UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

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ATTITUDES AND KNOWLEDGE ON PSYCHEDELICS AND PSYCHEDELIC-ASSISTED PSYCHOTHERAPY

DOCTORAL DISSERTATION

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Mentor: Prof. Darko Duplančić, MD, PhD

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Table of Contents

1 List of Abbreviations

2-CB – 4-Bromo-2,5-dimethoxyphenethylamine

5-HT2A – Serotonin 2A

APQ – Attitudes on Psychedelics Questionnaire

BDNF – Brain-derived neurotropic factor

CCC model – Claustro-cortical circuitry model

CFI – Comparative Fit Index

CI – Confidence interval

DMT – Dimethyltryptamine

FDA – Food and Drug Administration

HCW – Health care workers

IQR – Interquartile range

LSD – Lysergic acid diethylamide

Md – Median

MDMA – 3,4-Methylenedioxymethamphetamine

MDMA-AP – 3,4-Methylenedioxymethamphetamine-assisted psychotherapy

NMDA – N-methyl-D-aspartate

PAP – Psychedelic-assisted psychotherapy

RCT – Randomized controlled trial

REBUS model – Relaxed beliefs under psychedelics model

RMSEA – Root Mean Square Error of Approximation

SRMR – Standardized Root Mean Squared Residual

TLI – Tucker-Lewis Index

2 INTRODUCTION

Psychedelics are hallucinogenic psychoactive substances that cause sensory, affective, and perceptual alterations (1). The term "psychedelic" comes from the Greek words ψυχή (psyche, "soul, mind") and δῆλος (dêlos, "manifest, visible") and designates these substances as "mind-manifesting", i.e. manifesting the mind or soul within. It was first coined by Humphy Osmond, an English psychiatrist and one of the early clinical researchers working with psychedelics in the 1950s (2). However, there are multiple historical terms that are still sometimes used interchangeably for this group of substances, including: psychotomimetics, hallucinogens, and entheogens, among others (3).

Psychedelics constitute a sub-group of the larger and more heterogeneous pharmacological group of hallucinogens, which additionally include the sub-groups of dissociatives and the deliriants (4). According to a comprehensive review by Johnson et al. (5), we consider classic psychedelics to be substances with primary action at the serotonin 2A (5-HT2A) receptor. Generally, they are classified into two groups based on their molecular structure: tryptamines and phenethylamines. Some examples of tryptamine psychedelics are lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT). DMT is the psychoactive substance present in the South American sacramental beverage called ayahuasca, which is brewed as a combination of the *Banisteriopsis spp.* bark and the *Psychotria viridis* plant. An example of a phenethylamine is mescaline, the main psychoactive agent found in the peyote (*Lophophora wiliamsii*), Peruvian torch (*Echinopsis peruvianus*), and San Pedro (*Echinopsis pachanoi*) species of cacti. There are also a number of synthetic substances in the phenethylamine category, such as 4-Bromo-2,5-dimethoxyphenethylamine (2C-B), that can be categorized as psychedelics. Unlike the psychedelics previously mentioned, they do not occur in nature.

Although 3,4-methylenedioxymethamphetamine (MDMA) is not considered a classic psychedelic, it has certain similarities in its effects and chemical structure to traditional psychedelics, so it is frequently cited alongside them (5, 6). Some sources classify it as a stimulant, while others added it to a more refined category of an *empathogen* or *entactogen* (7). Ketamine is often also mentioned as part of the psychedelic group. However, relevant psychopharmacological literature classified it as a dissociative hallucinogen due to its mechanism of action on glutamate pathways in the brain, via N-methyl-D-aspartate (NMDA) receptor antagonism, and the subjective dissociation character of its effect (8).

The latest definitions used have thus grouped psychedelics into classic psychedelics, which we mentioned above, as well as atypical psychedelics, where we find ketamine and MDMA (9).

2.1 History of psychedelic research

The ritual use of psychoactive substances is ubiquitous in history, ranging from hunter-gatherer cultures to agriculture-based civilizations around the globe. Many of such practices were used for the purpose of religious rites, healing, or divination; often also associated with shamanism (10, 11). These practices, as confirmed by archaeological findings in which the presence of psychoactive plant sources can be detected, range far into Prehistory, some as early as 13000 BC (12, 13).

An example related specifically to psychedelics is present in the religious rituals of the ancient Greeks and, later, the ancient Romans. The Eleusinian Mysteriers were seasonal religious rites related to the cult of Demeter and Persephone, and included the ritual consumption of a drink called *kykeon.* Later archeometric analyses have demonstrated that the drink, consumed by all ritual participants, may have included ergot fungi which show LSD-like properties (12, 14). The Amazon region in South America is known for its ritual use of the DMT-containing beverage, ayahuasca. Indigenous tribes have a long-standing tradition of use of the plant in healing and initiation rituals. These usually take place in groups led by folk healers, witch-men often called *curanderos*. Similarly, divine mushrooms have been ritually consumed in the Yucatan peninsula since before the time of the Mayas, under the name of *teonanactl*, administered by shamans, sorcerers and, in the time of the Aztec and Maya empires, state-sanctioned priests.

In 1955, an American author and ethnomycologist, R. Gordon Wasson, managed to take part in a ceremony of a Mazatec Indian curandera, Maria Sabina, and consume a psychoactive mushroom. Upon returning to the United Stated, he wrote an article for *Life* magazine, where he detailed his experiences as a first-hand report. This was instrumental in reintroducing psilocybin-containing mushrooms to a wide audience in the West, and returning them to popular awareness (1). The biggest catalyst for the 20th century wave of psychedelic research, however, was the discovery of LSD by Swiss chemist, Dr Albert Hoffmann, working for the Sandoz pharmaceutical company. He synthetized it in 1938 and only discovered its consciousness-altering properties five years later, when he accidentally ingested the substance and experienced significant psychedelic effects. This led to Sandoz becoming interested in the

substance and handing out batches of LSDs to research groups which were interested in exploring its properties (15).

After this discovery, psychedelics, with a predominant focus on LSD, began to be explored for their effects in treating various mental illnesses. It is estimated that thousands of patients over a period of around 15 years received some form of psychedelic-assisted psychotherapy (1). In the United States, psychiatrist Humphry Osmond conducted studies on LSD as a method of treating alcoholism. Initial results showed high success rates of around 40-50%. However, with time, many of the patients relapsed, since no long-term follow-up was in place (15). The predominant model of these therapeutic efforts was the *psychedelic* model, with only one or two very high doses administered to patients, with the aim of eliciting a very intense experience that shifts one's personal narrative, as well as provides mystical elements of insight (10). LSD-associated psychotherapy was also popular in Europe, but there the dominant model was the *psycholytic* concept of therapy. In this therapy model, neurotic patients were given successively increasing doses of LSD and concomitantly underwent classic Freudian psychotherapy. The rationale was that administering LSD, based on what was known about its effects, could loosen a patient's psychological defense mechanisms, allow easier emergence of unconscious content, thus allowing inner conflicts to be resolved (10, 16). Around the same time, the United States government was interested in LSD as a potential agent in warfare. A secret project by the Central Intelligence Agency called MK-ULTRA, today associated with significant notoriety, was created to explore potential uses of LSD in interrogation and mind control, sometimes involving the dosing of individuals with LSD without their consent and, sometime without their knowledge (15).

However, a 25-year hiatus of psychedelic research followed after restrictive policies were gradually implemented. The halting of psychedelic research followed increased criminalization of psychedelics which happened because of the rise of widespread and uncontrolled use and manufacture of psychedelics outside the research setting. These new trends in psychedelic use led to concerns about public health and safety (17). Psychedelic use became increasingly associated to the counterculture movement, hippie sub-culture, and radical political movements. Here, one of the instrumental figures was Harvard psychologist Timothy Leary, who became interested in the consciousness-expanding properties of LSD, especially in the context of radical social change. He is known for his slogan urging youth to "Turn On, Tune In, Drop Out" and was generally advocating widespread use of LSD. He was terminated from his employment at Harvard, which caused him to gain even more publicity and notoriety. His

efforts led to a popularization of the use of LSD, especially widespread use among the public, as well as the rise of interest for exploring its effect among young researchers (15).

After the aforementioned long hiatus, psychedelic research is once again seeing resurgence today, with the highest emphasis placed on trials on the potential of psilocybin, MDMA, and ketamine to treat highly prevalent mental disorders such as major depressive disorder, post-traumatic stress disorder, and treatment-resistant depression. Since the early 2000s, the therapeutic safety and efficacy of using psychedelics as treatment has begun to be examined in a modern, clinical context. This is often referred to as the "new era of psychedelic research", sometimes even "the psychedelic renaissance" (6, 17).

Phase 2 clinical trials have shown the potential of these substances to have a therapeutic effect and even change an individual's personality characteristics, such as openness. These developments are also reported to have a potential to answer unknown questions about brain functions and the nature of consciousness (18). Since 2012, the US Food and Drug Administration (FDA) has designated two psychedelics as "breakthrough therapies": MDMA and psilocybin, for post-traumatic stress disorder and depression, respectively (19). MDMA, in particular, has reached phase 3 trials and has shown favorable effects in treating post-traumatic stress disorder when co-administered with psychotherapy, i.e. MDMA-assisted psychotherapy (MDMA-AP) (20, 21). An application to the Food and Drug Administration to allow the use of MDMA-AP in a medical context is currently underway and is expected to be filed in late 2023 (22).

2.2 Subjective effects and side effects of psychedelics

A quote by the writer Aldous Huxley, describing his mescaline experience in the book The Doors of Perception, is a suitable introduction into the subjectively perceived effects of psychedelics (23):

> *"The legs, for example, of that chair--how miraculous their tubularity, how supernatural their polished smoothness! I spent several minutes--or was it several centuries? -- -not merely gazing at those bamboo legs, but actually being them---or rather being myself in them; or, to be still more accurate (for "I" was not involved in the case, nor in a certain sense were "they") being my Not-self in the Not-self which was the chair."*

As evidenced by Huxley's described experience, psychedelics acutely cause significant alterations of consciousness. A systematic review of psychedelics' subjective effects by Breeksema et al. (24) describes that, under effect of psychedelics, participants reported altered physical and general sensory perception, often with synesthetic phenomena and characteristic fractal-like visual patterns which appear with eyes closes, and, at higher doses and experience intensities, also with open eyes. These can sometimes take the form of immersive visions, often of high personal significance, especially under the influence of psilocybin and ibogaine. Other perceptual alterations include alterations in the perception of passing time, which often appears as slowed or completely absent. Bodily sensations described as "strange" are sometimes reported, especially with ketamine. Finally, many individuals under the influence of psychedelics describe the phenomenology of their experience as ineffable, or difficult or impossible to describe in words.

On the psychological and emotional level, psychedelics are described as "magnifiers of consciousness", often amplifying and accentuating mental contents that are already present in an individual's mind (25). This magnifying effect can lead to increased emotional processing and an increased emotional spectrum. Individuals sometimes report gaining personal insight in the form of increased self-awareness and understanding and decreased self-criticism, as well as feeling connected to the universe and other people (24). At increasing doses, psychedelics can cause mystical-type experiences, where a person feels a sense of the unity of all people and things, a feeling of sacredness, and a sense of an authoritative truth behind the experience, the stripping away i.e. dissolution of one's ego, as well as feelings of euphoria and boundlessness (26, 27).

What seems to be very specific for psychedelic experiences is the co-called "set and setting" phenomenon. The idea behind it is that the expectations, emotional state, and personal history of the individual undertaking the experience (the "set") and the surroundings and context of where and how the experience takes place (the "setting") work together to determine the nature of the experience, as well as whether it tends to be pleasant or unpleasant, with significant variations of psychedelic effect among individuals (28, 29). This ties into the finding that psychedelics appear to increase a person's suggestibility, which could explain the significant influence of personal and external factors on a person's subjective experience of the psychedelic effect (30). This somewhat volatile nature of psychedelic effects, especially when combined with an uncontrolled setting that the participants perceives as unsafe, can sometimes lead to experiences which the literature calls "challenging", and which are characterized by

short-term distressing psychological symptoms such as fear, acute anxiety, feelings of panic and paranoia and an increased risk of exposing oneself to physical harm (31, 32).

In addition to acute effects, a systematic review by Goldberg et al. (33) explored the post-acute effects of psychedelics, defined as those that arise after more than 24 hours after the psychedelic experience. The review used reports from patients in experimental studies involving psychedelics (either randomized controlled trials or pre-and post-trials). Individuals often reported a reduction in depressive symptoms after PAP sessions. Psychedelics were also associated with reduced substance use among some of the individuals, in particular, decreased alcohol and tobacco consumption. There is also a possibility of long-lasting changes in patients' perspectives, values, and life priorities after the psychedelic experience, very commonly involving a greater appreciation for nature, e.g. higher nature-relatedness. Likewise, psychedelics appeared to enhance resilience and coping strategies, helping individuals better manage any stress and adversity that arose. There were also some effects on personality and mindfulness, but these results were considered to be less robust due to possible publication bias.

However, a systematic review on long-term effects of psychedelics by Aday et al. (34) warned that, although not many negative experiences have been reported in the research literature, the long-term effects of psychedelics are not known. Psychedelics are also specific because one cannot know how a person will respond to them, as this is highly context-dependent. This new era of psychedelic research that began in the 21st century, uses stringent research protocols that seek to minimize any harm to patients, which is likely to account for their favorable side effect profile. Additionally, their potential for causing addiction appears to be low (35, 36). The relationship between classical psychedelics and suicidality is unclear; there were several suicide cases in the very early wave of psychedelic research. A 2021 systematic review found no reports of increased suicidality in recent trials involving psychedelics, but rather found preliminary evidence for acute and sustained decreases in suicidality after treatment (37). However, a large phase 3 clinical randomized controlled trial (RCT) where a single dose of psilocybin was administered for treatment-resistant depression saw increased suicidal ideation both in the control and active treatment arms, restating caution on potential increases in suicidality within this format of therapy (38). Overall, a systematic review of side effects in trials with MDMA and psychedelics stated that many of the trial protocols did not include systematic monitoring of adverse events, and that more research is needed to systematically assess responses and potential side effects to these substances (39).

2.3 Psychedelic-assisted psychotherapy (PAP)

Psychedelic-assisted psychotherapy (PAP) is the term used for treatment using psychedelics, which includes their co-administration with psychotherapeutic support and supervision. As described in a comprehensive review of PAP by Schenberg (6), the combination of psychotherapy and the administration of psychoactive substances is an uncommon model in modern psychiatry, which usually uses daily therapy to correct neurochemical imbalances. Instead of psychedelics simply correcting functional imbalances in the brain through the activation of specific receptors, the goal is to use the acute drug effects to get the patient in a certain state where they are able, guided by psychotherapeutic support, to receive increased insight and personal emotional breakthroughs that would then lead to subsequent changes in behavior, brain function, and the patients' subjective experience of themselves and the world around them. The PAP format has been developed and received its name in the 21st century era of psychedelic research. A prototypical model of PAP has so far been used in trials of psilocybin, MDMA, and LSD.

PAP consists of 3 stages: preparation, dosing, and integration (40). After study volunteers for PAP are recruited and screened, they undergo several (usually including at least four meetings) of preparatory sessions with a therapist before a dosing session happens, in which a psychedelic is actually administered to the patient. At least one of these meetings is conducted in the room where the dosing session takes place, in order to prepare the participant by familiarizing them with the environment. The main purpose of these meetings is to establish therapist-patient rapport. The discussion usually revolves around the patient's personal history, feelings, and expectations, as well as explaining the study logistics. These meetings help prepare the patient for the upcoming psychedelic experience and often discuss strategies for dealing with any challenging feelings that may arise (41). The dosing sessions for both psilocybin and MDMA take place under the supervision of two therapists, one male and one female, in a living-room like environment that is aesthetically decorated in order to not appear as a hospital room. The dosing sessions often have music playing, which is carefully selected in advance, and a playlist is often standardized for all participants. Music has been recognized to a profound effect on the psychedelic experience, helping to facilitate patients to enter mystical states (42). Each dosing session is followed by an integration session, where the goal is to summarize the insights the patient received in the dosing sessions and help the patient apply these to their everyday life (40). The number and timing of dosing sessions varies by psychedelic substance and throughout different clinical trial protocols, but generally ranges from 1-3 sessions for MDMA

and psilocybin. So far, it seems that patients in studies that used multiple dosing sessions were more likely to have a positive treatment outcome (43).

A thematic synthesis by Breeksema et al. (24) summarized all qualitative studies with patients who underwent PAP in order to provide a perspective on what the format of PAP specifically provides to the psychedelic experience and the patients themselves. Patient reports within the study often described a cathartic emotional release, increased emotional insight, a sense of connection with others and the universe. Some patients also reported challenging or difficult moments during PAP sessions, which were typically attributed to the confrontation of personal traumas or fears. However, these challenging experiences were often seen as valuable for personal growth and healing, especially in the context of PAP, where the patients already initially had an intention to confront their trauma or other difficult feelings or memories. There was an emphasis on the fact that presence of trained therapists and a safe and supportive environment was crucial in ensuring a positive acute experience, thus differentiating it from psychedelic use in a recreational and/or uncontrolled setting.

2.4 Current theories of therapeutic mechanisms of PAP

There are several postulated mechanisms on why psychedelics, in treatment using PAP, contribute a therapeutic effect. According to a critical review by van Elk and Yaden (44), these can be sorted into three categories: pharmacological, neurocognitive, and psychological.

The most widely discussed feature of psychedelics' pharmacological effects is the *serotonergic model*, i.e. psychedelics' modulation of serotonergic activity within the brain through high binding activity to the 5HT-2A receptor. Psychedelics' intense visual effects and the stimulation of higher-order associative areas of the brain are likely due to the serotonergic activation, because those brain areas have a high density of 5HT-2A neurons. However, besides this primary effect, psychedelics also bind to many other different sub-types of serotonin and dopamine receptors, explaining the complexity of their action on mood and perception (44). Another highly discussed model of psychedelic effects in this category is the so-called *psychoplastogen model*, which states that psychedelics stimulate brain neuroplasticity. A systematic review by de Vos et al. (45) on studies exploring this hypothesis summarized that the repeated administration of psychedelics acutely stimulates neurogenesis and subacutely stimulates molecular neuroplasticity. Along with this, psychedelics seem to increase peripheral circulating levels of brain-derived neurotropic factor (BDNF), which could explain this effect. However, more studies are necessary to elaborate this hypothesis in more detail, although these

findings support the clinical observations of the acute antidepressant and anxiolytic effect of psychedelics and ketamine.

Different neuroscientific hypotheses have been proposed to explain the effects of psychedelics on the brain. The three main hypotheses are the thalamo-cortical filter theory, the relaxed beliefs under psychedelics (REBUS) model, and the claustro-cortical circuit model (CCC) model (44). The *thalamo-cortical filter theory* postulates that psychedelics release sensory filters, whereby the selective filtering of both interoceptive and exteroceptive stimuli by the thalamus is shut off, explaining the significant perceptual alterations during the psychedelic effect (46). The *REBUS model* proposes that psychedelics relax the brain's usual filtering mechanism, allowing a wider range of thoughts and perceptions to flood into consciousness, which can lead to the profound and unusual experiences associated with these substances (47). Finally, the *CCC model* is mostly based on neuroimaging observations. It describes that direct activation of 5-HT2A neurons in the claustrum, may cause a destabilization of usual brain network states and a reduction of executive functioning, causing some of the characteristics of psychedelic states like the feeling of ineffability. However, this model is still considered to be unexplored because it does not account for all of the observed acute effects of psychedelics (48).

One of the main psychological mechanisms behind psychedelic effects is their potential to cause altered and affective states, often with feelings of gaining new insight and perspective (44). These include the previously described mystical states, which are often considered by individuals as difficult to put into words, but at the same time some of the most important experiences in their lifetime, similar to the birth of a child or the loss of close relation (49, 50). The mystical aspects of the psychedelic experience may explain their therapeutic potential because the experience provides the person with a different perspective on their life, thereby enhancing its perceived meaning and purpose, especially important in conditions like major depressive disorder (49). Similar to this, psychedelics can also cause the experience of *ego-dissolution*, which is characterized by a complete loss of self-awareness and the loss of a definite “I” that is separate from the world around them (51). The concepts of mystical experiences, awe, and ego-dissolution overlap heavily, so this is still considered an area warranting exploration and more careful definition, especially when trying to see if these experiences are always of a positive emotional valence, as they are often presented in the literature (52).

Along with this, psychedelics also seem to increase health-promoting behaviors that can lead to taking up a healthier lifestyle, for example, through improving eating habits and quitting smoking (53). They have also been shown to increase psychological flexibility, defined as an adaptive response that individuals experience when faced with stressors that then result in value-driven action and increased problem-solving (54). Finally, psychedelics induce strong feelings being connected with other people, nature, and humanity or the universe as a whole. This can contribute to feeling one's experience as more meaningful and can encourage a more conscious way of life (55, 56).

2.5 Methodological limitations of clinical trials of PAP

Many clinical trials on PAP published so far have been criticized for having small samples, not having an extensive longitudinal design, and often including participants that already had a previous history of psychedelic use, which could be a confounding factor that influences their treatment experience (34). The safety of PAP has so far been observed only under very strict research protocols, controlled conditions, and with careful screening of participants. Since these strict patient eligibility criteria limit the studies' generalizability, it is not clear if such treatments could be widely used (57). A systematic review by Muttoni et al. (58) highlighted the fact that there are significant methodological issues with blinding in psychedelic trials. Since subjective effects of psychedelics at high doses are very specific, even patients in RCTs may be aware of treatment group allocation simply due to recognizing the presence or lack of certain phenomena, especially if the control group received inactive placebo. If patients have had previous personal experience with psychedelics, this effect could be more amplified. Study authors have, in part, managed to circumvent this by providing patients in the control group with inactive placebo, i.e. a low-dose psychedelic whose subjective effects can at least partially decrease the chance of the blind being broken, although issues still remain. In order to improve the methodological rigor of further psychedelic trials, Aday et al. (59) have suggested the following: recruiting patients who have previously not used psychedelics, study investigators emphasizing the uncertainty of the efficacy of PAP to minimize expectancy of positive results among participants, estimating the size of the placebo effect with special power calculations, as well as determining and measuring whether participants and therapists guessed the treatment group allocation correctly.

There are also many unknowns in terms of ideal protocols of PAP, including a concern that has been raised in 2023 that states that it is still currently unknown what the benefit of the

"psychotherapy" part of PAP is, and whether this psychotherapeutic support is an essential and relevant adjunct to the administration of the substances themselves. A recent criticism of the PAP model (60) emphasized that the current protocol of "psychotherapy" provided through that treatment model is not standardized, and includes general supportive and non-directive care that does not belong to any particular school of psychotherapy and can be influenced by the personal style of the psychotherapist. This criticism of PAP, focused primarily on psilocybin, concluded that the utility of the "psychotherapy" provided should be tested in clinical trials, and that, until its exact effects are known, it would be perhaps best to reconsider using the umbrella term "psychedelic-assisted psychotherapy". One option would be, in the case of psilocybin, to replace it with the name "psilocybin therapy," and leave an open option that such extensive inclusion of psychotherapists may not be necessary, thus also decreasing potential future costs of psychedelics as a treatment option.

2.6 Ethical issues in psychedelic research

Psychedelic research is unarguably currently subject to a high amount of hype and excitement that PAP could be a game-changing intervention in addressing unmet needs of treating difficult mental disorders. At the same time, psychedelics have certain properties that make their use in the therapeutic setting highly specific. Studies have reported that psychedelics increase suggestibility and that psychedelic use can also alter worldviews and various personal beliefs (28, 30, 51). For this reason, Anderson et al. (61), in a comment published in *The Lancet Psychiatry*, warned against dangers in the dynamic between investigators and patients, where both parties could experience grandiosity and wild enthusiasm about psychedelics that could ultimately harm the treatment process. The authors are psychedelic researchers themselves, and they described the drugs as having an "uncanny allure" to various individuals. For this reason, many potential trial participants could bring heightened and unrealistic expectations to their treatment. At the same time, therapists need to be responsible and keep strict ethical boundaries in the relationship with their patients.

The vulnerability of patients during a psychedelic experience can open them up to risks of boundary violations. For example, there are concerns about MDMA making individuals more vulnerable to sexual advances (62). In 2018, one patients from a MDMA-AP trial filed a lawsuit against her male PAP therapist for repeated sexual assault, which happened in the presence of his wife, who was the second PAP therapist present in the dosing sessions (63). A New York Times investigative journalism project was featured in the podcast called "Power Trip" and

released in 2021, resonating throughout the psychedelic community (64). It featured the anonymized testimonies of individuals who were harmed by unethical practices, both in underground psychedelic treatment, but also in MDMA-AP clinical trials. This podcast has stirred up discussion about the dark side of the psychedelics which has, for the most part, been ignored in the current wave of psychedelic research and enthusiasm.

An extensive review on ethical issues related to PAP by Smith and Appelbaum (65) also highlighted that psychedelics have a high potential for being exploited by commercial interests and a rush to apply for patents, that the push for legalization of recreational psychedelic use may be happening too fast, and that the safety limits in PAP research need to be reasonable and follow the evidence base in the field. They also mentioned a need for organizational structures to oversee therapeutic work with PAP that is emerging from underground scene, especially in the context of maintaining proper therapist-patient boundaries, as mentioned previously. There is also a question related to psychedelic legalization, on whom should retain regulatory power over psychedelics – whether it should be the FDA or that this should happen on a case-by-case basis through legalization laws via local governments.

Finally, Petranker et al. (66) warned against the risk of questionable research practices taking place within the psychedelic research community. Psychedelic science may be particularly vulnerable to them due to the presence of ideological conflicts of interest. This means that research stakeholders may be overly motivated by faith in the usefulness of psychedelics, making them subsequently more likely to be biased towards positive findings and more negative and suspicious towards negative findings. Psychedelics have not only elicited scientific and professional medical interest, but also that of political activists, philanthropists and entrepreneurs. This makes it likely that scientists will be called upon to comment on policy decisions regarding the decriminalization and legalization of psychedelics. Petranker et al. conclude this discussion by offering a research checklist that can help psychedelic scientists optimize their scientific rigor and transparency. It includes recommendations about making research data publicly available, pre-registering study protocols before data begin to be collected, encouraging the replication of studies, and that all papers on experiments with psychedelics should include a “constraints on generality” section, a structured replacement for the usual description of limitations in a discussion section of the paper.

2.7 Attitudes on psychedelics and PAP

Given the previously described cultural, historical, ethical, and methodological complexity of the use of psychedelics and PAP in general, it is not surprising that there is a rapidly rising research interest in evaluating what different groups, such as psychiatrists or patients, think about psychedelics. Psychiatrists, besides having relevant knowledge on psychopharmacology, are also potential treatment providers in case that PAP would enter into wider clinical application.

In particular, there have been several previous research studies aiming to survey what mental health professionals feel about psychedelics and PAP in the context of the controversial nature of such interventions and the novelty and fast pace of research on their therapeutic uses, mostly posed as preliminary and exploratory surveys with small sample sizes. A 2021 survey of psychiatrists showed that personal views on hallucinogens could influence professional opinions and the psychiatrists' willingness to implement them both in research and clinical practice (67). Overall, several surveys showed that mental health experts and psychologists are generally open to psychedelics in the context of medical use (67-72). Some of their main concerns with the use of psychedelics, however, are related to possible adverse events linked to psychedelic use, especially in terms of harms to cognition (68, 70). Despite general attitudes of openness, a certain proportion of the surveyed sample of professionals showed reserved attitudes and highlighted a strong need for regulation and supervision in relation to PAP (71, 73). It appears that it is younger psychiatrists and therapists who are more enthusiastic and optimistic about psychedelics in a therapeutic context. Such younger individuals source their information on the most recent research developments related to psychedelics from a wider variety of sources in comparison with their older colleagues (68, 71, 74).

Despite the baseline openness to new ideas in mental health treatment, such as the one offered by the current studies on psychedelics, there is still a gap between the how PAP is perceived and its possible implementation in practice. Psychiatrists in the UK, for example, do not feel ready or capable enough to talk to patients about psychedelics, nor do they feel that their knowledge about psychedelics is sufficient (74). Laypersons seem to have even more of a knowledge gap, although being younger and having previously used psychedelics is associated with higher self-assessed knowledge on psychedelics (75). Several studies so far have highlighted the need for enhanced education on psychedelics among mental health professionals, especially given that they are receiving more and more attention from various

sources (70, 74). A survey of a sample of psychiatrists at two international conferences showed that they would like to gain more knowledge on what PAP can bring, how PAP is conducted, and generally about the pharmacology and the potential harms of psychedelics (69).

The literature on attitudes on psychedelics is preliminary, and the methodology and methods of assessment in the studies mentioned above were highly heterogeneous. None of the studies so far used a validated psychometric instrument, and the majority showed their results as cross-sectional overviews of the percentage of responses for a certain response category for each question on psychedelics posed to survey participants, which does not allow for statistical comparison or the exploration of predictors of attitudes on psychedelics.

3 AIMS OF RESEARCH AND HYPOTHESES

3.1 Validation of a new instrument for assessing attitudes on psychedelics in the general population

The aim of this study was to develop and test the psychometric properties of a questionnaire to assess attitudes on psychedelics, the Attitudes on Psychedelics Questionnaire (APQ), on a sample of the Croatian general population.

3.2 Attitudes of European psychiatrists on psychedelics: A cross-sectional survey study

The aim of this study was to conduct a survey of a diverse sample of European psychiatrists using a previously validated instrument, the APQ, and applying it in English for the first time.

3.3 European psychiatrists' attitudes on psychedelic-assisted psychotherapy: a qualitative study

The aim of this study was to explore the perceptions of a diverse sample of European psychiatrists on psychedelic-assisted psychotherapy using a qualitative approach, thus enriching the findings obtained by quantitative surveys using the APQ.

4 METHODS

4.1 Validation of a new instrument for assessing attitudes on psychedelics in the general population

4.1.1 Study design and setting

This was an observational, cross-sectional study. This study was pre-registered at the Open Science Framework: https://osf.io/mj96r.

4.1.2 Development of the APQ

We generated an extensive set of 122 English items, both positively and negatively phrasing attitudes towards psychedelics. To help with the creation of the items, we applied the tripartite model of attitudes (affective, behavioural, and cognitive aspects) (76). Four people who were not involved in the study were given the item pool to review for face validity: an epidemiologist, a psychiatrist, a language expert, and a research methodology expert. Their comments were posted online as feedback. The items were re-evaluated in light of their feedback to make sure that each one is unambiguously positive or negative in its formulation and straightforward in its meaning. Uncertain or poorly worded items were not accepted. Following this procedure, we had a pool of 83 items – eight affective, fourteen behavioural, and fifty-four cognitive – that measured people's attitudes towards psychedelics. The answers were on a 5-point Likert-type scale, with 1 representing "completely disagree" and 5 representing "completely agree." One of the authors (MFŽ) translated these items into Croatian; to ensure translation accuracy, a language expert not involved in the study back translated the items into English.

4.1.3 Pilot testing of item characteristics

We performed a pilot survey on 116 students from the Faculty of Humanities and Social Sciences in Split in order to evaluate the features of the 83 questionnaire items that were still available after expert input. Respondents completed the online survey in Croatian using the SurveyMonkey platform (SurveyMonkey Inc., San Mateo, CA, USA). Principal component analysis (PCA) was used to conduct content examination of the 83 items we created, dividing them into sub-scales that represent various facets of attitudes towards psychedelics. We looked at item-total and inter-item correlations in addition to the reliability of each item and each item within a sub-scale. We also computed the mean score for each of these items in order to determine which items were extreme, i.e. those with a deviation in the response distribution

towards answers that were either extremely positive or negative. The structural model of the instrument, which was subsequently tested in the APQ's main validation survey, was constructed using the findings of this pilot analysis.

4.1.4 Validation survey of APQ structure

By employing a convenience snowballing sampling technique, we were able to assemble a sizable and heterogeneous sample of Croatian citizens. Participants completed the online validation survey using the SurveyMonkey platform (SurveyMonkey Inc., San Mateo, CA, USA) in Croatian. The participant had to be older than eighteen to meet the inclusion criteria. Both laypeople and healthcare professionals (HCWs) were included. By excluding those who did not finish the entire survey, any problems with missing data were avoided. In order to reduce the possibility that respondents would read about psychedelics during the survey and potentially introduce bias into their responses, we also eliminated all participants whose survey completion times exceeded 45 minutes. We determined that this was a fair maximum amount of time for survey completion, giving respondents about a minute to complete each question on the knowledge test and questionnaires.

The period of data collection was July 20, 2021 – November 1, 2021. Members of nine distinct groups and associations received invitations to participate in the survey through email or social media groups (the complete list and the timeline of sampling can be found in **Appendix 1**). Contact details obtained from social media or websites that were open to the public were used to send out invitations to groups and associations to distribute the survey. Each author actively distributed the survey on their own through personal connections and social media, because we anticipated that this would yield a high response rate.

The survey was anonymous and comprised three sections: demographic data, a basic knowledge section on psychedelics, and a section on attitudes on psychedelics that included items from our 20-item hypothesised APQ and the Barnett et al. questionnaire (68). Participants were given access to all items in each section (the knowledge and attitudes surveys, respectively) in a randomised order. We gathered demographic data on participants, including age, gender, and highest level of education attained, as well as whether or not they were HCWs and, if so, what kind of work they did. We used conditional reporting to present participants who were HCWs with an additional 5 questions on their attitudes on psychedelics that relate to their healthcare practice (**Table 1**). These questions were only informative and were not considered as a part of the APQ.

Table 1. Additional items for the health care workers' subgroup of survey participants*

Item no.	Item text
1	I would be worried if my institution took part in research with psychedelics. **(R)**
2	I would feel uncomfortable recommending psychedelic treatment to a patient, even if there is evidence for its effectiveness and safety. **(R)**
3	As a health professional, I would be interested in witnessing a psychedelic session with a patient.
4	If I knew that a psychiatrist used psychedelics, I would be less likely to refer my patient to them. **(R)**
5	If I knew a psychiatrist who supported the legalization of psychedelics, I would be less likely to refer my patient to them. **(R)**

*Negatively worded items that are reversely coded are marked by (R).

For the assessment of convergent validity, we included seven items from a previous study by Barnett et al. (68) on attitudes towards psychedelics. Their items were most similar to the APQ's goal, but they were not validated as a scale. Barnett et al. used the term "hallucinogens" in their study, so we modified the item phrasing to "psychedelics" instead of "hallucinogens" so that a proper comparison with our original items could be made (**Table 2**).

Table 2. Modified items by Barnett et al. (68) that were included in our survey*

Item no.	Item text
1	The use of psychedelics increases the risk for subsequent psychiatric disorders. **(R)**
2	The use of psychedelics increases the risk for long-term cognitive impairment. **(R)**
3	The use of psychedelics should be illegal for recreational purposes. **(R)**
4	The use of psychedelics is unsafe even under medical supervision. **(R)**
5	The use of psychedelics shows promise in treating psychiatric disorders.
6	The use of psychedelics may improve outcomes when used during psychotherapy.
7	The use of psychedelics deserves future research for the treatment of psychiatric disorders.

*Negatively worded items that are reversely coded are marked by (R).

A 5-point Likert-type scale, with 1 denoting "completely disagree" and 5 denoting "completely agree," was used to collect responses. The English items were back-translated into Croatian.

In order to verify that participants accurately classified substances as psychedelics and, consequently, that their responses in the attitudes section of psychedelics questionnaires truly referred to psychedelics, we devised a short test measuring participants' basic knowledge of psychedelic substances. The term "psychedelics" was defined more broadly, encompassing not only traditional psychedelics but also substances like MDMA and ibogaine (5).

We created a list of 22 substances, seven of which were psychedelics. The other substances included stimulants, other drugs of abuse, and different psychotropic medications. The substances were given to the participants in a randomised order, and they were asked to check "Yes" or "No" next to each one. "Yes" indicated that they thought the substance belonged in the psychedelic category (see **Table 3**).

Table 3. The basic knowledge on psychedelics test

Substance	**Response options – whether the substance is a psychedelic or not**	
Cocaine	Yes	No
LSD	Yes	No
Psilocybin	Yes	No
Imipramine	Yes	No
Heroin	Yes	No
Ibogaine	Yes	No
Phenobarbital	Yes	No
Methamphetamine	Yes	No
MDMA (ecstasy)	Yes	No
DMT	Yes	No
Digoxin	Yes	No
Mescaline	Yes	No
Modafinil	Yes	No
Ketamine	Yes	No
Haloperidol	Yes	No
Dextroamphetamine	Yes	No
Gamma-hydroxybutyrate (GHB)	Yes	No
Peyote	Yes	No
Rohypnol	Yes	No
Oxycodone	Yes	No
Opium	Yes	No
Mexazolam	Yes	No

They were unable to change their responses once they had been submitted by moving on in the survey. The right answers, along with more details (pharmacological class and mechanism of action) about each non-psychedelic substance, were then shown to them on the next page. The knowledge test served as a quick educational intervention in this way as well. Since we thought that many participants would choose not to answer if given the option, we did not include a "I don't know" response option on the test. We were better able to assess any misunderstandings participants might have about psychedelics thanks to the yes/no forced choice question format (for example, thinking that heroin is a psychedelic drug, even though it is not).

Although it was impossible to guarantee that respondents would not browse the Internet for information about psychedelics while completing the survey, as a precaution, all respondents who took longer than 45 minutes to complete the survey were disqualified. The complete information on the basic knowledge test for psychedelics can be found in **Appendix 2**. The number of incorrect answers (a non-psychedelic answer mistakenly identified as a psychedelic)

deducted from the number of correct answers (psychedelic answer correctly identified) was used to calculate the total knowledge score on psychedelics. We chose this method of calculation because it prevented a participant from obtaining the highest score by marking all substances as psychedelics. The theoretical scale range was from -15 (all answers incorrect) to 7 (all answers correct). To make the interpretation of total scores easier, we converted these scores to a scale ranging from 0 to 100 (conversion formula in **Appendix 2**).

Since we thought that any outliers in attitude scores might actually represent participants' extreme positive or negative attitudes, we included them all in the analysis. It was not possible for the same people to participate more than once because we restricted completion to unique visitors only.

4.1.5 Statistical analysis

All statistical tests were performed using JASP v. 0.14 (JASP Team, 2020, Amsterdam, Netherlands), SPSS Statistics v.22.0 (IBM, Armonk, NY, 2013), R software v.4.1.1. (R Foundation for Statistical Computing, 2021, Vienna, Austria) and MedCalc v. 19.5.3 (MedCalc Software Ltd, 2020, Ostend, Belgium). We assessed the normality of data distribution for all continuous variables through the Shapiro-Wilk test and by observing Q-Q plots. We considered P-values <0.05 as statistically significant.

We showed all demographic information using frequencies and percentages (N, %) except for age, which was shown with median (Md) and interquartile range (IQR). The response rate was obtained by dividing the number of participants with a fully completed survey by the total number of participants who accessed the survey and either completed the survey or gave up on filling it out before the end.

We performed a confirmatory factor analysis (CFA) for different structural models of the APQ to assess the instrument's construct validity. To do this, we used the diagonally weighted least squares (DWLS) estimation method with a polychoric correlation matrix, as recommended by Li et al. for models with ordinal observed variables (77). We assessed the results using the following model fit indices and cut-off values for acceptable model fit (78): Root Mean Square Error of Approximation (RMSEA)$\leq$0.06, Standardized Root Mean Squared Residual (SRMR) $\leq$0.08, Comparative Fit Index (CFI)$\geq$0.95, and the Tucker-Lewis Fit Index (TFI) $\geq$0.95. We expressed the RMSEA using a 95% confidence interval (CI). We used the likelihood ratio test

($\Delta\chi 2/\Delta df$) to compare model fit (79). We also calculated changes in the RMSEA (ΔRMSEA) to additionally compare the models.

We performed a reliability analysis using McDonald's omega (ω) and 95% confidence interval (CI) for the model that was determined to have the best fit. In order to check the instrument's convergent validity, we estimated the correlation (expressed as Pearson's r and a P-value) between the APQ model with the best fit (and its sub-scales) with the total score on the modified version of the Barnett et al. items (68). We evaluated the Barnett et al. items' psychometric properties by conducting an EFA with oblimin rotation, reliability analysis using ω and 95% CI, and CFA to assess model fit (with the same cut-off criteria for model fit as described above).

We used Md, IQR and 95% CI to show scores on the APQ, each of its sub-scales, and the total of the modified Barnett et al. items. We calculated all scale and sub-scale totals as a sum of all items with no weights applied. We showed scores from the basic knowledge test using Md, IQR and 95% CI. We used frequencies and percentages to show the number of correct or incorrect responses for each substance in the test.

We used the Mann-Whitney test for age and the chi-square test for gender and education level to compare demographic data between the included and excluded participants in order to address any potential attrition bias. We used Pearson's r to estimate the correlation between knowledge on psychedelics scores and APQ scores. A linear regression model was constructed with gender, age, education level and HCW status (yes/no) as covariates and APQ scores and each of its sub-scales as the dependent variable, respectively. We expressed the results of this model as standardized regression coefficients (β) and P-values. Coefficients of determination (R^2) were reported for significant predictors. We also conducted a subgroup analysis by using the Mann-Whitney test to compare knowledge and attitude scores between HCWs and non-HCW participants. We presented the response categories of the 5 items for HCWs with Md, IQR, and 95% CI.

We calculated that we needed a minimum sample size of 385 participants. This was done with a sample size calculator set to an unlimited population, a 95% confidence level, a 5% margin of error, and a 50% population proportion (80).

4.1.6 Ethical considerations

We obtained the ethics approval for conducting the study from the Ethics Committee of the USSM (document No. 2181-198-03-04-21-0077). The survey was anonymous. Participants provided their informed consent to both the pilot and validation survey by checking a box to confirm that they want to participate in the survey. They were free to quit the survey at any time and received no special incentives to participate. We did not collect the participants' IP addresses in order to ensure full anonymity.

4.1.7 Deviations from the pre-registered protocol

We determined that it was more appropriate to present the correlation between the Barnett et al. questionnaire and the APQ as a measure of convergent instead of criterion validity. Since we did not establish cut-off points for APQ scores, we refrained from categorizing any of the results as representing favourable or unfavourable attitudes towards psychedelics.

4.2 Attitudes of European psychiatrists on psychedelics: A cross-sectional survey study

4.2.1 Study design and setting

This was a cross-sectional survey study. We collected data through a web-based survey, the SurveyMonkey data collection platform (SurveyMonkey Inc., San Mateo, CA, USA). The study protocol was pre-registered on the Open Science Framework before any of the study data were collected: https://osf.io/upkv3.

4.2.2 Participants

All psychiatrists or psychiatry trainees currently practicing within the European territories were eligible to take part in this study. We considered the following countries as European territories (not restricted to the European Union): Albania, Andorra, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Moldova, Monaco, Montenegro, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Russia, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom. There were no other restrictions or exclusion criteria for participants.

4.2.3 Determination of minimum sample size

According to the most recent information available at eurostat (81), we estimated the number of psychiatrists in Europe to be 100,000. With population of that size, a 5% margin of error and a confidence level of 95%, we determined that we needed a sample of at least 383 participants. The sample size calculation was performed using the SurveyMonkey Sample Size Calculator (82).

4.2.4 Data collection and sampling

We made contact with all European organisations representing psychiatrists that are members of the European Psychiatric Association, which encompasses psychiatrists working in different European nations. We also made contact with trainees in psychiatry via the European Federation of Psychiatry Trainees and all of its affiliated organisations, which encompass its national sub-divisions. We also used a technique called snowballing sampling in which each author shared the survey on social media and with their professional networks and partners. Full information on all the contacted institutions and different means of disseminating the survey are included in **Appendix 3**.

Participants gave their informed consent by checking a box to confirm their participation. We determined that we would stop the sampling after we have surpassed the minimum sample size by at least 100 participants to ensure that we obtained an adequate response rate.

4.2.5 Survey information

The survey consisted of three parts: demographic data, a basic knowledge on psychedelics test, and the 20-item Attitudes on Psychedelics Questionnaire (APQ) previously developed and described within this dissertation (83). We collected the following demographic information: age, gender, country of residence, educational status, primary place of work, primary treatment approach, number of published peer-reviewed articles, previous experience of conducting psychedelic research or therapy (yes/no), self-assessment of personal knowledge on psychedelics, religiosity/spirituality, personal experience with psychedelics. The basic knowledge on psychedelics test and the APQ were previously already described in our dissertation-based published study, and their total scores and sub-scale scores were calculated as described in the study publication (83). The response options within the APQ were based on a 5-point Likert-type scale ranging from 1 – “Strongly disagree” to 5 – “Strongly agree”, making its theoretical score range is 20-100. Questions within the knowledge and attitudes

survey segments were shown to participants in a randomized order. The full survey that was given to participants is provided in the **Appendix 4**.

4.2.6 Statistical analysis

For continuous variables, we assessed the normality of data distribution using the Shapiro-Wilk test. We described categorical variables as frequencies and percentages. Continuous variables were described using mean or median (Md) ± 95% CI and standard deviation or IQR, depending on data normality distribution. All P-values <0.05 were considered as statistically significant. As the survey was web-based, we determined the response rate by dividing the number of participants with a fully completed survey with the total number of participants who accessed the survey and either completed the survey or stopped filling it out midway.

Demographic information was analysed descriptively for the full sample, and then compared by subgroups (psychiatrists who have no experience with psychedelic research or therapy vs. psychiatrists who have self-reported previous experience with psychedelic research or therapy) using the Mann-Whitney (continuous variables) and chi-square tests (categorical variables). We excluded all participant survey responses that were not fully complete i.e. if any part of the survey was missing. We did not exclude any outliers, as these values were considered to potentially represent extremes in either knowledge or psychedelics scores that occurred naturally within the sample population. We conducted an additional analysis of the possibility of attrition bias by comparing all available demographic information of participants who completed the survey vs. those who did not complete it fully.

We estimated the correlation between APQ scores and scores on the basic knowledge test using Spearman's rho (ρ). We created a linear regression model to assess the association of demographic variables, the basic knowledge on psychedelics test score, and the participants' self-reported perception of their own knowledge with scores on the APQ (i.e. participants' attitudes on psychedelics.).

Since this was the first use of the APQ among psychiatrists (and the first use in English), we once again validated the questionnaire in this sample using CFA and a reliability analysis (of the total scale and for each of its sub-scales). For the CFA, we used model fit index cut-offs to assess adequate model fit as defined by Hu and Bentler (78). The method used was the DWLS estimation method with a polychoric correlation matrix. RMSEA was expressed using a 95%

CI. We also used McDonald's ω and a 95% CI to assess the reliability of the APQ (overall and for each sub-scale), where results >0.70 were considered satisfactory.

4.2.7 Deviations from the pre-registered protocol

We rephrased the question "Are you a psychedelic researcher?" into "Do you have any previous experience with psychedelic-assisted treatment or research involving psychedelics?" to allow a broader range of participants who consider themselves skilled or experienced in this field to be identified through this question. We did this out of practical reasons because we estimated that we would not survey a large number of participants who are exclusively psychedelic researchers, and the rephrased question would allow a more robust comparison group. Additionally, one of the pre-registered co-authors withdrew from the study due to time constraints and a change in their primary workplace (IB). We also conducted an additional analysis after we obtained the results of the linear regression modelling in which we compared participants of male and female gender by demographic variables that were predictive of APQ scores in order to explore gender differences in attitudes towards psychedelics in more detail.

4.3 European psychiatrists' attitudes on psychedelic-assisted psychotherapy: a qualitative study

4.3.1 Study design and theoretical framework

This was a qualitative study that took place through web-based interviews with participants. All interviews took place via scheduled video calls on the Microsoft Teams online meeting platform. We used Braun and Clarke's six-phase guide to performing thematic analysis (84) as a method of analysis and overall followed a pragmatist approach. This approach was considered to be best suited to our study aim where we focused on the practical implications of our study. Our study was publicly pre-registered at the Open Science Framework: https://osf.io/2pu4s.

4.3.2 Research question

Our topic of interest was psychedelic-assisted psychotherapy seen through the perspective of psychiatrists and psychiatry trainees working within Europe. We broke down our research question according to the SPIDER formulation (85):

(S)ample – European psychiatrists

(P)henomenon of (I)nterest – Psychedelic-assisted psychotherapy

(D)esign – Interviews

(E)valuation – Perceived issues and implications for clinical practice, the design of future clinical trials, as well as policy

(R)esearch type – Qualitative

Therefore, our research objectives were formulated as the following questions: How do European psychiatrists perceive psychedelic-assisted psychotherapy? What do they see as facilitators or barriers to research on this topic, as well as the implementation of such therapies in a clinical setting? What do they consider to be the implications of psychedelic research and/or the real-world implementation of psychedelic-assisted psychotherapy for psychiatry and their personal practice?

4.3.3 Participant selection and recruitment

Our sample was made up of European psychiatrists or psychiatry trainees. There were no age limits or any other exclusion criteria for participants. Participants were invited to the study via

e-mail by the principal investigator and interviewer within the study (MFŽ). To reach eligible participants, we used different types of sampling.

We used our personal and professional contact to reach eligible participants (via e-mail, social media etc.). We contact authors who have a European affiliation and invited those who are also psychiatrists. The purposive sampling approach was generally used to obtain a heterogeneous sample, as we aimed for a diverse group of participants in regard to their location, age, treatment approach and level of experience in psychiatry.

The research team also conducted a survey using an instrument to measure attitudes on psychedelics in European psychiatrists. Participants who filled out the survey were invited to leave their contact e-mail in case they were interested in participating in an interview for this study. This was a type of convenience opportunity sampling.

Individuals (via any of the sampling methods above) who agreed to be interviewed were asked to consider whether they had any colleagues who may be interested in being interviewed. In this way, we also used a snowballing sampling method. This helped us to reach participants in remote locations or countries where it was difficult to reach possible interview candidates through the other sampling methods described above.

Previous research conducted by Barnett et al. (68) suggested that there are differences in attitudes on psychedelics between younger and older psychiatrists, as well as trainees vs. more experienced professionals. We targeted our sampling so that participants from varying age groups, levels of competence, and working experience in psychiatry were represented. The demographic characteristics of the participants were continually reassessed as new interviews were conducted. This was used as a basis for a decision on which individuals to invite to the next interview.

4.3.4 Data collection

Data were collected by conducting interviews and recording them during the ongoing conversation. The main rationale for using interviews is that psychedelics and psychedelic-associated psychotherapy may be a controversial topic for participants, which is why we chose not to use focus groups. These recordings were used to subsequently transcribe the interviews. The verbatim interview transcriptions were then further used for data analysis. We decided to stop data collection i.e. conducting new interviews once both data saturation and meaning saturation were achieved, according to the advice and parameters described by Hennink et al.

(86). Both these parameters were also considered when choosing new interview participants, along with the context of our study aim and the demographic diversity of the targeted sample.

4.3.5 Data analysis

We coded the data as new interviews were conducted and constructed a preliminary codebook after six interviews. This codebook was continually refined until the data collection was completed. Consensus was reached on the interpretation and coding choices by all three authors at multiple points throughout the iterative coding process, and once again after the final themes and sub-themes were determined. Themes were not identified in advance but were derived based on data from interviews and developed during coding. During data coding, we used an inductive approach.

We used the NVivo (QSR International Pty Ltd., London, UK) qualitative data analysis software to conduct the analysis. All other authors of the final publication who did not participate in the coding read all of the transcripts to verify that the final themes resulting from the analysis fairly represented the data set.

4.3.6 Research team and reflexivity

All interviews were conducted by Marija Franka Žuljević (MFŽ), the principal investigator of the study. MFŽ is a medical doctor and had been employed as a teacher at the University of Split School of Medicine at the time when the study was conducted. She had received previous training in qualitative research by attending the Autumn School of Qualitative Research which took place in Split, Croatia in October 2021 and had experience with interviews from previous research studies she worked on.

All participants were informed that MFŽ was conducting a PhD on the topic of psychedelics and psychedelic-assisted psychotherapy. Three of them knew of MFŽ through some personal contacts but had not had any significant previous interaction before the interview.

Reflexivity was one of the chosen strategies of increasing the credibility of the study due to the controversial nature of the topic of psychedelics and psychedelic-assisted psychotherapy. For this reason, the author conducting the interviews and coding (MFŽ) kept a reflective diary throughout the data collection and analysis process to identify any potential personal biases that may influence communication with participants, as well as by identifying any personal attitudes held on psychedelic-assisted psychotherapy that could influence data analysis. This reflective diary also helped ensure a rich and balanced interpretation as the end-product of data

analysis within the study. Two other co-authors experienced in qualitative methodology were actively involved in the coding process where they provided support and supervision throughout the data analysis process, as well as the creation of thematic maps, in order to ensure high methodological integrity and quality.

5 RESULTS

5.1 Validation of a new instrument for assessing attitudes on psychedelics in the general population

5.1.1 Participants' demographic information and response rate

There were 1153 participants in the final analysis (response rate: 69.2%). Based on predetermined exclusion criteria, n=514 participants were eliminated from the pool of n=1667 participants who began completing the survey (**Figure 1**).

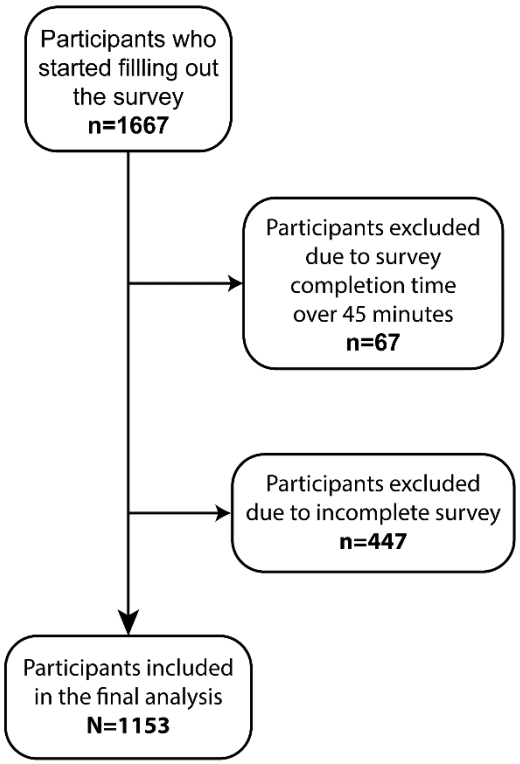

Figure 1. Flowchart showing the number of participants at each stage in the study.

The majority of the participants (n=716, 62.1%) were female, and the majority had either completed a high school degree (n=398, 34.5%) or a graduate/university degree (n=429, 37.2%). The median age of the participants was 31 years old (IQR: 23–40). Physicians (n=108, 60.3%) made up the majority of the HCWs (n=179), who made up 15.5% of the total participants (see **Tables 4** and **5**).

Table 4. Descriptive analysis of demographic information of all included study participants (n=1153)

Variable	**n (%)**
Gender	
Male	426 (36.9)
Female	716 (62.1)
Undisclosed	11 (1.0)
Completed education level	
No primary school education	0 (0.0)
Primary school education	8 (0.7)
High school	398 (34.5)
Undergraduate studies	183 (15.9)
Graduate studies	429 (37.2)
Postgraduate studies	51 (4.4)
PhD studies	84 (7.3)
Health care worker N (%)	
Yes	179 (15.5)
No	974 (84.5)

Table 5. Descriptive analysis of different professions of health care workers who were included in the study (n=179)

Type of health care worker	**n (%)**
Physician	108 (60.3)
Dentist	29 (16.2)
Nurse	21 (11.7)
Pharmacist	13 (7.3)
Physiotherapist	7 (3.9)
Radiology technician	1 (0.6)

5.1.2 Validation of the Attitudes on Psychedelics Questionnaire (APQ)

No item had a mean score of less than 2.0 or more than 4.0. For every sub-scale, we retained an equal number of items with positive and negative wording as well as items that, based solely on their meaning, were obviously part of that sub-scale. We considered the fact that the tripartite model of attitudes included a minimum of two items for each of the affective, behavioural, and cognitive categories. We also looked at the reliability of the overall scale, within particular sub-scales, and the reliability score in the event that an item is dropped, with a significant increase being defined as one of at least 0.05. This was done as part of an iterative procedure that started with the removal of individual items and continued with constant adjustment and re-evaluation of these variables as well as the face validity of the items and scale structure until a workable proposed model of the questionnaire was created. Because of its poor reliability, one hypothesised subscale—the four-item Prejudices Against Psychedelics—was eliminated. The pilot survey produced a hypothesised version of the APQ, with four sub-scales of five items each, comprising 20 items total (2 affective, 4 behavioural, and 14 cognitive) (see **Table 6**). The items in Croatian are provided in **Appendix 5**.

Table 6. The hypothesized model of the Attitudes on Psychedelics Questionnaire (APQ) in English*

Sub-scale	Item no.	Item text
Legal Use of Psychedelics	1	Legalizing psychedelics would benefit public health.
	2	Those who want to legalize psychedelics have a hidden agenda behind their actions. **(R)**
	3	The use of psychedelics for justified medical reasons should be legal.
	4	Administering psychedelics to psychiatric patients is safe as long as the treatment conditions are carefully controlled.
	5	Administering psychedelics to patients will eventually lead to bad outcomes. **(R)**
Effects of Psychedelics	6	Psychedelic use is linked to creativity.
	7	If more people used psychedelics, the world would be a better place.
	8	Recreational use of psychedelics has no practical benefit. **(R)**
	9	I am afraid of the effects of psychedelics on physical health. **(R)**
	10	Psychedelics can provide valuable spiritual experiences.
Risk Assessment of Psychedelics	11	Using psychedelics is safe.
	12	The use of psychedelics can damage the nervous system. **(R)**
	13	Psychedelics are less dangerous than other illegal drugs.
	14	A wider use of psychedelics would cause an increase in mental problems. **(R)**
	15	Administering psychedelics to patients is not problematic as long as it is performed by a professional.
Openness to Psychedelics	16	I am optimistic about psychedelic research.
	17	I would not agree to use psychedelics for mental health purposes. **(R)**
	18	If psychedelic-assisted psychotherapy enters into regular practice, I would be interested in learning more about it.
	19	I would be interested in learning about other people's experiences with psychedelics.
	20	I don't think that learning about psychedelics is worth my time. **(R)**

*Negatively worded items that are reversely coded are marked by (R).

We conducted a CFA on the following structural models of the APQ:

1. The hypothesized 4-factor model structure;

2. A hierarchical 4-factor model, i.e. a version of the 4-factor model that included a second-order factor accounting for covariance between first-order factors;

3. A 3-factor model, constructed by observing the highest factor covariance (0.935) in the hypothesized model (Legal Use of Psychedelics and Risk Assessment of Psychedelics were constrained into a single factor);

4. A 2-factor model, constructed by again observing the highest factor covariance in the 3-factor model (Legal Use of Psychedelics, Risk Assessment of Psychedelics, and Effects of Psychedelics were constrained into a single factor).

Nested models 2-4 were compared to the hypothesized 4-factor model (see **Table 7**).

Table 7. Model fit indices for all assessed nested structural models of the APQ (n=1153)*

Model	RMSEA (95% CI)	SRMR	CFI	TLI	χ^2 (df)	$\Delta\chi^2/\Delta df$†	ΔRMSEA‡
4-factor model	**0.042 (0.038-0.046)**	**0.054**	**0.992**	**0.991**	**496.16 (164)**	**-**	**-**
Hierarchical 4-factor model	0.043 (0.039-0.047)	0.055	0.991	0.990	518.95 (166)	+22.79/+2	+0.001
3-factor model	0.044 (0.039-0.048)	0.056	0.991	0.990	531.52 (167)	+35.36/+3	+0.001
2- factor model	0.046 (0.042)	0.058	0.990	0.989	575.17 (169)	+79.01/+5	+0.002

Abbreviations: RMSEA=Root Mean Square Error of Approximation, CI=confidence interval, SRMR=Standardized Root Mean Squared Residual, CFI=Comparative Fit Index, TFI=Tucker-Lewis Fit Index, χ2=chi-square, df=degrees of freedom.*The model with the best fit is shown in bold.
†Likelihood ratio test, shown as a change in χ2/df values relative to the parent model i.e. the hypothesized 4-factor model (top row).
‡Change in RMSEA value relative to the parent model i.e. the hypothesized 4-factor model (top row).

Every structural model fit the data in a satisfactory way. But compared to other models, the proposed 4-factor model had lower likelihood ratio test (χ2/df) results and lower RMSEA values, which made it appear more favourable.

The 20 APQ items showed excellent reliability (ω=0.949, 95% CI=0.944-0.953), as did all sub-scales in the hypothesized 4-factor model: Legal Use of Psychedelics (ω=0.842, 95% CI=0.828-0.856), Effects of Psychedelics (ω=0.881, 95% CI=0.870-0.892), Risk Assessment of Psychedelics (ω=0.841, 95% CI=0.826-0.855), and Openness to Psychedelics (ω=0.843, 95% CI=0.829-0.858) (see **Table 8**).

Table 8. Reliability analysis of the hypothesized 4-factor model with sub-scale ω values if an item is removed and correlations of each item with total of all other items in the sub-scale (n=1153)*

Subscale reliability (McDonald's ω, 95%CI)	Item no.	Item text	McDonald's ω if item dropped	Item-rest correlation
Legal Use of Psychedelics (ω=0.842, 95%CI=0.828-0.856)	1	Legalizing psychedelics would benefit public health.	0.786	0.708
	2	Those who want to legalize psychedelics have a hidden agenda behind their actions. **(R)**	0.829	0.570
	3	The use of psychedelics for justified medical reasons should be legal.	0.802	0.674
	4	Administering psychedelics to psychiatric patients is safe as long as the treatment conditions are carefully controlled.	0.825	0.573
	5	Administering psychedelics to patients will eventually lead to bad outcomes. **(R)**	0.804	0.674
Effects of Psychedelics (ω=0.881, 95%CI=0.870-0.892)	6	Psychedelic use is linked to creativity.	0.866	0.657
	7	If more people used psychedelics, the world would be a better place.	0.838	0.783
	8	Recreational use of psychedelics has no practical benefit. **(R)**	0.866	0.665
	9	I am afraid of the effects of psychedelics on physical health. **(R)**	0.865	0.673
	10	Psychedelics can provide valuable spiritual experiences.	0.842	0.772
Risk Assessment of Psychedelics (ω=0.841, 95%CI=0.826-0.855)	11	Using psychedelics is safe.	0.787	0.725
	12	The use of psychedelics can damage the nervous system. **(R)**	0.802	0.689
	13	Psychedelics are less dangerous than other illegal drugs.	0.811	0.669
	14	A wider use of psychedelics would cause an increase in mental problems. **(R)**	0.846	0.640

	15	Administering psychedelics to patients is not problematic as long as it is performed by a professional.	**0.846**	0.472
Openness to Psychedelics (ω=0.843, 95%CI=0.829-0.858)	16	I am optimistic about psychedelic research.	0.813	0.641
	17	I would not agree to use psychedelics for mental health purposes. **(R)**	0.841	0.578
	18	If psychedelic-assisted psychotherapy enters into regular practice, I would be interested in learning more about it.	0.810	0.666
	19	I would be interested in learning about other people's experiences with psychedelics.	0.803	0.693
	20	I don't think that learning about psychedelics is worth my time. **(R)**	0.795	0.700

*Values in bold indicate items those where overall reliability rises if the item is dropped. Negatively worded items that are reversely coded are marked by (R).

The hypothesized 4-factor model demonstrated good convergent validity, because its total score showed a high positive correlation with the total score on the Barnett et al. questionnaire (r=0.885, P<0.001). All sub-scales on the APQ did as well: Legal Use of Psychedelics (r=0.859, P<0.001), Effects of Psychedelics (r=0.792, P<0.001), Risk Assessment of Psychedelics (r=0.822, P<0.001), and Openness to Psychedelics (r=0.736, P<0.001).

According to our analysis, the originally proposed 20-item questionnaire with four sub-scales, a theoretical total score range of 20-100, and a theoretical score range of 5-25 for each sub-scale is the best model of the APQ. We believe that high observed factor covariances justify a computation of the scale total using the sum of scores on all sub-scales, even though we did not select the hierarchical 4-factor model (see **Figure 2**).

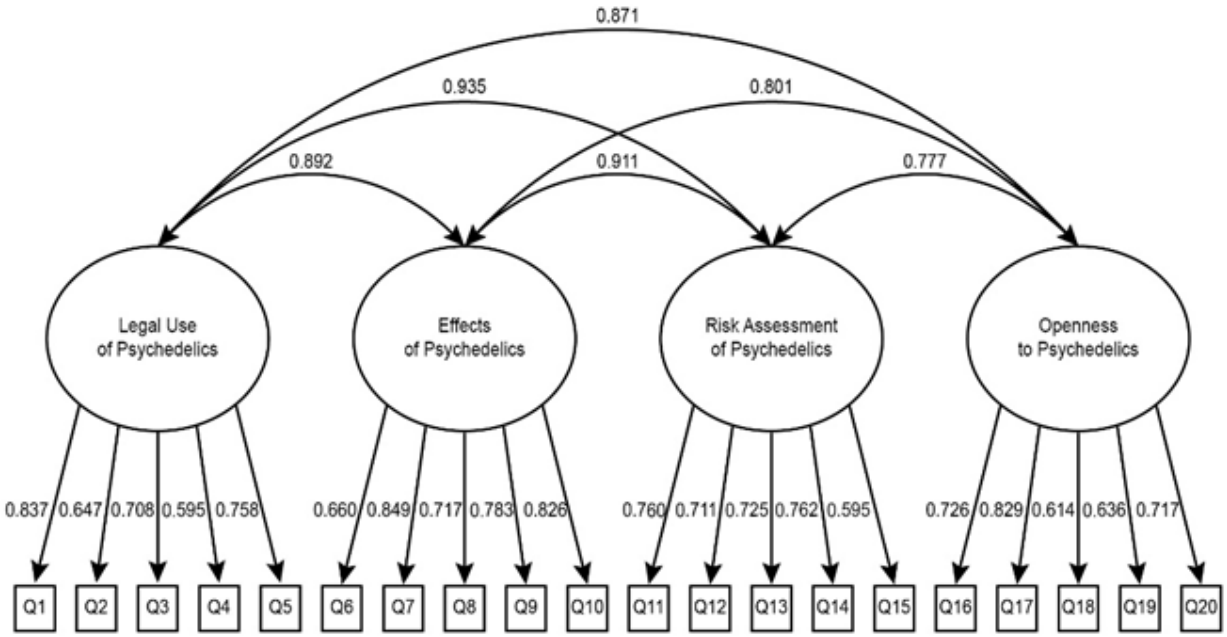

Figure 2. Structural representation of the final model of the APQ, with factor covariances and standardized item loading estimates for each factor.

5.1.3 Attitudes on psychedelics scores

The median total score on the APQ was Md=65.0 (IQR=56.0-77.0, 95% CI=64.0-66.0). Median scores on sub-scales were the following: Legal use of Psychedelics Md=17.0 (IQR=15.0-20.0, 95% CI=17.0-18.0), Effects of Psychedelics Md=15.0 (IQR=11.0-19.0, 95% CI=14.0-15.0), Risk Assessment of Psychedelics Md=15.0 (IQR=12.0-17.0, 95% CI=14.0-15.0), and Openness to Psychedelics Md=19.0 (IQR=16.0-22.0, 95% CI=19.0-20.0).

The median score on the Barnett et al. questionnaire (scale range 7-35) was Md=23.0 (IQR=16.0-30.0, 95% CI=23.0-24.0). The item and factor structure of the modified Barnett et al. questionnaire showed satisfactory psychometric properties (see **Tables 9, 10 and 11**).

Table 9. Results of exploratory factor analysis for 7 items from the Barnett et al. questionnaire (n=1153)*

Item no.	Item text	Loading on Factor 1
1	The use of psychedelics increases the risk for subsequent psychiatric disorders. **(R)**	**0.654**
2	The use of psychedelics increases the risk for long-term cognitive impairment. **(R)**	**0.736**
3	The use of psychedelics should be illegal for recreational purposes. **(R)**	**0.466**
4	The use of psychedelics is unsafe even under medical supervision. **(R)**	**0.790**
5	The use of psychedelics shows promise in treating psychiatric disorders.	**0.796**
6	The use of psychedelics may improve outcomes when used during psychotherapy.	**0.799**
7	The use of psychedelics deserves future research for the treatment of psychiatric disorders.	**0.707**

*Factor loadings over 0.3 are shown in bold. Applied rotation method is oblimin. Negatively worded items that are reversely coded are marked by (R).

Table 10. Reliability analysis of the Barnett et al. questionnaire with scale ω value if an item is removed and correlations of each item with total of all other items in the sub-scale (n=1153)*

Total scale reliability (McDonald's ω, 95%CI)	Item no.	Item text	McDonald's ω if item dropped	Item-rest correlation
(ω=0.863, 95%CI=0.851-0.875)	1	The use of psychedelics increases the risk for subsequent psychiatric disorders. **(R)**	0.846	0.614
	2	The use of psychedelics increases the risk for long-term cognitive impairment. **(R)**	0.837	0.690
	3	The use of psychedelics should be illegal for recreational purposes. **(R)**	**0.883**	0.441
	4	The use of psychedelics is unsafe even under medical supervision. **(R)**	0.829	0.724
	5	The use of psychedelics shows promise in treating psychiatric disorders.	0.837	0.716
	6	The use of psychedelics may improve outcomes when used during psychotherapy.	0.835	0.720
	7	The use of psychedelics deserves future research for the treatment of psychiatric disorders.	0.845	0.639

Abbreviations: CI=confidence interval.

*Values in bold indicate items those where overall reliability rises if the item is dropped. Negatively worded items that are reversely coded are marked by (R).

Table 11. Model fit indices for two assessed structural models of the Barnett et al. questionnaire (n=1153)*

Model	RMSEA (95%CI)	SRMR	CFI	TLI	χ^2 (df)	ΔRMSEA
Modified Barnett et al. questionnaire	0.081 (0.064-0.100)	0.065	0.984	0.970	69.01 (8)	-
Barnett et al. questionnaire	**0.063 (0.050-0.078)**	**0.058**	**0.987**	**0.978**	**73.37 (13)**	**-0.018**

Abbreviations: RMSEA=Root Mean Square Error of Approximation, CI=confidence interval, SRMR=Standardized Root Mean Squared Residual, CFI=Comparative Fit Index, TFI=Tucker-Lewis Fit Index, χ2=chi-square, df=degrees of freedom.
* The model with the best fit is shown in bold. The modified version of the questionnaire has item 3 removed and a total of 6 items.

5.1.4 Basic knowledge on psychedelics scores

The median score on the knowledge on psychedelics test was Md=63.6 (IQR=50.0-81.8, 95% CI=64.9-68.2). The three most commonly correctly recognized psychedelics were LSD (n=1038, 90.0%), MDMA (n=866, 75.1%), and psilocybin (n=829, 71.9%). Three substances most commonly mistaken for psychedelics were opium (n=690, 59.8%), methamphetamine (n=665, 57.7%), and heroin (n=543, 47.1%). Responses for each substance are shown in **Table 12**.

Table 12. Descriptive analysis of participants' responses on the knowledge on psychedelics test (n=1153)

Substance	**Response, n (%)**	
Psychedelics	**Correctly identified as a psychedelic**	**Incorrectly identified as non-psychedelic**
Lysergic acid dithylamide (LSD)	1038 (90.03)	115 (9.97)
MDMA (ecstasy)	866 (75.11)	287 (24.89)
Psilocybin	829 (71.90)	324 (28.10)
DMT	796 (69.04)	357 (30.96)
Mescaline	736 (63.83)	417 (36.17)
Peyote	672 (58.28)	481 (41.72)
Ibogaine	431 (37.38)	722 (62.62)
Non-psychedelics	**Incorrectly identified as a psychedelic**	**Correctly identified as a non-psychedelic**
Opium	690 (59.84)	463 (40.16)
Methamphetamine	665 (57.68)	488 (42.32)
Heroin	543 (47.09)	610 (52.91)
Cocaine	512 (44.41)	641 (55.59)
Dextroamphetamine	510 (44.23)	643 (55.77)
Ketamine	454 (39.38)	699 (60.62)
Gamma-hydroxybutyrate (GHB)	428 (37.12)	725 (62.88)
Rohypnol	339 (29.40)	814 (70.60)
Oxycodone	315 (27.32)	838 (72.68)
Haloperidol	313 (27.15)	840 (72.85)
Mexazolam	307 (26.63)	846(73.37)
Phenobarbital	282 (24.46)	871 (75.54)
Modafinil	244 (21.16)	909 (78.84)
Imipramine	178 (15.44)	975 (84.56)
Digoxin	155 (13.44)	998 (86.56)

5.1.5 Additional analyses

The study's excluded participants did not differ in terms of age or gender distribution from the included participants. An examination of the groups' educational characteristics using the post-hoc chi-square test revealed no discernible differences (see **Table 13**).

43.4% (n=194) of the 447 participants who were eliminated for not finishing the survey gave up on the psychedelic knowledge test. According to participant feedback, some people left the survey during the knowledge test because they realised they didn't know enough about psychedelics to be able to answer correctly (see details on participant feedback in **Appendix 1**). The APQ scores were found to be associated with male gender (standardised regression coefficient (β)=-0.171, P<0.001), younger age (β=-0.218, P<0.001), and lower educational status (β=-0.124, P<0.001), but these factors alone only explained 12.6% of the variance in scores. HCW status was linked to the sub-scale totals for Legal use of Psychedelics and Effects of Psychedelics but not with APQ scores (β=-0.049, P=0.091) (see **Table 14**).

Table 13. Comparison of demographic data between included and excluded participants (n=1621)*

	Included (n=1153)	**Excluded (n=468)**	
		n, %	P†
Gender			0.277
Male	426 (36.9)	171 (36.5)	
Female	716 (62.1)	288 (61.5)	
Undisclosed	11 (1.0)	9 (1.9)	
		n, %	P†
Education			**0.012**
No primary school education	0 (0.0)	2 (0.4)	
Primary school education	8 (0.7)	4 (0.9)	
High school	398 (34.5)	194 (41.5)	
Undergraduate studies	183 (15.9)	70 (15.0)	
Graduate studies	429 (37.2)	152 (32.3)	
Postgraduate studies	51 (4.4)	25 (5.3)	
PhD studies	84 (7.3)	21 (4.5)	
		Median, IQR, 95% CI	P‡
Age			0.717
	31.0 (IQR=25.0-42.0, 95% CI=30.0-32.0)	30.0 (IQR=24.0-43.0, 95% CI=28.0-32.0)	

Abbrevations: IQR=interquartile range, CI=confidence interval.
*Significant P-values are shown in bold. Only excluded participants that provided demographic data (468/514, 91.0%) were included in this analysis.
†Chi-square test. Post-hoc analysis showed that there was no significant difference for any education levels between the two groups.
‡Mann-Whitney test.

Table 14. Results of linear regression modelling used to explore the association of demographic factors with the total APQ score and the scores of all sub-scales (n=1153)*

Outcome variables	**Predictor variables (β, P-value)**				R^2
	Age	Gender	Education level	HCW status (yes/no)	
Total APQ score	**-0.218, P<0.001**	**-0.171, P<0.001**	**-0.124, P<0.001**	-0.049, P=0.091	0.126
Legal use of Psychedelics score	**-0.211, P<0.001**	**-0.159, P<0.001**	**-0.072, P=0.027**	**-0.075, P=0.011**	0.102
Effects of Psychedelics score	**-0.204, P<0.001**	**-0.199, P<0.001**	**-0.117, P<0.001**	**-0.061, P=0.036**	0.130
Risk Assessment of Psychedelics score	**0.131, P<0.001**	**-0.164, P<0.001**	**-0.145, P<0.001**	-0.023, P=0.444	0.089
Openness to Psychedelics score	**-0.233, P<0.001**	**-0.079, P=0.005**	**-0.108, P=0.001**	-0.014, P=0.641	0.097

Abbreviations: APQ=Attitudes on Psychedelics Questionnaire, β=Standardized regression coefficient, R^2=Coefficient of determination.
*Results with significant P-values are shown in bold. R^2 shows the percentage of score variance explained by statistically significant predictor variables.

We estimated a positive correlation between total scores on knowledge and attitudes on psychedelics (r=0.494, P<0.001). The knowledge of psychedelics scores between non-HCW participants (n=974) and HCWs (n=179) did not differ significantly (P=0.711); however, non-HCWs had slightly more positive attitudes than HCWs (P<0.001) regarding psychedelics scores (see **Table 15**). The majority of responses to questions intended exclusively for healthcare workers (HCWs) had a neutral median score when it came to either supporting or referring patients to psychiatrists who use psychedelics or who use them. There was general interest in seeing sessions of psychedelic-assisted psychotherapy, as well as little concern about prescribing or recommending psychedelics to patients if their safety and efficacy were established (see **Table 16**).

Table 15. Comparison of scores in knowledge and attitudes on psychedelics between HCW and non-HCW participants (n=1153)*

Variable (theoretical range)	Median, IQR, 95% CI		P†
	Non-HCW (n=974)	HCW (n=179)	
Total APQ score (20.0-100.0)	66.0 (IQR=56.0-78.0, 95% CI=65.0-67.1)	62.0 (IQR=53.0-71.8, 95% CI=60.0-64.0)	**<0.001**
Knowledge test score (0.0-100.0)	65.9 (IQR=50.0-81.8, 95% CI=63.6-68.2)	63.6 (IQR=50.0-81.8, 95% CI=59.1-72.7)	0.711

Abbreviations: APQ=Attitudes on Psychedelics Questionnaire, HCW=health care worker, IQR=interquartile range, CI=confidence interval.
*Significant P-values are shown in bold
†Mann-Whitney test.

Table 16. Descriptive analysis of health care workers' responses to the additional set of questions for their sub-group (n=179)*

Item text	Median score (95%CI)	IQR
I would be worried if my institution took part in research with psychedelics. **(R)**	4.0 (4.0-5.0)	3.0-5.0
I would feel uncomfortable recommending psychedelic treatment to a patient, even if there is evidence for its effectiveness and safety. **(R)**	4.0 (3.0-4.0)	3.0-4.0
As a health professional, I would be interested in witnessing a psychedelic session with a patient.	4.0 (4.0-4.0)	3.0-5.0
If I knew that a psychiatrist used psychedelics, I would be less likely to refer my patient to them. **(R)**	3.0 (2.0-3.0)	2.0-4.0
If I knew a psychiatrist who supported the legalization of psychedelics, I would be less likely to refer my patient to them. **(R)**	3.0 (3.0-4.0)	2.0-5.0

Abbreviations: CI=confidence interval, IQR=interquartile range.
*Negatively worded items that are reversely coded are marked by (R). For negatively worded items, interpretation of response scores is as follows: Completely agree=1, Agree=2, Neither agree nor disagree=3, Disagree=4, Completely disagree=5. For non-reversed/positive items, the scoring is: Completely disagree=1, Disagree=2, Neither agree nor disagree=3, Agree=4, Completely agree=5.

5.2 Attitudes of European psychiatrists on psychedelics: A cross-sectional survey study

5.2.1 Participants' demographic information and response rate

In total, 680 surveys were recorded on the SurveyMonkey platform. With 419 of those eligible for study inclusion, the response rate was 61.6%. 261 surveys (38.4%) in total were eliminated; most of these (n=186, 71.3%) were because the survey was not completed, and a smaller percentage were because the participants were either not based in Europe (n=7, 2.7%), or they were not psychiatrists (n=68, 26.1%).

Thirty-seven European countries provided data for our survey. Of these, the ten most represented (in descending order of frequency) were: Italy (n=33, 7.9%), Croatia (n=30, 7.2%), Germany (n=24, 5.7%), the Netherlands (n=22, 5.3%), Slovenia (n=17, 4.1%), Czech Republic and Estonia (n=17, 4.1% each), Bosnia and Herzegovina, North Macedonia, and Romania (n=16, 3.7% each). This survey collected data from thirty European countries. An exhaustive breakdown of responses across all countries can be found in **Table 17**.

Table 17. Locations of all survey participants by country, in order of descending frequency (n=419)

Country (n=33)	**n, %**
Poland	55 (13.1)
United Kingdom	35 (8.4)
Italy	33 (7.9)
Croatia	30 (7.2)
Germany	24 (5.7)
the Netherlands	22 (5.3)
Country (n=33)	**n, %**
Sweden	19 (4.5)
Slovenia	17 (4.1)
Czech Republic	17 (4.1)
Estonia	17 (4.1)
Bosnia and Herzegovina	16 (3.8)
North Macedonia	16 (3.8)
Romania	16 (3.8)
France	14 (3.3)
Portugal	12 (3.9)
Norway	10 (2.4)
Switzerland	9 (2.1)
Latvia	8 (1.9)
Belarus	7 (1.7)
Greece	6 (1.4)
Belgium	5 (1.2)
Denmark	4 (1.0)
Austria	3 (0.7)
Finland	3 (0.7)
Hungary	3 (0.7)
Moldova	3 (0.7)
Malta	3 (0.7)
Spain	3 (0.7)
Lithuania	2 (0.5)
Russia	2 (0.5)
Serbia	2 (0.5)
Turkey	2 (0.5)
Iceland	1 (0.2)

The majority of the participants in our sample (55.4%) were male, with a median age of 38. The majority of the participants (65.6%) were specialists in psychiatry, with the majority working in hospitals (67.3%) and using a treatment approach that combined biological and psychotherapeutic techniques (57.8%). A lesser percentage of participants (19.6%) said they had prior experience with PAP or psychedelic research. Nearly two-thirds of participants said they were either agnostic (27.4%) or an atheist (32.2%).

On a theoretical range of 0-100, the self-assessed level of knowledge about psychedelics was moderate (Md=52.0), and the median number of scientific publications was Md=2.0. 34.4% (n=144) of the participants reported having used a psychedelic in the past, with psilocybin being the most often used (24.3%), followed by MDMA (20%), and cannabis being tried by 58.9% of the participants. **Table 18** presents a comprehensive summary of the demographic data.

Table 18. Demographic information for study participants (n=419)

Variable		**Md, IQR**
Age (in years)*		38.0 (31.0-47.8)
Number of published scientific papers		2.0 (0.0-15.0)
Self-assessed knowledge on psychedelics (range 0-100)		52.0 (30.0-70.0)
		n, %
Gender		
	Male	232 (55.4)
	Female	182 (43.4)
	I don't want to answer this question	2 (0.5)
	Other	3 (0.7)
Education**		
	Psychiatry trainee	144 (34.4)
	Psychiatry specialist	275 (65.6)
	Psychotherapy trainee	55 (13.1)
	Licenced psychotherapist	55 (13.1)
	PhD	81 (19.3)
	Other	23 (5.5)
Place of work		
	Hospital	282 (67.3)
	Private hospital	10 (2.4)
	Private practice	35 (8.4)
	University	48 (11.5)
	Other	44 (10.5)
Primary treatment approach		
	Biological	145 (34.6)
	Psychotherapeutic	22 (5.3)
	Both biological and psychotherapeutic	242 (57.8)
	This does not apply to me	10 (2.4)
Previous experience with psychedelic-assisted psychotherapy or psychedelic research		
	Yes	82 (19.6)
	No	337 (80.4)
Religious beliefs**		
	Religious	72 (17.2)

	Spiritual	110 (26.3)
	Atheist	135 (32.2)
	Agnostic	115 (27.4)
	Other	58 (13.8)
Past personal experience with using psychoactive substances†		
	Cannabis	247 (58.9)
	LSD	81 (19.3)
	Psilocybin	102 (24.3)
	Ayahuasca	19 (4.5)
	DMT	17 (4.1)
	Mescaline	7 (1.7)
	Ibogaine	3 (0.7)
	MDMA	84 (20.0)
	None of the above	163 (38.9)

*n=2 participant had missing data. One participant wrote "0" as their age, and another stated their age as 18, which was incompatible with the other information provided in the survey. As their surveys had all other information filled out, we decided not to exclude them, only to remove the value from the Age column to avoid skewing the results.
†The percentages do not add up to 100, as the participants could select multiple answers.

5.2.2 Psychometric characteristics of the APQ

The four-factor structural model of the APQ had the following CFA model fit indices: RMSEA=0.031 (95% CI=0.021-0.040), SRMR=0.060, CFI=0.994, and TLI=0.993, all of which showed an acceptable model fit based on predetermined cut-off criteria. Each of the four sub-scales of the APQ, including Legal Use of Psychedelics (ω=0.812, 95% CI=0.783-0.840), Effects of Psychedelics (ω=0.835, 95% CI=0.810-0.860), Risk Assessment of Psychedelics (ω=0.795, 95% CI=0.764-0.826), and Openness to Psychedelics (ω=0.832, 95% CI=0.806-0.857), all demonstrated good reliability when taken as a whole. These results are consistent with our preliminary APQ validation study (83).

5.2.3 Attitudes on psychedelics scores

On the APQ scale, which has a theoretical score range of 20 to 100, the median total score was Md=66.0 (IQR=56.5-75.0). The subscale titled "Openness to Psychedelics" had the highest median attitude scores (Md=20.0, IQR=12.0-17.0). The other subscales, which had theoretical score ranges of 5–20, were "Legal use of Psychedelics" (Md=18.0, IQR=15.0–20.0), "Effects of Psychedelics" (Md=14.0, IQR=12.0–18.0), and "Risk Assessment of Psychedelics" (Md=14.0, IQR=12.0-17.0).

The Openness to Psychedelics sub-scale displayed a discernible trend towards greater agreement with its items when examining the frequencies of response options for individual APQ items. Conversely, participants tended to exhibit the highest level of uncertainty regarding agreement or disagreement with items on the Effects of Psychedelics and Risk Assessment of Psychedelics sub-scales. **Figure 3** provides a comprehensive summary of response frequencies for every question on the APQ.

Figure 3. Visual representation showing frequencies of response options marking participants' degree of agreement or disagreement with different items on the APQ. Note: the results of reversely worded questions are shown in their unreversed form to ease readers' comprehension.

5.2.4 Basic knowledge on psychedelics scores

The theoretical score range for the knowledge test on psychedelics was 0-100, with a median of Md=86.0 (IQR=82.0-91.0). The three psychedelics that were most frequently identified correctly were mescaline (n=385, 91.9%), LSD (n=409, 97.6%), and psilocybin (n=411, 98.1%). The three non-psychedelic substances that were most frequently referred to as psychedelics were gamma-hydroxybutyric acid (GHB) (n=109, 26.0%), methamphetamine (n=107, 25.5%), and ketamine (n=264, 63.0%). The responses for each substance are displayed in **Table 19**.

Table 19. Descriptive analysis of participants' responses on the knowledge on psychedelics test (n=419)*

Substance group	**Response, n (%)**	
Psychedelics	**Correctly identified as a psychedelic**	**Incorrectly identified as non-psychedelic**
Psilocybin	411 (98.1)	8 (1.9)
LSD	409 (97.6)	10 (2.4)
Mescaline	385 (91.9)	34 (8.1)
Ayahuasca	377 (90.0)	42 (10.0)
MDMA	291 (69.5)	128 (30.5)
Ayahuasca	377 (90.0)	42 (10.0)
DMT	316 (75.4)	103 (24.6)
Ibogaine	215 (51.3)	204 (48.7)
Non-psychedelics	**Incorrectly identified as a psychedelic**	**Correctly identified as a non-psychedelic**
Ketamine	264 (63.0)	155 (37.0)
Methamphetamine	107 (25.5)	312 (74.5)
Gamma hydroxybutyrate (GHB)	109 (26.0)	310 (74.0)
Dextroamphetamine	93 (22.2)	326 (77.8)
Opium	71 (16.9)	348 (83.1)
Rohypnol	55 (13.1)	364 (92.6)
Cocaine	54 (12.9)	365 (87.1)
Heroin	52 (12.4)	367 (87.6)
Oxycodone	31 (7.4)	388 (92.6)
Phenobarbital	25 (6.0)	394 (94.0)
Digoxin	23 (5.5)	396 (94.5)
Modafinil	19 (4.5)	400 (95.5)
Mexazolam	18 (4.3)	401 (95.7)
Haloperidol	11 (2.6)	408 (97.6)
Imipramine	9 (2.1)	410 (97.9)

Abbreviations: LSD=lysergic acid diethylamide; MDMA=3,4-Methylenedioxymethamphetamine; DMT=N, N dimethyltryptamine; GHB=Gamma hydroxybutyrate.
*Substances are shown in decreasing frequency of participants who identified them as a psychedelic for each substance group.

5.2.5 Additional analyses

A moderate correlation was observed between the APQ scores and the total score on the psychedelics basic knowledge test (ρ=0.310, P<0.001), as well as between the APQ scores and the self-assessed knowledge score (ρ=0.371, P<0.001). Because self-assessed knowledge and knowledge test scores showed collinearity, self-assessed knowledge was excluded from the linear regression analysis. With the total APQ score serving as the criterion variable and all gathered demographic variables serving as potential predictors, we tested a stepwise multiple linear regression model. 31.3% of the variance in APQ scores was explained by the model (R^2=0.313).

According to the relative order of magnitude, the following were statistically significant predictors: having used psychedelics in the past lifetime (β=0.286, P<0.001), having higher basic knowledge test scores (β=0.237, P<0.001), being younger (β=-0.248, P<0.001), considering oneself as spiritual (β=0.165, P<0.001), having previously worked with PAP or psychedelic research (β=0.112, P=0.008), and being male (β=-0.086, P=0.042). The same predictors were significant when the criterion variable was the sub-scale scores of the APQ, with the exception of the following: male gender was only related to the sub-scales on Legal Use of Psychedelics and Risk Assessment of Psychedelics; all sub-scales but Legal Use of Psychedelics were related to considering oneself as spiritual; and all sub-scales but Openness to Psychedelics were related to having prior experience with PAP and psychedelic research (see **Table 20**).

Table 20. Results of a linear regression analysis of predictors of scores on the APQ and its sub-scales (n=419)

Outcome variables	**Significant predictor variables (β, P-value)**	Adjusted R^{2*}
Total APQ score	**Previous psychedelic use** (β=0.286, P<0.001), **higher scores on the basic knowledge on psychedelics test** (β=0.237, P<0.001), **younger age** (β=-0.248, P<0.001), **considering oneself as spiritual** (β=0.165, P<0.001), **having previous experience with PAP or psychedelic research** (β=0.112, P=0.008), and **male gender** (β=-0.086, P=0.042)	0.313
Legal Use of Psychedelics score	**Previous psychedelic use** (β=0.211, P<0.001), **higher scores on the basic knowledge on psychedelics test (**β=0.207, P<0.001), **younger age** (β=-0.236, P<0.001), **male gender** (β=-0.135, P=0.003), **having previous experience with PAP or psychedelic research** (β=0.104, P=0.023)	0.198
Effects of Psychedelics score	**Previous psychedelic use** (β=0.311, P<0.001), **considering oneself as spiritual** (β=0.217, P<0.001), **higher scores on the basic knowledge on psychedelics test (**β=0.192, P<0.001), **younger age** (β=-0.200, P<0.001), **having previous experience with PAP or psychedelic research** (β=0.131, P=0.002)	0.306
Risk Assessment of Psychedelics score	**Previous psychedelic use** (β=0.236, P<0.001), **higher scores on the basic knowledge on psychedelics test (**β=0.180, P<0.001), **considering oneself as spiritual** (β=0.162, P<0.001), **younger age** (β=-0.177, P<0.001), **having previous experience with PAP or psychedelic research** (β=0.128, P=0.004), **male gender** (β=-0.101, P=0.025)	0.221
Openness to Psychedelics score	**Previous psychedelic use** (β=0.253, P<0.001), **higher scores on the basic knowledge on psychedelics test (**β=0.264, P<0.001), **younger age** (β=-0.236, P<0.001), **considering oneself as spiritual** (β=0.123, P=0.004)	0.244

Abbreviations: APQ=Attitudes on Psychedelics Questionnaire, β=Standardized regression coefficient, R^2=Adjusted coefficient of determination.

Psychiatrists who reported prior experience with PAP or psychedelic research published more scientific papers, evaluated their knowledge of psychedelics more highly, were more likely to be male, worked more frequently in private hospitals, identified more frequently as spiritual, and were more likely to have used cannabis, LSD, psilocybin, ayahuasca, DMT, mescaline, or MDMA in the past than those who did not (**Table 21**). Psychiatrists who did not finish the survey but still submitted their demographic data (n=50) were substantially less likely to have ever tried cannabis or psychedelics in general ($P<0.001$) when we examined the potential for attrition bias (**Table 22**).

Table 21. Comparison of demographic information between participants with self-reported previous experience with PAP or psychedelic research and those who reported to have none (n=419)*

		Previous experience with PAP or psychedelic research (n=82)	**Without experience with PAP or psychedelic research (n=337)**	P†
		Median, IQR		
Age		40.0 (32.0-52.0)	37.0 (3146.0)	0.057
Number of published scientific papers		11.0 (0.3-60.5)	1.0 (0.0-10.0)	**<0.001**
Self-assessed knowledge on psychedelics (range 0-100)		70.0 (53.5-86.0)	50.0 (25.0-68.0)	**<0.001**
		n, %		P‡
Gender				
	Male	57 (69.5)	175 (51.9)	**0.032**
	Female	25 (30.5)	157 (46.6)	
	I don't want to answer this question	0 (0.0)	2 (0.6)	
	Other	0 (0.0)	3 (0.9)	
Education§				
	Psychiatry trainee	23 (28.0)	121 (35.9)	0.179
	Psychiatry specialist	59 (72.0)	216 (64.1)	0.179
	Psychotherapy trainee	6 (7.3)	49 (14.5)	0.082
	Licenced psychotherapist	13 (15.9)	42 (12.5)	0.415
	PhD	22 (26.8)	59 (17.5)	0.055
	Other	6 (7.3)	17 (5.0)	0.527
Place of work				
	Hospital	41 (50.0)	241 (71.5)	**<0.001**
	Private hospital	4 (4.9)	6 (1.8)	
	Private practice	6 (7.3)	29 (8.6)	
	University	6 (7.3)	24 (7.1)	
	Other	7 (8.5)	37 (11.0)	
Primary treatment approach				
	Biological	22 (26.8)	123 (36.5)	0.431

	Psychotherapeutic	5 (6.1)	17 (5.0)	
	Both biological and psychotherapeutic	53 (64.6)	189 (56.1)	
	This does not apply to me	2 (2.4)	8 (2.4)	
Religious beliefs§				
	Religious	10 (12.2)	62 (18.4)	0.182
	Spiritual	29 (35.4)	81 (24.0)	**0.037**
	Atheist	22 (26.8)	113 (33.5)	0.244
	Agnostic	23 (28.0)	92 (27.3)	0.892
	Other	14 (17.1)	44 (13.1)	0.345
Past personal experience with using specific psychoactive substances§				
	Cannabis	65 (79.3)	182 (54.0)	**<0.001**
	LSD	36 (43.9)	45 (13.4)	**<0.001**
	Psilocybin	39 (47.6)	63 (18.7)	**<0.001**
	Ayahuasca	15 (18.3)	4 (1.2)	**<0.001**
	DMT	11 (13.4)	6 (1.8)	**<0.001**
	Mescaline	4 (4.8)	3 (0.9)	**0.012**
	Ibogaine	1 (1.2)	2 (0.6)	0.546
	MDMA	30 (36.6)	54 (16.0)	**<0.001**
	None of the above	15 (18.3)	148 (43.9)	

Abbreviations: PAP=psychedelic-assisted psychotherapy; LSD=lysergic acid diethylamide; DMT=N, N dimethyltryptamine; MDMA=3,4-Methylenedioxymethamphetamine.
*Significant P-values are highlighted in bold.
†Mann-Whitney test for independent samples.
‡Chi-square test.
§The percentages do not add up to 100, as the participants could select multiple answers.

Table 22. Comparison of demographic data between participants who submitted an incomplete survey (n=50) and included participants (n=419)*

Variable		Included surveys (n=419)	Incomplete surveys with demographic data (n=50)	P†
		Median, IQR		
Age		38.0 (31.0-47.8)	38.5 (31.3-54.5)	0.586
Number of published scientific papers		2.0 (0.0-15.0)	3.0 (0.3-9.3)	0.427
Self-assessed knowledge on psychedelics (range 0-100)		52.0 (30.0-70-0)	49.5 (31.0-63.3)	0.223
		n, %		P‡
Gender				0.019
	Male	232 (55.4)	17 (34.0)	
	Female	182 (43.4)	32 (64.0)	
	I don’t want to answer this question	2 (0.5)	1 (2.0)	
	Other	3 (0.7)	0 (0.0)	
Education§				
	Psychiatry trainee	144 (34.4)	23 (46.0)	0.104
	Psychiatry specialist	275 (65.6)	29 (58.0)	0.285
	Psychotherapy trainee	55 (13.1)	6 (12.0)	0.829
	Licenced psychotherapist	55 (13.1)	7 (14.0)	0.863
	PhD	81 (19.3)	11 (22.0)	0.653
	Other	23 (5.5)	0 (0.0)	N/A
Place of work				
	Hospital	282 (67.3)	37 (74.0)	0.123
	Private hospital	10 (2.4)	1 (2.0)	
	Private practice	35 (8.4)	7 (14.0)	
	University	48 (11.5)	5 (10.0)	
	Other	44 (10.5)	0 (0.0)	
Primary treatment approach				
	Biological	145 (34.6)	18 (36.0)	0.707
	Psychotherapeutic	22 (5.3)	2 (4.0)	
	Both biological and psychotherapeutic	242 (57.8)	30 (60.0)	
	This does not apply to me	10 (2.4)	0 (0.0)	

Previous experience with psychedelic-assisted psychotherapy or psychedelic research				
	Yes	82 (19.6)	10 (20.0)	0.942
	No	337 (80.4)	40 (80.0)	
Religious beliefs§				
	Religious	72 (17.2)	9 (18.0)	0.885
	Spiritual	110 (26.3)	10 (20.0)	0.338
	Atheist	135 (32.2)	15 (30.0)	0.750
	Agnostic	115 (27.4)	9 (18.0)	0.152
	Other	58 (13.8)	9 (18.0)	0.427
Past personal experience with using psychoactive substances§				
	Cannabis	247 (58.9)	9 (18.0)	**<0.001**
	LSD	81 (19.3)	2 (4.0)	**0.007**
	Psilocybin	102 (24.3)	1 (2.0)	**<0.001**
	Ayahuasca	19 (4.5)	0 (0.0)	0.124
	DMT	17 (4.1)	0 (0.0)	0.147
	Mescaline	7 (1.7)	0 (0.0)	0.357
	Ibogaine	3 (0.7)	0 (0.0)	0.548
	MDMA	84 (20.0)	2 (4.0)	**0.006**
	None of the above	163 (38.9)	3 (6.0)	**<0.001**

Abbreviations: PAP=psychedelic-assisted psychotherapy; LSD=lysergic acid diethylamide; DMT=N, N dimethyltryptamine; MDMA=3,4-Methylenedioxymethamphetamine.
*Significant P-values are highlighted in bold.
†Mann-Whitney test for independent samples.
‡Chi-square test.
§The percentages do not add up to 100, as the participants could select multiple answers.

Finally, we compared participants of male and female gender by all variables which were predictive of APQ scores in the regression model in order to identify possible reasons for gender differences in attitudes on psychedelics (non-significant comparisons not shown). We found that men in our sample had a higher median age (Md=40.0, IQR=32.0-52.0) than women (Md=36.0, IQR=30.0-44.0) (P<0.001), higher median basic knowledge test scores (Md=91.0, IQR=82.0-95.0 vs. Md=86.0, IQR=77.0-91.0 for women, P<0.001), and assessed their knowledge on psychedelics as higher (Md=60.0, IQR=31.8-72.0 vs. Md=50.0, IQR=25.0-65.0). Men also reported having experience with PAP and psychedelic research more often (n=57, 24.6% vs. n=25, 13.7%, P=0.006). Participants who did not want to disclose their gender (n=2, 15%) and those who marked their gender as “Other” (n=3, 0.7%) were not included in this analysis because the sample size was too small.

5.3 European psychiatrists' attitudes on psychedelic-assisted psychotherapy: a qualitative study

We conducted 12 interviews with participants from 9 different countries. Overall, we defined four main themes and 14 sub-themes within the collected data (see **Figure 4**). Participant quotes are provided within each sub-theme and the basic demographic information for each participant from P01 to P12 is shown in **Table 23**.

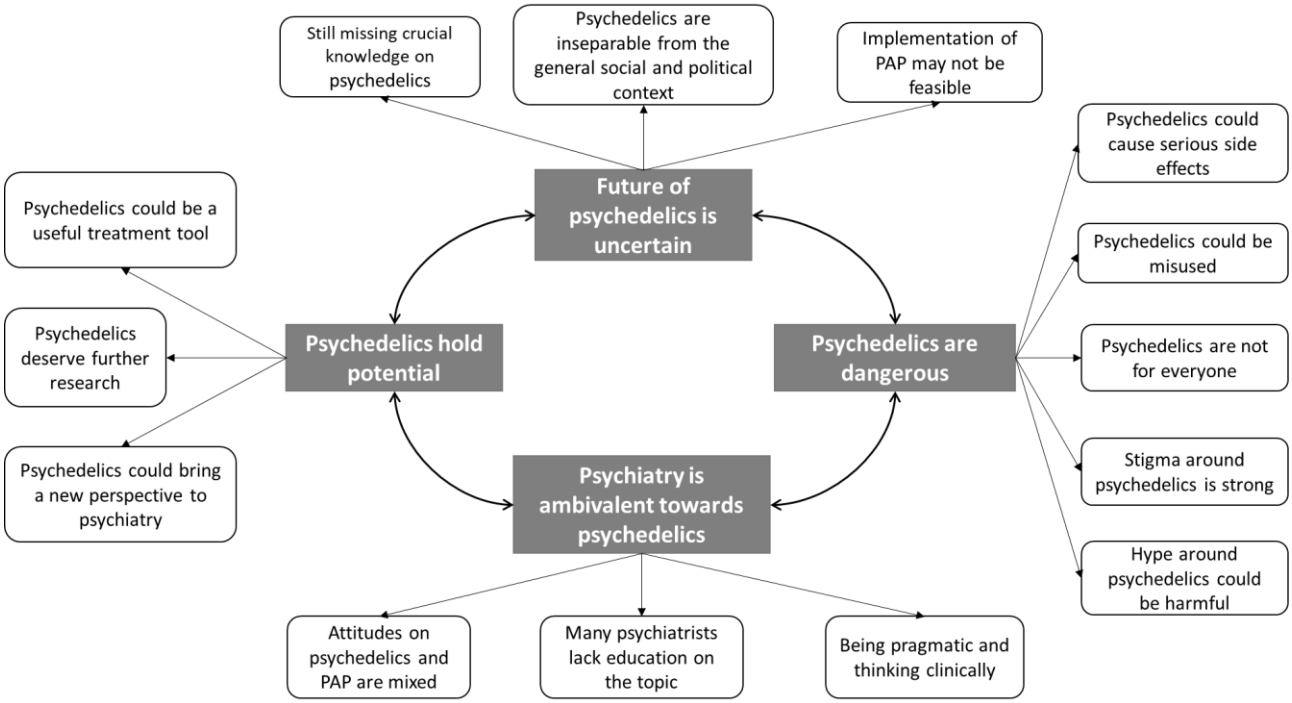

Figure 4. Thematic map of findings, showing relationships between themes and sub-themes within the analysis.

Table 23. Demographic information of all 12 interview participants

	Country	Gender and age	Education	Primary place of work	Primary treatment approach	Number of published articles	Estimated knowledge on psychedelics
P01	Croatia	Male, 30	Psychiatry trainee, psychotherapy trainee	Hospital	Biological	0	Low to moderate
P02	Croatia	Female, 43	Licenced psychotherapist, psychiatry specialist, PhD	Currently unemployed	Both biological and psychotherapeutic	13	Moderate
P03	Poland	Female, 34	Psychiatry trainee	Hospital	Biological	0	Good
P04	Poland	Male, 30	Psychiatry trainee, psychotherapy trainee	Hospital	Both biological and psychotherapeutic	10	Good
P05	Sweden	Male, 39	Psychiatry specialist, licenced psychotherapist, psychotherapy trainee	Outpatient clinic	Psychotherapeutic	5	Good
P06	Netherlands	Male, 40	Psychiatry specialist, PhD	University	Both biological and psychotherapeutic	70	Good
P07	Croatia	Female, 39	Psychiatry specialist	Hospital	Both biological and psychotherapeutic	10	Good
P08	Ireland	Female, 48	Psychiatry specialist	Hospital	Both biological and psychotherapeutic	1	Low to moderate
P09	Italy	Male, 31	Psychiatry specialist, PhD student	Hospital	Both biological and psychotherapeutic	17	Good

P10	Sweden	Female, 35	Psychiatry specialist, PhD	University	Both biological and psychotherapeutic	11	Good
P11	United Kingdom	Male, 34	Psychiatry trainee, psychotherapy trainee	Outpatient addictions centre, inpatient addictions ward	Both biological and psychotherapeutic	0	Good
P12	France	Female, 36	Psychiatry specialist, PhD	University	Both biological and psychotherapeutic	18	Good

5.3.1 Psychedelics hold potential

The first theme encompasses all positive mentions of psychedelics, their worth or utility. It captures the statements of participants on certain positive attributes of psychedelics that make them carry potential, in relation to treating patients, providing new insights into the mind, or a new treatment model of psychiatry. Within this theme, we identified three sub-themes.

Psychedelics could be a useful treatment tool

Participants highlighted many of the characteristics of psychedelics' effects and of the PAP model as potentially facilitating and speeding up the treatment process. Psychedelics were mentioned as a tool that could help access unconscious contents, "get to the root of the problem" (P11), and generally bring back the focus on patients and their insight and emotional processing:

> *P05:The positive things are indeed that some people have, speaking of symptoms of post-traumatic stress and the avoidance issues, sometimes it is really difficult for people to verbally process the traumatic experience and the feelings that are associated with it, and in these cases I think that for some people this psychotherapy supported by psychedelics can really in some way make it possible to access those experiences more easily, of course with a therapist, a guide as they call them, who is present there…. I think I see some advantage there, that it is a method for people who cannot do exposure [therapy] in a classical way.*

P03: I would say that [PAP] allows us to kind of explore our psyche or consciousness at different levels and different dimensions. So it kind of lets us find out more about the mind as kind of treating that individual as a whole, as a complex person, really kind of lets us go into the different areas of our mind. So in that sense, it helps us better understand the person, maybe better understand the symptoms that that person is having, better understand the causes like the why, which is always a very important question in psychiatry. So it helps us answer many questions. We get to learn more about that individual as a whole, and I think that helps us better target the treatment when we understand more.

Overall, this theme highlighted that psychedelics and PAP have certain unique advantages that make them useful and give them strong potential as treatment methods.

Psychedelics could bring a new perspective to psychiatry

The treatment potential psychedelics hold was described as potentially very attractive in the current context of psychiatry. Psychiatry was described as needing innovation and in need of new treatment methods:

P08: I mean, our SSRI's and that class or family, they're all over 30 years old at this point, and we haven't really developed any new or different antidepressant therapy, apart from esketamine, which is starting to be used in day-to-day clinical practice. So I think we need to explore other antidepressant therapies and other sort of neurochemical modalities and ways of working.

P12: So because there is this lack of research in pharmaceutical industry, we are now stuck in a period where we don't have new treatments to propose to patients. And this is quite hard. [When] you are a doctor, you have people that are really troubled and you can only propose SSRI (laughs) or older treatment. And then it's electroconvulsive therapy -- I mean, just painkilling for very sick people. And this is not enough, we need new treatments. We need to think out of the box of what we have. (...) And I think people go back to the interest in psychedelics because they are desperate and they say, "well, maybe we missed something at that time".

P03: When it comes to the development of psychopharmacological agents, it seems that we have kind of come to a standstill of this innovative approach, and we're not

really creating that many new drugs that are helpful. So in a way, we are ready for another approach to enter and to use that.

The new approach of using psychedelics as therapeutics was likewise mentioned as providing a new, non-conventional model of treatment that could bridge the existing gap between psychiatry and psychotherapy and bring back focus on psychotherapy in general, as a contrast to the existing predominance of pharmacotherapy:

P10: I think in general that the people are always interested when it comes to new types of treatments. This should be, I think, is interesting because it goes in a whole different type than other studies and treatments. It's not like a new antidepressant. (…) It's not like a new neuroleptic, it's a whole different kind of track. And I think that may be gaining some interest as a whole new, different way of thinking about psychotherapy, in a way.

P02: The idea of a new therapy [like PAP], that's effective, sounds great (laughs). Now, I would definitely not be someone who will push for something until everything is regulated, but I am looking forward to new approaches to treatment, especially this integration of psychiatry and psychotherapy because, unfortunately, psychotherapy is not given enough space and more and more people are talking about the importance of integrating it, which is, I guess, logically implied, but it is so difficult to implement in practice. And this would be something that would force it… so maybe more psychiatrists would not be so proud to call themselves, as they say, "biologically" oriented.

P11: I think that it offers something is different to modern psychiatry models of medical interventions, mental health. So where as a general practitioner or a psychiatrist might prescribe an antidepressant, someone takes every day for months or even years. The model used for psychedelic therapy is that the participant -- the patient would only maybe have two to three or four doses of the of the medicine and the sort of guidance and the support and supervision of a therapist and possibly a doctor as well. And the idea is to start to try and, I guess, treat the roots of the disorder, treat the roots of the distress, rather than treating the symptoms and taking something every day that can sort of ease the symptoms a little bit.

The need to improve outcomes for patients in psychiatry for new solutions was seen as a highly relevant reason for the ongoing consideration of psychedelics as potential therapy, and personally staying attentive for further interesting research results.

Psychedelics deserve further research

Furthermore, the research on psychedelics conducted so far was described as "promising" (P03), interesting" (P04, P06), and "exciting" (P11).

Participants also expressed that psychedelics deserve further attention because further research in this field could help provide useful insight into how the human mind functions. Additionally, the involvement of respectable institutions in the field was reported to inspire interest and confidence:

> *P03: So from the information that I gathered, basically the psychedelic substance, it's something that really lets us kind of zoom in on the mind. And find - discover that depth to our mind, different levels and different dimensions to our mind. So I think it's just something that it will help us better understand one's mind and better understand the symptoms and the causes of the disease. So that's kind of one area why it's very promising, because it's - it's kind of a different approach to the mind,*
>
> *P12: I think it will lead us to a better understanding of what is a change in the human mind, but not on a biological point of view because it's not so interesting, but also, in the dynamic way, in the interaction, when you change a little bit of something, the perspective of someone, how you can affect his feelings and the way he is in the world and with others.*
>
> *P05: When I hear that Johns Hopkins took on something [like this], that they started so many projects, well, I think there's something interesting there. (...) It's good that serious institutions are working on this.*

5.3.2 Psychedelics are dangerous

Although some participants highlighted positive benefits and potentials of psychedelics, the idea that psychedelics are dangerous was very present and covered multiple aspects, from the side effects and potential for abuse they were perceived as having, to the general stigma they carry as drugs, and the way that the hype and enthusiasm around them can be harmful. This theme covers both the personal perceptions of the participants, their observations about what

other individuals think, as well as participants' impressions of the ongoing events in society and research. Overall, we identified five sub-themes within this theme.

Psychedelics could cause serious side effects

Psychedelics as substances were perceived by the participants as having numerous potential side effects, especially the risk of addiction, and of patients manipulating to gain access to the substances:

> *P02: I believe it would be safer to use [psychedelics] with people who are not prone to addiction. (...) [Psychedelic therapy] has not been done enough, it is still not used enough, we do not know how much addiction to those good trips we would see, and a certain feeling of some kind of connection with everything, with the whole universe... so, I believe that that feeling, it can be something that people who are deep in the throes of addiction might want to return to.*
>
> *P03: One of [the risks] would be that maybe that individual would be prone to use the substance on their own, outside of therapy, because maybe when they don't fully understand how it should be done, they would be interested in obtaining this substance and using it on their own.*
>
> *P05: Ketamine is researched a lot in psychiatry for the treatment of depression and other conditions. But ketamine is also highly addictive and must be kept under lock and key. Allegedly, some people were breaking into some clinics to steal ketamine and stuff - so it can potentially be a good drug under controlled conditions and stuff, but that doesn't change the fact that it's highly addictive, like methadone, potentially.*
>
> *P01: So there is a certain personality structure in people who tend to simulate a certain psychiatric condition in order to get what they want. If we open the way for them so that, instead of going to a dealer, paying for psilocybin, LSD, whatever -- we enable them to get it at the expense of the state because they get a diagnosis – those things will definitely happen.*
>
> *P08: There's the potential of abuse by staff on the medication and then the potential abuse that patients manipulate their history to gain access to it.*

However, not all participants agreed with the view of psychedelics as addictive:

P09: I read and I am quite confident that the dependence that has been raised as a reason to not to do psychedelic assisted psychotherapy is not a real threat.

P04: And I suppose maybe a few sessions [for substance users] with psychedelics like psilocybin, DMT, LSD would change their view of the world what is important and maybe it would change them as a whole (...) so that they could finally notice what's important in life, change their goals and maybe it would be easier for them to not to come back to drugs once and for all.

Participants also said they were worried that using psychedelics within PAP could cause traumatic experiences the patient would not be able to handle such as a "too heavy fragmentation or ego dissolution" (P09) and that psychedelics could exacerbate existing or underlying psychotic or manic phenomena:

P07: In [psychedelic] states, people can do different things that they are not aware of, they can enter into some kind of psychotic decompensation and so on, so it's not to be taken lightly.
P12: Patients with treatment resistant depression, they don't have the same brain and their brain is very vulnerable. And some may be – like, close to psychosis, hence I'm afraid that the psychedelic could push them into psychosis. The last step to psychosis.

P11: I think that there is reasonable evidence to show that if someone has a family history or a direct history of potentially psychosis or manic phases, then they can trigger that response in people.

Overall, participants concluded that the risks for patient decompensation, if present, could be decreased by taking increased safety measures, such as a "good medical interview" (P04) or a "general history taking" (P03) to screen patients, "a safe setting" (P07), or "good medical ethics committees that are checking the studies" (P06).

Psychedelics could be misused

Besides the immediate side effects of psychedelics, participants reported concern about the general misuse of psychedelics in ways that were not intended by PAP protocols. They highlighted a risk that therapists providing psychedelics could abuse their role and power, especially if not trained or supervised properly:

P03: And another factor that could be of concern, because when we - when one ingests the psychedelic and it's in that non ordinary state of consciousness, they are of course very susceptible and prone to suggestions. So, again, who is administering this session to us? Can we trust them and will it be just used for our own good? Or it could have a different purpose, if not used in the right, right way.

P02: Another thing that was also mentioned was the possibility of abuse by therapy providers- since patients are in some kind of altered state of consciousness, for example - could therapists have some kind of non-therapeutic approach? How can we ensure that there is no harm done to the patient?

P06: [There could be] people that are not eligible for this specific treatment because they do not have insurance or that they just that this hospital is not offering it because it's still very modest. So you get a lot of obscurity with maybe psychologists that are going to do it with psychedelics, but not on recipe, but just in private practice. I think that will be a danger.

Psychedelics were also perceived as having the risk of misuse that goes beyond physical addiction or side effects. Some participants were concerned that they could be a means of escapism or that patients could start relying on them too much instead of doing the therapeutic work themselves:

P04: But there are also many patients who just want to get high and it's no matter - it doesn't matter for them what substance is it. And it can be, for example, psychedelics or alcohol or anything else. And in these patients, psychedelics can be harmful in a way that they just want to get high and then they don't want to be sober because of some reason. And yeah, but they use psychedelics just like any other substance. So then they can also be harmful, but because they are using everything that's available.

P03: And maybe another risk factor could be kind of dependency of that individual. So maybe start really relying just on this substance rather than looking at the therapy as a whole, that it's not just about ingesting the psychedelic but undergoing the session as well.

Some solutions to these risks were that participants highlighted that therapists could be in "in supervision groups" (P11) and that they should be "checked in some way" (P06). A way patients could be protected from therapists is that "[psychedelic] séances could be filmed"

(P02) and that PAP should stay "within the walls of a hospital" (P06). Likewise, patients should "understand why they're doing [PAP]" (P03) and that "one should define what the goal of the therapy is" (P05).

Psychedelics are not for everyone

The risks and side effects of psychedelics also translated into a general view that psychedelics are not for everyone. This could be seen through accounts of participants when they talked about how it's difficult to choose which patients would be eligible for PAP, both psychologically and physically:

> *P11: But I guess another risk with addiction problems would be that often, particularly people with alcohol problems, have a sort of slightly older biological age. Then it's actually their age just because of the impact of alcohol on one's physical health. So often people are a little bit more frail, so I guess we need to be making sure that people are physically and physically safe to get it.*

> *P11: And I think that, at the moment, things like personal or family history of psychosis or personal family history of bipolar tend to be ruled out, although there's a strong movement of people in the bipolar community to say that that's actually being a little overly cautious. I think some people are feeling that some people in the bipolar community are feeling quite excluded from the psychedelic research and the feeling that you're doing more harm by excluding people, when there's people with, you know, bipolar depression, manic phases. And there are case studies to show that psychedelics could be good for some people with bipolar disorder. So it's very complex.*

> *P01: There's a problem with patient selection. How big can this group [of patients] be, how applicable it is. You can't exclude the social aspect in these things, they are a big factor in treatment. For example, are you giving a shaman in Africa what you are giving to someone in London, their experience of it is completely different. So there's geographical variability, too.*

Additionally, since psychedelics can lead to changes in personal beliefs and views, this was seen as something that certain individuals don't want or need:

P04: I think I agree that they can change like the more, more important domains. Like, for example, how someone is thinking about religion, about political views, because the feeling after psychedelics, it's this feeling that you are connected with the world, that everything is one or some kind of other mystical experience. And it can also change the very concepts of how- what do you think about the world? So it can change you as a person as a whole. And actually therapy should just change, for example, symptoms. Should make someone not depressed, for example, and not change his point of view of the world, for example. (...) It can be also desirable. Maybe the patient would be grateful for this change, but we have to be aware that it is possible and maybe not everybody would like to change his point of view in some other domains.

Some participants also highlighted that psychedelics and PAP are not interesting to them because for now they don't have potential therapeutic applications to the patient group they are mostly seeing.

Stigma around psychedelics is strong

Psychedelics were described as "controversial" (P07), carrying a "social stigma" (P01), having a "bad reputation" (P10), and people having "prejudice" against them (P06).

In particular, the message "all drugs are bad" was mentioned as key to their stigmatized position in society:

P04: Drugs are treated as a whole. So there is alcohol which is accepted in our society. Of course, people know it's harmful, but in small amounts, for most, it's not harmful. And tobacco, which we know is harmful but not harmful to mental health, and there are drugs which are completely harmful. Maybe some know that cannabis is less harmful than others, of course it's not 100% true, but some of them, some people think like that. But in general, drugs, drugs are harmful. And it doesn't matter if these are psychedelics or opioid stimulants.

P05: There is a generally a negative attitude towards addictive substances. Especially in... I won't say "Western" psychiatry because it sounds stupid, but… like these more developed countries that have a slightly higher GDP, for example, they have a very developed aversion towards drugs of addiction.

P10: But I would say in general, my personal guess is that people in general are quite sceptical to substances that are classified as narcotics. (…) For example, for established treatment like with ADHD medication, there's enough scepticism that's connected. So unfortunately, psychiatry has a lot of stigma connected to its treatments.

This stigma was described as confusing when combined with the new idea that psychedelics as drugs could be used for treatment:

P08: The message for so long has been that drugs are bad. And it's a criminal offense to use drugs or to be found with drugs. So it's criminalized. And so, you know, I have the narrative where, it's illegal to use this substance in the community or to be found in possession of the substance in the community. But now you're telling me that it's OK to come into the centre and to use [it as therapy]. (laughs) (…) There's the risk of mixed messages when we tell the public about, you know, "don't use drugs" and yet we use drugs in a clinical setting. So it'll have to be a very nuanced and balanced discussion if it was to be introduced into mainstream clinical practice. (..) But there could be a stigma if you approach, you know, a middle-aged lady with anxiety symptoms and panic attacks and you say, "Well, actually, what you really need is to come in for some psychedelic psychotherapy." You know, there may be some resistance.

P07: It would be very unusual for me [to do PAP], honestly, I can't even imagine. So for us [in addiction psychiatry] patients - the prerequisite for coming for treatment is that they are sober, that they are clean. You can't do psychotherapy with him if he's spazzing out, right? So it's a very unusual concept actually, I don't know how it would... it would be weird, yes. (laughs) (…) Generally, if you ask me, it's the complete opposite, because you're taking it - if you have some kind of psychotic shift, you give something to make the person more present, not to hallucinate, to be present, and this is actually a kind of reverse path.

The stigma was not only related to drugs, but also to psychedelics' cultural and historical notoriety, most often mentioned in relation to their role in the counterculture movement of the 60s, the MK-ULTRA experiments, and the New Age spirituality movement:

P01: For example, we hear quite often, from the hippies of the 60s onwards... we heard that, when it comes to psychedelics, they open the third eye, they act on, I don't

know, the chakras in the body... they are the way to some transcendental experience and so on. (…) We know of, for example, of spontaneous trips that occur in people who have taken some psychoactive drug even once - LSD is very specific here. Which, without any external trigger... years, decades later, people can go into some kind of spontaneous trip or something.

P04: I heard that one researcher said that we have to be careful because psychedelics were also used in CIA programs in the fifties and sixties and in these, which are documented. There are many for which it's supposed that they were conducted, but MK-ULTRA was documented and it is possible that they can be also used for brainwashing.

P09: There is I think that there is a historical heritage of the fact that the psychedelics at some point were considered dangerous because they were taken outside the context of therapy or a controlled context. So there also has been - have been problems with that, for example, with MDMA in the United States in the 80s and also some cases of suicide attempts or a suicide completed during LSD trips. But it's easy to be critical. It's also true that the SSRIs increase the risk of suicide. So I think that there is more fear of something that maybe… may change your mind in a way like psychedelics do that may make you more connected with the other, connected with the world, with the nature, more peaceful. And that may have scared the leaders of the countries in the past.

The media was also described a risk factor in further propagating the public stigmatization of psychedelics through the generation of negatively slanted and sensationalist news:

P04: I suppose if it happens that we will have some psychedelic-assisted psychotherapy, there will be some stories about people who went to therapy or, I don't know, got the psychedelics and wanted to make their own therapy but something bad happened to them, that they went to the hospital.

P06: Because if you have one big case with a suicidal patient, for example, that is on psychedelics, then people will be - the media and the overall sentiment against psychedelics would be big.

Some of the solutions offered to disassociate psychedelics from their stigma was "rebranding (…) [by] changing the name so that it wasn't associated with the street drug" (P08), to "solve

the dichotomy [between drugs and medical use]" (P05), and reduce the "mixed messaging" (P08).

Hype around psychedelics could be harmful

Moving beyond the negative image of psychedelics from the past, participants also focused on serious concerns about the hype present around the current wave of psychedelic research, which generates unrealistic expectations of psychedelics as "cure-all" among researchers, physicians, and especially for patients:

> *P11: I think there may be a risk of over-inflating the benefits as well. I think that for such a long time since the 60s, really there were scare stories about drugs and lots of propaganda and "drugs are bad, stay away from LSD" type of thing that I think has maybe swung the other way now. The media hype is being overly positive and there's been a lot of headlines out of, not all that many trials, or not larger trials. So I think that there's maybe a little bit of overhype and that can lead people to think that these are a miracle cure or like a golden pill that is going to fix everything for them in one dose, which is not often the case. So I think that maybe, yeah, there are risks of over inflating the benefits, and that can leave some people sort of feeling quite helpless or feel quite disappointed if it doesn't work the way that it works, like on a documentary for one person or in any story for somebody as well.*
>
> *P06: So the main the main risk is that it's like people really jumped the bandwagon. And this means that we think - and this is- it happens all the time in psychiatry that we think "wow, we have this new thing. This is really going to change the world and we're going to do a lot of things" and, eventually, the result is that it works, the effect sizes are not really big because for some people it works and for other people does not work, which is also logical, which also was for antidepressants, which also was for other types of substances.*
>
> *P12: And [patients] already tried also. A lot of patients, they say they see the name of the drugs in the journal. They want the treatment in the hospital. Even if we say, no, you are not a good candidate for ketamine. I know some of them buy it in the black market and try, it's uncontrolled, and sometimes the drug is really a bad quality. And this is dangerous for people. But this is why I never advocate drugs in the public media.*

Furthermore, the media was also seen as playing a role in the hype and exerting pressure on researchers:

> *P12: The media put pressure on the researchers and doctors to say that it is interesting and important and blah, blah, and then their colleagues who are really enthusiastic, they have no inhibition (laughs). (…) Yes, the journalists come and say, "OK, do you think the psychedelic is the new therapy?" And they say, "Oh yes, of course." But they don't have this public health way of seeing the thing. I mean, when you say this in the most read journal of France, what are you doing now? (…) I think both researchers and doctors have the responsibility [with] public talking. So you can say something with your colleagues, door closed. "I think that psilocybin is the next revolution". But saying this in a public place, TV shows or whatever, this is dangerous.*

Besides the responsibility when speaking about psychedelics publicly which was pointed out by P12, some of the solutions participants offered to the risks carried by the hype were to "stay humble (…) [and] always aim for more research" (P06), "always be a bit cautious" (P10), and "be very, very transparent in research" (P09).

5.3.3 The future of psychedelics is uncertain

The third theme revolved around the general sentiment that it was unclear whether psychedelics and PAP would be, ultimately, successful in reaching clinical practice. This theme describes general unknowns which remain in relation to psychedelics, and which relate to research findings, social and political factors, and perceived factors influencing real-life implementation attempts. Overall, we identified three sub-themes.

Still missing crucial knowledge on psychedelics

Participants said that the current evidence about psychedelics and PAP was still insufficient, in their eyes. They especially emphasized the need for larger studies, especially randomized controlled trials:

> *P12: And for me, I am very cautious with drugs and I just - I need data. I need data and I need to see [with] my eyes first and then bigger data trials. Well done, multicentred with good outcomes. I want to see effect on suicide. I want to see effect on going back to work, going out of the hospital, for instance, on suicidal ideation. I want to see this data. (…) I'm not involved a lot in this research because I think it's—*

for me, this is only pilot studies, but they are sold in the paper as phase three or phase four trials. This is bad science. It's too early, too few - samples are ridiculous.

P02: [PAP would be more convincing with] more positive results from these clinical studies. So there is already something, but it's mostly still very small numbers, at least what I've read, is still relatively small numbers of subjects so there should be a certain number of positive results. preferably compared to conventional treatments.

P06: What is needed, I think more evidence, more evidence is needed because then the taxpayer or the health insurance companies will pay. So there's just more evidence needed.

Participants also expressed the idea that certain key questions about psychedelics and PAP are still unanswered, making any speculation about the future more difficult. Some of these unknowns were reported as increasing the perceived risk of PAP:

P03: I would worry about what happens if one, kind of, continuously over their life goes for these sessions, and then ingests the substance. What kind of effect will it have then on our psyche? (…) So that would be something to think about as to the quantity, the amount of times that we do this with a patient.

P06: So the biggest risk factor would probably be that we do something and we still don't know exactly how it works.

P02: It seems to me that there are still no clear guidelines regarding dosage, frequency, treatment. (…) A lot of a kind of...preparatory work [is needed] before it can be applied on a wider scale.

Participants also mentioned methodological issues with psychedelic trials that may be confounding true results, such as the effect and the role of psychotherapy and the therapist or which outcomes are measured in clinical trials:

P06: And I also think that the next step would also be that that you don't do psychotherapy anymore, you just use psychedelics and see whether that will help you as well. So that is another development that's probably going to start. Like the same goes for ketamine, right? Because the ketamine, you don't do it with psychotherapy, you just give ketamine and it works for suicidality. (…) I think it also is very dependent

on the therapist if he knows what he or she knows what to do with these types of patients, then you have more chances that it's actually effective.

P09: I think that there is not yet a standardized training, for example, for assisted psychotherapy and those in the past when it was tested, it was more up to the clinician, up to the therapist. So that's not fully - that's not good to me. I think that there is the need of a framework.

P12: The FDA wants the Hamilton [scale] and the MADRS [scale] to be measured for market access, for the drug to go to the markets to be authorized [for treatment-resistant depression]. (...) And I think these outcomes are like, no, they don't say everything about depression. They are really debatable. This is not the whole picture of depression. They missed important dimensions that can be helped by, for instance, other drugs. These outcomes were tailored to show efficacy of tricyclic and SSRI. So Hamilton for tricyclics and MADRS for SSRI. So it's just like impossible to show something in this case when you try something else. Even psychotherapy or restoration, because these are more targeted therapies and specific dimensions that are not captured or they are blended by other items of the scale.

Some practical solutions to address these unanswered questions were to "include patients when designing research" (P09) and "collect exploratory data with qualitative interviews [with patients]" (P12).

Psychedelics are inseparable from the general social and political context

Psychedelics were described as an issue deeply embedded in a social context. Participants said that any implementation of PAP was also inseparable from questions about the legal status of psychedelics. Likewise, research involving psychedelics was seen as potentially limited as long as psychedelics remained controlled substances in most countries worldwide:

P01: You will have lobbies of pharmaceutical companies that will push for it to be legalized as soon as possible, but there will be lobbies of conservative parties that will be about "let's save our children, say no drugs" and so on, and there will be a fight on that level. Then it is it's a matter of time who will be the first to concede. (...) As I said, the pharmaceutical lobbies have great interests in this, insurance companies have great interests in this. That means money - a lot of money can be spent there, so it's

not likely to always be criminalized, it will definitely go in that direction, that it will eventually be implemented.

P09: I think [legalization and research] are connected, and I would agree with the liberalization and maybe also… legalization because of two reasons. The first reason is that we would be more free to investigate the substances and the second reason is that the people would take [them] for recreational use anyway, so it's better to provide them with control and safe substance rather than a dirty or mixed compound that may be dangerous.

Along with this, participants emphasized that financial interests are something that could influence the future of PAP. They stated that psychedelics and PAP have the potential to be commercialized and subject to market-driven interests, but also that, if this area got more funding, this could be more interesting and relevant for them:

P09: I am a bit afraid that these kinds of substances, psychedelics that are mostly present in nature may be heavily commercialized, heavily traded, so it may be kind of speculation on that, that are not natural products, so it could be quite cheap to get.

P10: I know in the US a lot of, for example, IT companies have been pouring money into psychedelic research, and that also helps. I mean, where there is money that's also going to be increased research.

P11: I would like to see a commitment to more funding for this type of research. I work in Scotland, which is like even worse than the rest of the UK in terms of its addiction problems and drug related deaths. (…) [My personal involvement] largely depends on funding, really. If it's something that likely to be funded if it's something that the government will fund, or even mental health charities or bodies are likely to get interested in funding. Then I think that I'll be a lot more likely to work on it.

P1: In fact, I think you would see a boom [if PAP would be implemented]. I don't know, if you a school for that opens - I would be the first to apply because I definitely see that there is a market there.

Finally, psychedelics were described as connected to the current historical moment and zeitgeist and that their future would both influence and be influenced by ongoing changes in society and psychiatry:

P09: And yeah, from the social and the political perspectives, it's more difficult to say what's needed [to approach psychedelics in the right way]. I think that at some point there are bigger interests from the, yeah - the top people in the world, and these are very difficult to understand and to change. For example, I listened to some interview of people that had a, for example, psychedelic trip or a psychedelic treatment, and they suggest also and they report increased connection with nature. So in the era of ambientalism, ecologism and so on it may be useful also for that, from a social perspective rather than a therapy setting.

P03: [Where psychedelic research will go] is kind of something that we don't know much about, and when it comes to our mind, a very vast subject, I would kind of maybe a little, be a little bit hesitant as to what dimensions are we tapping into and what are we discovering, and are we ready, kind of, to discover these different dimensions? What will we do with this knowledge? And are we really - will it really be used in the right ways?

P01: [When thinking of how psychedelic research will look like in 10 years] I think that at that moment there are more other factors to take into account. The development of new medicines, what will society look like in 10 years? (...) Now, in 10 years, and we are talking about a significant scientific advance from today, the question is, that's why it is difficult for me to predict, the question is where this moment... which we are talking about, where will it be then, given that the competition [of other treatments] with which it competes during those 10 years is quite strong.

This theme generally tied in with the sentiment expressed earlier that psychedelics are controversial, so some participants compared the situation with psychedelics with issues around cannabis legalization (P04, P09).

Implementation of PAP may not be feasible

Participants expressed that real-world clinical implementation of the PAP model that is currently being explored may not be feasible. Primary, they stated that this is due to high staffing, administrative, time and resource requirements:

> *P10: And also, one thing when it comes to PTSD and psychotherapy, as I understand it, the psychedelic is like an individual therapist and patient treatment. That's also not very staff-efficient. Aa lot I know [from what] we do here [is that] a lot of the PTSD treatment is in group therapy. Not for everybody can work, of course, but when it comes to patients, these things seem to be quite the same as individual therapy, at least for PTSD. And you're going to have much less staff resources and you can treat more patients. That's also important to me, that if you do treatment and it's a benefit for as many as possible. (…) And also, you need to have the administration of the psychedelic and the patient needs to be a certain time in hospital, as I understand. And then for observation afterwards, maybe not for a long time, but it's a whole different way of setting up the care that I think is going to be logistically [difficult].*

> *P12: This is very expensive, so you have it will be done in very specific departments as the one as I work, where we have a lot of money and you can pay psychologists to do this session. But basically, I don't think we have the means to pay so much psychotherapy. So, it will be… I don't think the cost effectiveness of this therapy, that it's worth it.*

> *P01: If something is going to be officially introduced as a medicine, then it has to be included in state regulations, not only state regulations but insurance company regulations. For PAP you would have enough red tape from here to the Moon and back. (laughs)*

There was also a sentiment that such a complex treatment is not compatible with current infrastructure which is, in many places, already heavily overburdened:

> *P02: I believe that it would be a lot, purely for these legal reasons, easier to organize [PAP] in some kind of hospital environment. On the other hand, mostly all these public systems are so overloaded that there is not even room for psychotherapy, let alone... for psychotherapy supported by psychedelics, because as far as I know from those in some of the articles I've seen, it's mostly important that the setting is not*

overstimulating, that in fact... that one can dedicate himself to that client or that patient he would work with, so I don't really know how it would be, at least not in public hospitals, maybe in some private ones.

P10: But at least in Sweden, in my clinic, I mean, there's already a lack of therapists for regular, more established PTSD treatments. For example, exposure, CBT. There's currently a two-year waiting list just to get to especially psychiatry, you know, CBT for trauma here. And so I'm like, if we can't even provide the regular basic PTSD treatment for psychotherapy, I don't know if we have the resources to add additional treatments under investigation, because then we need to train therapists in new ways and set up different facilities. (...) No, I think it's more important and urgent to add new treatment methods for categories of patients that have more severe symptoms, that are harder to treat with the methods already have. I think that's a higher priority. If we have other functional treatments for other disorders, we should focus on trying to make our work at a base level first.

P12: But in reality, we don't have a nurse in the hospital. So one third of the beds are closed because we don't have enough [staff]. So let's talk about psychedelic psychotherapy, it's impossible to do.

Additionally, some participants were confirmed that the current model of PAP with its high resource requirements may be very expensive and may only be available for patients who are well-off:

P09: I have the fear that it will become something that only rich people may have access to, because psychotherapy is already very expensive and a new substances used as medication usually cost a lot of money at the beginning of the trading. So that's what I expect. Like what happened for esketamine, for example, that starting from ketamine an enantiomer was taken and just commercialized at a much higher price, whereas ketamine was far cheaper.

P12: I am not involved in the RCTs of psychedelics because I know it's really niche and it has no future to be spread around the world like major therapy. What I am evaluating, though, is more digital therapeutics. All those applications that claims to do psychotherapy, democratized psychotherapy, etc. I think the idea is good, but I just

want to evaluate it to see if it works more than this for people, because I can see a bigger access to care; while for these kinds of drugs, I can only see health inequalities.

5.3.4 Psychiatry is ambivalent towards psychedelics

Psychedelics were described as a topic that creates a lot of divided opinions and debates within the field of psychiatry. The "50/50" split was not only expressed in terms of attitudes, but also significant discrepancies among individuals in the level of interest and knowledge on psychedelics and PAP. This theme referred to both opinions held by participants themselves, as well as those they describe their colleagues or, more generally, wider groups of psychiatrists as having. We identified three sub-themes within this theme.

Attitudes on psychedelics and PAP are mixed

When asked about the potential introduction of PAP in real-life clinical practice, the possible reaction of psychiatry as a whole was described as likely to be "ambivalent" (P10), "split" (P09), or "divided" (P02, P03).

Some of the reasons for being opposed to psychedelics as a psychiatrist was fear, either due to having insufficient data on a potentially risky intervention, or a general resistance to novelty and changes:

P08: And where that, I suppose, the reason I talked about the past use is that there have been novel treatments in psychiatry, all going through the years that the last hundred years and some have not been successful. (…) With any novel treatment they look for the evidence base and they want to see, well, what is the practice? What are the numbers? What are the studies, before their own practice changes? So people are slightly wary, I think, of novel treatments until they're seen to be safe and effective.

P04: But I think in general, most of psychiatrists would disapprove it, but they also don't use the newest drugs, which seem better or better tolerated. And many of them don't know how to do polypharmacotherapy. So it's because of that I would say that they don't read, they don't learn, they just do. They just treat patients like they did 20 or 15 years ago.

P11: In mainstream psychiatry, people are quite fearful and sometimes I speak to my colleagues about it. Addiction colleagues are quite open to the idea that psychedelics could be helpful. People in general psychiatry and adult inpatient wards seem to be a

little bit more cautious, and I think that's probably because they work in inpatient units, they said they often see when drugs go wrong, when people who probably shouldn't be taking psychedelics take them and end up in hospital.

P06: Another is that people don't know, so they don't want to prescribe it, so people are scared of prescribing new stuff, so that's also the reason why it really takes care before it really gets implemented in a country.

Some psychiatrists were described as more open than others, especially those who were younger or already generally more open to novelty:

P04: Most of my colleagues, but I mean colleagues in my age, I don't say anything about most of older psychiatrists, but in my clinic especially, I think people are open minded and would be very grateful if they can use this possibility of new drugs and new treatments.

P03: Some people who are maybe very like in favour of rapidly evolving treatments and kind of being on top of everything, up to date, maybe they would be for it.

P10: I think it is very different even now, just for the past five years, I see a shift in attitudes, especially with the younger generation.

Although the opinions on psychedelics were described as mixed and likely to stay that way, many participants expressed that awareness about them is rising.

Many psychiatrists lack education on the topic

Knowledge on psychedelics and PAP was a topic with significant division present in psychiatry, where mostly personally motivated individuals are reading about new research developments. Education on psychedelics was often described as lacking overall within one's professional training, although some participants reported increasing awareness and discussion of the topic within the field. However, some participants said their colleagues could profit from more education when considering the topic:

P03: I would think that probably the average psychiatrist probably had or has a similar level of knowledge that I had before this, because it's not something that is covered in depth, obviously, in medical school, and it's not something that is the main area of focus in our residency training because there is so much other material we

have to learn and especially when it comes to our daily interactions with patients. So we tend to focus on those approaches, the drugs that we use on a daily basis and psychotherapeutic approaches. So I think it's rather limited, their knowledge.

P06: Yeah, I think [the knowledge] is very basic still. It's not very well developed yet. So training will take time before it's actually there.

A significant number of participants also expressed the personal view that they didn't often encounter psychedelic users in their practice nor receive sufficient education on psychedelics during their medical school or psychiatry training. Any knowledge on the subject was described as left up to personal interest and initiative:

P03: So as far my psychiatry residency training for now, it has not really been addressed. I haven't come across the psychedelic group of substances in terms of, like, theoretical lectures. And the only kind of knowledge that I have would be very superficial and brief knowledge from my medical studies when we had a chapter in pharmacology on different drugs for recreational use, what kind of effects they can have. So LSD, for example was covered. So that is just very limited and superficial knowledge that I have from my medical studies.

P07: I don't even remember that they were mentioned, maybe they were mentioned... well, LSD was the only one that was mentioned during my studies, and during my residency... I was in addiction psychiatry for a long time, but there were no such patients, the education was not somehow formalized then. So formally, no. It was left to me, right?

P11: There was a mention that I mean, I think if it was mention of LSD or magic mushrooms, it would have been called by our teacher as negative and [that] these are things that can make people mad, make people psychotic and end up in hospital. There is certainly nothing like absolutely nothing on any sort of positive benefits, of drugs in general, but particularly on psychedelics. (...) Medical students tend to know more about it than the old sort of doctors that have been working for years on it or in psychiatry.

P09: I studied [psychedelics] in like a one-hour module within "substances of abuse". So kind of an odd context, because they are now studied for the treatment and they don't have the peculiarities of the substances of abuse, but still they are there in the

juridical and legal regulations. So I think that's the reason why they are put inside that model.

Some solutions to this lack of knowledge that participants suggested were "continuing professional education programs" (P11), "discussing it on most [psychiatry] conferences" (P04), "have psychiatrists witness these sessions" (P03). Likewise, the lack of knowledge and education was connected by participants with the base scepticism and resistance many psychiatrists feel towards psychedelics.

Being pragmatic and thinking clinically

Finally, participants expressed a pragmatic viewpoint, stating that, in the end, their primary focus is on their patients and clinical outcomes. This view encompassed that, if they were presented with adequate evidence and backed by the field, they would be open to apply it in treatment. There was also a consideration that, if professional organizations would give a positive judgement of PAP, this kind of consensus would make it more acceptable to them. The distinction of thinking like a clinician rather than involving their personal attitudes was a significant difference emphasized within this view:

P12: So I think that there is this feeling in the youth that are interested in psychedelics, but for me, it's not as a doctor, it's not a question of psychedelics or not. It is: do you have a new tool to help my patients or not?

P07: I think that there would have to be a high level of evidence and the absence of another method that could do it, in which case [PAP] would probably be accepted. (...) I [personally] would like to see that it is effective, that it has a low profile of side effects, that it is feasible, that patients are satisfied with it, and that the profession supports it, that's it.

P10: I think also what we're interested in is "How this is going to change my current work clinically?". I think people are interested, but you know, it's still as we're early in the field so we're going to see where it actually goes.

P08: And you know, most psychiatrists are pragmatic people in the end, and if they find a medication that is evidence-based, safe and effective, they will use it. That would be my opinion.

P01: If someone were to offer me concrete scientific evidence about the usefulness and safety of [PAP], I would accept it in the same way as I accept transcranial magnetic stimulation and so on, but until I see this, until it becomes generally accepted, I don't think I would be a pioneer in that area.

Overall, participants, despite naming significant cautions towards psychedelics on the most part, were open to new developments and a general change of attitudes or paradigm that could follow in their field.

6 DISCUSSION

The studies within this PhD dissertation demonstrated that psychedelics remain a controversial therapy even today. This was shown to be the case for the Croatian general population, for European psychiatrists, and as well in a qualitative study with European psychiatrists. We also developed a validated instrument to assess attitudes on psychedelics.

6.1 Validation of a new instrument for assessing attitudes on psychedelics in the general population

6.1.1 Summary of main study findings

We presented the construction and preliminary psychometric characteristics of a new scale measuring attitudes towards psychedelics, the APQ, within this study. The construct validity of our new instrument has been confirmed by confirmatory factor analysis, which has also validated the factor structure of four sub-scales: Legal Use of Psychedelics, Effects of Psychedelics, Risk Assessment of Psychedelics, and Openness to Psychedelics. All four sub-scales, as well as the overall APQ scale, have shown a high degree of internal consistency. Strong correlations with the results of the modified Barnett et al. questionnaire (68) provided support for the convergent validity of the study. In the basic knowledge on psychedelics test, opium, methamphetamine, and heroin were most frequently misidentified as psychedelics. LSD, MDMA, and psilocybin were the most commonly recognised psychedelics. The APQ scores and knowledge of psychedelics showed a positive correlation. Having a lower level of education, male gender, and younger age were linked to more positive sentiments regarding psychedelics. HCW status was only connected with more negative sentiments regarding the legal status of psychedelics and the perception of their effects, although general response trends in this sample indicated openness and interest towards psychedelic-assisted psychotherapy. HCWs and the general public had the same basic ability to recognize psychedelics and differentiate them from substances that aren’t psychedelics.

6.1.2 Strengths and limitations of the study

As is typical with survey research, the primary limitation within this study was the possibility of selection bias. We made an effort to prevent this by selecting participants from a diverse range of backgrounds, reminding those who were invited to solve the survey, highlighting the equal value of all viewpoints on psychedelics, and offering the survey in the participants' native tongue. However, given Croatia's high degree of ethnic and cultural homogeneity, a caveat is

necessary about the generalizability of our survey results. Since our results are limited to the Croatian context, we encourage future research to validate and analyse APQ scores in ethnically, geographically, and culturally varied settings. In addition to this, the snowball sampling technique we used did not allow us to determine the demographic makeup of all invited participants, the number of individuals who did not access the survey, nor the precise response rate of the survey. Nevertheless, an examination of attrition bias for those who did access the survey revealed that demographic information about survey respondents who stopped midway through did not differ from that of respondents who were ultimately included in the study. As a result of these limitations, we took care to avoid attempting to characterise or establish any cut-off values for our instrument because we are unable to guarantee that it fully represents the target sample. Overall, since the primary aim of this study was initial validation of a new instrument, we encourage further studies to assess attitudes on psychedelics within smaller groups of participants where an exact response rate can be determined.

6.1.3 Placing the study findings into the context of previous research

Our findings were generally in line with the previously published surveys on attitudes on psychedelics. An association of younger age and male gender with more positive attitudes on psychedelics that we found was also previously observed by Barnett et al. (68). Reynolds et al. also carried out a qualitative study with HCWs who worked with patients who were terminally ill. They found that interviewees' attitudes and conversations regarding psychedelics were influenced by their knowledge (87). Our observation of the relationship between interviewees' attitudes and knowledge about psychedelics validates and quantifies their field observations. The validity of our findings is additionally strengthened by the strong correlation of APQ scores with the Barnett et al. questionnaire on attitudes on psychedelics, especially since the items developed Barnett et al. also showed good psychometric properties in our sample (68). The added value of the APQ compared to the items by Barnett et al. is that it offers a wider and more detailed scope and that is has sub-scales which can be separately used in a statistical analysis. Although the majority of the APQ is made up of cognitive items, it also includes items that address attitudes on psychedelics through behavioural and affective components.

Research by Davis et al. has demonstrated that even mental health professionals know very little about psychedelics (70). This was also the case in our study, where HCWs' knowledge of psychedelics was no greater than that of the general public. The fact that a large number of our participants were misinformed about what substances qualify as psychedelics is also not

surprising. Despite the fact that hallucinogens are generally known to have a low potential for dependency (35, 36), a survey of college students' attitudes towards them revealed that the majority of them believed that they lead to addiction (88). It makes sense that there is a lack of general knowledge about psychedelics because this field of study has only recently come back into vogue and knowledge about these subjects is slowly making its way into the general public (3, 17). A significant portion of our participants dropped out of the knowledge test, and their feedback made this clear—those who did so explicitly said they did not know enough to complete the survey. We come to the conclusion that even though the APQ has been validated in a general population sample, it cannot be given to participants who essentially know nothing about psychedelics. Approximately half of the participants in our study had average to above-average knowledge of psychedelics, according to the distribution of knowledge scores on a 0–100 scale. Still, a sizable portion of our participants believed that drugs like heroin are psychedelics, suggesting that people have very little understanding of the distinction between legal and illegal substances as well as the effects of psychedelics. However, we were able to be more certain that our participants' responses are representative and do, in fact, reflect their attitudes towards psychedelics, rather than other substances, because we provided them with the correct test answers.

6.1.4 Implications of the study findings and suggestions for further research

There are several more ways to apply our findings and the APQ. First of all, it is commonly known that expectancy bias and other extra-pharmacological factors influence the degree of the psychedelic experience experienced by participants in trials involving psychedelics (89, 90). Using the APQ to measure pre-existing attitudes and beliefs, it could be possible to determine whether treatment response or the intensity of the psychedelic experience is related to the baseline attitudes on psychedelics held by participants in psychedelic-assisted psychotherapy trials. Secondly, according to a study by Davis et al., US psychologists expressed interest in using psychedelics as medical treatments, but they only had a limited understanding of their characteristics and effects (70). Their research made clear how important it is for mental health professionals to receive education, particularly in light of the ongoing public conversation about psychedelics. The correlation we observed between attitudes and knowledge regarding psychedelics suggests that further research should focus on educational interventions. The APQ has the capacity to offer a metric for helpful before-and-after comparisons of various educational interventions in addition to comparisons between groups. The APQ should also be independently validated among health professionals, such as

psychologists and psychiatrists, since knowledge of their attitudes and beliefs is crucial to comprehending the ramifications of any psychedelic use outside of research settings. We also recommend using our knowledge test (where the substances can be changed as needed) when administering the APQ, as early results and participant feedback have shown that a basic understanding of psychedelics is required to complete the survey. In this way, the knowledge test can function as a means of participant screening. In addition, we held back from asking about prior recreational psychedelic use among participants out of concern for selection bias or socially acceptable answers that might distort the findings of our study, which had validation as its main goal. The study's demographic factors only partially explained the variance in APQ scores, suggesting that psychedelic use may be a significant but understudied predictor of attitudes towards psychedelics. Subsequent research endeavours could examine the potential correlation between APQ scores and self-reported recreational psychedelic use, in addition to any other demographic variables deemed relevant. Finally, since it is difficult to obtain samples that are, for example, truly representative of the general population of a country, future studies should define standard cut-offs for APQ scores by conducting the questionnaire in specific smaller and more well-defined settings.

6.2 Attitudes of European psychiatrists on psychedelics: A cross-sectional survey study

6.2.1 Summary of main study findings

In our survey, European psychiatrists demonstrated generally moderate attitudes towards psychedelics and were able to distinguish psychedelics from a group of psychoactive substances, particularly mescaline, psilocybin, and LSD. Particularly, younger male psychiatrists who classified as spiritual, were more adept at identifying and categorising substances as psychedelics, and had used psychedelics in the past exhibited more positive attitudes. Remarkably, attitudes towards psychedelics were unrelated to any professional variables other than self-reported prior experience with PAP or psychedelic research. Additionally, we found a strong positive correlation between APQ scores and self-assessed and objectively tested basic knowledge of psychedelics, respectively.

6.2.2 Strengths and limitations of the study

It is important to evaluate these results in the context of potential response and sample bias. Numerous participants reported having experimented with cannabis and psychedelics; prior use of these substances was also linked to more positive attitudes, suggesting that those with more positive attitudes were more likely to take the survey. It is possible that we lost participants who would have skewed the APQ scores in favour of those expressing more negative attitudes because we also discovered that the individuals who dropped out had less experience with cannabis and psychedelics. Given the large number of organisations that were initially contacted with an invitation to distribute the survey and the small number of organisations that agreed to do so, our actual response rate is probably very low (<10%), and we are unable to account for those who declined to respond. The psychiatrist population is difficult to reach, so we employed a number of thorough sampling techniques to compile a sizable sample that was diverse in terms of geography and culture. Our study's strength lies in its large sample size, as our response rates are unsurprising when compared with those of other web-based surveys assessing attitudes on PAP (70, 74). In this way, rather than claiming to represent all European psychiatrists, we offer a comprehensive and perceptive dataset along with analyses that are grounded in a validated psychometric tool. The APQ's sub-scales, which let us distinguish between various aspects of the psychiatrists' attitudes, are a benefit of using it.

6.2.3 Contextualizing and interpreting the study findings

The median APQ scores of psychiatrists fell between the middle of the APQ scale (66.0 vs.65.0), which was similar to the scores of the general population evaluated in our prior study (83). Openness to Psychedelics was the sub-scale with the highest score, and Risk Assessment of Psychedelics had the lowest score. These results complement and quantify earlier research by mental health experts, which indicated baseline openness to psychedelics and PAP, but also a significant degree of caution and uncertainty about potential risks and side effects of psychedelic use (68, 70, 74). There was no discernible difference in knowledge between laypeople and healthcare professionals of all specialties, according to our prior general population survey (83). In contrast to these two groups, the current sample of psychiatrists demonstrated a higher level of basic knowledge regarding psychedelics (86.0 vs. 63.6). The most widely acknowledged psychedelics in our investigation were LSD, psilocybin, and mescaline, which were also identified in the UK psychiatrist survey conducted by Page et al. (74). When it came to classification, ketamine had the most polarised scores; even so, half of the participants continued to classify it as a psychedelic. This research suggests that a broad and widely-accepted agreement regarding the classification of psychedelics is needed. A consensus like this can aid in standardising professional education and dispelling any misunderstandings regarding an already complicated problem. In contrast to our survey of the Croatian general population, where participants frequently mistakenly believed substances like heroin, methamphetamine, and opium to be psychedelics, this survey saw methamphetamine and GHB as the most frequently misidentified as psychedelics, a significantly less alarming finding (83). Overall, the knowledge results are consistent with expectations given psychiatrists' superior psychopharmacological expertise and their higher level of hallucinogen knowledge compared to other medical professionals (67).

Consistent with earlier research, our results also show that younger ages and male gender were linked to more positive attitudes regarding psychedelics (68, 71, 83). In line with earlier psychological research (91) and supported by the higher percentage of males in our sample who had previously used psychedelics, our study found that male gender was only associated with higher scores on the Risk Assessment of Psychedelics and Legal Use of Psychedelics sub-scales of the APQ. This may indicate that men are less risk-averse than females when it comes to psychedelics. Despite the small but significant difference in median scores between male and female participants in the basic knowledge test (91.0 vs. 86.0 on a scale 0-100), male participants in our sample seemed more confident in their self-assessed knowledge on

psychedelics. Additionally, men reported having more experience with PAP and psychedelic research, suggesting that they may interact with psychedelic resources and information more frequently. The "war-on-drugs" propaganda that began in the 1960s and focused primarily on the negative effects and risks of psychedelics may have contributed to the lower APQ among older participants (2, 92). The conversation about psychedelics is currently becoming much more open and, though still somewhat polarised, we are witnessing a shift in culture and society that may have an impact on the younger generations, whose attitudes are still susceptible to the current cultural climate (93). Regardless of one's background and training in psychiatry, our findings that prior psychedelic use and personal experience with PAP and psychedelic research were both strongly associated with more positive attitudes on psychedelics are consistent with the widely accepted hypothesis that prior behaviour is the strongest predictor of subsequent attitudes (94). Further to what is known about psychedelic use shifting one's beliefs to be more geared towards panpsychism, belief in reincarnation and the afterlife, and attributing consciousness to living and non-living entities, there is an association between spirituality and past psychedelic use and more positive attitudes (95-97).

6.2.4 Implications of the study findings and suggestions for further research

We estimated an association between knowledge and attitudes about psychedelics, just as we had in our prior validation study of the APQ. This finding supports and underscores all of the previous recommendations for raising awareness and educating people about psychedelics and PAP (70, 74, 83). Higher levels of self-assessed psychedelic knowledge were also linked to more optimistic and positive viewpoints in this case. In our surveys, psychiatrists scored significantly lower on their self-assessed knowledge than on the basic knowledge test (66.0 vs. 86.0, both on a 0-100 scale). This suggests that the information they took into account for their self-evaluation was more complex than simply understanding what psychedelics are. Following this replication of our original discovery, we propose creating a standardised knowledge test for psychedelics that extends beyond simple material recognition and categorization. To accomplish this, we must investigate and specify the minimal levels of understanding necessary to comprehend psychedelics and their effects. The basic knowledge test was originally created by our research team to help with the interpretation of the APQ, but the insights it has yielded thus far may justify additional research on this construct, particularly in light of the need to create formalised educational materials on psychedelics and PAP that are replicable in a practical setting, as well as a scientific one. However, designing an intervention to deliver impartial, balanced information without unintentionally influencing attitudes in a positive or

negative way is a major challenge with this kind of initiative. Finding interventionists who are completely unbiased is probably challenging, especially given that attitudes towards psychedelics also have an emotional component—as evidenced by the contrast between enthusiasm and fear and fear and prejudice. Education aided by artificial intelligence is one potential solution to this problem.

All things considered, this is the first time the APQ has been validated in English and among psychiatrists. Its metrics match those of our first validation study (83), which is encouraging for further use in this group. By thoroughly applying the APQ in smaller, more intimate settings (e.g., specific departments, institutions, or single countries), where response rates are likely to be higher, future studies could attempt to mitigate some of the response bias and sampling challenges we encountered and concentrate on setting-specific and culturally specific nuances in knowledge and attitudes. Future research using structural modelling may examine the impact of past psychedelic use, which appeared to be the strongest predictor of attitudes in our study, on other variables like spirituality. It would be beneficial to investigate the circumstances surrounding the comparatively high frequency of prior psychedelic use among our respondents and whether any of it was done for self-experimentation or self-treatment (98, 99). In order to inform any relevant and so far undiscovered constructs for further quantitative analyses, some of the open questions regarding attitudes towards psychedelics and PAP in younger vs. older individuals could be thoroughly investigated using qualitative approaches. In addition, we propose a qualitative method to investigate gender variations in perceptions of psychedelic use. Based on our current research, particular attention should be paid to how gender influences how interested individuals are to learn about psychedelics and psychedelic research, as well as how confident they are in their knowledge of the topic.

6.3 European psychiatrists' attitudes on psychedelic-assisted psychotherapy: a qualitative study

6.3.1 Summary of main study findings

Through interviews with European psychiatrists, we found that psychedelics were seen through a very ambivalent lens, with both caution and enthusiasm present. Psychedelics were seen as holding potential by being a possibly very useful and interesting treatment tool that could bring a new perspective and theoretical insights to psychiatry, which is in need of innovations. At the same time, participants expressed caution about many different risks of psychedelics, including serious side effects like physical and psychological addiction, risks of psychotic and manic decompensation, and physical harms to frail patients. In general, they were seen as not suitable for everyone and open to misuse for non-treatment related goals by both patients and therapists. They were reported as carrying historical and drug-related stigma, which was contrasted by the ongoing hype around their potential, something that could be equally as harmful by giving patients and the public unrealistic expectations. Their future was seen as quite uncertain, and participants were concerned that some key scientific findings and a significant volume of evidence was still missing, while, at the same time, the implementation of PAP was also seen as potentially not feasible due high resource requirements. PAP was also seen as something psychiatry had very mixed feelings about, which were amplified by a general lack of knowledge and systemic education on psychedelics. However, many of our participants expressed that, if presented with enough evidence and with support from their profession, both they and their colleagues would be likely to apply PAP if it meant that they could help their patients.

6.3.2 Strengths and limitations of the study

Psychedelics and PAP are currently an emerging topic without a large body of modern-era clinical evidence, leading to many unknowns and uncertainties as to what the future will bring to this line of research. This makes the discussion around them a highly nuanced and controversial topic (7, 18, 100). The qualitative approach as such allows for in-depth exploration of new phenomena, and the reflexive thematic analysis approach we applied to analyse our data allows for a very flexible approach in defining the overarching themes among the complex discussion of topics provided by participants (84, 101). Therefore, the main strength of this study is that we used a flexible method that is appropriate for the complexity of the topic and that we included participants from 9 different countries and of different gender,

age and treatment approach, along with varying levels of knowledge on psychedelics and different levels of experience in science, as measured by their number of peer-reviewed publications.

However, our study is not without limitations. Our study included 12 participants, which may still give only a limited perspective on psychedelics and PAP. The representability of our findings for the whole population of European psychiatrists cannot be ascertained, as it is possible that some key voices were not included. However, we attempted to remove this limitation as much as possible by using multiple sampling techniques and by ensuring a demographic diversity of participants. The final number of participants was also determined by data and meaning saturation and, therefore, was based on richness of our findings from the interviews rather than trying to reach a quantitative cut-off. Overall, this study is not meant to give an overarching and final overview of the attitudes of all European psychiatrists, but to point to the complexities and main issues in the discussion around psychedelics and PAP, providing ideas for further research and debate. Future qualitative studies on this topic could target more specific expert or psychiatrist sub-groups, such as individuals working with treatment-resistant patients or substance users in order to differentiate the nuances of their particular perspectives on PAP.

6.3.3 Placing participants' accounts into the context of current insights on psychedelics and PAP

Overall, our themes and sub-themes seemed to be consistent with insight from surveys so far conducted with psychiatrists. The general openness to using psychedelics in practice that previous surveys identified was also seen in our participants' accounts (68, 69, 72). However, our findings added the fact that this openness depended on future developments of the psychedelic field and depends on the implications carried by new evidence coming in. Similar to this, the caution towards possible risks and side effects of psychedelics was also described among participants in our study (68, 70). This comparison shows that there are various nuances to psychiatrists' attitudes that have not been captured through survey-based studies. Although physical addiction to psychedelics is not considered a risk within the scientific literature (34-36), our participants highlighted concerns about addiction that could be on the psychological level, of looking for easy solutions and escapism. The idea expressed by participants that patients could continue to use psychedelics after receiving them within PAP is supported by the findings that more side effects of psychedelics are present in unregulated and unsupervised

use (32, 102). Participants' concerns about psychosis and other forms of decompensation upon the use of psychedelics are partially supported by the lack of definite information on side effects such as psychosis, although the new era of clinical trials on psychedelics has minimized harms for participants by using strict safety and screening protocols (34, 103). Finally, our finding of younger individuals being more personally engaged and open to PAP follow previous quantitative observations (68, 74). Interestingly, participants in our study who were younger offered many of the potential solutions and ideas in response to negative aspects on PAP and psychedelics that were being discussed.

6.3.4 Implications of the findings for further research and initiatives

Overall, the attitudes expressed by participants was that evidence on PAP needs to be more robust and convincing, especially in terms of bigger sample sizes and comparisons of PAP to standard treatments. This goes in line with the sub-theme that many psychiatrists tend to think about the issue of PAP pragmatically and in terms of what these new findings bring to their patients. An important suggestion in this regard would be to communicate evidence and new findings to psychiatrists by focus on clinically relevant information, such as patient-centred outcomes. Our participants also gave many suggestions for further research, such as the inclusion of patients in study designs, something that has already been emphasized generally as an important initiative in classic clinical trial research (104). Besides simply providing more evidence, certain unresolved key questions should be addressed in future research, such as, for example, how much psychotherapy within PAP contributes to clinical outcomes and how much variability exists due to differences in therapist style and skill. This concern has also recently been voiced in the literature by an authority within the field of psilocybin research (60).

Another important word of caution expressed by participants in our study was the discrepancy between the stigma of psychedelics as illegal substances, often connected with their use by hippies in the 60s and New Age ideas, and their newly emerging image as medical treatments given by professionals in a clinical setting. The dichotomy and discrepancy between these two is something the psychedelic research movement should address, especially in communicating evidence to the public. Negative examples provided by study participants of researchers being used by the media to generate additional positive hype on psychedelics and PAP are a significant consideration as well, highlighting the need for significant responsibility and accountability from the psychedelic research community. This is consistent with the findings of a survey which showed that patients would view psychedelic researchers more favorably if

they didn't personally use psychedelics or, if they did use them personally, that this would be publicly and transparently disclosed (56). A notable comment by Anderson et al. (61) on the risks of bias within the psychedelic research communities has also voiced concerns about the impartiality of scientists who personally use psychedelics and at the same time perform clinical experiments where they aren't supposed to favour a positive outcome. Overall, our findings underscore the importance increased personal transparency among psychedelic researchers. PAP appears to be a topic where non-medical discussions points and factors have the potential to complicate discussions around their medical use. The representation of multiple perspectives on psychedelic conferences could ameliorate this issue and bring the focus back to the evidence instead of merely encouraging further enthusiasm. Generally, a criticism of the current pitfalls of psychedelic research is using terms such as "consciousness" vaguely and including religious icons in the psychedelic therapy process (105). If the present cultural stigma towards psychedelics wants to be decreased, such a criticism is likely to be valid and should be seriously considered and applied by using well-grounded terms when speaking of concepts related to psychedelics or consciousness.

This study once again demonstrated the importance of educating professionals such as psychiatrists on psychedelics, as there does not seem to be enough knowledge in the field to follow the pace of research developments related to PAP. The perspectives of our participants highlighted the fact that psychedelics are not represented in the curriculum of either medical studies or psychiatry training and that information given on conferences so far is somewhat superficial. Initiatives such as including educational packages on psychedelics on conferences or continuing professional development courses are an interesting consideration to improve the knowledge in the field. The findings within the field of psychedelic research may still be too preliminary to include PAP as a part of the education curricula of higher education institutions, but this is a valid consideration in the case that future evidence will justify their clinical utility.

7 CONCLUSIONS

1. The newly created APQ is a valid and reliable instrument that opens up multiple research opportunities in exploring the context of the ongoing revival of psychedelic research. In particular, it can help evaluate the effect of educational interventions on psychedelics, as well as how attitudes on psychedelics affect patients' treatment outcomes in PAP.

2. Attitudes on psychedelics showed a consistent positive association with knowledge on psychedelics in both quantitative surveys that were conducted.

3. European psychiatrists' attitudes on psychedelics seemed to be wholly dependent on personal factors, while professional variables related to one's work in psychiatry did not seem to have a significant influence on them.

4. Past personal use of psychedelics was the most significant predictor of holding positive attitudes on psychedelics, demonstrating that psychedelics and PAP are a topic where it is difficult to remain impartial.

5. General knowledge on psychedelics and their effects is very poor and should be improved through educational initiatives, especially for mental health professionals such as psychiatrists, for whom this is most immediately relevant.

6. Before education initiatives on psychedelics are implemented, further research is needed to determine the content of such a curriculum, especially since it may be very challenging to design a bias-free intervention that does not preferentially influence an individual's attitudes on psychedelics towards the positive or negative.

7. In-depth interviews with European psychiatrists showed that they do not review the current evidence base on psychedelics and PAP as robust enough. However, if evidence showed their safety and efficiency, they were likely to think pragmatically and be open to the implementation of PAP.

8. Psychedelics and PAP are difficult to separate from their historical, social and political context, influencing and complicating discussions around this their medical use by introducing non-medical arguments and factors.

9. It is important to increase the transparency and accountability of psychedelic research, especially in the context of current high levels of enthusiasm and the potential for personal attitudes to introduce bias among mental health professionals towards the topic.

8 SAŽETAK

Ciljevi: Istraživanja opisana u ovoj disertaciji imala su za cilj stvoriti i validirati standardizirani upitnik za procjenu stavova o psihodelicima, taj upitnik primijeniti u ispitivanju skupine europskih psihijatara o njihovim stavovima te nadopuniti te nalaze provođenjem ciljanih intervjua s europskim psihijatrima o istoj temi.

Metode: Prvo i drugo istraživanje bili su presječnog nacrta te su koristili online anketu. Treće je istraživanje bilo kvalitativno, temeljeno na refleksivnoj tematskoj analizi polustrukturiranih intervjua.

Rezultati: Prvo istraživanje je pokazalo validnost novog standardiziranog i dalo preliminarne podatke o stavovima hrvatske opće populacije o psihodelicima, gdje se pokazalo da mnogo osoba nema niti osnovno znanje o psihodelicima. Drugo istraživanje je pokazalo da su europski psihijatri otvoreni prema psihodelicima, ali da su najviše nesigurni oko mogućih nuspojava i zloporabe tih supstanci. Pozitivniji stavovi kod te skupine bili su vezani uz prethodno osobno korištenje psihodelika, veće znanje o psihodelicima, mlađu dob, muški spol i duhovnost. Varijable vezane uz stručnu izobrazbu i rad nisu pokazale značajan utjecaj na stavove o psihodelicima. Treće istraživanje prikazalo je kompleksnost stavova o psihodelicima i njihovu duboku vezanost uz društveni, politički i povijesni kontekst. Stavovi u psihijatriji o psihodelicima su miješani, a veliki broj psihijatara smatra da dokazi o njihovoj terapeutskoj učinkovitosti još uvijek nisu dovoljno uvjerljivi.

Zaključci: Novi instrument koji smo validirali ima široki potencijal primjene u budućim istraživanjima. Opće znanje o psihodelicima je loše, a psihijatri navode da je ta tema premalo zastupljena u njihovom obrazovanju. To bi trebalo promijeniti kako bi se moglo imati kvalitetne i informirane rasprave o budućnosti terapije psihodelicima. Naši nalazi upućuju na to da su psihodelici tema gdje je teško ostati nepristran, posebno kao osoba koja prenosi znanje o njima ili provodi terapiju.

9 SUMMARY

Objectives: The studies described in this dissertation aimed to create and validate a standardized questionnaire for the assessment of attitudes about psychedelics, to apply this questionnaire by assessing a group of European psychiatrists about their attitudes, and to complement these findings by conducting selected interviews with European psychiatrists on the same topic.

Methods: The first and second studies were cross-sectional and used an online survey. The third study was a qualitative study, based on a reflective thematic analysis of semi-structured interviews.

Results: The first research showed the validity of the new instrument and provided preliminary data on the attitudes of the Croatian general population about psychedelics, where it was shown that many people do not even have basic knowledge about psychedelics. The second study showed that European psychiatrists are open to psychedelics, but are concerned about the possible side effects and abuse of these substances. More positive attitudes in that group were associated with previous personal use of psychedelics, greater knowledge about psychedelics, younger age, male gender, and spirituality. Variables related to professional training and practice did not show a significant influence on attitudes on psychedelics. The third study showed the complexity of attitudes on psychedelics and their deep connection to the social, political and historical context. Attitudes on psychedelics in psychiatry are mixed and a large number of psychiatrists believe that the evidence for their therapeutic effectiveness is still not sufficiently convincing.

Conclusions: The new instrument we validated has a many potential uses for future research. General knowledge about psychedelics is poor, and psychiatrists state that this topic is underrepresented in their education. This should be improved in order to hold high-quality informed discussions about the future of psychedelic therapy. Our findings suggest that psychedelics are a topic where it is difficult to remain impartial, especially as an education or treatment provider.

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11 APPENDICES

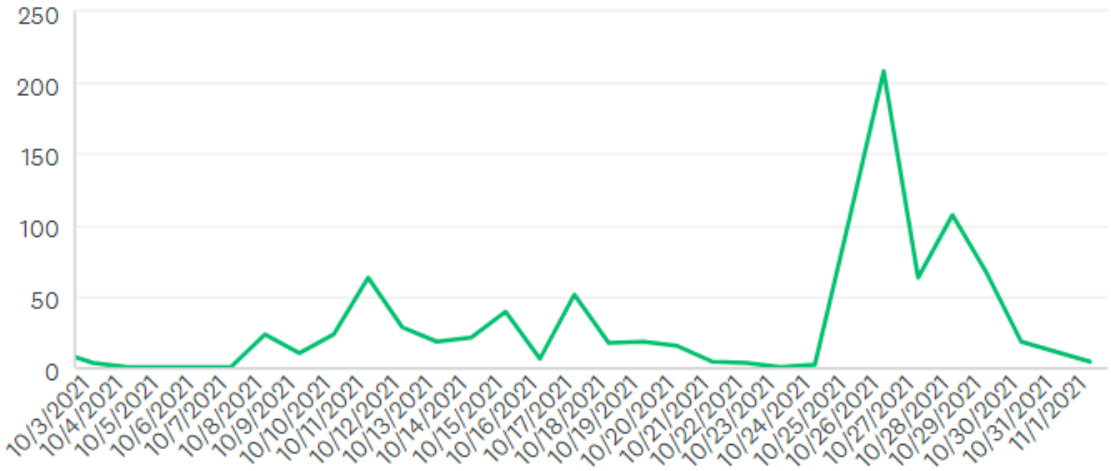
11.1 Appendix 1: Sampling methods and timeline, survey response trends, and participant feedback (first study)

Our survey was disseminated within the following organizations or social media groups between July and October 2021:

- CroMSIC Split, a medical student association (disseminated on their Facebook page to around 1400 followers on July 28);
- SplitMisli, a youth and student association (disseminated on their Facebook page to around 1300 followers on October 14);
- Udruga ATMA, an independent lifestyle news portal and association (disseminated on their Facebook page to around 207.000 followers on October 14);
- Udruga MoSt, a non-governmental, non-profit organization with aid programs for the homeless and impoverished (disseminated to their members via mailing list on October 14, number unknown);
- The Croatian Association for the Promotion of Patients' Rights, a non-governmental, non-profit patients' rights organization (disseminated on their Facebook page to around 10.300 followers on October 19);
- Psihodelični Vrt, a closed Facebook group for discussion on psychedelics (disseminated within the Facebook group to around 1700 members on October 27);
- Psihodelično društvo Balkana, an open Facebook group for discussion on psychedelics (disseminated within the Facebook group to around 650 members on October 27);
- Soba, a closed Facebook group for underground clubbing events (disseminated within the Facebook group to around 1700 members on October 27);
- Nepopularna Psihologija, a psychology blog and website (disseminated on their Facebook page to around 10.200 followers on October 28).

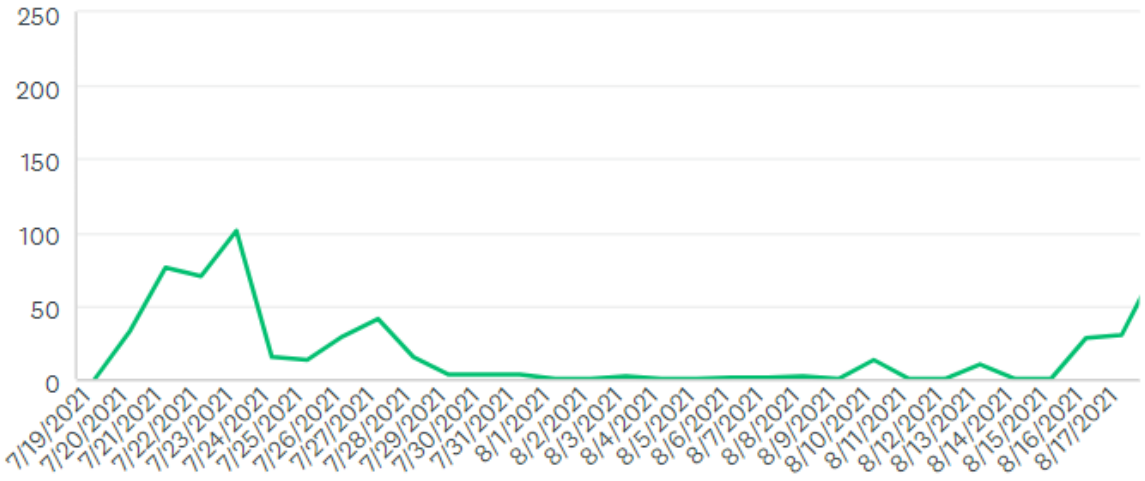
As mentioned above, dissemination in groups related to psychedelics happened on October 27, 2021. We see a rise in survey responses around this date after another previous peak (see

Supplementary Figure 1). However, as our sampling method is snowballing, we are unable to pinpoint if this is only due to members from these groups responding more to the survey (or also from the psychology blog and website that advertised the survey a day later). An upward trend of responses is visible around this time period, but all images of response trends in this document are informative only.



Supplementary Figure 1. Frequency of survey responses by day for the time period from October 3 to November 1, 2021.

To contrast the response trends from October, we show the second largest peak in responses per day at the beginning of data collection, in July (see **Supplementary Figure 2**).



Supplementary Figure 2. Frequency of survey responses by day for the time period from October 3 to November 1, 2021.

Participant feedback

When we sent out the survey, we received feedback from some participants directly, or the feedback was provided to the person disseminating the survey via the snowballing method (who shared the feedback with the research team).

Here we provide some de-identified responses of participants that were of interest that relate to their inability to answer the survey due to poor or non-existent knowledge on psychedelics.

Quote 1: "*I simply cannot respond to a survey about substances that I have no idea about or any sort of knowledge, except that I often heard about cocaine and heroin and I don't know if they are psychedelics.*"

Quote 2: "*I would gladly answer the survey questions but I must admit that I haven't heard about 90% of the listed substances. Likewise, I don't even know if this substance that is unknown to me is even a psychedelic. And I've only been offered the answers Yes and No?! So, I would have to be offered the response option – don't know.*"

Quote 3: "*One small comment, without an intention to criticize, but my personal opinion in any case. The topic [of the survey] is interesting and unfortunately currently relevant. However, I gave up on filing the survey until the end, because [my survey] would not faithfully represent my attitude, and even less my knowledge on psychedelics to you. Namely, I am missing the*

response "don't know" in most of the survey, because, if I don't know about something, I cannot agree or disagree. Yet I may agree with the question if it was explained to me what it was about. Otherwise, I am forced to choose either don't agree or agree for something I don't actually know about, and that completely changes the whole result of the survey."

11.2 Appendix 2: Full information on the basic knowledge on psychedelics test

After participants marked their answers on the survey, they moved on to the next page in SurveyMonkey and were presented with the following text:

"From the substances presented in the previous question, the following belong to the group of psychedelic substances (psychedelics): Lysergic acid diethylamide (LSD), psilocybin, ibogaine, MDMA (ecstasy), DMT, mescaline, peyote.

Other substances from the list do not belong to psychedelics: cocaine (stimulant), imipramine (tricyclic antidepressant), heroin (opioid), phenobarbital (barbiturate sedative), methamphetamine (stimulant), digoxin (cardiac glycoside), modafinil (eugeroic i.e. wakefulness-promoting drug), ketamine (anaesthetic, NMDA receptor antagonist in the brain), haloperidol (antipsychotic), dextroamphetamine (stimulant), gamma-hydroxybutyrate (GHB) (central nervous system depressant), rohypnol (benzodiazepine sedative), oxycodone (opioid), opium (natural substance used to produce opioid drugs), mexazolam (benzodiazepine sedative).

The total knowledge on psychedelics score was determined by the number of incorrect answers (a non-psychedelic incorrectly identified as a psychedelic) subtracted from the number of correct answers (correctly identified psychedelic). We chose this calculation method because it prevented a participant from getting the highest score by marking all substances as psychedelics. The theoretical scale range was from -15 (all answers incorrect) to 7 (all answers correct). To ease the interpretation of scoring on the knowledge on psychedelics survey, we converted scores from a scale from -15 to 7 to a scale of 0-100. We used the following formula:

*(S-m)/(M-m)*100*, where S – the total score/result, m – minimum theoretical value, M – maximal theoretical value.

In our case (scale range -15 to 7), the formula applied to each participant's score (S) in knowledge on psychedelics was:

*(S-(-15)/(7-(-15))*100=(S+15)/(7+15)*100*

11.3 Appendix 3: List of contacted institutions and different means of disseminating the survey (second study)

When disseminating the survey, we contacted major European psychiatric and psychotherapeutic organizations, a large number of individual psychiatrists' e-mails, psychiatrist-related social media groups, and hospitals in Croatia and Poland (due to these being the locations of the study authors).

Psychiatric and psychotherapeutic organizations

We contacted the European Psychiatric Association (EPA) and all of its member associations (32 in total). Two e-mails were returned with the e-mail not sent. Four member organizations (response rate 13.3%, 4/30) replied and agreed to disseminate the survey. We also contacted the European Federation of Psychiatry Trainees (EFPT) and all of its member associations (32 in total). The EFPT sent out an e-mail to all of its members with an invite to the survey. Additionally, 9 member organizations disseminated the survey within their countries (response rate 28.1%, 9/32). The original invite to all organizations was sent in English, with the exception of Croatia (initially sent in Croatian). For German, Swiss, Austrian and French organizations which did not respond to the message, we repeated the message after 5 months in German and French, respectively. No other reminders were sent.

As an additional sampling method, we e-mailed 110 psychotherapeutic organizations throughout Europe which belonged to various psychotherapeutic schools (psychoanalytic, integrative, general psychotherapeutic association etc.) and invited them to disseminate the survey to their members who are psychiatrists. Here, the British Psychoanalytic Council (BAP) kindly agreed to disseminate the survey to their members. The response rate here was very low, but this was not entirely unexpected, as only few of these groups exclusively have psychiatrists as members.

Individual psychiatrists

We aimed to collect individual psychiatrists' e-mails and send out the survey to them personally. A subset of e-mails was retrieved from BAP Meeting Abstract Books from 2011-2022 using web scraping methods. We also used the search function on the Web of Science (WoS) database to search for authors by searching in the WoS Category "Psychiatry" combined with the keyword "European". We retrieved the first 100000 records which were available as a result of the search (the WoS platform did not allow retrieving search results over that

number). The BAP and WoS e-mails were combined in a table and deduplicated, leaving a total of 25785 e-mails. We then used a script written in Python 3.8.8 to remove e-mails with endings that primarily indicate non-European countries (".edu", "126.com", "163.com", .jp", ".nih.gov"), leaving a total of 20447 e-mails to which an invite to the survey in English was sent.

Social media groups

We additionally posted an invite to the survey in 5 Facebook groups with the permission of the group's administrators:

- Young Psychiatrists' Network (around 8900 members)
- World Network of Psychiatric Trainees (around 800 members)
- Psychedelic Society of Edinburgh (around 4000 members)
- Young Psychiatrists (around 3600 members, group in Polish)
- Psychiatrists - a group for doctors only (around 900 members, group in Polish)

Here we cannot adequately gauge the impact of the sampling, as we cannot be sure how many of the group members are truly active.

Hospitals

A total of 124 hospitals were contacted in Poland with a message sent in Polish. The list of psychiatric hospitals came from the official website of the National Health Fund of Poland: https://gsl.nfz.gov.pl/GSL/GSL/Szpitale (specialty - psychiatric treatment). From these, 4 e-mails were returned with the e-mail not sent.

A total of 3 hospitals were contacted in Croatia through personal contacts of the study authors with a message sent in Croatian.

11.4 Appendix 4: Full survey given to participants (second study)

DEMOGRAPHIC INFORMATION

1.Age (please enter as a number): _____

2. Gender:

a) Male

b) Female

c) Other (please specify)

3. What is your current country of residence? _____

4. Please select all educational titles which apply to you (you can select more than one):

a) Psychiatry trainee (currently in training as resident/specialist in psychiatry)

b) Resident psychiatrist (completed residency/specialization in psychiatry)

c) Psychotherapy trainee (currently enrolled in training in one of the psychotherapeutic approaches)

d) Licensed psychotherapist (completed education within a psychotherapeutic approach)

e) Doctor of science (PhD)

f) Other (please specify, if necessary): _____

5. What is your primary place of work (where you spend the majority of your working hours)?

a) Hospital

b) Private hospital

c) Private practice

d) University

e) Other/this does not apply to me (please specify, if necessary): _____

6. How would you describe your primary treatment approach, if applicable?

a) Biological

b) Psychotherapeutic

d) Both biological and psychotherapeutic (in equal measure)

e) This does not apply to me

7. How many peer-reviewed articles have you published so far? Please enter your answer as a number. _____

8. Do you have any previous experience with psychedelic-assisted treatment or research involving psychedelics?

a) Yes

b) No

9. How would you assess your personal knowledge on psychedelics? Please try to express your estimate by using the slider below.

10. Which of the following do you feel describes you? You can choose more than one.

a) Religious

b) Spiritual

c) Atheist

d) Agnostic

d) None of the above

11. You will find various substances listed below. Please choose for each one of them if you think the substance is a psychedelic or not by choosing yes or no.

1. Cocaine **YES/NO**
2. Lysergic acid diethylamide (LSD) **YES/NO**
3. Psilocybin **YES/NO**
4. Imipramine **YES/NO**
5. Heroin **YES/NO**
6. Ibogaine **YES/NO**
7. Phenobarbital **YES/NO**
8. Methamphetamine **YES/NO**
9. 3,4-Methylenedioxymethamphetamine (MDMA)**YES/NO**
10. N, N-Dimethyltryptamine (DMT) **YES/NO**
11. Digoxin **YES/NO**
12. Mescaline **YES/NO**
13. Modafinil **YES/NO**
14. Ketamine**YES/NO**
15. Haloperidol **YES/NO**
16. Dextroamphetamine **YES/NO**
17. Gamma-hydroxybutyrate (GHB) **YES/NO**

18. Ayahuasca **YES/NO**

19. Rohypnol **YES/NO**

20. Oxycodone **YES/NO**

21. Opium **YES/NO**

22. Mexazolam **YES/NO**

12. Have you ever had any experience with any of the following substances (either recreationally or for medical purposes)? You can select more than one.

a) Cannabis

b) Lysergic acid diethylamide (LSD)

c) Psilocybin

d) Ayahuasca

e) N, N-Dimethyltryptamine (DMT)

f) Mescaline

g) Ibogaine

h) 3,4-Methylenedioxymethamphetamine (MDMA)

i) None of the above

ATTITUDES ON PSYCHEDELICS QUESTIONNAIRE (APQ)

For each statement, please choose the number which corresponds to how much you agree or disagree with the statement. The meanings of numbers are as follows:

1	2	3	4	5
Completely disagree	**Disagree**	**Neither agree nor disagree**	**Agree**	**Completely agree**

Statement	**Completely disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Completely agree**
Legalizing psychedelics would benefit public health.	1	2	3	4	5
Those who want to legalize psychedelics have a hidden agenda behind their actions.	1	2	3	4	5
The use of psychedelics for justified medical reasons should be legal.	1	2	3	4	5
Administering psychedelics to psychiatric patients is safe as long as the treatment conditions are carefully controlled.	1	2	3	4	5
Administering psychedelics to patients will eventually lead to bad outcomes.	1	2	3	4	5
Psychedelic use is linked to creativity.	1	2	3	4	5
If more people used psychedelics, the world would be a better place.	1	2	3	4	5

Recreational use of psychedelics has no practical benefit.	1	2	3	4	5
I am afraid of the effects of psychedelics on physical health.	1	2	3	4	5
Psychedelics can provide valuable spiritual experiences.	1	2	3	4	5
Using psychedelics is safe.	1	2	3	4	5
The use of psychedelics can damage the nervous system.	1	2	3	4	5
Psychedelics are less dangerous than other illegal drugs.	1	2	3	4	5

11.5 Appendix 5: APQ items in Croatian

Molimo Vas da za svaku tvrdnju **označite broj** koji odgovara stupnju Vaše suglasnosti s pojedinom tvrdnjom. Brojevi znače:

1	2	3	4	5
Potpuno se ne slažem	**Ne slažem se**	**Ni slažem se ni ne slažem se**	**Slažem se**	**Potpuno se slažem**

Tvrdnja	**Potpuno se ne slažem**	**Ne slažem se**	**Niti se slažem niti ne slažem**	**Slažem se**	**Potpuno se slažem**
1. Uporaba psihodelika povećava rizik za naknadne psihijatrijske poremećaje.	1	2	3	4	5
2. Uporaba psihodelika povećava rizik za dugotrajna kognitivna oštećenja.	1	2	3	4	5
3. Uporaba psihodelika u rekreativne svrhe trebala bi biti ilegalna.	1	2	3	4	5
4. Uporaba psihodelika nije sigurna čak ni pod medicinskim nadzorom.	1	2	3	4	5
5. Uporaba psihodelika pokazuje potencijal u liječenju psihijatrijskih poremećaja.	1	2	3	4	5
6. Uporaba psihodelika može poboljšati ishode kada se koristi tijekom psihoterapije.	1	2	3	4	5
7. Uporaba psihodelika zaslužuje buduća	1	2	3	4	5

istraživanja za liječenje psihijatrijskih poremećaja.					
8. Legalizacija psihodelika pridonijela bi javnom zdravstvu.	1	2	3	4	5
9. Osobe koje žele legalizirati psihodelike imaju skriveni plan u pozadini svojih postupaka.	1	2	3	4	5
10. Uporaba psihodelika iz opravdanih medicinskih razloga trebala bi biti legalna.	1	2	3	4	5
11. Davanje psihodelika psihijatrijskim bolesnicima sigurno je dok su god uvjeti liječenja pažljivo kontrolirani.	1	2	3	4	5
12. Davanje psihodelika pacijentima s vremenom dovodi do loših ishoda.	1	2	3	4	5
13. Korištenje psihodelika povezano je s kreativnošću.	1	2	3	4	5
14. Kada bi više ljudi koristilo psihodelike, svijet bi bio bolje mjesto.	1	2	3	4	5
15. Rekreacijsko korištenje psihodelika nema praktičnu korist.	1	2	3	4	5
16. Strah me učinaka psihodelika na tjelesno zdravlje.	1	2	3	4	5
17. Psihodelici mogu pružiti vrijedna duhovna iskustva.	1	2	3	4	5
18. Uporaba psihodelika je sigurna.	1	2	3	4	5
19. Uporaba psihodelika može oštetiti živčani sustav.	1	2	3	4	5

20. Psihodelici su manje opasni od ostalih ilegalnih droga.	1	2	3	4	5
21. Šira uporaba psihodelika dovela bi do povećanja broja mentalnih problema.	1	2	3	4	5
22. Davanje psihodelika pacijentima nije problematično dok god to radi stručna osoba.	1	2	3	4	5
23. Optimističan/na sam oko znanstvenih istraživanja o psihodelicima.	1	2	3	4	5
24. Ne bih pristao/la koristiti psihodelike u svrhe vezane za mentalno zdravlje.	1	2	3	4	5
25. Da psihoterapija potpomognuta psihodelicima uđe u svakodnevnu praksu, zanimalo bi me doznati više o njima.	1	2	3	4	5
26. Bio bih zainteresiran/na za učenje o iskustvima drugih ljudi s psihodelicima.	1	2	3	4	5
27. Mislim da upoznavanje s psihodelicima nije vrijedno moga vremena.	1	2	3	4	5

12 RESUME

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