skills already acquired in psychedelic therapy will be taken into account through transitional provisions in the introduction of the certificate of competence.

Self-awareness

The historically widespread but never empirically investigated assumption that psychedelic self-awareness must be assumed by therapists for high-quality and safe psychedelic therapy needs to be examined more closely. While several authors have described the potential benefits of psychedelic self-awareness (including enhanced empathy and understanding, improved therapeutic outcomes, increased credibility and trust, informed training and

supervision, and better navigation of altered states of consciousness) (Nielson and Guss, 2018). However, no study to date has systematically investigated the impact of therapists' personal psychedelic experiences on treatment outcomes. So far, there are only self-reports from therapists indicating that they have benefited personally and professionally from their own psychedelic experiences (Nielson, 2024). Therefore, based on current evidence, the requirement of psychedelic self-experience as a quality criterion is not justifiable (Emmerich and Humphries, 2023; McGovern et al., 2023; Villiger, 2024). Furthermore, the use of most psychedelics in the context of self-awareness is illegal.

Conclusion

The treatment of mental illnesses with psychedelics has been carried out on a case-by-case basis by the FOPH in Switzerland since 2014. The clinical study situation with modern methods increasingly supports its use. Internationally, there are already completed or ongoing efforts to implement the treatment in everyday clinical practice. On the other hand, the therapeutic field is still poorly regulated and guidelines and treatment recommendations have not yet been agreed. In this respect, this study aims to make a fundamental contribution to the future coordinated evidence-based use of psychedelics in psychiatry and psychotherapy in Switzerland.

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Statements

Thank you(s)

We would like to thank Prof. Dr. med. Matthias Liechti, Clinical Pharmacology, University Hospital Basel, for reviewing the manuscript, especially with regard to the pharmacological aspects of psychedelic therapy.

We would also like to thank the psychiatric societies that were involved in the development of these treatment recommendations under the leadership of the Swiss Society of Psychiatry and Psychotherapy (SGPP): Swiss Conference of Academic Psychiatry (SCAP), Swiss Association of Psychiatric Chief Physicians (SVPC), Swiss Society for Anxiety and Depression (SGAD), Swiss Society of Biological Psychiatry (SGBP), Swiss Society of Interventional Psychiatry (SGIP), Swiss Society for Addiction Medicine (SSAM), Swiss Society for Drug Safety in Psychiatry (SGAMSP), Swiss Society for Bipolar Disorders (SGBS), Swiss Medical Association for Psycholytic Therapy (SÄPT).

Author Contributions

RK: Responsible for the process Development of treatment recommendations, drafting, discussion and implementation of consultation comments. ES: Consultation SGPP; RK, RB, AB, JH, GH, MH, UH, DH, AK, FM, SO, FR, MV, SW, ES: Significant contributions to the design of the work, revision, discussion, finalization.

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