



**UNIVERSITÀ DEGLI STUDI
DI MESSINA**

Dipartimento di Scienze Cognitive,
Psicologiche, Pedagogiche e degli Studi
Culturali e Sociali



MAASTRICHT UNIVERSITY

Faculty of Psychology and
Neuroscience,
Department of Neuropsychology &
Psychopharmacology

PHD COURSE IN COGNITIVE SCIENCE - XXXVI CYCLE

Trip the pain away: Psychedelic therapies for physical and mental pain

Candidate:
Mauro Cavarra

Supervisors:
Prof. Dr. Jan G. Ramekers

Prof. Dr. Carmela Mento

PhD course coordinator:
Prof. Dr. Alessandra Falzone

ACADEMIC YEAR 2022/2023

Trip the pain away:
Psychedelic therapies for
physical and mental pain



Mauro Cavarra

Cover image: Clara Holt, [@clara.holt.ceramics](#)

© Mauro Cavarra 2023

*Trip the pain away: psychedelic therapies for
physical and mental pain*

DISSERTATION

to obtain the degree of Doctor at Maastricht
University, on the authority of the Rector
Magnificus, Prof.Dr. Pamela Habibović and the
degree of Dottore di Ricerca in Scienze Cognitive
at the Università degli Studi di Messina on the
authority of the Rector Magnificus Prof.ssa
Giovanna Spatari in accordance with the decision
of the Board of Deans, to be defended in public
on Friday 15 November 2024, at 13.00 hours

by Mauro Cavarra

Supervisor:

Prof. Dr. Johannes G. Ramaekers, Maastricht University, The Netherlands

Prof. Dr. Carmela Mento, University of Messina, Italy

Co-Supervisors

Dr. Kim P. C. Kuypers, Maastricht University, The Netherlands

Dr. Eef L. Theunissen, Maastricht University, The Netherlands

Assessment Committee

(Please list the members of the Assessment Committee. First the chair, next other members in alphabetical order):

Chair:

Prof. Dr. Arjan Blokland, Maastricht University, The Netherlands

Members:

Prof. Dr. Ivan Formica, University of Messina, Italy

Prof. Dr. Kees Kramers, Radboud University, Nijmegen, The Netherlands

Prof. Dr. Madelon Peters, Maastricht University, The Netherlands

Dr. Monique van Velzen, Leiden University Medical Center, The Netherlands

Contents

Contents	7
Chapter 1 - General introduction	9
History of clinical research with psychedelics	9
Psychedelic therapies for pain	11
Aims of this dissertation	14
Outline of the dissertation	14
References	16
Chapter 2 - Potential analgesic effects of psychedelics on select chronic pain conditions: A survey study	27
Introduction.....	28
Methods.....	30
Results	34
Discussion	45
Limitations	48
Conclusions.....	49
References	50
Chapter 3 - A placebo-controlled study of the effects of LSD microdosing (15 µg) on pain perception in healthy volunteers	62
Introduction.....	63
Materials and Methods.....	64
Results	69
Discussion	75
References	78
Supplementary Materials	85
Chapter 4 - Psychedelic-Assisted Psychotherapy—A Systematic Review of Associated Psychological Interventions	89
Introduction.....	89
Methods.....	91
Results	92
Discussion	121
Conclusion.....	128
References	129
Chapter 5 - The therapeutic process of a fibromyalgia patient after a psychedelic retreat: a single case, 6 months follow-up study	148

Introduction	148
Methods	151
Discussion.....	163
Limitations	166
Conclusion	167
Ethical approval.....	168
References.....	169
Supplementary materials	177
Chapter 6 - Psychedelic therapies to treat mental pain	193
Definition, causes, and mental health implications of mental pain	194
The second wave of psychedelic research.....	195
Psychedelic-assisted psychotherapy for mental pain	196
Therapeutic mechanisms.....	205
Conclusion	207
References.....	208
Chapter 7 - Discussion.....	226
The potential of psychedelic microdosing in the treatment of chronic pain	226
The potential of full psychedelic doses in the treatment of chronic pain ..	228
Where to go from here?	237
Impact: the potential societal impact of psychedelic therapy for chronic pain	238
References.....	241
Summary	250
Samenvatting	252
Acknowledgments	256

Chapter 1

General introduction

History of clinical research with psychedelics

Psychedelics are a group of substances that can markedly change perception, cognition, and mood, leading to profound shifts in consciousness and, in some instances, mystical or transcendent experiences (Griffiths et al., 2008; Nichols, 2016). This category includes LSD, psilocybin, mescaline, and DMT, primarily affecting the brain by binding to serotonin (5-HT) 2 receptors (Vollenweider & Kometer, 2010). The initial wave of research on the therapeutic potential of psychedelics emerged in the 1960s. During this period, these substances were investigated in diverse clinical conditions, such as neuroses (Crocket et al., 1963), alcoholism (Smith, 1958; Leuner, 1967), end-of-life anxiety (Kast, 1967; Grof et al., 1973; Grof and Halifax, 1978), and chronic pain (Fanciullacci et al., 1977), and produced promising results.

The methods used to deliver such therapeutic interventions varied, and at the time, a systematisation attempt categorised them into three categories. The first one, *psychedelic chemotherapy* implied one or more psychedelic sessions employing doses large enough to produce intense changes in consciousness with limited or no

formal psychotherapeutic work before or after (Pahnke et al., 1970). Secondly, *psycholytic therapy resembled* more traditional psychotherapeutic practices as the patient received smaller doses of psychedelic substances during psychotherapy sessions to facilitate “*the emergence of unconscious material*” (Pahnke et al., 1970). Finally, *psychedelic-peak therapy* (PPT) was a three-stage process that included a preparation phase in which one or more non-drug sessions were held to discuss themes relevant to therapy, preparing the patient for the experience, and establishing therapeutic alliance (Pahnke et al., 1970). Preparation was then followed by the psychedelic session(s), in which patients were usually asked to lie down, wear a blindfold and music headphones, and invited to shift their attention inwards, relax, and surrender to the experience. After each psychedelic session, one or more integration sessions were held to discuss the contents of the psychedelic experience and integrate potential insights into the patient’s life.

Currently, only limited evidence supports the necessity of adding psychotherapy to clinical psychedelic interventions (Johnson et al., 2008; Koslowski et al., 2021) and no definitive agreement currently exists on the necessary psychotherapeutic elements to incorporate (Cavarra et al., 2022). Furthermore, preliminary results suggest that psychedelic pharmacotherapy alone could result in significant clinical improvement (Reckweg et al., 2023). Still, most clinical trials aiming at investigating the effectiveness of psychedelic therapies

employ psychedelic-assisted psychotherapy (PAP) models that follow in the PPT footsteps (Cavarra et al., 2022), likely for safety-related reasons (Johnson et al., 2008). As made evident by the list of conditions targeted by clinical psychedelic research, considerable attention was dedicated to revitalise research to test the potential of such models of treatment for psychiatric disorders. On the contrary, less emphasis was placed on testing their effectiveness on another area of clinical significance that was already proposed during the first wave of studies: pain.

Reviewing the early literature on psychedelic therapy shows that models in which some kind of preparation and integration phases were included were more frequently used (e.g., Crockett et al., 1963) and the reason for this can be traced back to what is known as *set and setting theory* (Hartogsohn, 2017). The theory (likely first formulated by Timothy Leary in 1961) posits that the acute and long-term effects of psychedelic drugs are determined by individual factors such as personality, expectations, intentions, previous knowledge, and beliefs that constitute the set, and by setting: the physical, relational and cultural environment surrounding the psychedelic experience (Hartogsohn, 2017). Such considerations are not original to the modern Western world as the traditional use of mind-altering substances has been associated with phases of preparation aimed at acting upon the set and ritual manipulations of the environment where the substance was consumed (Beyer, 2010; Helman, 2001).

Despite some promising results obtained by early research, in the 1970s psychedelic use was outlawed, and researching its effects and potential therapeutic applications became increasingly harder (Nutt, 2015). Due to safety concerns, the supposed potential for abuse, and a politically stigmatising climate, such substances were labelled as dangerous, with no potential therapeutic application. Furthermore, the discovery that thalidomide (whose commercial name was Softenon in the U.S.) was causing phocomelia in newborns led to tougher requirements to run drug studies (Royal Pharmaceutical Society, 2011; NIHR CRN CC, 2013). As a consequence, researchers lost the support of pharmaceutical companies that produced the substances (MAPS, 1999). This sequence of events ultimately led to a quasi-standstill of psychedelic research (Nutt, 2015).

In recent years, a renewed interest in the therapeutic possibilities of psychedelics has led to a second wave of psychedelic research. From the 1990s to the 2010s, the volume of scientific publications on various aspects related to psychopharmacology (Kometer et al., 2012; Passie et al., 2002; Preller et al., 2017; Valle et al., 2016; Vollenweider et al., 1998), neuroimaging (Carhart-Harris et al., 2012; Muthukumaraswamy et al., 2021; Riba et al., 2004; Vollenweider, 1997), cognitive and psychological functioning (Kuypers et al., 2016), and clinical research for conditions like anxiety linked with life-threatening illnesses (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), addictions

(Bogenschutz et al., 2015; Johnson et al., 2014), and depression (Carhart-Harris et al., 2016), consistently increased. This stimulated advocacy efforts to legalise these drugs for medical use (Nutt, 2015).

Psychedelic therapies for pain

Chronic pain (CP) stands as a primary contributor to disability (Burke et al., 2015), impacting roughly 20% of the population (Goldberg & McGee, 2011). Its effects ripple across psychological well-being, diminishing social functioning (Dueñas et al., 2016), and dampening productivity (Cohen et al., 2021). Additionally, CP intertwines with the emergence or worsening of psychiatric symptoms, including depression (Cohen et al., 2021), anxiety (Dueñas et al., 2016), and substance use (Voon et al., 2017).

The societal costs are very high as common CP conditions account for many years lost to disability and remarkable costs for families and healthcare systems (Zia et al., 2023). Suggested pharmacological treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) (Yekkirala et al., 2017), opioids, anticonvulsants, and antidepressants (Edinoff et al., 2022). Although these remedies exhibit some effectiveness in providing relief, a considerable portion of patients do not experience substantial benefits (Johannes et al., 2010). Notably, opioids carry numerous undesirable effects, have a high potential for addiction (Coussens et al., 2019), are linked to a

heightened occurrence of severe adverse events (Els et al., 2017), overdose (Zia et al., 2023), and may potentially induce opioid-induced hyperalgesia (i.e., heightened pain sensitivity, Nijs et al., 2014).

Considering that the latest understanding of the nature of CP characterises it as a complaint originating from the interaction of abnormal neural signalling and biopsychosocial dimension, adjunct psychological therapy is often recommended. This is also supported by the fact that several psychosocial factors that modulate the intensity and invasiveness of pain in daily life widely overlap with those modulating the severity of psychiatric conditions such as depression that tend to respond to psychological treatments (Cuijpers et al., 2023). While psychological therapies appear to contribute to improved pain management (Hann & McCracken, 2014; Hoffman et al., 2007), their impact is moderate when compared to no treatment and smaller or statistically insignificant when juxtaposed with other interventions, such as active controls (e.g., physical therapy, education, medical regimes), or diverse forms of 'treatment as usual' (Williams et al., 2020; Hann & McCracken, 2014).

Early research on psychedelics and pain

During the first wave of psychedelic research, six studies were conducted. Of these, two combined LSD (25 µg - 500 µg) with psychotherapy (Kurland, 1985; Grof et al., 1973), two with

psychological support (Kast, 1967; Kurland et al., 1972), and two did not use any additional psychological intervention (Fanciullacci et al., 1977; Kast and Collins, 1963). All studies were conducted with patients suffering from chronic pain caused by life-threatening illnesses (Kurland, 1985; Grof et al., 1973; Kast, 1967; Kurland et al., 1972; Kast and Collins, 1963) or phantom limb pain (Fanciullacci et al., 1977). Findings suggested that such treatments led to long-lasting reductions (up to 21 days) in pain, reduced depression, feelings of isolation, anxiety, fear of death, and analgesic use. With the exception of Kast and Collins (1963), who compared the effectiveness of LSD (100 µg) with two other substances (2 mg of dihydromorphinone, and 100 mg of meperidine) in a double-blind design, all the other above-cited sources are case studies.

Modern research on psychedelics and pain

Recently, we witnessed a new wave of interest regarding the analgesic potential of psychedelics. Such resurgence was partially motivated by the results of qualitative and survey studies showing that people suffering from chronic pain conditions such as cluster headaches reported improvements when using both high and low, non-hallucinogenic doses of psychedelics such as LSD and psilocybin (Sewell et al., 2006; Schindler et al., 2015; Di Lorenzo et al., 2016; Andersson et al., 2017). More recent survey studies showed this was the case in samples of people living with chronic

pain (PLCP) (Bonnelle et al., 2022; Glynos et al., 2022). Findings from these survey studies are also supported by case studies which show that psychedelics may help manage phantom limb pain (Ramachandran et al., 2018), FM and chronic fatigue (Ona et al., 2018), and cluster headaches (Johnson and Black, 2020).

Though research into using psychedelics for pain management trails the exploration of their potential in treating mental health conditions like depression, notable findings have emerged, some interesting results have been produced. More specifically, a recent RCT showed that a non-hallucinogenic dose of LSD can enhance pain tolerance and decrease the perceived unpleasantness in healthy volunteers to a degree comparable in effect to oxycodone or morphine (Ramaekers et al., 2021). Also, modern clinical research on the effects of psychedelics is still in its infancy and current results support the effectiveness of psilocybin in reducing headache frequency in a sample of patients suffering from migraines (Schindler et al., 2021).

Aims of this dissertation

This dissertation aims to expand our understanding of the potential for psychedelics to function as pain-relieving agents. Despite wide public interest in the analgesic potential of psychedelics (e.g., Andersson et al., 2017; Soussan & Kjellgren, 2016), there is still a dearth of knowledge in this field. Therefore, we conducted several

studies adopting a variety of methodologies to contribute to a more complete understanding of the phenomenon. More specifically, the reader will be presented with survey data adding more granularity on use patterns and perceived effectiveness of psychedelics in specific chronic pain populations, experimental results on the analgesic effectiveness of low doses of LSD in healthy volunteers, a review of PAP models currently used in clinical studies which could potentially be used in psychedelic pain research, and a case study documenting the effects of a retreat-based PAP program. Additionally, considering the similarities in how the brain processes physical and mental pain (MP) (Shneidman, 1993), and the significance of mental pain in predicting severe self-harm, we explored how psychedelic therapy principles could be used in treating MP.

Outline of the dissertation

Chapter 2 will present the results of a survey study aiming at investigating the reported analgesic effects of psychedelics on a sample of people living with chronic pain suffering from specific CP conditions, some of which have been the object of study for the first time: FM, arthritis, migraine and tension-type headache (TTH).

Chapter 3 will report on the results of the first placebo-controlled study aiming at testing the analgesic effects of a microdosing schedule (i.e., repeated administration of low doses of psychedelics) on a sample of healthy volunteers. Considering that

there currently is no consensus on how to deliver PAP for any potentially treatable condition, and being PAP an approach that could potentially be explored in pain research, **Chapter 4** will present a literature review of the PAP models currently explored in clinical research. Following the topic of Chapter 4, **Chapter 5** will present an example of the application of PAP in the treatment of a CP condition: FM. More specifically, it will report on the qualitative and quantitative results of a case study involving an FM patient who took part in a retreat-based PAP program. Finally, **Chapter 6** will discuss how psychedelic therapies have the potential to tackle mental pain, a construct relevant to the understanding and prediction of suicidal intention and behaviors that share many similarities with physical pain both in terms of neural correlates and subjective experience.

References

Andersson, M., Persson, M., & Kjellgren, A. (2017). Psychoactive substances as a last resort—A qualitative study of self-treatment of migraine and cluster headaches. *Harm Reduction Journal*, 14(1), 60. <https://doi.org/10.1186/s12954-017-0186-6>

Beyer, S. V. (2010). *Singing to the Plants: A Guide to Mestizo Shamanism in the Upper Amazon* (Reprint edition). University of New Mexico Press.

Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Psychopharmacology*, 29(3), 289–299. <https://doi.org/10.1177/0269881114565144>

Bonnelle, V., Smith, W. J., Mason, N. L., Cavarra, M., Kryskow, P., Kuypers, K. P. C., Ramaekers, J. G., & Feilding, A. (2022). Analgesic potential of macrodoses and microdoses of classical psychedelics in chronic pain sufferers: A population survey. *British Journal of Pain*, 13.

Burke, A. L. J., Mathias, J. L., & Denson, L. A. (2015). Psychological functioning of people living with chronic pain: A meta-analytic review. *British Journal of Clinical Psychology*, 54(3), 345–360. <https://doi.org/10.1111/bjc.12078>

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *The Lancet Psychiatry*, 3(7), 619–627. [https://doi.org/10.1016/S2215-0366\(16\)30065-7](https://doi.org/10.1016/S2215-0366(16)30065-7)

Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., Tyacke, R. J., Leech, R., Malizia, A. L., Murphy, K., Hobden, P., Evans, J., Feilding, A., Wise, R. G., & Nutt, D. J. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences*, 109(6), 2138–2143. <https://doi.org/10.1073/pnas.1119598109>

Cavarra, M., Falzone, A., Ramaekers, J. G., Kuypers, K. P. C., & Mento, C. (2022). Psychedelic-Assisted Psychotherapy—A Systematic Review of Associated Psychological Interventions. *Frontiers in Psychology*, 13. <https://www.frontiersin.org/article/10.3389/fpsyg.2022.887255>

Cohen, S. P., Vase, L., & Hooten, W. M. (2021). Chronic pain: An update on burden, best practices, and new advances. *The Lancet*, 397(10289), 2082–2097. [https://doi.org/10.1016/S0140-6736\(21\)00393-7](https://doi.org/10.1016/S0140-6736(21)00393-7)

Coussens, N. P., Sittampalam, G. S., Jonson, S. G., Hall, M. D., Gorby, H. E., Tamiz, A. P., McManus, O. B., Felder, C. C., & Rasmussen, K. (2019). The Opioid Crisis and the Future of Addiction and Pain Therapeutics. *Journal of Pharmacology and Experimental Therapeutics*, 371(2), 396–408. <https://doi.org/10.1124/jpet.119.259408>

Crocket, R., Sandison, R. A., & Walk, A. (1963). *Hallucinogenic drugs and their psychotherapeutic use* (1st ed.). Royal Medico-Psychological Association.

Cuijpers, P., Miguel, C., Harrer, M., Plessen, C. Y., Ciharova, M., Ebert, D., & Karyotaki, E. (2023). Cognitive behavior therapy vs. control conditions, other psychotherapies, pharmacotherapies and combined treatment for depression: A comprehensive meta-analysis including 409 trials with 52,702 patients. *World Psychiatry*, 22(1), 105–115. <https://doi.org/10.1002/wps.21069>

Di Lorenzo, C., Coppola, G., Di Lorenzo, G., Bracaglia, M., Rossi, P., & Pierelli, F. (2016). The use of illicit drugs as self-medication in the treatment of cluster headache: Results from an Italian online survey. *Cephalalgia*, 36(2), 194–198. <https://doi.org/10.1177/0333102415583145>

Dueñas, M., Ojeda, B., Salazar, A., Mico, J. A., & Failde, I. (2016). A review of chronic pain impact on patients, their social environment

and the health care system. *Journal of Pain Research*, 9, 457–467.
<https://doi.org/10.2147/JPR.S105892>

Edinoff, A. N., Fort, J. M., Singh, C., Wagner, S. E., Rodriguez, J. R., Johnson, C. A., Cornett, E. M., Murnane, K. S., Kaye, A. M., & Kaye, A. D. (2022). Alternative Options for Complex, Recurrent Pain States Using Cannabinoids, Psilocybin, and Ketamine: A Narrative Review of Clinical Evidence. *Neurology International*, 14(2), 423–436. <https://doi.org/10.3390/neurolint14020035>

Els, C., Jackson, T. D., Kunyk, D., Lappi, V. G., Sonnenberg, B., Hagtvedt, R., Sharma, S., Kolahtooz, F., & Straube, S. (2017). Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: An overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews*, 10. <https://doi.org/10.1002/14651858.CD012509.pub2>

Fanciullacci, M., Bene, E. D., Franchi, G., & Sicuteri, F. (1977). Phantom Limb Pain: Sub-Hallucinogenic Treatment With Lysergic Acid Diethylamide (LSD-25). *Headache: The Journal of Head and Face Pain*, 17(3), 118–119. <https://doi.org/10.1111/j.1526-4610.1977.hed1703118.x>

Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., & Brenneisen, R. (2014). Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated

With Life-threatening Diseases. *Journal of Nervous & Mental Disease*, 202(7), 513–520.
<https://doi.org/10.1097/NMD.000000000000113>

Glynos, N. G., Pierce, J., Davis, A. K., McAfee, J., & Boehnke, K. F. (2022). Knowledge, Perceptions, and Use of Psychedelics among Individuals with Fibromyalgia. *Journal of Psychoactive Drugs*, 1–12. <https://doi.org/10.1080/02791072.2021.2022817>

Goldberg, D. S., & McGee, S. J. (2011). Pain as a global public health priority. *BMC Public Health*, 11(1), 770. <https://doi.org/10.1186/1471-2458-11-770>

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, 30(12), 1181–1197. <https://doi.org/10.1177/0269881116675513>

Griffiths, R. R., Richards, W., Johnson, M. W., McCann, U., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology*, 22(6), 621–632. <https://doi.org/10.1177/0269881108094300>

Grob, C. S., Danforth, A. L., Chopra, G. S., Hagerty, M., McKay, C. R., Halberstadt, A. L., & Greer, G. R. (2011). Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. *Archives of General Psychiatry*, 68(1), 71. <https://doi.org/10.1001/archgenpsychiatry.2010.116>

Grof, S., Goodman, L. E., Richards, W. A., & Kurland, A. A. (1973). LSD-Assisted Psychotherapy in Patients with Terminal Cancer. *International Pharmacopsychiatry*, 8(3), 129–144. <https://doi.org/10.1159/000467984>

Grof, S., & Halifax, J. (1978). *The human encounter with death*. E.P. Dutton.

Hann, K. E. J., & McCracken, L. M. (2014). A systematic review of randomized controlled trials of Acceptance and Commitment Therapy for adults with chronic pain: Outcome domains, design quality, and efficacy. *Journal of Contextual Behavioral Science*, 3(4), 217–227. <https://doi.org/10.1016/j.jcbs.2014.10.001>

Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law*, 3, 205032451668332. <https://doi.org/10.1177/2050324516683325>

Helman, C. (2001). Placebos and nocebos: The cultural construction of belief. 3–16. <https://doi.org/10.1016/B978-0-443-06031-1.50004-6>

Hoffman, B. M., Papas, R. K., Chatkoff, D. K., & Kerns, R. D. (2007). Meta-analysis of psychological interventions for chronic low back pain. *Health Psychology*, 26(1), 1–9. <https://doi.org/10.1037/0278-6133.26.1.1>

Human Psychedelic Research: A Historical And Sociological Analysis. (1999, April 1). Multidisciplinary Association for Psychedelic Studies - MAPS. <https://maps.org/1999/04/01/human-psychedelic-research-a-historical-and-sociological-analysis/>

Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The Prevalence of Chronic Pain in United States Adults: Results of an Internet-Based Survey. *The Journal of Pain*, 11(11), 1230–1239. <https://doi.org/10.1016/j.jpain.2010.07.002>

Johnson, M. W., Garcia-Romeu, A., Cosimano, M. P., & Griffiths, R. R. (2014). Pilot study of the 5-HT 2A R agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology*, 28(11), 983–992. <https://doi.org/10.1177/0269881114548296>

Johnson, M. W., Richards, W., & Griffiths, R. R. (2008). Human hallucinogen research: Guidelines for safety. *Journal of*

Psychopharmacology, 22(6), 603–620.
<https://doi.org/10.1177/0269881108093587>

Johnson, S., & Black, Q. C. (2020). Can Psychedelics Alleviate Symptoms of Cluster Headache and Accompanying Mental Health Problems? A Case Report Involving Hawaiian Baby Woodrose. *Journal of Psychoactive Drugs*, 52(4), 319–323.
<https://doi.org/10.1080/02791072.2020.1762023>

Kast, E. C. (1967). Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide. *The Psychiatric Quarterly*, 41(4), 646–657. <https://doi.org/10.1007/BF01575629>

Kast, E. C., & Collins, V. J. (1963). Study of Lysergic Acid Diethylamide as an Analgesic Agent. *Anesthesia and Analgesia*, 43(3), 285–291.

Kometer, M., Schmidt, A., Bachmann, R., Studerus, E., Seifritz, E., & Vollenweider, F. X. (2012). Psilocybin Biases Facial Recognition, Goal-Directed Behavior, and Mood State Toward Positive Relative to Negative Emotions Through Different Serotonergic Subreceptors. *Biological Psychiatry*, 72(11), 898–906.
<https://doi.org/10.1016/j.biopsych.2012.04.005>

Koslowski, M., Johnson, M. W., Gründer, G., & Betzler, F. (2021). Novel treatment approaches for substance use disorders:

therapeutic use of psychedelics and the role of psychotherapy. *Current Addiction Reports*, 1-11. <https://doi.org/10.1007/s40429-021-00401-8>

Kurland, A. A. (1985). LSD in the Supportive Care of the Terminally Ill Cancer Patient. *Journal of Psychoactive Drugs*, 17(4), 279–290. <https://doi.org/10.1080/02791072.1985.10524332>

Kurland, A. A., Grof, S., Pahnke, W. N., & Goodman, L. E. (1972). Psychedelic drug assisted psychotherapy in patients with terminal cancer. *Journal of Thanatology*, 2(1–2), 644–691.

Kuypers, K. P. C., Riba, J., de la Fuente Revenga, M., Barker, S., Theunissen, E. L., & Ramaekers, J. G. (2016). Ayahuasca enhances creative divergent thinking while decreasing conventional convergent thinking. *Psychopharmacology*, 233(18), 3395–3403. <https://doi.org/10.1007/s00213-016-4377-8>

Leuner, H. (1967). Present state of psycholytic therapy and its possibilities. *The Use of LSD in Psychotherapy and Alcoholism*, 101.

Muthukumaraswamy, S., Forsyth, A., & Lumley, T. (2021). Blinding and Expectancy Confounds in Psychedelic Randomised Controlled Trials. <https://doi.org/10.31234/osf.io/q2hzm>

Nichols, D. E. (2016). Psychedelics. *Pharmacological Reviews*, 68(2), 264–355. <https://doi.org/10.1124/pr.115.011478>

NIHR CRN CC | History of research standards | Thalidomide. (2013, December 3). https://web.archive.org/web/20131203020225/http://www.crncc.nihr.ac.uk/workforce_development/learning_and_development/gcp/gcp_resource/research_standards/history/thalidomide

Nijs, J., Malfliet, A., Ickmans, K., Baert, I., & Meeus, M. (2014). Treatment of central sensitization in patients with ‘unexplained’ chronic pain: An update. *Expert Opinion on Pharmacotherapy*, 15(12), 1671–1683. <https://doi.org/10.1517/14656566.2014.925446>

Nutt, D. (2015). Illegal Drugs Laws: Clearing a 50-Year-Old Obstacle to Research. *PLOS Biology*, 13(1), e1002047. <https://doi.org/10.1371/journal.pbio.1002047>

Ona, G., & Troncoso, S. (2019). Long-lasting analgesic effect of the psychedelic drug changa: A case report. *Journal of Psychedelic Studies*, 3(1), 7–13. <https://doi.org/10.1556/2054.2019.001>

Pahnke, W. N., Kurland, A. A., Unger, S., Savage, C., & Grof, S. (1970). The Experimental Use of Psychedelic (LSD)

Psychotherapy. JAMA, 212(11), 1856–1863.
<https://doi.org/10.1001/jama.1970.03170240060010>

Passie, T., Seifert, J., Schneider, U., & Emrich, H. M. (2002). The pharmacology of psilocybin. *Addiction Biology*, 7(4).
<https://doi.org/10.1080/1355621021000005937>

Preller, K. H., Herdener, M., Pokorny, T., Planzer, A., Kraehenmann, R., Stämpfli, P., Liechti, M. E., Seifritz, E., & Vollenweider, F. X. (2017). The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. *Current Biology*, 27(3), 451–457.
<https://doi.org/10.1016/j.cub.2016.12.030>

Ramachandran, V., Chunharas, C., Marcus, Z., Furnish, T., & Lin, A. (2018). Relief from intractable phantom pain by combining psilocybin and mirror visual-feedback (MVF). *Neurocase*, 24(2), 105–110. <https://doi.org/10.1080/13554794.2018.1468469>

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., Liechti, M. E., Feilding, A., & Kuypers, K. P. C. (2021). A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of Psychopharmacology*, 35(4), 398–405. <https://doi.org/10.1177/0269881120940937>

Reckweg, J. T., Leeuwen, C. J., Amelsvoort, T., Theunissen, E., Mason, N. L., Paci, R., Terwey, T., & Ramaekers, J. G. (2023). A Phase 1/2 Trial to Assess Safety and Efficacy of a Vaporized 5-Methoxy-N,N-Dimethyltryptamine Formulation (GH001) in Patients with Treatment-Resistant Depression. *Frontiers in Psychiatry*, 14. <https://doi.org/10.3389/fpsy.2023.1133414>

Riba, J., Anderer, P., Jané, F., Saletu, B., & Barbanoj, M. J. (2004). Effects of the South American Psychoactive Beverage Ayahuasca on Regional Brain Electrical Activity in Humans: A Functional Neuroimaging Study Using Low-Resolution Electromagnetic Tomography. *Neuropsychobiology*, 50(1), 89–101. <https://doi.org/10.1159/000077946>

Ross, S. (2018). Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress. *International Review of Psychiatry*, 30(4), 317–330. <https://doi.org/10.1080/09540261.2018.1482261>

Royal Pharmaceutical Society. The evolution of pharmacy, Theme E, Level 3. Thalidomide and its aftermath. (2011, October 2011) <https://web.archive.org/web/20111014114005/https://www.rpharm.s.com/museum-pdfs/e3a-thalidomide-and-its-aftermath-2011.pdf>

Schindler, E. A. D., Gottschalk, C. H., Weil, M. J., Shapiro, R. E., Wright, D. A., & Sewell, R. A. (2015). Indoleamine Hallucinogens in

Cluster Headache: Results of the Clusterbusters Medication Use Survey. *Journal of Psychoactive Drugs*, 47(5), 372–381. <https://doi.org/10.1080/02791072.2015.1107664>

Schindler, E. A. D., Sewell, R. A., Gottschalk, C. H., Luddy, C., Flynn, L. T., Lindsey, H., Pittman, B. P., Cozzi, N. V., & D'Souza, D. C. (2021). Exploratory Controlled Study of the Migraine-Suppressing Effects of Psilocybin. *Neurotherapeutics*, 18(1), 534–543. <https://doi.org/10.1007/s13311-020-00962-y>

Sewell, R. A., Halpern, J. H., & Pope, H. G. (2006). Response of cluster headache to psilocybin and LSD. *Neurology*, 66(12), 1920–1922. <https://doi.org/10.1212/01.wnl.0000219761.05466.43>

Shneidman, E. S. (1993). *Suicide as Psychache: A Clinical Approach to Self-destructive Behavior*. Jason Aronson.

Smith, C. M. (1958). A New Adjunct to the Treatment of Alcoholism: The Hallucinogenic Drugs. *Quarterly Journal of Studies on Alcohol*, 19(3), 406–417. <https://doi.org/10.15288/qjsa.1958.19.406>

Soussan, C., & Kjellgren, A. (2016). The users of Novel Psychoactive Substances: Online survey about their characteristics, attitudes and motivations. *International Journal of Drug Policy*, 32, 77–84. <https://doi.org/10.1016/j.drugpo.2016.03.007>

Valle, M., Maqueda, A. E., Rabella, M., Rodríguez-Pujadas, A., Antonijoan, R. M., Romero, S., Alonso, J. F., Mañanas, M. À., Barker, S., Friedlander, P., Feilding, A., & Riba, J. (2016). Inhibition of alpha oscillations through serotonin-2A receptor activation underlies the visual effects of ayahuasca in humans. *European Neuropsychopharmacology*, 26(7), 1161–1175. <https://doi.org/10.1016/j.euroneuro.2016.03.012>

Vollenweider, F. (1997). Positron Emission Tomography and Fluorodeoxyglucose Studies of Metabolic Hyperfrontality and Psychopathology in the Psilocybin Model of Psychosis. *Neuropsychopharmacology*, 16(5), 357–372. [https://doi.org/10.1016/S0893-133X\(96\)00246-1](https://doi.org/10.1016/S0893-133X(96)00246-1)

Vollenweider, F. X., & Kometer, M. (2010). The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. *Nature Reviews Neuroscience*, 11(9), 642–651. <https://doi.org/10.1038/nrn2884>

Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F. I., Bäbler, A., Vogel, H., & Hell, D. (1998). Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *NeuroReport*, 9(17), 3897.

Voon, P., Karamouzian, M., & Kerr, T. (2017). Chronic pain and opioid misuse: A review of reviews. *Substance Abuse Treatment*,

Prevention, and Policy, 12(1), 36. <https://doi.org/10.1186/s13011-017-0120-7>

Williams, A. C. de C., Fisher, E., Hearn, L., & Eccleston, C. (2020). Psychological therapies for the management of chronic pain (excluding headache) in adults. The Cochrane Database of Systematic Reviews, 2020(8). <https://doi.org/10.1002/14651858.CD007407.pub4>

Yekkirala, A. S., Roberson, D. P., Bean, B. P., & Woolf, C. J. (2017). Breaking barriers to novel analgesic drug development. Nature Reviews Drug Discovery, 16(8), Article 8. <https://doi.org/10.1038/nrd.2017.87>

Zia, F. Z., Baumann, M. H., Belouin, S. J., Dworkin, R. H., Ghauri, M. H., Hendricks, P. S., Henningfield, J. E., Lanier, R. K., Ross, S., & Berger, A. (2023). Are psychedelic medicines the reset for chronic pain? Preliminary findings and research needs. Neuropharmacology, 233, 109528. <https://doi.org/10.1016/j.neuropharm.2023.109528>

Chapter 2

Potential analgesic effects of psychedelics on select chronic pain conditions: A survey study

Cavarra M., Mason N. L., Kuypers K. P. C., Bonnelle V., Smith W. J., Feilding A., Kryskow P., Ramaekers J. G.

Background: Chronic pain is a major cause of suffering and disability and is often associated with psychiatric complications. Current treatments carry the risk of severe side effects and may lead to limited or no relief at all in a relevant portion of this patient population. Preliminary evidence suggests that classical psychedelics (e.g., LSD and psilocybin) may have analgesic effects in healthy volunteers and in certain chronic pain conditions and observational studies reveal that they are used in naturalistic settings as a means to manage pain. Methods: In order to gain insight on the potential effectiveness of such compounds in chronic pain conditions, we set up a survey addressed to people living with chronic pain inquiring about psychedelic use and the relief levels achieved with both conventional treatments, full psychedelic doses and microdoses. We analysed data related to five conditions selected based on diagnostic homogeneity within each of them:

fibromyalgia, arthritis, migraine, tension type headache and sciatica. Results: Except for sciatica, volunteers reported that psychedelics led to better pain relief compared to conventional medication in all examined conditions. More specifically, full doses performed better than conventional medication. Microdoses led to significantly better relief compared to conventional medication in migraines and achieved comparable relief in the remaining three categories. Implications for future research are discussed. Conclusions: Full doses and microdoses may hold value in the treatment of some specific chronic pain conditions.

Published in: European Journal of Pain, 2023; 28(1), 163-165

Introduction

Improving treatment outcomes for people living with chronic pain (PLCP) patients represents a pressing challenge. CP is a leading cause of disability (Burke et al., 2015), it affects about 20% of the population (Goldberg & McGee, 2011), impacts psychological well being while decreasing social functioning (Dueñas et al., 2016) and productivity (Cohen et al., 2021). Furthermore, CP is associated with the onset or exacerbation of psychiatric symptoms such as depression (Cohen et al., 2021), anxiety (Dueñas et al., 2016) and substance use problems (Voon et al., 2017).

Recommended pharmacological therapies include nonsteroidal anti-inflammatory drugs (NSAIDs) (Yekkirala et al., 2017), opioids, anticonvulsants, and antidepressants (Edinoff et al., 2022). While these have some degree of success in achieving relief, a significant portion of patients does not benefit from them (Johannes et al., 2010). Opioids in particular cause several unwanted effects, can be highly addictive (Coussens et al., 2019), are associated with a greater frequency of (serious) adverse events (Els et al., 2017), and may lead to opioid-induced hyperalgesia (i.e., increased sensitivity to pain) (Nijs et al., 2014). Psychological therapies also seem to contribute to better pain management (Hann & McCracken, 2014; Hoffman et al., 2007). However, the magnitude of their effect is small to medium compared to no treatment and smaller or non-significant when compared to other interventions such as active

controls (e.g., physical therapy, education, medical regimes), or different forms of “treatment as usual” (Williams et al., 2020; Hann & McCracken, 2014).

Alternative or complementary treatments are often sought and classic psychedelic drugs have recently gained the PLCP’s attention as shown by the numerous articles, posts, and discussions published on online fora (e.g., Andersson et al., 2017; Soussan & Kjellgren, 2016). Classic psychedelics are a class of psychoactive compounds that produce profound alterations to perception, cognition, and emotion through agonism of serotonergic receptors (de Vos et al., 2021). Their use pattern is classically categorised into full dose use, in which doses large enough to generate such alterations are taken, and microdosing, in which doses small enough not to generate perceivable alterations of consciousness (microdoses) are taken repeatedly over the course of several days or weeks (Kuypers et al., 2019). Research to test their analgesic effects began before the war on drugs era (Reiff et al., 2020) and evidence of their efficacy was gathered in neuropathic, ischemic, or cancer-related pain (Grof et al., 1973; Kast & Collins, 1963), life-threatening illnesses (Kast, 1967), and phantom limb pain (Fanciullacci et al., 1977). More recent retrospective studies have revealed that individuals suffering from cluster headache who have used psychedelics report improvements even when using low, non-hallucinogenic doses (Schindler et al., 2015; Sewell et al., 2006). Furthermore, a recent

40

randomised controlled trial with healthy volunteers showed that a non-hallucinogenic dose of LSD can improve pain tolerance and ratings of unpleasantness to an extent comparable to oxycodone or morphine (Ramaekers et al., 2021). The responsible mechanisms are still unclear but a reasonable hypothesis points to the psychedelic-induced activation of serotonin receptors (5-HT_{2A}), which may upregulate genes that promote neuroplasticity and suppress inflammatory factors (Castellanos et al., 2020; de Vos et al., 2021). This may help to compensate for the malfunction of the descending inhibitory 5-HT pathways, a supposed cause of hyperalgesia and allodynia in chronic pain and a contributing factor in increasing inflammatory pain (Castellanos et al., 2020). A recent review focusing on the potential mechanisms supporting the pain regulating effects of psychedelics pointed to the fact that psilocin (an active metabolite of psilocybin) binds to several 5-HT receptors and evidence exist of a potential role of both 5-HT_{2A} and 5-HT₃ in nociception (Zia et al., 2023). Furthermore, the reduction in 5-HT_{2A} receptors number caused by the use of such compounds may also contribute to decreased signalling in pathways responsible for nociception (Zia et al., 2023). The authors also add that 5-HT_{2A} agonists may promote the internalisation of such receptors potentially resulting in less perceived pain (Zia et al., 2023).

To summarise, while classic psychedelics seem to have potential in the management of CP, their actual effectiveness and mechanisms are still unclear. To better understand the perceived

analgesic effects that psychedelics have on CP patients who self-medicate, an online survey (Bonnelle et al., 2022) was set up. Results suggested that psychedelic use led to pain relief, that full doses appeared to work better than microdoses, and that these changes were unrelated to the mood improvement that these substances typically induce nor to the degree in which participants considered themselves advocates for psychedelic use (Bonnelle et al., 2022). The present paper will be focused on results concerning specific CP conditions selected based on homogeneity within each individual survey category: fibromyalgia (FM), arthritis, migraine, tension-type headache (TTH) and sciatica (See Supplemental material 1 for a description of the conditions).

Methods

Participants

The sample was recruited via an online survey that was disseminated through the Beckley Foundation website and social media platforms from August 2020 to July 2021 (Bonnelle et al., 2022). The advertisement was addressed to individuals who had microdosed and had been or were currently suffering from chronic pain. Eligible participants were at least 18 years of age, had already had experience with psychedelics, and were suffering or had suffered from CP. Once informed about the study, respondents were presented with the consent form. The Ethics Review

Committee of Psychology and Neuroscience at Maastricht University (NL) approved the protocol (ERCPN-226_101_08_2020) and the survey was presented via Qualtrics.

Test battery

The test battery included a questionnaire inquiring about demographic information, history of psychedelic use, pain complaints, reported pain relief from conventional medication and cannabis, and reported pain relief from psychedelic use.

Demographic information

Respondents' age group, sex, and work status (i.e., full-time, part-time, unemployed, unemployed due to pain, home duties, on leave due to pain, studying, other) were gathered.

History of psychedelic use

Participants indicated whether they had experience with psychedelics and, if they had, what compound they were most experienced with (LSD/1p-LSD, psilocybin-containing truffles or mushrooms, DMT, ayahuasca, 5-MeO-DMT, mescaline, or other). Finally, they indicated the frequency and duration of their psychedelic use for both microdoses and full doses.

Pain complaints

Respondents indicated current or past painful complaints requiring pain management interventions. Complaints were grouped as follows: Musculoskeletal, Inflammatory, Neuropathic, Headache & orofacial, Pain caused by cancer, Visceral, or Other type. Participants could enter multiple conditions and pain severity was then recorded on a Visual Analogue Scale (VAS) ranging from 0 to 10 while pain frequency was recorded on a 4-point Likert scale ranging from “all the time” to “less than once a week”). Respondents who indicated no present or past complaints were redirected to the survey end page.

This paper will present the data obtained regarding a subset of such complaints (for the full list, refer to Supplementary material 2). The selection was based on presumed diagnostic homogeneity within the indicated category (i.e., while the “back pain” complaint may potentially include very diverse conditions, the “migraine” one may include a more homogeneous subsample of patients). Based on this criterion, results from the following conditions were analysed: FM, arthritis, migraine, TTH, and sciatica.

Reported effectiveness of conventional medication and cannabis

The survey required participants to indicate which conventional medication they used most often from a predefined list including

drugs both acute (i.e., over-the-counter pain relievers/NSAIDs, opioids) and preventive drugs (i.e., antidepressants, anticonvulsants), as well as cannabis which seems to have both prophylactic and abortive effects (Okusanya et al., 2022). Given that cannabis is gaining increasing acceptance as an effective pain management treatment and the fact that several countries are now allowing its prescription, it was included in this category (Häuser et al., 2018). Participants also rated the extent of pain relief they got from such medication on a Visual Analogue Scale (VAS) ranging from 0 (no pain relief) to 10 (complete relief).

Reported effectiveness of psychedelics in pain relief

Respondents reported the degree of relief they obtained from microdoses and full doses on a Visual Analogue Scale (VAS) ranging from 0 (no pain relief) to 10 (complete relief), whether they used psychedelics to intentionally obtain pain relief and how long the potential benefits lasted on a multiple choice question which presented the following options: benefit on dosing day only, on dosing day and the following day, on dosing day plus 2 to 3 days after, on dosing day and for more than 3 days after.

Mood and expectation

Since mood and treatment expectations are considered important factors influencing pain perception (Hall et al., 2011), the survey required participants to report whether they experienced changes

in mood as a consequence of psychedelic use and whether they used them to intentionally treat pain.

Statistical analysis

Data were analysed in SPSS (version 26.0.0.0). Frequencies were computed for the following variables: gender, age, work status, number of concurrent pain complaints, most often used conventional medication, and psychedelic compound.

Pain relief scores after conventional medication, microdosing, and full doses were not normally distributed according to Komogorov-Smirnov and Shapiro-Wilk tests. Kruskal-Wallis tests were used to test for differences in pain relief obtained by the different classes of conventional medication across conditions. Related samples Friedman's two-way ANOVA was used to compare pain relief scores between Treatment Type (conventional medication, microdoses, and full doses). Contrasts were carried out via the Wilcoxon signed ranks test and the Bonferroni correction for multiple comparisons was performed. Effect sizes (Kendall's W for Friedman's ANOVAs and η^2 for Kruskal-Wallis) and p -values were reported and the latter tested against a Bonferroni corrected α level. To determine whether changes in mood were associated with reductions in pain, Pearson's correlation analyses were run between mood change ratings and relief ratings. To determine whether expectations played a role in determining relief scores Mann-Whitney U tests were run comparing the degree of relief

obtained by participants who reported taking psychedelics to intentionally self-treat pain and those who did not.

Results

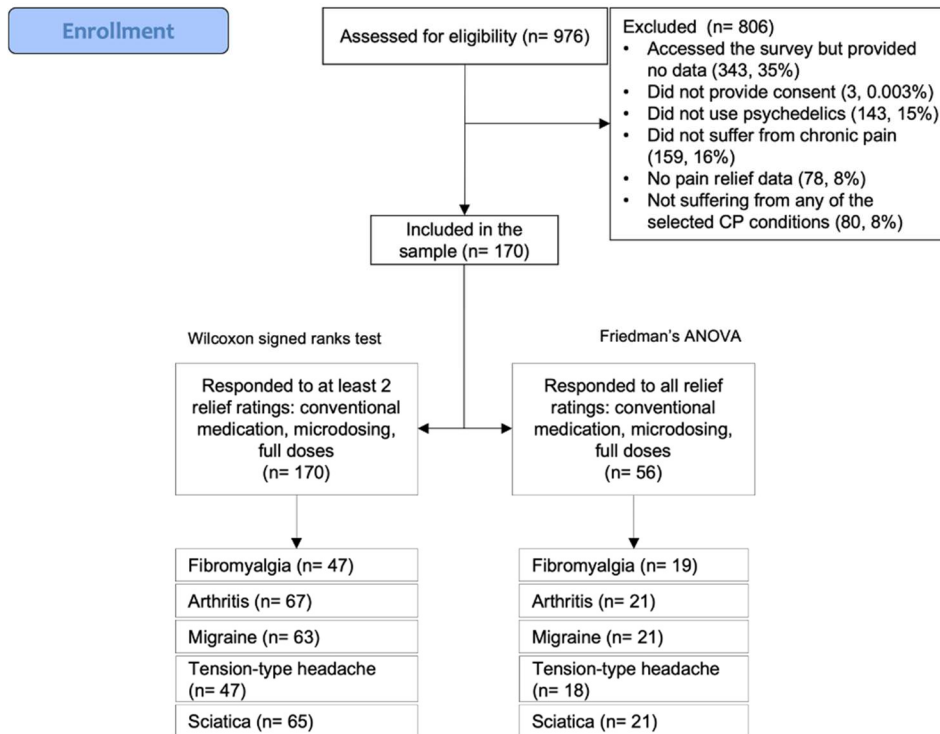


Figure 1. Enrollment flowchart detailing how many participants fulfilled inclusion criteria, provided pain relief data and suffered from at least 1 of the selected CP conditions. Friedman’s ANOVA was run including participants who provided all 3 relief measures (i.e., conventional medication, microdosing and full doses) while contrasts between each treatment pair were run via Wilcoxon signed ranks test considering the whole sample.

Demographics

Data on this sample were published in another paper (Bonnelle et al., 2022) and are briefly summarised here. Out of 976 respondents, 170 completed the survey and met the inclusion criteria (Figure 1). Respondents who did not consent to participate, were younger than 18 years of age, did not provide relief data, or were not suffering from one of the selected CP conditions were excluded. There were 93 females and 70 males (7 preferred not to say). The majority (33%) fell into the 31-40 age range (n=56), followed by the 18-30 (n=40; 24%), 41-50 (n=29; 17%), 51-60 (n=24; 14%) and finally 61-70 (n=21; 13%). Thirty-five (21%) declared to be unemployed due to pain and 2 (1%) of being on leave from work because of pain. The average number of concurrent pain complaints was 5.88 (sd=4.23).

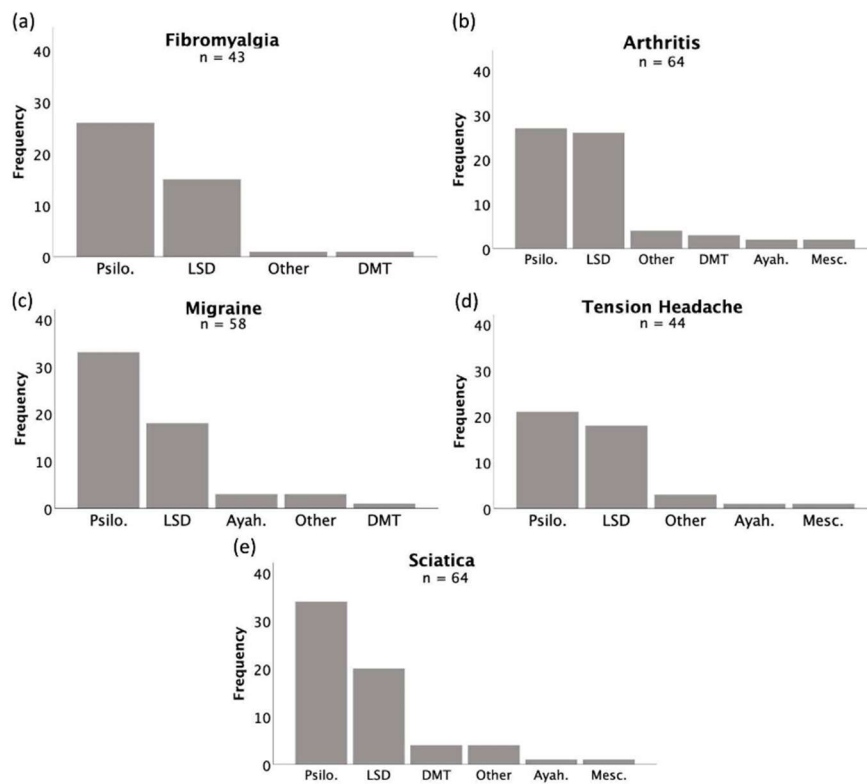


Figure 2. Frequencies of most used psychedelics in each condition and sample sizes: a) fibromyalgia, b) arthritis, c) migraine, d) tension headache, e) sciatica. Psilo. = psilocybin, LSD = lysergic acid diethylamide, Ayah. = ayahuasca, DMT = N,N-dimethyltryptamine, Mesc. = mescaline.

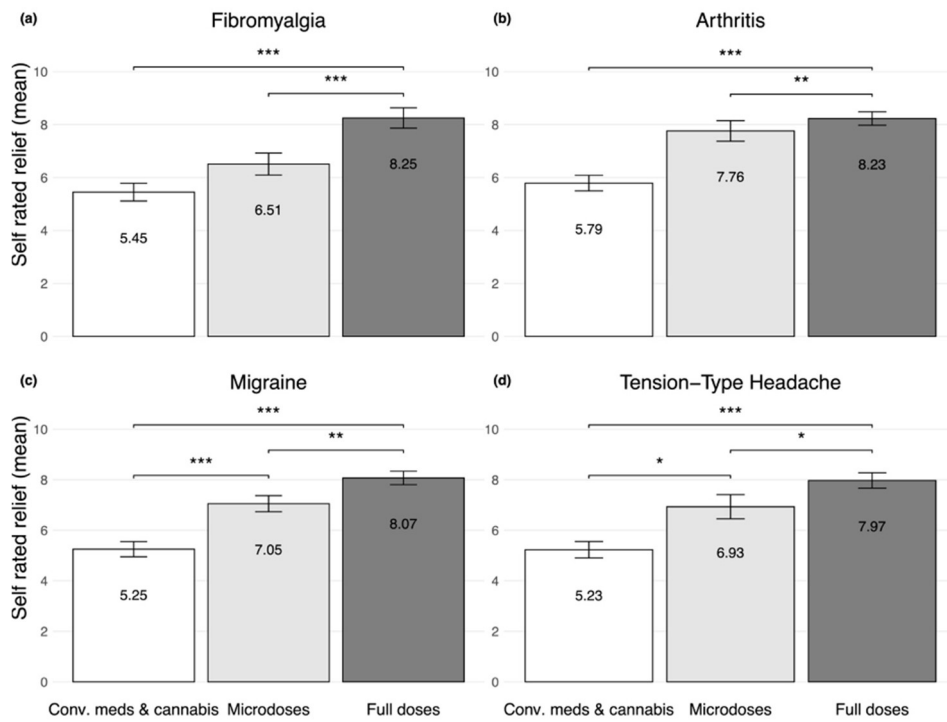


Figure 3. Mean self-rated relief from conventional medication plus cannabis, microdoses and full doses for each condition, sample sizes and 95% confidence intervals. Statistically significant differences between groups are denoted by ** (<.005) and * (<.01). a) fibromyalgia, b) arthritis, c) Migraine, d) tension headache.

Fibromyalgia

Demographics

Of the 170 participants, 47 (18.8%; 34 females and 11 males, 2 preferred not to say) participants reported to be suffering from FM. The majority (38.3%) fell into the 31-40 age range (n=18), followed by the 18-30 (n=12; 25.5%), 41-50 (n=9; 19.1%), 51-60 (n=7; 14.9%) and finally 61-70 (n=1; 2.1%). Seventeen participants (34.7%) declared to be unemployed due to pain and 2 (4.1%) of being on leave from work because of pain. The average number of concurrent pain complaints was 8.55 (sd=5.18).

Pain relief with conventional medication

Regarding the most used conventional medications, 5 participants in this subsample reported the use of over-the-counter (OTC)/NSAIDs medication (mean relief = 4.4; sd=2.32), 16 reported use of opioids (mean relief = 5.38; sd=2.71), 11 of cannabis (mean relief = 6.18; sd=1.4), 10 of other medications (mean relief = 5.3; sd=1.89). The latter category included amitriptyline (n=1), anticonvulsants (n=3), ketamine (n=2), serotonin-norepinephrine reuptake inhibitors (SNRIs) (n=2), codeine/paracetamol (n=1), 1 participant did not specify. Seven participants did not respond. No significant differences were found in obtained relief between conventional treatments ($H(3)=2.66$, $p=.447$, $\eta^2=.11$).

Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample (n=26), followed by LSD (n=15), DMT (n=1), other (n=1). In the other category, 1 participant indicated LSD and mescaline (n=1; Figure 2a). Four participants flagged the other category but in the free text field, they indicated compounds that are not considered classical psychedelics (MDMA and ketamine (n=1), ketamine (n=2), THC (n=1)) and were therefore excluded from subsequent analyses investigating relief. Most participants in the FM subsample made alternate use of microdoses and full doses (n=39; 83%) as opposed to just microdoses (n=7; 14.9%) or full doses (n=1; 2.1%).

A significant effect of Treatment Type ($F(2)=19.042$, $p<.001$) with a medium effect size ($W=.5$) was found. Pairwise comparisons were conducted including data from participants who completed at least 2 of the 3 relief measures (i.e., relief from conventional medication, microdosing and full doses) via a Wilcoxon signed ranks test with a Bonferroni adjusted α level. Results showed a significantly greater relief from full doses ($M=8.25$) compared to both conventional medication ($M=5.32$; $p<.001$) and microdoses ($M=6.51$; $p<.001$) (Figure 3a). Considering this subsample, 68.4% (n=13) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 31.6% (n=6) reported a benefit on the dosing day only, 21.1% (n=4) also on the following day, 21.1% (n=4) on the following 2 to 3 days, and 26.3% (n=5) reported benefits beyond the 3rd day. In terms of benefit

duration for low doses, 52.6% (n=10) reported a benefit on the dosing day only, 31.6% (n=6) also on the following day, 10.5% (n=2) on the following 2 to 3 days and 5.3% (n=1) reported benefits beyond the 3rd day. Pearson correlation analyses revealed no significant association between pain relief and mood change scores for full doses ($r=.025$; $p=.919$) and microdoses ($r=.180$, $p=.461$).

Arthritis

Demographics

Of the 170 participants, 67 (26.8%; 37 females, 29 males, 1 preferred not to say) participants reported suffering from arthritis. The majority (28.4%) fell into the 31-40 age range (n=19), followed by the 61-70 range (n=15; 22.4%), 41-50 (n=14; 20.8%), 51-60 (n=12; 17.9%) and finally 18-30 (n=7; 10.5%). Sixteen participants (23.9%) declared to be unemployed due to pain and 2 (4.1%) of being on leave from work because of pain. The average number of concurrent pain complaints was 6.93 (sd=4.95).

Pain relief with conventional medication

Regarding the most used conventional medications, 14 participants in this subsample reported the use of OTC/NSAIDs (mean relief = 4.79; sd=2.19), 22 of opioids (mean relief = 6.14; sd=2.36), 16 of cannabis (mean relief = 6.56; sd=1.71) 4 of other medications (mean relief = 5.75; sd=2.5). The latter category included anticonvulsants (n=2), hydroxychloroquine (n=1), and SSRIs (n=1).

Eleven participants did not respond. No significant differences in obtained relief between conventional treatments were found ($H(3)=8.08$, $p=.044$, $\eta^2=.098$).

Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample ($n=27$), followed by LSD ($n=26$), other ($n=4$), DMT ($n=3$), ayahuasca ($n=2$), mescaline ($n=2$; Figure 2b). In the other category, participants indicated the following substances respectively: LSD and psilocybin ($n=3$), LSD and mescaline ($n=1$). Four participants flagged the other category but in the free text field, they indicated compounds that are not considered classical psychedelics (ketamine ($n=1$), methamphetamine ($n=1$), THC ($n=1$)) and were therefore excluded from subsequent analyses investigating relief. Most participants in the Arthritis subsample made alternate use of microdoses and full doses ($n=49$; 73.1%) as opposed to only microdoses ($n=4$; 6%) or only full doses ($n=13$; 19.4%).

A significant effect of Treatment Type ($Fr(2)=12.873$, $p=.002$) with a medium effect size ($W=.31$) was found. Pairwise comparisons were conducted including data from participants who completed at least 2 of the 3 relief measures (i.e., relief from conventional medication, microdosing and full doses) via a Wilcoxon signed ranks test (Figure 3a) with a Bonferroni adjusted α level. Results showed a significantly greater relief from full doses ($M=8.23$) compared to both conventional medication ($M=5.79$; $p<.001$) and

microdoses ($M=7.76$; $p<.001$) (Figure 4b). Considering this subsample, 52.4% ($n=11$) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 33.3% ($n=7$) reported a benefit on the dosing day only, 14.3% ($n=3$) also on the following day, 23.8% ($n=5$) on the following 2 to 3 days and 28.6% ($n=6$) reported benefits beyond the 3rd day. In terms of benefit duration for low doses, 33.3% ($n=7$) reported a benefit on the dosing day only, 33.3% ($n=7$) also on the following day, 9.5% ($n=2$) on the following 2 to 3 days, and 23.8% ($n=5$) reported benefits beyond the 3rd day. Pearson correlation analyses revealed no significant association between relief and mood change scores for full doses ($r=-.083$; $p=.693$) and microdoses ($r=.194$, $p=.353$).

Migraine

Demographics

Of the 170 participants, 63 (25,2%; 42 females, 19 males, 2 preferred not to say) participants reported suffering from migraine. The majority (36.5%) fell into the 31-40 age range ($n=23$), followed by the 18-30 range ($n=16$; 25.4%), 41-50 ($n=14$; 22.2%), 51-60 ($n=5$; 7.9%) and finally 18-30 ($n=5$; 7.9%). Eleven participants (17.5%) declared to be unemployed due to pain and 1 (1.6%) of

being on leave from work because of pain. The average number of concurrent pain complaints was 6.63 (sd=4.87).

Pain relief with conventional medication

Regarding the most used conventional medications, 15 participants in this subsample reported the use of OTC/NSAIDs (mean relief = 4.13; sd=1.85), 16 of opioids (mean relief = 5.50; sd=2.42), 13 of cannabis (mean relief = 6.23; sd=1.96) 9 of other medications (mean relief = 5.22; sd=2.11). The latter category included anticonvulsants (n=2), triptans (n=4), and kratom (n=1). Two participants did not specify. Ten participants didn't respond. No significant differences in obtained relief between conventional treatments were found ($H(3)=6.72$, $p=.081$, $\eta^2=.063$).

Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample (n=33), followed by LSD (n=18), ayahuasca (n=3), other (n=3), DMT (n=1). In the other category, participants indicated the following substances respectively: LSD and mescaline (n=1), cannabis and psilocybin (n=1), LSD and psilocybin (n=1; Figure 2c). Two participants flagged the other category but in the free text field, they indicated compounds that are not considered classical psychedelics (THC (n=1), MDMA and ketamine (n=1)) and were therefore excluded from subsequent analyses investigating relief. Three participants did not respond. Most participants in the Migraine subsample made alternate use of microdoses and full

doses (n=42; 66.7%) as opposed to just microdoses (n=15; 23.8%) and full doses (n=3; 4.8%).

A significant effect of Treatment Type ($F(2)=19.973$, $p<.001$) with a medium effect size ($W=.48$) was found. Pairwise comparisons were conducted including data from participants who completed at least 2 of the 3 relief measures (i.e., relief from conventional medication, microdosing and full doses) via a Wilcoxon signed ranks test (Figure 3a) with a Bonferroni adjusted α level. Results showed a significantly greater relief from full doses ($M=8.07$) compared to both conventional medication ($M=5.25$; $p<.001$) and microdoses ($M=7.05$; $p<.001$). Microdoses also lead to significantly greater relief compared to conventional medication ($p<.005$) (Figure 4c). Considering this subsample, 61.9% (n=13) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 19% (n=4) reported a benefit on the dosing day only, 19% (n=4) also on the following day, 33.3% (n=7) on the following 2 to 3 days, and 28.6% (n=6) reported benefits beyond the 3rd day. In terms of benefit duration for low doses, 33.3% (n=7) reported a benefit on the dosing day only, 28.6% (n=6) also on the following day, 33.3% (n=7) on the following 2 to 3 days and 4.8% (n=1) reported benefits beyond the 3rd day. Pearson correlation analyses revealed no significant association between relief and mood change scores for full doses ($r=.041$; $p=.859$) and microdoses ($r=-.066$, $p=.777$).

Tension-Type Headache

Demographics

Of the 170 participants, 47 (18,8%; 31 females, 14 males, 2 preferred not to say) participants reported suffering from TTH. The majority (34%) fell into the 31-40 age range (n=16), followed by the 41-50 range (n=14; 29.8%), 18-30 (n=12; 25.5%), 51-60 (n=3; 6.4%) and finally 61-70 (n=2; 4.3%). Twelve participants (25.5%) declared to be unemployed due to pain. The average number of concurrent pain complaints was 8.08 (sd=5.22).

Pain relief with conventional medication

Regarding the most used conventional medications, 13 participants in this subsample reported the use of opioids (mean relief = 5.54; sd=1.81), 11 of OTC/NSAIDs (mean relief = 4.09; sd=1.7), 8 of cannabis (mean relief = 6.38; sd=1.51), 7 of other medications (mean relief = 5.14; sd=2.8). The latter category included anticonvulsants (n=2), SNRIs (n=2), ketamine (n=1), kratom (n=1), benzodiazepines (n=1). Eight participants did not specify.

No significant differences in relief between conventional treatments were found ($H(3)=6.950$, $p=.074$, $\eta^2=.092$).

Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample (n=21), followed by LSD (n=18), other (n=3), ayahuasca (n=1),

mescaline (n=1). In the other category, 3 participants indicated the following substances respectively: LSD and psilocybin (n=1), LSD and mescaline (n=2; Figure 2d). Two participants flagged the other category but in the free text field, they indicated compounds that are not considered classical psychedelics (MDMA and ketamine (n=1), and ketamine (n=1)) and were therefore excluded from subsequent analyses investigating relief. One participant did not respond. Most participants in the subsample made alternate use of microdoses and full doses (n=37; 78.7%) as opposed to microdoses (n=6; 12.8%) and full doses (n=3; 6.4%).

A significant effect of treatment ($F(2)=13.16$, $p<.005$) with a small effect size ($W=.13$) was found. Pairwise comparisons were conducted including data from participants who completed at least 2 of the 3 relief measures (i.e., relief from conventional medication, microdosing and full doses) via a Wilcoxon signed ranks test (Figure 3a) with a Bonferroni adjusted α level. Results showed a significantly greater relief from full doses ($M=7.97$) compared to conventional medication ($M=5.23$; $p<.001$) – and also revealed a significant difference in relief obtained with full doses compared to microdoses ($M=6.93$; $p<.01$) and with microdoses compared with conventional medication ($p<.01$) (Figure 4d). Considering this subsample, 66.7% (n=12) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 22.2% (n=4) reported a benefit on the dosing day only, 11.1% (n=2) also on the following day, 33.3% (n=6) on

the following 2 to 3 days and 33.3% (n=6) reported benefits beyond the third day. In terms of benefit duration for low doses, 27.8% (n=5) reported a benefit on the dosing day only, 27.8% (n=5) also on the following day, 27.8% (n=5) on the following 2 to 3 days, and 16.7% (n=3) reported benefits beyond the 3rd day. Pearson correlation analyses revealed no significant association between relief and mood change scores for full doses ($r=.105$; $p=.677$) and microdoses ($r=.467$, $p=.051$).

Sciatica

Demographics

Of the 170 participants, 65 (26%; 36 females, 26 males, 3 preferred not to say) participants reported suffering from sciatica. The majority (26.2%) fell into the 31-40 age range (n=17), followed by 41-50 (n=16; 24.6%), 18-30 (n=12; 18.5%), 51-60 (n=12; 18.5%) and finally 61-70 (n=8; 12.3%). Twenty participants (31.3%) declared to be unemployed due to pain and 1 (1.6%) of being on leave from work because of pain. The average number of concurrent pain complaints was 7.9 (sd=5.14).

Pain relief with conventional medication

Regarding the most used conventional medications, 16 participants in this subsample reported the use of opioids (mean relief = 5.81; sd=2.11), 15 of cannabis (mean relief = 6.67; sd=1.95), 11 of OTC/NSAIDs (mean relief = 4.91; sd=2.26), 10 of other medications

(mean relief = 5.30; sd=2.18). The latter category included anticonvulsants (n=5), ketamine (n=2), tricyclic antidepressants (n=1), and SNRIs (n=1). One participant didn't specify. Thirteen participants did not respond. No significant differences in relief between conventional treatments were found ($H(3)=5.795$, $p=.122$, $\eta^2=.046$).

Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample (n=34), followed by LSD (n=20), DMT (n=4), other (n=4), ayahuasca (n=1), mescaline (n=1). In the other category, 4 participants indicated the following substances: LSD and psilocybin (n=2), LSD and mescaline (n=1), and psilocybin and cannabis oil (n=1; Figure 2e). One participant flagged the other category but indicated compounds that are not considered classical psychedelics (MDMA and ketamine) in the free text field so this response was therefore excluded from subsequent analyses investigating relief. One participant did not respond. Most participants in the subsample made alternate use of microdoses and full doses (n=49; 75.4%) as opposed to just microdoses (n=10; 15.4%) and full doses (n=6; 9.2%). While there were differences in the mean degree of relief obtained with full doses (M=8.05), microdoses (M=7.05), and conventional medication (M=7), analyses did not reveal a significant main effect of Treatment Type on the degree of relief ($F(2)=5.4$, $p=.067$). Considering this subsample, 42.9% (n=9) of patients reported making use of

psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 33.3% (n=7) reported a benefit on the dosing day only, 9.5% (n=2) also on the following day, 23.8% (n=5) on the following 2 to 3 days, and 33.3% (n=7) reported benefits beyond the 3rd day. In terms of benefit duration for low doses, 38.1% (n=8) reported a benefit on the dosing day only, 33.3% (n=7) also on the following day, 9.5% (n=2) on the following 2 to 3 days and 19% (n=4) reported benefits beyond the 3rd day. Pearson correlation analyses revealed no significant association between relief and mood change scores for full doses ($r=.352$; $p=.117$) and microdoses ($r=-.039$, $p=.867$).

Expectations

Comparisons between individuals who intentionally took psychedelics to self-treat CP and those who did not report such intention across conditions resulted in a non-significant difference in both participants making use of microdoses ($U= 882$; $z=-.98$, $p=.328$) and full doses ($U= 1455$; $z=-.98$; $p=.325$).

Discussion

The aim of the present study was to investigate the perceived analgesic effects that psychedelics may have on selected CP conditions - namely FM, arthritis, migraine, TTH, and sciatica - when used in naturalistic settings. This is the first study to investigate the effect of the use of both psychedelic microdoses and

full doses in specific pain conditions and to compare their effects with that of conventional medications. Findings demonstrated reduced self-rated pain scores when self-administering psychedelics compared to conventional pharmacological pain treatments. This was true for all selected pain conditions except for those suffering from sciatica.

Participants suffering from migraine seemed to get better relief from microdosing compared to conventional medication and better relief from full doses compared to microdoses. This finding is consistent with an exploratory controlled study which suggested that psilocybin may be able to reduce migraine frequency even at sub or mildly hallucinogenic doses (Andersson et al., 2017; Schindler et al., 2021). The same response pattern was observed in participants with TTH.

Participants suffering from FM, and arthritis reported that full doses led to better relief than both microdoses and conventional medication while no significant difference was observed between microdoses and conventional medication. No controlled study has yet investigated the effect of psychedelics on FM but the present results are in line with another survey study that found that, among 12 FM sufferers, 11 reported improvement in symptoms after psychedelic use (Glynos et al., 2022). This is the first study to report a perceived analgesic effect of psychedelics on arthritis pain although their potential value in treating autoimmune diseases has

already been proposed (Flanagan & Nichols, 2018). According to survey participants suffering from FM and arthritis, full doses led to greater improvements compared to the other conventional treatments and microdoses, which suggests that this use type may have therapeutic value. This may be especially true if considering that full doses are usually taken sporadically in contrast to most conventional abortive pain medications such as NSAIDs or opioids and that several respondents reported a benefit duration that extended beyond the day of administration of both full doses and microdoses. In other words, psychedelics may be useful both to treat pain acutely and as a prophylactic agent as observed in migraine patients (Schindler et al., 2021). Still, in order to conclude that they have a preventive effect on paroxysmal pain disorders, future research should compare the pain baseline episode frequency with the post-treatment frequency (e.g., number of pain days per month). Furthermore, current treatment options often carry unwanted side effects that range from gastrointestinal ulcers and higher risk of cardiovascular diseases caused by NSAIDs (Edinoff et al., 2022) to addiction, hyperalgesia, constipation, dizziness, drowsiness, fatigue, hot flushes, diaphoresis, nausea, vomiting, and pruritus caused by opioids (Edinoff et al., 2022).

Interestingly, participants also reported that microdosing was as effective as (FM, arthritis) or more effective (migraine and TTH) than conventional treatments. It is unclear whether this effect is achieved through a common biological (e.g., the anti-inflammatory

action, increased neuroplasticity (Castellanos et al., 2020; de Vos et al., 2021) causal pathway. Earlier research found that mood (Griffiths et al., 2016) and expectation (Kirsch, 2018) may play a role in determining the perceived intensity of pain. This relationship was not observed in the present study, suggesting that the perceived analgesic effects of psychedelics may not be entirely explained by psychological factors. There may still be other psychological factors that mediate or moderate the relationship (e.g. psychological flexibility and personality profile).

Future research should aim at replicating such findings in a controlled setting and at disentangling the possible causal factors involved while considering the safety, effects of dose, type of psychedelic, frequency of administration, and potency. Furthermore, new research should investigate each condition separately and disentangle the acute analgesic effects from the preventive effects. Another interesting way to further the understanding of the potential effects of serotonergic psychedelics would entail to test different conditions that however share the same causal pathways (e.g., nociplastic pain) regardless of the location of pain itself. While the search for better avenues to manage CP should still aim at producing greater and more stable degrees of relief (Finnerup et al., 2015), results of the current survey suggest that patients may be able to achieve comparable levels of efficacy through substances that carry a potentially better side effect profile (Kuypers, 2020).

The effect of psychedelics on pain related to sciatica was statistically non-significant. This result may indicate that these substances hold promise only for certain kinds of pain conditions, presumably those in which the inflammatory and/or psychosomatic components play a more prominent role. Also, sciatica is caused by a well-understood structural pathology and, as may be the case with psychedelic-assisted psychotherapy (Cavarra et al., 2022), the greater benefit may be achieved by pairing psychedelics with already established treatments (e.g., physical therapy). Further research is needed to better understand the mechanisms that may account for pain relief.

In line with (Bonnelle et al., 2022), no association between measures of mood and pain relief in both microdoses and full doses was found suggesting that the perceived analgesic effect of psychedelics may be supported by different mechanisms.

The present results are in line with what was suggested by early research in the field (Fanciullacci et al., 1977; Grof et al., 1973; Kast, 1967; Kast & Collins, 1963), recent experimental studies on healthy volunteers (Ramaekers et al., 2021), survey studies focusing on headache disorders (Schindler et al., 2015, 2021), recent reviews (Castellanos et al., 2020; Elman et al., 2022) and they expand on previous reports suggesting that psychedelics administered in full doses and microdoses may have the potential to help in the management of CP (Bonnelle et al., 2022).

Limitations

The current study suffers from several limitations. First of all, this is a naturalistic survey study and as such it provides purely retrospective self-ratings from a self-selected sample of individuals who self-administer psychedelics. This design carries the risk of obtaining biased data and the generalizability of the produced results is only limited. It provides limited information to disentangle the role that different mechanisms play to achieve these perceived analgesic effects. While subjective reports on pain relief are still a valuable source of information given the nature of pain itself, in order to draw conclusions on the effects that psychedelics may have in this area, controlled studies are needed. Second, while there is consensus around the hypothesis that set and setting are important determinants of the outcomes of psychedelic use (Kettner et al., 2021), the survey did not inquire about the context of the administration nor other potentially relevant individual variables (e.g., personality traits) that may have served as mediators of the effects. Third, not all pain complaints had the same degree of homogeneity within the same category. As an example, this survey did not differentiate between different forms of arthritis (e.g., osteoarthritis vs. rheumatoid arthritis) that have different etiopathogeneses. Fourth, the survey did not inquire about doses or dosing schedules in the case of microdosing, which may limit the generalisability of the results. On the other hand, most psychedelic users in naturalistic settings are usually unaware of the dose they

are taking, therefore subjective effects were preferred as indicators of the dose range. Fifth, the study does not allow to properly distinguish the effects of psychedelics on paroxysmal pain from that of persisting pain, two categories of conditions that require different clinical management. Also, relevant especially for migraine and TTH, a measure of the frequency of attacks in the attacks per week or per month timescale was not included. Sixth, medications were not presented in separate lists based on them being abortives or preventives so this may not appropriately capture the effects of preventives like antidepressants that are not supposed to bring acute relief in case of a pain episode. Seventh, albeit participants had the opportunity to enter conventional medications other than those listed, gabapentinoids were not included in the medications list. Considering that they are the first-line treatment for sciatica prevention, analyses may not have been able to capture the comparison of obtained relief between such drug categories and psychedelics. Finally, the sample size for each condition was limited.

Conclusions

In conclusion, the present study suggests that psychedelics may hold value in the treatment of certain CP conditions. More specifically, participants reported that full doses seem to achieve better perceived results in pain relief than microdosing while microdosing's effectiveness seems comparable to that of

conventional medication according to survey participants. Future research should focus on building clinical studies that would allow for controlling doses, dosing schedules, and the monitoring of both biological and psychological measures to paint a clearer picture of the causal mechanisms that may lead to analgesic effects.

References

Alciati, A., Sgiarovello, P., Atzeni, F., & Sarzi-Puttini, P. (2012). Psychiatric problems in fibromyalgia: clinical and neurobiological links between mood disorders and fibromyalgia. *Reumatismo*, 64(4), 268-274.

Almutairi, K., Nossent, J., Preen, D., Keen, H., & Inderjeeth, C. (2021). The global prevalence of rheumatoid arthritis: A meta-analysis based on a systematic review. *Rheumatology International*, 41(5), 863–877. <https://doi.org/10.1007/s00296-020-04731-0>

Andersson, M., Persson, M., & Kjellgren, A. (2017). Psychoactive substances as a last resort—a qualitative study of self-treatment of migraine and cluster headaches. *Harm Reduction Journal*, 14, 1-10.

Applbaum, E., & Lichtbroun, A. (2019). Novel Sjögren's autoantibodies found in fibromyalgia patients with sicca and/or xerostomia. *Autoimmunity Reviews*, 18(2), 199-202.

Bendtsen, L., Evers, S., Linde, M., Mitsikostas, D. D., Sandrini, G., & Schoenen, J. E. F. N. S. (2010). EFNS guideline on the treatment of tension-type headache—Report of an EFNS task force. *European Journal of Neurology*, 17(11), 1318-1325.

Bonnelle, V., Smith, W. J., Mason, N. L., Cavarra, M., Kryskow, P., Kuypers, K. P., Ramaekers, J. G. & Feilding, A. (2022). Analgesic potential of macrodoses and microdoses of classical psychedelics in chronic pain sufferers: a population survey. *British Journal of Pain*, 16(6), 619-631.

Burke, A. L., Mathias, J. L., & Denson, L. A. (2015). Psychological functioning of people living with chronic pain: A meta-analytic review. *British Journal of Clinical Psychology*, 54(3), 345-360.

Casale, R., Boccia, G., Symeonidou, Z., Atzeni, F., Batticciotto, A., Salaffi, F., Sarzi-Puttini, P., Brustio, P. R. & Rainoldi, A. (2019). Neuromuscular efficiency in fibromyalgia is improved by hyperbaric oxygen therapy: looking inside muscles by means of surface electromyography. *Clinical and Experimental Rheumatology*, 37(1, suppl. 116), S75-S80.

Casale, R., Sarzi-Puttini, P., Botto, R., Alciati, A., Batticciotto, A., Marotto, D., & Torta, R. (2019). Fibromyalgia and the concept of resilience. *Clinical and Experimental Rheumatology*, 37(116), 105-113.

Castellanos, J. P., Woolley, C., Bruno, K. A., Zeidan, F., Halberstadt, A., & Furnish, T. (2020). Chronic pain and psychedelics: a review and proposed mechanism of action. *Regional Anesthesia & Pain Medicine*, 45(7), 486-494.

Cavarra, M., Falzone, A., Ramaekers, J. G., Kuypers, K. P., & Mento, C. (2022). Psychedelic-Assisted Psychotherapy—A Systematic Review of Associated Psychological Interventions. *Frontiers in Psychology*, 2996.

Charles, A. (2013). The evolution of a migraine attack—a review of recent evidence. *Headache. The Journal of Head and Face Pain*, 53(2), 413-419.

Charles, A. (2018). The pathophysiology of migraine: implications for clinical management. *The Lancet Neurology*, 17(2), 174-182.

Chen, B., He, Y., Xia, L., Guo, L. L., & Zheng, J. L. (2016). Cortical plasticity between the pain and pain-free phases in patients with episodic tension-type headache. *The Journal of Headache and Pain*, 17, 1-6.

Chen, W. T., Chou, K.-H., Lee, P.-L., Hsiao, F.-J., Niddam, D. M., Lai, K.-L., Fuh, J.-L., Lin, C.-P., & Wang, S.-J. (2018). Comparison of gray matter volume between migraine and “strict-criteria” tension-type headache. *The Journal of Headache and Pain*, 19, 1-11.

Chinn, S., Caldwell, W., & Gritsenko, K. (2016). Fibromyalgia pathogenesis and treatment options update. *Current Pain and Headache Reports*, 20, 1-10.

Clos-Garcia, M., Andrés-Marin, N., Fernández-Eulate, G., Abecia, L., Lavín, J. L., van Liempd, S., Cabrera, D., Royo, F., Valero, A., Errazquin, N., Vega, M. C. G., Govillard, L., Tackett, M. R., Tejada, G., González, E., Anguita, J., Bujanda, L., Orcasitas, A. M. C., Aransay, A. M., Maíz, O., López de Munain, A., Falcón-Pérez, J. M. (2019). Gut microbiome and serum metabolome analyses identify molecular biomarkers and altered glutamate metabolism in fibromyalgia. *EBioMedicine*, 46, 499–511. <https://doi.org/10.1016/j.ebiom.2019.07.031>

Cohen, S. P., Vase, L., & Hooten, W. M. (2021). Chronic pain: an update on burden, best practices, and new advances. *The Lancet*, 397(10289), 2082-2097.

Costantini, A., Giorgi, R., D'Agostino, S., & Pala, M. I. (2013). High-dose thiamine improves the symptoms of Friedreich's ataxia. *Case Reports*, 2013, bcr2013009424.

Coussens, N. P., Sittampalam, G. S., Jonson, S. G., Hall, M. D., Gorby, H. E., Tamiz, A. P., McManus, O. B., Felder, C. C., & Rasmussen, K. (2019). The opioid crisis and the future of addiction and pain therapeutics. *Journal of Pharmacology and Experimental Therapeutics*, 371(2), 396-408.

Davis, D., Maini, K., & Vasudevan, A. (2022). Sciatica. In StatPearls. StatPearls Publishing. <http://www.ncbi.nlm.nih.gov/books/NBK507908/>

De Vos, C. M., Mason, N. L., & Kuypers, K. P. (2021). Psychedelics and neuroplasticity: a systematic review unraveling the biological underpinnings of psychedelics. *Frontiers in Psychiatry*, 12, 724606.

Dueñas, M., Ojeda, B., Salazar, A., Mico, J. A., & Failde, I. (2016). A review of chronic pain impact on patients, their social environment and the health care system. *Journal of Pain Research*, 457-467.

Dworkin, R. H., Anderson, B. T., Andrews, N., Edwards, R. R., Grob, C. S., Ross, S., Satterthwaite, T. D., & Strain, E. C. (2022). If the doors of perception were cleansed, would chronic pain be relieved? Evaluating the benefits and risks of psychedelics. *The Journal of Pain*, 23(10), 1666-1679.

Edinoff, A. N., Fort, J. M., Singh, C., Wagner, S. E., Rodriguez, J. R., Johnson, C. A., Cornett, E. M., Murnane, K. S., Kaye, A. M., & Kaye, A. D. (2022). Alternative Options for Complex, Recurrent Pain States Using Cannabinoids, Psilocybin, and Ketamine: A Narrative Review of Clinical Evidence. *Neurology international*, 14(2), 423-436.

Elman, I., Pustilnik, A., & Borsook, D. (2022). Beating pain with psychedelics: Matter over mind?. *Neuroscience & Biobehavioral Reviews*, 134, 104482.

Els, C., Jackson, T. D., Kunyk, D., Lappi, V. G., Sonnenberg, B., Hagtvedt, R., Sharma, S., Kolahdooz, F., & Straube, S. (2017). Adverse events associated with medium-and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews*, (10).

Fanciullacci, M., Bene, E. D., Franchi, G., & Sicuteri, F. (1977). Phantom limb pain: Sub-hallucinogenic treatment with Lysergic Acid Diethylamide (LSD-25). *Headache: The Journal of Head and Face Pain*, 17(3), 118-119.

Finnerup, N. B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R. H., Gilron, I., Haanpää, M., Hansson, P., Jensen, T. S., Kamerman, P. R., Lund, K., Moore, A., Raja, S. N., Rice, A. S. C., Rowbotham, M., Sena, E., Siddall, P., Smith, B. H., & Wallace, M. (2015). Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *The Lancet Neurology*, 14(2), 162-173.

Flanagan, T. W., & Nichols, C. D. (2018). Psychedelics as anti-inflammatory agents. *International Review of Psychiatry*, 30(4), 363-375.

Galloway, J. B., & Scott, D. L. (2017). Management of common types of arthritis in older adults. In J.-P. Michel, B. L. Beattie, F. C. Martin, & J. Walston (Eds.), *Oxford Textbook of Geriatric Medicine*. Oxford, UK: Oxford University Press. <https://doi.org/10.1093/med/9780198701590.003.0075>

Gelonch Rosinach, O., Garolera i Freixa, M., Valls Marsal, J., Castellà, G., Varela, O., Rosselló Aubach, L., & Pifarré Paredero, J. (2018). The effect of depressive symptoms on cognition in patients with fibromyalgia. *Plos One*, 2018, vol. 13, núm. 7, e0200057.

Glynos, N. G., Pierce, J., Davis, A. K., McAfee, J., & Boehnke, K. F. (2022). Knowledge, perceptions, and use of psychedelics among individuals with fibromyalgia. *Journal of Psychoactive Drugs*, 1-12.

Goldberg, D. S., & McGee, S. J. (2011). Pain as a global public health priority. *BMC Public Health*, 11(1), 1-5.

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, 30(12), 1181-1197.

Pahnke, W. N., Kurland, A. A., Goodman, L. E., & Richards, W. A. (1969). LSD-assisted psychotherapy with terminal cancer patients. *Current psychiatric therapies*, 9, 144-152.

Hall, A. M., Kamper, S. J., Maher, C. G., Latimer, J., Ferreira, M. L., & Nicholas, M. K. (2011). Symptoms of depression and stress mediate the effect of pain on disability. *Pain*, 152(5), 1044-1051.

Hann, K. E., & McCracken, L. M. (2014). A systematic review of randomized controlled trials of Acceptance and Commitment Therapy for adults with chronic pain: Outcome domains, design quality, and efficacy. *Journal of Contextual Behavioral science*, 3(4), 217-227.

Häuser, W., Petzke, F., & Fitzcharles, M. A. (2018). Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management—An overview of systematic reviews. *European Journal of Pain*, 22(3), 455-470.

Haut, S. R., Bigal, M. E., & Lipton, R. B. (2006). Chronic disorders with episodic manifestations: focus on epilepsy and migraine. *The Lancet Neurology*, 5(2), 148-157.

Olesen, J., Bendtsen, L., & Goadsby, P. (2018). Comité de clasificación de la cefalea de la Sociedad Internacional de Cefaleas

(IHS), III edición de la clasificación internacional de las cefaleas. *Cephalalgia*, 38(1), 1-211.

Hoffman, B. M., Papas, R. K., Chatkoff, D. K., & Kerns, R. D. (2007). Meta-analysis of psychological interventions for chronic low back pain. *Health Psychology*, 26(1), 1.

Jensen, R. K., Kongsted, A., Kjaer, P., & Koes, B. (2019). Diagnosis and treatment of sciatica. *BMJ*, 367.

Jesus, C. A., Feder, D., & Peres, M. F. (2013). The role of vitamin D in pathophysiology and treatment of fibromyalgia. *Current Pain and Headache Reports*, 17, 1-7.

Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The prevalence of chronic pain in United States adults: results of an Internet-based survey. *The Journal of Pain*, 11(11), 1230-1239.

Kast, E. (1967). Attenuation of anticipation: a therapeutic use of lysergic acid diethylamide. *Psychiatric Quarterly*, 41(4), 646-657.

Kast, E. C., & Collins, V. J. (1964). Study of lysergic acid diethylamide as an analgesic agent. *Anesthesia & Analgesia*, 43(3), 285-291.

Kettner, H., Rosas, F. E., Timmermann, C., Kärtner, L., Carhart-Harris, R. L., & Roseman, L. (2021). Psychedelic communitas: intersubjective experience during psychedelic group sessions predicts enduring changes in psychological wellbeing and social connectedness. *Frontiers in Pharmacology*, 234.

Kirsch, I. (2018). Response Expectancy and the Placebo Effect *International Review of Neurobiology*, Vol. 138.

Konstantinou, K., Dunn, K. M., Ogollah, R., Vogel, S., & Hay, E. M. (2015). Characteristics of patients with low back and leg pain seeking treatment in primary care: baseline results from the ATLAS cohort study. *BMC Musculoskeletal Disorders*, 16(1), 1-11.

Kuypers, K. P. (2020). The therapeutic potential of microdosing psychedelics in depression. *Therapeutic Advances in Psychopharmacology*, 10, 2045125320950567.

Kuypers, K. P., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., ... & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology*, 33(9), 1039-1057.

Leistad, R. B., Sand, T., Westgaard, R. H., Nilsen, K. B., & Stovner, L. J. (2006). Stress-induced pain and muscle activity in patients with migraine and tension-type headache. *Cephalalgia*, 26(1), 64-73.

Lima, L. O. de, Zicarelli, C. A. M., Matsumura, A. S., Moroti-Perugini, L. R., Teixeira, D. de C., Fernandes, K. B. P., Perrucini, P. D. de O., & Poli-Frederico, R. C. (2020). Lower limb muscle strength and serotonin receptor gene polymorphism as factors associated in women with fibromyalgia. *Advances in Rheumatology*, 59.

Littlejohn, G. (2015). Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. *Nature Reviews Rheumatology*, 11(11), 639-648.

Long, H., Liu, Q., Yin, H., Wang, K., Diao, N., Zhang, Y., Lin, J., & Guo, A. (2022). Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. *Arthritis & Rheumatology*, 74(7), 1172-1183.

Lorenz, J., Grasedyck, K., & Bromm, B. (1996). Middle and long latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia syndrome. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, 100(2), 165-168.

Marmura, M. J., Silberstein, S. D., & Schwedt, T. J. (2015). The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache: The Journal of Head and Face Pain*, 55(1), 3-20.

Mascarenhas, R. O., Souza, M. B., Oliveira, M. X., Lacerda, A. C., Mendonça, V. A., Henschke, N., & Oliveira, V. C. (2021). Association of therapies with reduced pain and improved quality of life in patients with fibromyalgia: a systematic review and meta-analysis. *JAMA Internal Medicine*, 181(1), 104-112.

Jeng, C. J., Chuang, L., & Shen, J. (2014). A comparison of progestogens or oral contraceptives and gonadotropin-releasing hormone agonists for the treatment of endometriosis: a systematic review. *Expert Opinion on Pharmacotherapy*, 15(6), 767-773.

Okusanya, B. O., Lott, B. E., Ehiri, J., McClelland, J., & Rosales, C. (2022). Medical cannabis for the treatment of migraine in adults: a review of the evidence. *Frontiers in Neurology*, 13.

Pednekar, D. D., Amin, M. R., Azgomi, H. F., Aschbacher, K., Crofford, L. J., & Faghieh, R. T. (2019, July). A system theoretic investigation of cortisol dysregulation in fibromyalgia patients with chronic fatigue. In 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) (pp. 6896-6901). IEEE.

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., ... & Kuypers, K. P. (2021). A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of Psychopharmacology*, 35(4), 398-405.

Regland, B., Forsmark, S., Halaouate, L., Matousek, M., Peilot, B., Zachrisson, O., & Gottfries, C. G. (2015). Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia. *PLoS One*, 10(4), e0124648.

Reiff, C. M., Richman, E. E., Nemeroff, C. B., Carpenter, L. L., Widge, A. S., Rodriguez, C. I., Kalin, N. H., McDonald, W. M., & the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research. (2020). Psychedelics and psychedelic-assisted psychotherapy. *American Journal of Psychiatry*, 177(5), 391-410.

Sakarya, S. T., Akyol, Y., Bedir, A., & Canturk, F. (2011). The relationship between serum antioxidant vitamins, magnesium levels, and clinical parameters in patients with primary fibromyalgia syndrome. *Clinical Rheumatology*, 30, 1039-1043.

Schindler, E. A., Gottschalk, C. H., Weil, M. J., Shapiro, R. E., Wright, D. A., & Sewell, R. A. (2015). Indoleamine hallucinogens in cluster headache: results of the clusterbusters medication use survey. *Journal of Psychoactive Drugs*, 47(5), 372-381.

Schindler, E. A. D., Sewell, R. A., Gottschalk, C. H., Luddy, C., Flynn, L. T., Lindsey, H., Pittman, B. P., Cozzi, N. V., & D'Souza, D. C. (2021). Exploratory controlled study of the migraine-suppressing effects of psilocybin. *Neurotherapeutics*, 18(1), 534-543.

Schwartz, B. S., Stewart, W. F., Simon, D., & Lipton, R. B. (1998). Epidemiology of tension-type headache. *JAMA*, 279(5), 381-383.

Sewell, R. A., Halpern, J. H., & Pope, H. G. (2006). Response of cluster headache to psilocybin and LSD. *Neurology*, 66(12), 1920-1922.

Smith, H. S., Harris, R. E., & Clauw, D. J. (2011). Fibromyalgia. In *Essentials of Pain Medicine E-book* (pp. 345–350). Elsevier Health Sciences.

Song, T. J., Cho, S. J., Kim, W. J., Yang, K. I., Yun, C. H., & Chu, M. K. (2016). Anxiety and depression in tension-type headache: a population-based study. *PloS One*, 11(10), e0165316.

Soussan, C., & Kjellgren, A. (2016). The users of novel psychoactive substances: online survey about their characteristics, attitudes and motivations. *International Journal of Drug Policy*, 32, 77-84.

Steel, S. J., Robertson, C. E., & Whealy, M. A. (2021). Current understanding of the pathophysiology and approach to tension-type headache. *Current Neurology and Neuroscience Reports*, 21, 1-12.

Stewart, W. F., Shechter, A., & Lipton, R. B. (1994). Migraine heterogeneity. Disability, pain intensity, and attack frequency and duration. *Neurology*, 44(6 Suppl 4), S24-39.

Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, 17(11), 954-976.

Theis, K. A., Murphy, L., Hootman, J. M., & Wilkie, R. (2013). Social participation restriction among US adults with arthritis: a population-based study using the International Classification of Functioning, Disability and Health. *Arthritis Care & Research*, 65(7), 1059-1069.

van Elk, M., & Yaden, D. B. (2022). Pharmacological, neural, and psychological mechanisms underlying psychedelics: A critical review. *Neuroscience & Biobehavioral Reviews*, 104793.

Voon, P., Karamouzian, M., & Kerr, T. (2017). Chronic pain and opioid misuse: A review of reviews. *Substance Abuse Treatment, Prevention, and Policy*, 12(1), 36. <https://doi.org/10.1186/s13011-017-0120-7>

Vos, T., Allen, C., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, A., Carter, A., Casey, D. C., Charlson, F. J., Chen, A. Z., Coggeshall, M., Cornaby, L., Dandona, L., Dicker, D. J., Dilegge, T., Erskine, H. E., Ferrari, A. J., Fitzmaurice, C., Fleming, T., ... Murray, C. J. L. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, 388(10053), 1545-1602.

Williams, E. M., Walker, R. J., Faith, T., & Egede, L. E. (2017). The impact of arthritis and joint pain on individual healthcare expenditures: findings from the Medical Expenditure Panel Survey (MEPS), 2011. *Arthritis Research & Therapy*, 19(1), 1-8.

Williams, A. C. d. C., Fisher, E., Hearn, L., & Eccleston, C. (2020). Psychological therapies for the management of chronic pain (excluding headache) in adults (Review). *Cochrane Database of Systematic Reviews*, (8), Art. No.: CD007407. <https://doi.org/10.1002/14651858.CD007407.pub4>

Wolfe, F., Clauw, D. J., Fitzcharles, M.-A., Goldenberg, D. L., Katz, R. S., Mease, P., Russell, A. S., Russell, I. J., Winfield, J. B., & Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care & Research*, 62(5), 600-610.

Wolfe, F., Walitt, B., Perrot, S., Rasker, J. J., & Häuser, W. (2018). Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. *PloS One*, 13(9), e0203755.

Yekkirala, A. S., Roberson, D. P., Bean, B. P., & Woolf, C. J. (2017). Breaking barriers to novel analgesic drug development. *Nature Reviews Drug Discovery*, 16(8), 545-564.

Zia, F. Z., Baumann, M. H., Belouin, S. J., Dworkin, R. H., Ghauri, M. H., Hendricks, P. S., Henningfield, J. E., Lanier, R. K., Ross, S., & Berger, A. (2023). Are psychedelic medicines the reset for chronic pain? Preliminary findings and research needs. *Neuropharmacology*, 233, 109528. <https://doi.org/10.1016/j.neuropharm.2023.109528>

Chapter 3

A placebo-controlled study of the effects of LSD microdosing (15 µg) on pain perception in healthy volunteers

Cavarra M., Hutten N.R.P.W., Schepers J., Mason N.L, Theunissen E.L., Liechti M. E., Kuypers K.P.C., Bonnelle V., Feilding A., Ramaekers J.G.

This study investigated the potential analgesic effects of an LSD microdosing regimen on pain tolerance and subjective pain perception in healthy participants. Utilizing a randomised, placebo-controlled design, participants received 15 µg of LSD or placebo over four administrations. Pain tolerance was assessed using the Cold Pressor Task, and self-reported painfulness, unpleasantness, and stress were recorded in addition. No analgesic effects of LSD were found on any of these measures in the whole sample. However, after removal of a sizeable fraction of participants that displayed plateau pain tolerance at baseline and throughout treatment, marginal but significant effects of LSD were found on measures of pain tolerance and unpleasantness as indicated by Treatment x Test day interactions. Visual inspection suggested that LSD increased pain tolerance and reduced unpleasantness after

the first dose. Such trends were not visible after the fourth dose. Under LSD, variations in blood pressure correlated positively with variations in pain tolerance, but these did not account for the Treatment x Test day interactions as shown by covariance analysis. Subjective experience under LSD did not correlate with pain tolerance. The present study provided marginal evidence for analgesic effects of 15µg LSD. It is conceivable that the current LSD dose was at or just below the threshold dose that is needed to produce a solid and consistent analgesic effect. Future research with larger samples and higher doses is recommended to further elucidate LSD's analgesic effects and its application in clinical settings.

Submitted to: British Journal of Pain

Introduction

Classic psychedelics such as psilocybin and lysergic acid diethylamide (LSD) are substances that cause marked changes to perception, cognition, and emotion through their agonist action on serotonergic receptors ([de Vos et al., 2021](#)). These substances are used recreationally ([Erritzoe et al., 2019](#)) and have come to the attention of clinical researchers for their potential in the treatment of several psychiatric conditions such as treatment-resistant depression (TRD) ([Carhart-Harris et al., 2018](#)), addiction ([Garcia-Romeu et al., 2014](#); [Johnson et al., 2017](#)), anxiety and depression in end-of-life settings ([Griffiths et al., 2016](#); [Grob et al., 2011](#); [Holze et al., 2023](#)).

Another area of potential clinical interest is the treatment of painful conditions that are refractory to current therapies. Retrospective studies show that individuals suffering from cluster headaches report improvements in their pain levels as a consequence of psychedelic use in both psychedelic ('high') and lower doses ([Schindler et al., 2015](#); [Sewell et al., 2006](#)). More recently, a survey study in chronic pain patients showed that the reported improvements associated with psychedelic use were greater than those achieved with conventional pain medication ([Bonnelle et al., 2022](#)). Another survey study conducted among users of low doses of psychedelics found higher effectiveness in the treatment of a variety of medical complaints compared to conventional medication

[\(Hutten et al., 2019\)](#). Supporting evidence was also provided by a recent exploratory, small sample (n=10), double-blind, placebo-controlled, crossover study in migraine patients. Compared to baseline, participants who took two doses of psilocybin (10 mg) two weeks apart had a significantly greater reduction in the number of attacks than that experienced with placebo in the two weeks after the last administration [\(Schindler et al., 2021\)](#).

The analgesic potential of LSD in end-of-life settings and in phantom limb pain was already explored and confirmed during the first wave of psychedelic research [\(Fanciullacci et al., 1977; Grof et al., 1973; Kast, 1967; Kast & Collins, 1963\)](#). A more recent controlled study in healthy participants showed that a low LSD dose (20 µg), led to increased tolerance to experimentally-induced pain and reduced self-ratings of pain and unpleasantness, compared to placebo, without severely disrupting consciousness [\(Ramaekers et al., 2021\)](#). Given this finding, it could be argued that low, non-hallucinogenic doses of psychedelics may be more suited to treat chronic pain as preserving a state of consciousness that allows for normal daily functioning is of primary importance in the pain patient population.

Repeated administration of low doses of psychedelics (microdosing) to self-medicate is practised by individuals suffering from a variety of mental health and medical conditions [\(Bonnelle et al., 2022; Hutten et al., 2019; Kuypers et al., 2019\)](#). Still, no

placebo-controlled study has been conducted to test the analgesic potential of a repeated microdosing regimen. In the present study, the aim was to test the potential of an LSD microdosing schedule to improve pain tolerance and perception in a sample of healthy participants. The above-cited controlled study testing the analgesic effects of LSD in a sample of healthy volunteers found that 20 µg of LSD was effective in reducing pain while 10 µg was not ([Ramaekers et al., 2021](#)). Since 20 µg also produced noticeable (albeit small) changes in consciousness ([Ramaekers et al., 2021](#)), a dose of 15 µg LSD was chosen to minimise subjective, psychedelic effects while aiming to retain analgesic effects. Finally, considering that variations in BP and HR and subjective effects were previously associated with pain experience ([Ramaekers et al., 2021](#)), we sought to test whether such relationships also existed within the present sample.

Materials and Methods

Participants

In total, 48 (24 female, 24 male) healthy adults (18 to 65 years of age; mean age 36.9, SD=16.6), were recruited from the general population. Inclusion criteria were: proficient use of the English language, no use of psychotropic medications, previous use of a psychedelic drug but not in the past 3 months, and a body mass index between 18 and 28. Exclusion criteria included past history of

drug addiction, use of psychoactive substances during the study, previous experience of serious side effects to psychedelic drugs, pregnancy or lactation, history of psychiatric disorders, and family history of psychotic disorders. Levels of education included high-school degree (N=17, 35%), university bachelor's degree (N=13, 27%), university master's degree (N=15, 31%), and Ph.D. (N=3, 6%). Most of the participants were university students (N=26, 54%), while the others were employed (N=17, 35%), or not working (N=5, 10%).

Lifetime psychedelic use (i.e., used a psychedelic at least once) was reported by 28 (58.3%) participants and 14 (29%) of them used a psychedelic at least once in the past year. In this context, the use of psilocybin was reported most frequently (n=18, 38%) followed by LSD (n=9, 19%) and ayahuasca (n=3, 6%). The use of alcohol was reported by 45 (94%) participants. Use of cannabis (n=33, 69%), cocaine (n=18, 38%), ecstasy (n=10, 21%), amphetamines (n=8, 17%), and other substances (n=5, 10%) was also reported.

All participants were informed about the procedures and risks associated with the study before signing the informed consent. The study was conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Fortaleza (Brazil, October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and was approved by the Academic Hospital and University's

Medical Ethics committee. All participants were fully informed about all procedures, possible adverse reactions, legal rights and responsibilities, expected benefits, and their right to voluntary termination without consequences. The study was registered in the Netherlands Trial Register (Trial NL70508.068.19). Participants in the study were financially compensated for the time they invested .

Study design and treatments

The study was conducted according to a randomised, placebo-controlled, between-subjects design, including two treatment groups; one receiving microdoses of LSD (15 µg) two times a week for 2 consecutive weeks (4 doses in total) and one receiving a placebo according to the same treatment schedule. LSD base (15 µg) was formulated as an oral solution in 0.6mL 96% ethanol, according to GMP ([Holze et al., 2019](#)). Placebo consisted of a 0.6mL ethanol solution only. Treatments were administered at 10 AM.

Procedure

Prior to the first study day, participants were medically screened and, if healthy, were then familiarised with tests and study procedures. Participants were instructed to refrain from drug use (≥ 7 days) and alcohol use (≥ 24 h). They were also instructed not to consume caffeinated or alcoholic beverages on test days and the

evening before, and to arrive well-rested at the test facility. On arrival, participants were screened for the presence of drugs (THC, opiates, cocaine, amphetamine, MDMA) in urine and for alcohol. An additional pregnancy test was given to female participants. If all tests were found to be negative, participants were allowed to proceed.

The study consisted of a baseline, 4 treatment days, and a follow-up over the course of 4 weeks (Figure 1). Participants received 15 µg of LSD on treatment days 1 to 4. At baseline, treatment day 1, treatment day 4, and follow-up, data on pain was collected at 2 time points (1h and 5h after administration) so that, in case we detected an analgesic effect of LSD we would be able to evaluate its acute duration. Vital signs (BP and HR), and subjective drug experience were also collected multiple times (Figure 1). On test days, the participants remained at our facilities for 6.5 hours. On treatment days 2 and 3, only subjective drug experience data were collected and the participants stayed in the lab for 1.5 hours.

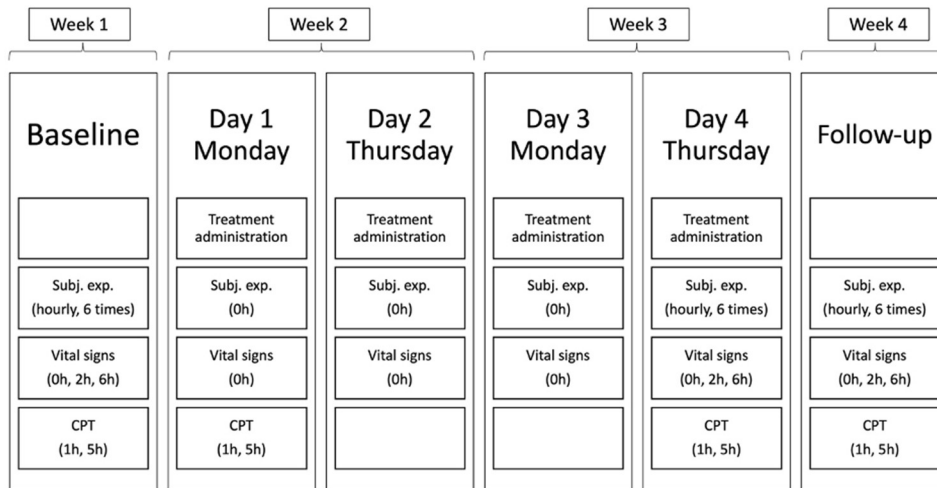


Figure 1. Graphical representation of study days and activities. Test days lasted 6.5-hours except for test days 2 and 3 which lasted 1.5 hours.

Pain measures

The Cold Pressor Task (CPT) ([Smeets et al., 2012](#)) was used to induce a painful sensation. Participants were asked to keep the dominant hand submerged in cold water (about 3°C) for as long as possible. They were informed that the procedure could be painful and that they could stop at any time. The maximum duration of immersion (pain tolerance) was set at 180 seconds and in case the maximum time was reached, the researcher would instruct participants to remove their hand from the water. Participants were

unaware of the time limit and the duration of immersion was used as a measure of pain tolerance. Immediately after the end of the test, participants were asked to rate painfulness, unpleasantness, and stress during the task on a visual analogue scale (VAS). They were presented as 100 mm long horizontal lines marked with “not at all” on the left and “extremely” on the right. CPT was performed at 1h and 5h post-treatment on test days 1 and 4, and at similar timepoints at baseline and follow-up.

Subjective experience

Beginning at baseline and then every hour, participants were presented with a VAS asking to rate the extent to which they felt “under the influence”. It was presented as a 100 mm long horizontal line marked with “not at all” on the left and “extremely” on the right. Subjective experience was recorded once every hour.

LSD concentration in blood plasma

Blood samples were taken 2 hours after treatment administration. The blood was centrifuged, and pipetted plasma was frozen at -20°C until analysis. LSD and O-H-LSD concentrations were determined using ultra high-performance liquid chromatography-tandem mass spectrometry (UHPLC–MS/MS) as previously described ([Holze et al., 2019](#)).

Statistical analysis

To investigate the effects of treatment on pain outcome measures, statistical analysis was conducted with IBM SPSS Statistics 26 using a Linear Mixed Models (LMM) analysis. The model included Fixed effects for Treatment (placebo vs LSD), Test day (baseline, treatment day 1, treatment day 4, follow-up), Time (1h and 5h post-administration) and Treatment x Test day, Treatment x Time, Test day x Time, and Treatment x Test day x Time interactions. A random subject intercept was included to account for the dependency between the two daily measurements (i.e., factor Time) and an unstructured covariance matrix was estimated to account for dependencies between Test days. Given that the study included a baseline measurement, statistical evidence for a treatment effect would appear as a significant Treatment x Test day interaction or as a Treatment x Test day x Time interaction. If these significant interaction effects were detected, further single-degree-of-freedom interaction contrasts were conducted.

Since variations in BP and HR were shown to have an effect on pain experience in a previous study with acute doses of LSD ([Ramaekers et al., 2021](#)), we ran additional LMM analyses including vital signs measures as covariates to test their potential role as mediators, in case evidence for an effect of treatment was found. Since the intensity of subjective effects of LSD was also shown to be associated with pain perception ([Ramaekers et al., 2021](#)), we

ran additional LMM analyses including the under the influence score as covariate to test its potential role as mediator. To test the association between vital signs and pain measures, correlation analyses between systolic BP, diastolic BP, HR and pain tolerance were run. Additionally, canonical correlation analyses between a first canonical variable composed of measures of vital signs (i.e., systolic BP, diastolic BP and HR) and a second one composed of all pain measures (i.e., pain tolerance, painfulness, unpleasantness and stress) were also run.

To test the effects of 15 mg of LSD on subjective experience, we ran LMM analyses on a model that included Fixed effects for Treatment (placebo vs LSD), Test day (baseline, treatment day 1, treatment day 4, follow-up), Time (0h to 5h post-administration) and Treatment x Test day, Treatment x Time, Test day x Time, and Treatment x Test day x Time interactions and the under the influence scale as dependent variable. A random subject intercept was included to account for the dependency between the daily measurements (i.e., factor Time) and an unstructured covariance matrix was estimated to account for dependencies between Test days. In case a significant Treatment x Time interaction was found, the same LMM was run on data obtained on treatment day 1 and 4 to test for potential effects related to LSD tolerance building.

Results

The following section will report the main findings related to the study's hypothesis. For the complete results refer to Supplemental Tables S1 and S2.

Whole sample

LSD concentration in blood plasma

Mean (SD) concentrations of LSD 2 h after dose 1 and dose 4 were 302 (105) pg/mL and 326 (117) pg/mL, respectively. Mean (SD) concentrations of O-H-LSD after dose 1 and dose 4 were 17 (7.2) pg/ml and 17 (4.9) pg/mL, respectively.

Pain Tolerance

Means (SE) for pain tolerance, unpleasantness, pain intensity and stress are shown in Figure 2. LMM revealed no significant Treatment x Test day ($p=.198$) nor a Treatment x Test day x Time interaction ($p=.959$) on pain tolerance (Figure 2 a). For the detailed results refer to Supplemental Table S1.

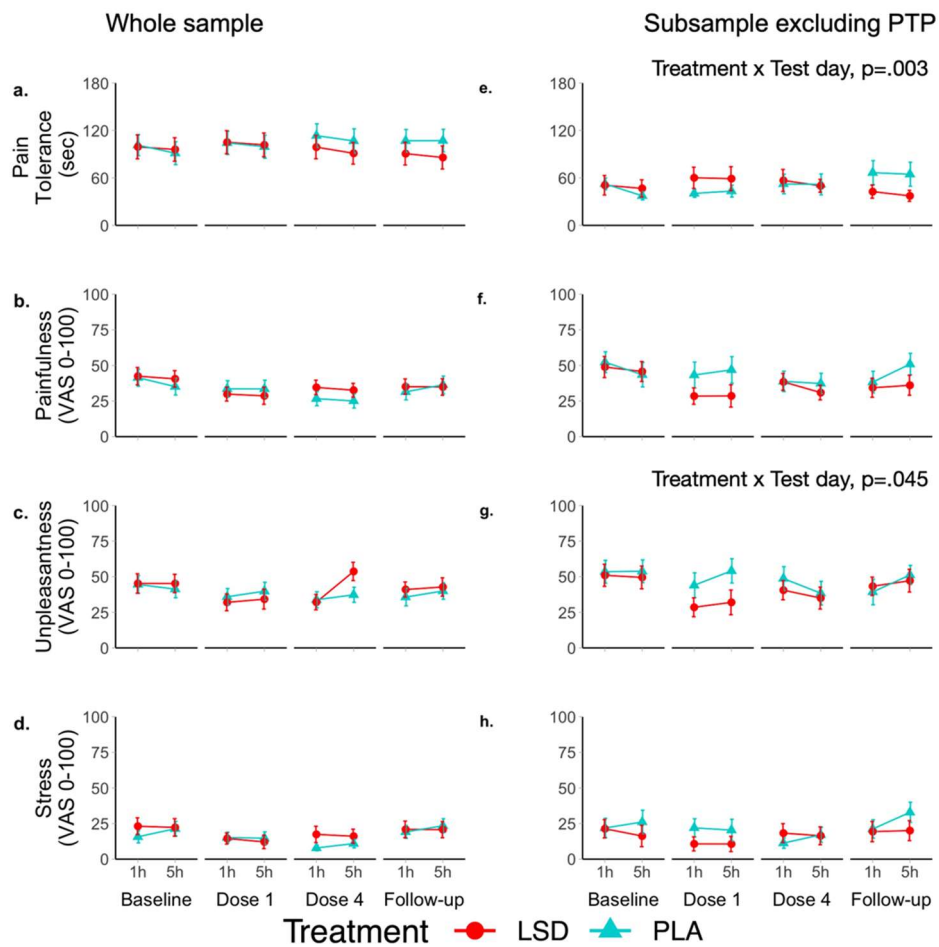


Figure 2. Mean pain (SE) tolerance (a,e) and subjective ratings of painfulness (b,f), unpleasantness (c,g), and stress (d,h) as a function of treatment group, test day and time in the whole sample and in the subsample obtained by excluding pain resistant volunteers.

Self-rated pain, unpleasantness, and stress

LMM revealed no significant Treatment x Test day nor a Treatment x Test day x Time interaction on self-reported painfulness ($p = .085$ and $p = .762$ respectively) (figure 2 b) unpleasantness ($p = .370$ and $p = .812$ respectively) (figure 2 d) and stress ($p = .096$ and $p = .941$ respectively).

Detailed results are provided Supplemental Table S1.

Selected sample without “pain-resistant” participants

Pain tolerance

An unexpectedly high proportion of participants (42%) was able to sustain the cold water immersion for 180s, which is the task’s maximal duration. Since such a ceiling effect may have masked potential Treatment effects, analyses were repeated after excluding pain-resistant participants, that is, participants in both treatment groups who displayed plateau pain tolerance at baseline ($n=18$) or during 3 out of 4 (75%) CPT administrations ($n=2$) on treatment days. After this filtering, a subsample of $n=28$ (14 placebo; 14 LSD) volunteers remained.

LMM revealed a significant Treatment x Test day interaction ($F(3, 55)=5.196$, $p=.003$) (Figure 2 e). Single degree of freedom

interaction contrasts revealed that the effect was mainly driven by the difference observed at follow-up ($\beta=29.47$, $p= .013$). For the detailed results refer to Supplemental Table S2.

Self-rated pain, unpleasantness, and stress

LMM revealed no significant Treatment x Test day interaction nor Treatment x Test day x Time interaction on self-reported painfulness ($p= .328$ and $p= .521$ respectively) (Figure 2 f) and stress ($p= .138$ and $p= .592$ respectively) (Figure 2 g). A significant Treatment x Test day interaction on unpleasantness ($F(3, 42)=2.925$, $p= .045$) was observed (Figure 2 h). As a follow-up, single degree of freedom interaction contrasts were conducted but none of these comparisons turned out significant.

Detailed results are provided Supplemental Table S2.

Relationship between vital signs and pain measures

Variations in vital signs measures (Figure 3) all occurred within the normal range. LMM analyses showed a significant Treatment x Test day interaction on systolic BP ($F(5, 234)= 2.7$; $P=.022$).

Spearman correlation revealed a significant association of pain tolerance with systolic ($\rho_{214}=.305$, $p=.000$) and diastolic ($\rho_{214}=.297$, $p=.000$) BP in the LSD group (Figure 4). Canonical

correlation between measures of BP and HR on the one hand and pain measures on the other indicated a significant positive association ($F(44, 343)=1.94$, $p=.001$, canonical $r=.41$) that explained 16% of the total variance. More specifically, the higher HR and BP, the stronger the analgesic effect.

The Treatment x Test day interactions in the LMM on measures of pain tolerance ($F(3, 55)=4.845$, $p=.005$) and unpleasantness($F(3, 41)=2.949$, $p=.044$), however remained significant after the inclusion of vital signs measures as covariates.

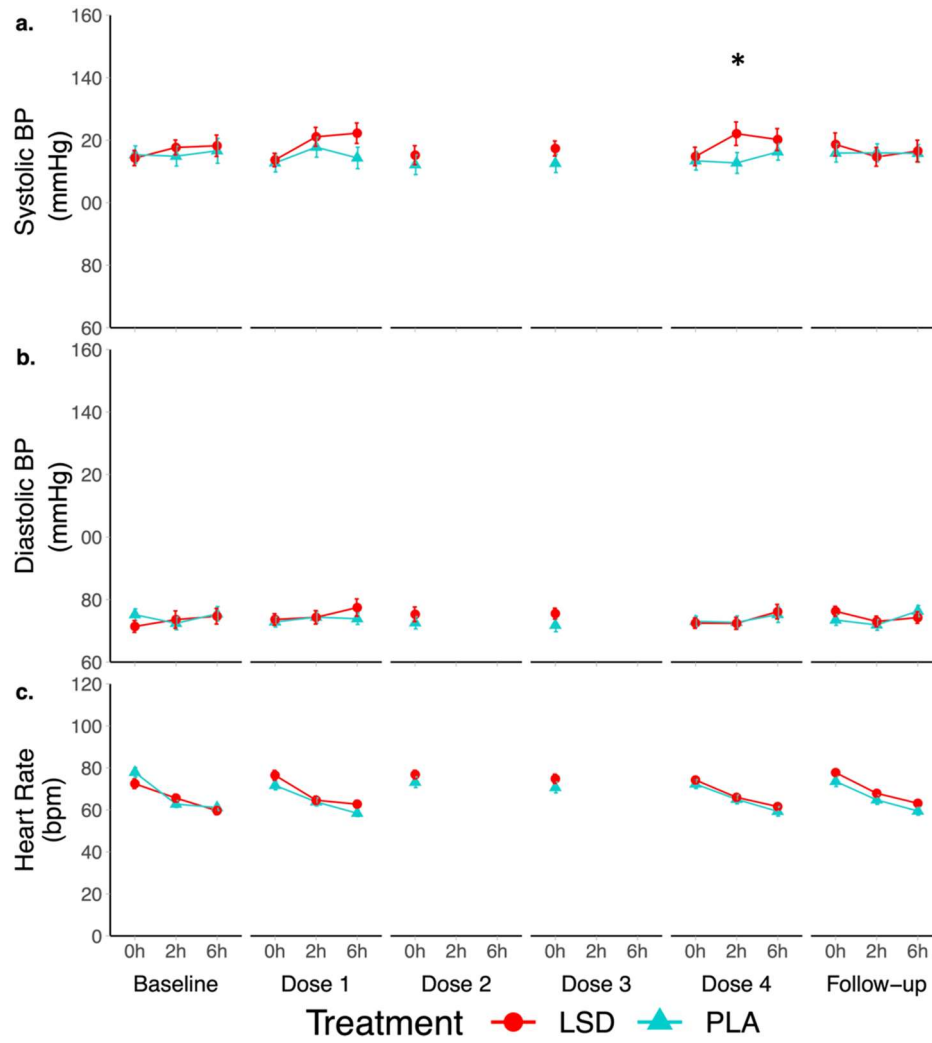


Figure 3. Mean systolic blood pressure (a), diastolic blood pressure (b) and heart rate (c) each test day, administration time and treatment group.

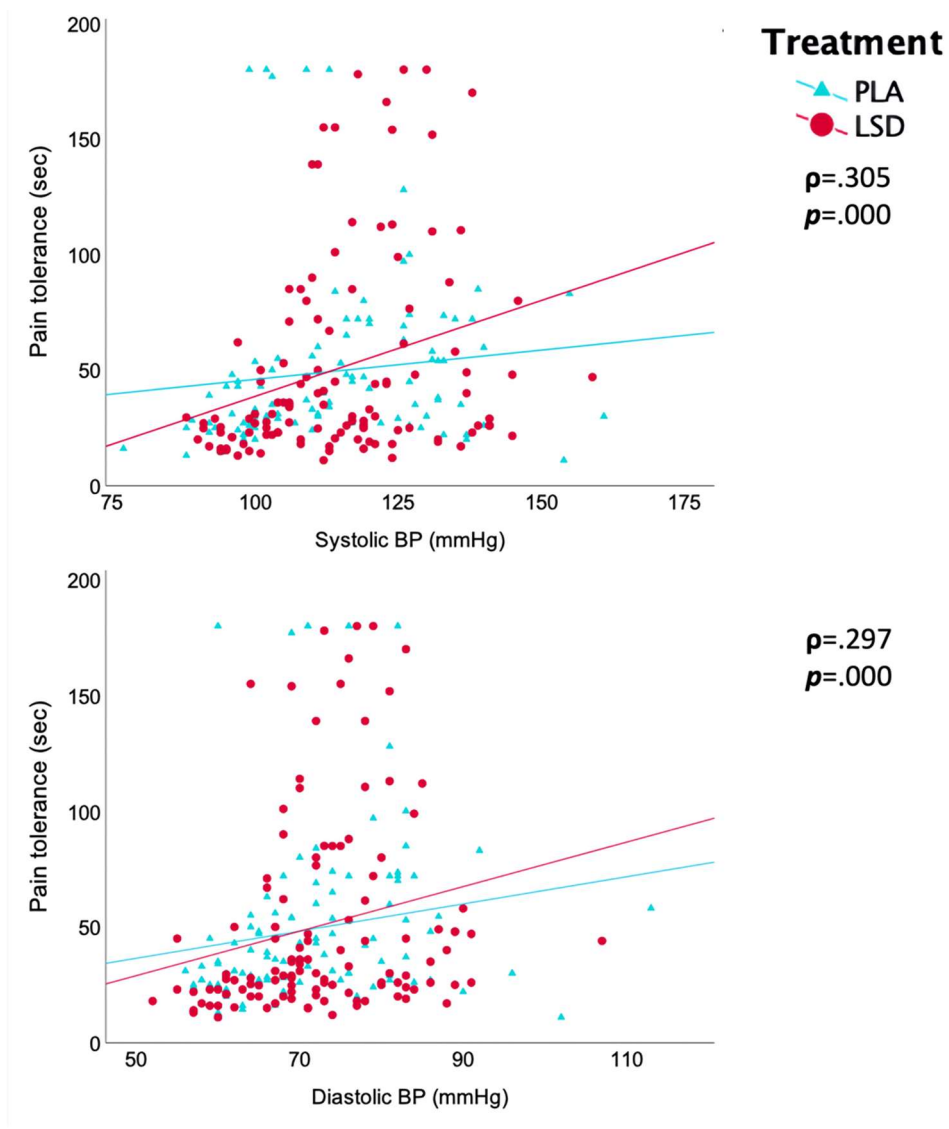


Figure 4. Correlations between systolic/diastolic blood pressure and pain tolerance in both treatment groups.

Subjective experience in the whole sample

Mean under the influence scores are shown in Figure 5. LMM analyses showed a significant Treatment x Test day interaction on the under the influence score ($F(3, 95)=3.43, p=.02$). An additional LMM utilising only data from treatment day 1 and 4 was ran to test for potential tolerance effects. This analysis only yielded a significant main effect of treatment ($F(1, 48)=4.125, p=.048$), suggesting the absence of tolerance. Under the influence scores did not correlate with measures of pain. The Treatment x Test day interactions in the LMM on measures of pain tolerance ($F(3, 55)=5.186, p=.003$) and unpleasantness ($F(3, 42)=2.974, p=.042$) remained significant even after the inclusion of under the influence scores as covariates.

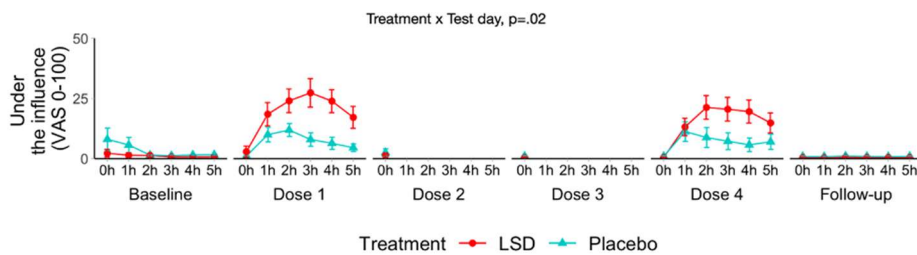


Figure 5. Mean (SE) ratings of 'under the influence' as a function of treatment, day of treatment and time to administration (** $p<.001$).

Discussion

This study set out to investigate the effects of a LSD microdosing regimen on pain tolerance and perception in a sample of healthy volunteers. It was hypothesised that microdosing with 15 µg LSD would improve pain tolerance and subjective ratings of painfulness, unpleasantness and stress in response to a pain-evoking task. We found only marginal evidence supporting this expectation in that Treatment x Test day interactions were found for measures of pain tolerance and unpleasantness in a selected subsample.

Initial analyses showed no significant differences between LSD and placebo groups on any of the pain measures in the whole sample. After removing a large fraction of participants that displayed plateau pain tolerance at baseline and throughout treatment (42%), a smaller subsample remained in which 2 indications of a treatment effect emerged as indicated by Treatment x Test day interactions. These interactions pertained to the measures of pain tolerance and unpleasantness. Visual inspection of these parameters suggested increased pain tolerance and decreased ratings of unpleasantness after the first dose of LSD, as compared to placebo. Moreover, there appeared to be an increase in pain tolerance in the placebo group during follow-up. Simple interaction contrasts, however, were generally non-significant, except at follow-up. It is likely, however, that the selected subsample was too small to provide sufficient statistical power to consistently detect treatment differences with

simple contrasts. It should be noted that no ‘trends’ were apparent on the fourth dosing day. This might suggest that participants had developed some tolerance (Yamauchi et al., 2006) to the ‘mild’ analgesic effects that were trending after the first dose. Alternatively, this might suggest that 15 µg of LSD is close to a threshold dose at which mild signs of analgesic effects might appear in some but not in others, to degrees that may fluctuate over time.

Systolic blood pressure slightly increased in the LSD group but remained within the normal range. This finding is in line with earlier studies that demonstrated LSD safety at low doses ([Bershad et al., 2019](#), [Ramaekers et al., 2020](#), [Hutten et al., 2020](#)). Present findings also showed a positive correlation between LSD-induced variations in blood pressure and pain tolerance, suggesting that changes in blood pressure might account for the Treatment x Test day interactions observed for pain tolerance and unpleasantness. The possibility that increased blood pressure may induce analgesia was already suggested in both animal and human studies ([Bruehl et al., 2010](#); [Ghione, 1996](#); [Saccò et al., 2013](#)) and while the underlying mechanism is still unclear, it may be related to the stimulation of baroreceptors and consequent activation of descending inhibitory pathways from the dorsal raphe nucleus leading to serotonin release ([De Gregorio et al., 2016](#)). However, the addition of blood pressure as a covariate to the LMM models of pain tolerance and unpleasantness did not alter the significance of the original

108

Treatment x Test day interactions. This indicates that the interaction effect was not mediated by blood pressure, and represent a direct effect of LSD on pain experience.

LSD also produced slight but noticeable subjective effects. Yet, subjective ratings of drug experience did not alter the main Treatment x Test day interactions observed for pain tolerance and unpleasantness when added to the LMM model as a covariate. This suggests that these main interactions were not mediated by subjective effects, but rather by a pharmacological mechanism of action. Still, the current dose might have been too low to exert a solid analgesic effect. A previous study demonstrated analgesic effects of LSD in healthy volunteers at a 20 µg but not at a 10 µg dose, suggesting that the minimal dose for inducing a reliable analgesic effect may be closer to 20 µg of LSD or higher ([Ramaekers et al., 2021](#)). At such doses, LSD may be used as a novel therapeutic tool for chronic pain patients. This possibility is especially intriguing if we consider that its side effects profile seems more favourable compared to other widely prescribed drugs such as opioids ([Kertesz & Gordon, 2019](#)). While chronic pain can develop from acute pain, the processes underlying the two are different ([Feizerfan & Sheh, 2015](#)). Considering the role that changes in both the peripheral and central nervous systems play in establishing central sensitisation ([Feizerfan & Sheh, 2015](#)), psychedelics such as LSD may hold promise in light of their psychoplastogen action ([Castellanos et al., 2020](#); [de Vos et al.,](#)

[2021; Ly et al., 2018](#)). Future research should investigate their therapeutic potential in clinical studies with patients suffering from chronic pain conditions. Effectiveness of LSD and other psychedelics could be tested in a therapeutic microdosing schedule format in which low doses are administered repeatedly over the course of multiple weeks to assess generalisability of earlier analgesic findings in healthy volunteers ([Ramaekers et al., 2021](#)) and to determine whether analgesic effects sustain over time or are subject to tolerance ([Yamauchi et al., 2006](#)). Considering the multifactorial nature of chronic pain ([Bervers et al., 2016](#)) and the fact that many patients may obtain relief by engaging in psychotherapy ([Ehde et al., 2014](#)) or other psychological pain management interventions such as mindfulness ([Hilton et al., 2017](#)) and hypnosis ([Adachi et al., 2014](#)), further research may also investigate the effects microdosing schemes in the context of psychedelic-assisted (psycho)therapy ([Cavarra et al., 2022](#)).

The present study is limited by the fact that a large number of volunteers displayed plateau pain tolerance in the CPT at baseline and throughout treatment, which made it impossible to assess the potential of LSD to induce improvements in this group. Removal of these participants from the statistical analysis resulted in a smaller subsample of participants that showed some marginal improvement in subjective experience of pain, but this subsample may have resulted in an underpowered design for studying the full scope of analgesic effects. Future research should make sure to adopt

experimental procedures that screen suitability of participants for CPT measures at screening ([Reddy et al., 2012](#)) in order to avoid ceiling effects during treatments.

In sum, the present study provided marginal support for the analgesic effect of 15 µg LSD during a repeated dosing regimen. Future research with larger samples, in patient populations and with higher doses is recommended to further elucidate LSD's analgesic effects and its application in clinical settings.

References

Adachi, T., Fujino, H., Nakae, A., Mashimo, T., & Sasaki, J. (2014). A Meta-Analysis of Hypnosis for Chronic Pain Problems: A Comparison Between Hypnosis, Standard Care, and Other Psychological Interventions. *International Journal of Clinical and Experimental Hypnosis*, 62(1), 1–28. <https://doi.org/10.1080/00207144.2013.841471>

Bershad, A. K., Schepers, S. T., Bremmer, M. P., Lee, R., & de Wit, H. (2019). Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers. *Biological Psychiatry*, 86(10), 792–800. <https://doi.org/10.1016/j.biopsych.2019.05.019>

Bervers, K., Watts, L., Kishino, N., & Gatchel, R. (2016). The Biopsychosocial Model of the Assessment, Prevention, and

Treatment of Chronic Pain. *US Neurology*, 12, 98.
<https://doi.org/10.17925/USN.2016.12.02.98>

Bonnelle, V., Smith, W. J., Mason, N. L., Cavarra, M., Kryskow, P., Kuypers, K. P. C., Ramaekers, J. G., & Feilding, A. (2022). Analgesic potential of macrodoses and microdoses of classical psychedelics in chronic pain sufferers: A population survey. *British Journal of Pain*, 13.

Bruehl, S., Burns, J. W., Chung, O. Y., Magid, E., Chont, M., Gilliam, W., Matsuura, J., Somar, K., Goodlad, J. K., Stone, K., & Cairl, H. (2010). Hypoalgesia associated with elevated resting blood pressure: Evidence for endogenous opioid involvement. *Journal of Behavioral Medicine*, 33(2), 168–176.
<https://doi.org/10.1007/s10865-009-9241-4>

Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., & Nutt, D. J. (2018). Psilocybin with psychological support for treatment-resistant depression: Six-month follow-up. *Psychopharmacology*, 235(2), 399–408.
<https://doi.org/10.1007/s00213-017-4771-x>

Castellanos, J. P., Woolley, C., Bruno, K. A., Zeidan, F., Halberstadt, A., & Furnish, T. (2020). Chronic pain and

psychedelics: A review and proposed mechanism of action. *Regional Anesthesia & Pain Medicine*, 45(7), 486–494. <https://doi.org/10.1136/rapm-2020-101273>

Cavarra, M., Falzone, A., Ramaekers, J. G., Kuypers, K. P. C., & Mento, C. (2022). Psychedelic-Assisted Psychotherapy—A Systematic Review of Associated Psychological Interventions. *Frontiers in Psychology*, 13. <https://www.frontiersin.org/article/10.3389/fpsyg.2022.887255>

De Gregorio, D., Posa, L., Ochoa-Sanchez, R., McLaughlin, R., Maione, S., Comai, S., & Gobbi, G. (2016). The hallucinogen d-lysergic diethylamide (LSD) decreases dopamine firing activity through 5-HT1A, D2 and TAAR1 receptors. *Pharmacological Research*, 113, 81–91. <https://doi.org/10.1016/j.phrs.2016.08.022>

de Vos, C. M. H., Mason, N. L., & Kuypers, K. P. C. (2021). Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics. *Frontiers in Psychiatry*, 12, 724606. <https://doi.org/10.3389/fpsyg.2021.724606>

Ehde, D. M., Dillworth, T. M., & Turner, J. A. (2014). Cognitive-behavioral therapy for individuals with chronic pain: Efficacy, innovations, and directions for research. *American Psychologist*, 69(2), 153–166. <https://doi.org/10.1037/a0035747>

Erritzoe, D., Smith, J., Fisher, P. M., Carhart-Harris, R., Frokjaer, V. G., & Knudsen, G. M. (2019). Recreational use of psychedelics is associated with elevated personality trait openness: Exploration of associations with brain serotonin markers. *Journal of Psychopharmacology*, 33(9), 1068–1075. <https://doi.org/10.1177/0269881119827891>

Fanciullacci, M., Bene, E. D., Franchi, G., & Sicuteri, F. (1977). Phantom Limb Pain: Sub-Hallucinogenic Treatment With Lysergic Acid Diethylamide (LSD-25). *Headache: The Journal of Head and Face Pain*, 17(3), 118–119. <https://doi.org/10.1111/j.1526-4610.1977.hed1703118.x>

Feizerfan, A., & Sheh, G. (2015). Transition from acute to chronic pain. *Continuing Education in Anaesthesia Critical Care & Pain*, 15(2), 98–102. <https://doi.org/10.1093/bjaceaccp/mku044>

Garcia-Romeu, A., Griffiths, R. R., & Johnson, M. W. (2014). Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. *Current Drug Abuse Reviews*, 7(3), 157–164. <https://doi.org/10.2174/1874473708666150107121331>

Ghione, S. (1996). Hypertension-Associated Hypalgesia. *Hypertension*, 28(3), 494–504. <https://doi.org/10.1161/01.HYP.28.3.494>

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, 30(12), 1181–1197. <https://doi.org/10.1177/0269881116675513>

Grob, C. S., Danforth, A. L., Chopra, G. S., Hagerty, M., McKay, C. R., Halberstadt, A. L., & Greer, G. R. (2011). Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. *Archives of General Psychiatry*, 68(1), 71. <https://doi.org/10.1001/archgenpsychiatry.2010.116>

Grof, S., Goodman, L. E., Richards, W. A., & Kurland, A. A. (1973). LSD-Assisted Psychotherapy in Patients with Terminal Cancer. *International Pharmacopsychiatry*, 8(3), 129–144. <https://doi.org/10.1159/000467984>

Hilton, L., Hempel, S., Ewing, B. A., Apaydin, E., Xenakis, L., Newberry, S., Colaiaco, B., Maher, A. R., Shanman, R. M., Sorbero, M. E., & Maglione, M. A. (2017). Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. *Annals of Behavioral Medicine*, 51(2), 199–213. <https://doi.org/10.1007/s12160-016-9844-2>

Holze, F., Duthaler, U., Vizeli, P., Müller, F., Borgwardt, S., & Liechti, M. E. (2019). Pharmacokinetics and subjective effects of a novel oral LSD formulation in healthy subjects. *British Journal of Clinical Pharmacology*, 85(7), 1474–1483. <https://doi.org/10.1111/bcp.13918>

Holze, F., Gasser, P., Müller, F., Dolder, P. C., & Liechti, M. E. (2023). Lysergic Acid Diethylamide–Assisted Therapy in Patients With Anxiety With and Without a Life-Threatening Illness: A Randomized, Double-Blind, Placebo-Controlled Phase II Study. *Biological Psychiatry*, 93(3), 215–223. <https://doi.org/10.1016/j.biopsych.2022.08.025>

Hutten, N. R. P. W., Mason, N. L., Dolder, P. C., & Kuypers, K. P. C. (2019). Self-Rated Effectiveness of Microdosing With Psychedelics for Mental and Physical Health Problems Among Microdosers. *Frontiers in Psychiatry*, 10, 672. <https://doi.org/10.3389/fpsy.2019.00672>

Hutten, N. R. P. W., Mason, N. L., Dolder, P. C., Theunissen, E. L., Holze, F., Liechti, M. E., Feilding, A., Ramaekers, J. G., & Kuypers, K. P. C. (2020). Mood and cognition after administration of low LSD doses in healthy volunteers: A placebo controlled dose-effect finding study. *European Neuropsychopharmacology*, 41, 81–91. <https://doi.org/10.1016/j.euroneuro.2020.10.002>

Johnson, M. W., Garcia-Romeu, A., & Griffiths, R. R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. *The American Journal of Drug and Alcohol Abuse*, 43(1), 55–60. <https://doi.org/10.3109/00952990.2016.1170135>

Kast, E. C. (1967). Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide. *The Psychiatric Quarterly*, 41(4), 646–657. <https://doi.org/10.1007/BF01575629>

Kast, E. C., & Collins, V. J. (1963). Study of Lysergic Acid Diethylamide as an Analgesic Agent. *Anesthesia and Analgesia*, 43(3), 285–291.

Kertesz, S. G., & Gordon, A. J. (2019). A crisis of opioids and the limits of prescription control: United States. *Addiction*, 114(1), 169–180. <https://doi.org/10.1111/add.14394>

Kuypers, K. P. C., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Pani, L., Soula, A., & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology*, 33(9), 1039–1057. <https://doi.org/10.1177/0269881119857204>

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Soltanzadeh Zarandi, S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-

McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics Promote Structural and Functional Neural Plasticity. *Cell Reports*, 23(11), 3170–3182. <https://doi.org/10.1016/j.celrep.2018.05.022>

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., Liechti, M. E., Feilding, A., & Kuypers, K. P. C. (2021). A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of Psychopharmacology*, 35(4), 398–405. <https://doi.org/10.1177/0269881120940937>

Reddy, K. S. kumar, Naidu, M. U. R., Rani, P. U., & Rao, T. R. K. (2012). Human experimental pain models: A review of standardized methods in drug development. *Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences*, 17(6), 587–595.

Saccò, M., Meschi, M., Regolisti, G., Detrenis, S., Bianchi, L., Bertorelli, M., Pioli, S., Magnano, A., Spagnoli, F., Giuri, P. G., Fiaccadori, E., & Caiazza, A. (2013). The Relationship Between Blood Pressure and Pain. *The Journal of Clinical Hypertension*, 15(8), 600–605. <https://doi.org/10.1111/jch.12145>

Schindler, E. A. D., Gottschalk, C. H., Weil, M. J., Shapiro, R. E., Wright, D. A., & Sewell, R. A. (2015). Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters Medication Use

Survey. *Journal of Psychoactive Drugs*, 47(5), 372–381.
<https://doi.org/10.1080/02791072.2015.1107664>

Schindler, E. A. D., Sewell, R. A., Gottschalk, C. H., Luddy, C., Flynn, L. T., Lindsey, H., Pittman, B. P., Cozzi, N. V., & D'Souza, D. C. (2021). Exploratory Controlled Study of the Migraine-Suppressing Effects of Psilocybin. *Neurotherapeutics*, 18(1), 534–543. <https://doi.org/10.1007/s13311-020-00962-y>

Schlereth, T., & Birklein, F. (2008). The sympathetic nervous system and pain. *Neuromolecular Medicine*, 10(3), 141–147. <https://doi.org/10.1007/s12017-007-8018-6>

Sewell, R. A., Halpern, J. H., & Pope, H. G. (2006). Response of cluster headache to psilocybin and LSD. *Neurology*, 66(12), 1920–1922. <https://doi.org/10.1212/01.wnl.0000219761.05466.43>

Smeets, T., Cornelisse, S., Quaedflieg, C. W. E. M., Meyer, T., Jelacic, M., & Merckelbach, H. (2012). Introducing the Maastricht Acute Stress Test (MAST): A quick and non-invasive approach to elicit robust autonomic and glucocorticoid stress responses. *Psychoneuroendocrinology*, 37(12), 1998–2008. <https://doi.org/10.1016/j.psyneuen.2012.04.012>

Yamauchi, M., Miyara, T., Matsushima, T., & Imanishi, T. (2006). Desensitization of 5-HT_{2A} receptor function by chronic

administration of selective serotonin reuptake inhibitors. *Brain Research*, 1067(1), 164–169.
<https://doi.org/10.1016/j.brainres.2005.10.075>

Supplementary Materials

Tables

Supplemental Table S1. LMM results for ratings of painfulness, unpleasantness, and stress on the whole sample: coefficients, df, and p-values.

Pain tolerance (sec)			
	F	df	p
Treatment	0.167	1, 48	.685
Treatment x Test day	1.585	3, 96	.198
Treatment x Time	0.054	3, 96	.817
Treatment x Test day x Time	0.101	3, 96	.959

Painfulness rating VAS (0 - 100)			
Treatment	0	1, 47	.986
Treatment x Test day	2.284	3, 87	.085
Treatment x Time	0.023	3, 88	.879
Treatment x Test day x Time	0.388	3, 88	.762
Unpleasantness rating VAS (0 - 100)			
Treatment	0.001	1, 48	.978
Treatment x Test day	1.062	3, 83	.370
Treatment x Time	1.027	3, 84	.318
Treatment x Test day x Time	0.318	3, 84	.812
Stress rating VAS (0 - 100)			
Treatment	0.113	1, 47	.739
Treatment x Test day	2.182	3, 86	.096

Treatment x Time	5.943	3, 86	.021
Treatment x Test day x Time	0.132	3, 86	.941

Supplemental Table S2. LMM results for ratings of painfulness, unpleasantness and stress on the selected sample: coefficient, df and p-values.

Pain tolerance (sec)			
	F	df	p
Treatment	0	1, 28	.984
Treatment x Test day	5.196	3, 55	.003
Treatment x Time	0.019	3, 56	.892
Treatment x Test day x Time	0.424	3, 56	.737
Painfulness rating VAS (0 - 100)			
Treatment	1.202	1, 26	.283
Treatment x Test day	1.178	3, 49	.328
Treatment x Time	1.105	3, 50	.304
Treatment x Test day x Time	0.761	3, 50	.521

Unpleasantness rating VAS (0 - 100)			
Treatment	0.79	1, 28	.382
Treatment x Test day	2.925	3, 42	.045
Treatment x Time	0.433	3, 42	.517
Treatment x Test day x Time	0.082	3, 42	.970
Stress rating VAS (0 - 100)			
Treatment	0.592	1, 28	.448
Treatment x Test day	1.918	3, 50	.138
Treatment x Time	3.944	3, 50	.069
Treatment x Test day x Time	0.641	3, 50	.592

Chapter 4

Psychedelic-Assisted Psychotherapy— A Systematic Review of Associated Psychological Interventions

Cavarra M., Falzone A., Ramaekers J. G., Kuypers Kim P. C., Mento C.

Modern clinical research on psychedelics is generating interesting outcomes in a wide array of clinical conditions when psychedelic-assisted psychotherapy is delivered to appropriately screened participants and in controlled settings. Still, a number of patients relapse or are less responsive to such treatments. Individual and contextual factors (i.e., set and setting) seem to play a role in shaping the psychedelic experience and in determining clinical outcomes. These findings, coupled with data from literature on the effectiveness of psychotherapy, frame the therapeutic context as a potential moderator of clinical efficacy, highlighting the need to investigate how to functionally employ environmental and relational factors. In this review, we performed a structured search through two databases (i.e., PubMed/Medline and Scopus) to identify records of clinical studies on psychedelics which used and described a structured associated psychotherapeutic intervention.

The aim is to construct a picture of what models of psychedelic-assisted psychotherapy are currently adopted in clinical research and to report on their clinical outcomes. Ad-hoc and adapted therapeutic methods were identified. Common principles, points of divergence and future directions are highlighted and discussed with special attention toward therapeutic stance, degree of directiveness and the potential suggestive effects of information provided to patients.

Published in: Frontiers in Psychology, 2022; 13:887255

Introduction

We are currently witnessing a growth in interest in psychedelic substances and their potential use for the promotion of mental health (Nutt et al., 2020). After an early phase set between the '50s and the '70s of the previous century when applications were being tested in psychotherapy (Abramson, 1960; Grof et al., 1973) and, more specifically, for the treatment of neuroses (Crocket et al., 1963), alcoholism (Smith, 1958; Leuner, 1967), end-of-life anxiety (Kast, 1967; Grof et al., 1973; Grof and Halifax, 1978) and chronic pain (Fanciullacci et al., 1977), psychedelic research almost got to a standstill. While modern clinical studies are obtaining promising results in some of the most difficult to treat psychiatric populations (for recent reviews see (Wheeler and Dyer, 2020; Andersen et al., 2021), a portion of patients do not seem to benefit from psychedelic-

assisted therapies (PAT) or end up relapsing (Nutt et al., 2020). While this issue may arise in part due to the limited number of sessions that are admissible in a clinical trial (Grof, 2016), such variability urges researchers to find ways to ways to increase response rates and the stability of clinical improvement.

Several authors hypothesised that the therapeutic effects of psychedelics cannot be explained by their pharmacological properties only (a model referred to as psychedelic chemotherapy; Pahnke et al., 1970) but rather that individual ('set') and contextual ('setting') factors play a pivotal role in some of the observed clinical gains with psychedelics (Leary, 1961; Pahnke et al., 1970; Hartogsohn, 2017). Classic psychedelics seem to increase neuroplasticity (Ly et al., 2018; de Vos et al., 2021; Hutten et al., 2021) and environmental sensitivity or suggestibility (Carhart-Harris et al., 2015; Carhart-Harris and Nutt, 2017; Carhart-Harris and Friston, 2019) both during the dosing session itself and in the following days (Majić et al., 2015). In a way, psychedelics seem to open a window of flexibility (Kuypers et al., 2016) that may relax higher level priors and increase sensitivity to bottom-up information (Carhart-Harris et al., 2018b; Carhart-Harris and Friston, 2019). In the context of psychotherapy, this could imply that patients are offered a window of opportunity to become more effective in modifying rigid behaviours, thought patterns, and emotional reactions and that psychotherapy itself must be carefully honed to take advantage of this fertile state.

Despite evidence and theoretical reasons supporting the importance of set and setting (Carhart-Harris et al., 2018b), we still lack a model identifying the specific factors on which to focus to maximise the effectiveness of PAT. Modern research still has to tackle the delicate matter of clearly describing the role of the therapist during dosing sessions and in the wider context of PAT. Current suggestions emphasise the importance of building rapport, “letting go” of resistance, promoting openness and reliance on unconscious processes in the context of a non-directive relationship (Johnson et al., 2008; Richards, 2015; Roseman et al., 2018). In the light of such considerations, the current review aims at collecting and describing the psychotherapeutic models that have been already used in clinical studies to provide a picture of current practices adopted by clinicians and researchers in the context of clinical research. Outcomes of such studies will be reported and common principles, points of divergence and future directions will be highlighted and discussed. All models will be presented using the name that the respective authors used to refer to them.

Methods

We performed the following searches in Pubmed/Medline and Scopus databases: “psychedelic AND assisted AND psychotherapy”, “substance name AND assisted AND psychotherapy”, “psychedelic AND enhanced AND psychotherapy”, “substance name AND enhanced AND psychotherapy”. We

restricted our search to clinical studies (i.e., which involved patients suffering from a psychiatric condition or psychological distress), written in English, which made use of a psychedelic or empathogen substance (i.e., LSD, psilocybin, MDMA, ayahuasca, ketamine, DMT, 5-MeO-DMT, mescaline), which contained a description of a structured associated psychological intervention and were published before September 2021. A total of 15.959 articles resulted from the search and 15.470 unique articles were identified. Two of the authors (M.C., C.M.) independently screened the articles to determine eligibility and when judgment differed discussions were held until consensus was reached. After screening titles and abstracts according to the above-mentioned criteria, 15.079 were excluded and 391 retained. Forty-five articles were retained after full-text screening, 7 were added after an iterative reference list search and 3 were added thanks to comments received during the paper review process. The resulting number of included papers is therefore 55 (Figure 1). We decided to organise the psychotherapeutic models in two main categories: ad-hoc therapeutic models (i.e., models that were originally devised for use with psychedelics compounds) and adapted models (i.e., models that were devised in a more “traditional” psychotherapeutic setting and were later adopted for PAT).

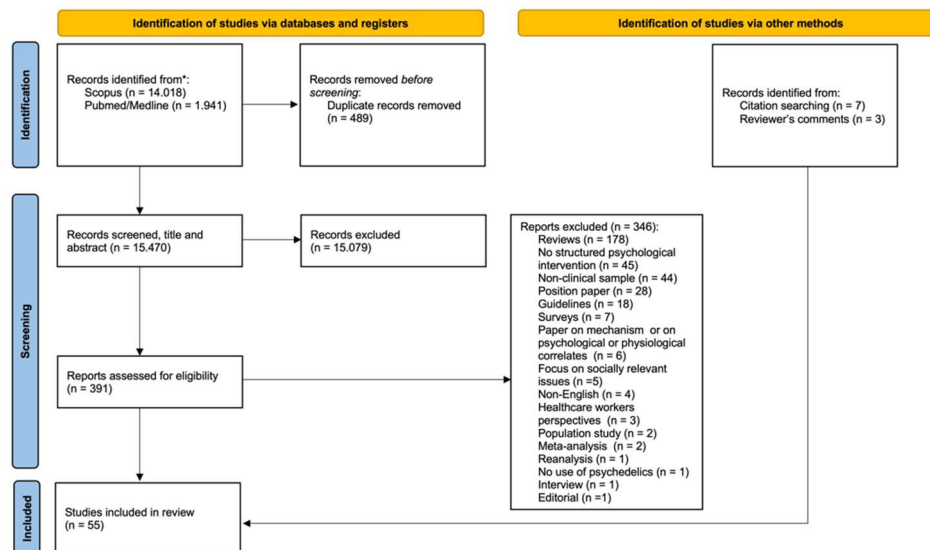


Figure 1. PRISMA flowchart

Results

We identified a total of 55 papers (Table 1) that reporting the results of a total of 26 studies in which the following therapeutic models were used: Cognitive Behavioural Conjoint Therapy (CBCT; n=3; 1 open-label study), Cognitive Behavioural Therapy (CBT; n=7; 1 case study, 2 open-label, 1 RCT), Human Relations Training Laboratory Group (HRTL; n=1; 1 open-label), Ketamine Enhanced Therapy/Ketamine Psychedelic Therapy (KET/KPT; n=5; 1 case study, 1 case series, 1 observational study, 2 RCTs), Medication-Assisted Psychotherapy (MAP; n=7, 1 RCT, 1 pre-post, 1 case series), MDMA-Assisted Therapy plus Mindfulness Skills Training (MDMA-ATM; n=1; 1 open-label), MDMA-Assisted Psychotherapy

(MDMA-AP; n=14; 1 case series; 1 small sample within-subjects, 3 RCTs, 1 pooled analysis of 6 RCTs), Motivational Enhancement Therapy (MET; n=5; 1 open-label, 1 pilot RCT), Preparation Support Integration (PSI; (n=7; 1 open-label), Supportive-Expressive Group Therapy (SEGT; n=3; 1 open-label), Trauma Interventions using Mindfulness Extinction and Reconsolidation (TIMBER; n=2; 1 RCT). In this pool, PAT's efficacy was tested in TRD, depression, opioid addiction, tobacco addiction, PTSD, AUD, issues related to life-threatening conditions, social anxiety in autistic adults and demoralisation in HIV-infected patients. Notably, 45 papers were excluded because they did not provide a description of a structured psychological intervention. This was the case for studies which did not employ psychotherapy (e.g., Palhano-Fontes et al., 2019), used generic labels (e.g., Müller et al., 2020) or referenced guidelines for safety (e.g., Griffiths et al., 2016).

Ad-hoc Therapeutic models

Ketamine Enhanced Psychotherapy

Our search identified 5 studies investigating the efficacy of different versions of KET: 1 case series on AUD (Kolp et al., 2006), 1 case study on end-of-life distress (Kolp et al., 2007), 2 RCTs on heroin dependence (Krupitsky et al., 2002; Kolp et al., 2007), and 1 observational study on AUD (Krupitsky and Grinenko, 1997).

KEP, also sometimes referred as KPT or Ketamine Assisted Psychotherapy, was first introduced (albeit with a different name: affective contra attribution) in a 1992 clinical study on the treatment of alcoholism. It made use of other drugs in addition to ketamine (i.e., aethimizol and bemegrade) during a single drug session to enhance emotional experiences and promote the consolidation of memories (Krupitsky et al., 1992; Krupitsky and Grinenko, 1997). Despite ketamine being a dissociative agent that does not act on 5-HT2A receptors as classical psychedelics do (Green et al., 2011), the authors often refer to it and to the experiences it produces as psychedelic. The model was developed in an attempt to integrate the establishment of aversive associations with a previously appetitive stimulus (i.e., aversive conditioning) with the shift in attitudes toward alcohol that psychedelic therapy seemed to promote in earlier studies (Krupitsky et al., 1992). In a later review article (Krupitsky and Grinenko, 1997), the authors describe this three-step approach in greater detail.

In the first stage, preparation is carried out over a three-month period and aims at preparing patients by informing them about the different states of consciousness they will experience. An exploration of personal motives and goals for treatment along with beliefs concerning the cause of the disease is also carried out. Establishing positive expectations toward the outcome of the experience is considered another important part of preparation together with the co-construction of the therapeutic myth; the latter

refers to a therapeutic narrative constructed by the therapist and the patient that could describe and explain the patients' suffering and hint at ways to resolve it (Frank and Frank, 1993). The session should integrate elements from the patients' personal life in an atmosphere of confidence and understanding. More specifically, patients are told that they may experience insights (e.g., on their personal problems, values, beliefs about themselves or the world) leading to adaptive changes in personality and that the psychedelic experience is instrumental in acknowledging the negative effects of alcohol abuse and the positive aspects of sobriety. Furthermore, they are instructed to fully surrender to the experience and are informed that the causes for their alcoholism are unconscious in nature, related to more central personality issues and that such causes will manifest themselves during the experience in symbolic form.

The second stage is the drug session, which is conducted by a psychiatrist and an anaesthesiologist. It includes the use of aethimizol (1.5% 3 ml, i.m.) to promote the consolidation of memory, bemegride (0.5% 10 mL, i. v.) to intensify emotional experience, and ketamine (2.5 mg/kg, i.m.) to achieve a psychedelic experience lasting between 45 and 60 minutes. During the session, new age/soothing instrumental music (Krupitsky and Grinenko, 1997; Krupitsky et al., 2002) is used with the intention to promote symbolic resolution of inner conflicts and facilitating cathartic experiences. Additionally, patients are exposed to so-

called “psychotherapeutic influences”, i.e., therapist interventions that are “based on the concrete data of the patient's case history and [are] directed toward the resolution of the patient's personality problems and toward the formation of a stable orientation towards sobriety”. At the peak of the experience, while the therapist aims at shifting the focus of the experience toward the dysfunctional aspects of alcohol abuse (e.g., “Your fear is a result of vodka. It is vodka that has led you to the edge of the abyss”), patients are given the chance to smell alcohol to establish aversion towards the substance. Once the dissociative effects subside, the experience is discussed and interpretations are offered. Finally, patients are asked to write down a detailed report of the session (Krupitsky and Grinenko, 1997).

The third and final stage of KPT consists of a variable number of group psychotherapy sessions carried out the day after the drug session. In this context, the psychiatrist promotes integration via discussion, interpretation of the experience and consideration of lifestyle changes.

In the original 1992 paper, the authors employed this model to treat 86 male AUD patients and reported a remission rate of 69.8% at 1 year compared to 24% of the control group. KPT (in combination with existential psychotherapy) was also used to treat heroin addiction (Krupitsky et al., 2002) and was subsequently adapted to Ketamine-Enhanced Psychotherapy (KEP) to reportedly “extend it

into another cultural context: the US” (Kolp et al., 2007). In this latter form, the treatment was used to treat end-of-life anxiety with the following structure: 3 weekly preparation sessions (75-80 min), one ketamine session (1-3 hours) and a final integration session (75-80 min). KEP was also offered to patients suffering from alcoholism in two other formats: outpatient and intensive. The outpatient format consists of 3 preparation sessions, one of which is devoted to the formulation of a “psychospiritual” goal: a therapeutic objective that integrates the patients’ personal motives for treatment, their goals for their future sober life and spiritual growth (Wolfson and Hartelius, 2016). By the latter, authors refer to a multitude of feelings, experiences and attitudes that usually concern feeling unity with others and the universe, increased chance of converting to a religion, experiencing a so-called “separation of consciousness from the body”, the feeling of being in contact with a higher power, the belief in the existence of “other dimensions or worlds that are parallel to ours” and similar other transpersonal phenomena. The treatment then proceeds with 1 ketamine session and 3 integration sessions (Kolp et al., 2006; Krupitsky et al., 2007). All integration sessions had the same structure and lasted 50 minutes; the ketamine session lasted for 3 hours.

The intensive format had the same general structure of outpatient KPT and added daily all-day activity programs including psychotherapeutic and psychoeducation groups along with training in mind-body techniques. Initial data were collected in a clinical

study in Russia in which the percentage of abstinent patients at 1 year post-treatment in a KPT group was compared with that of a control group (Krupitsky et al., 2007). The authors of the Russian study reported that 65% of patients in the KPT group (n = 111) remained abstinent compared to 24% (n = 100) in the control group. In the U.S., several adaptations of this model were created in an attempt to replicate results and progressively improve its efficacy even more (Kolp et al., 2006). In the first attempt the authors maintained the same structure of KPT as described above but condensed it in a 10-session, 10-week program which comprised 1 screening session, 4 preparation sessions, 1 goal-setting session, 1 ketamine session and 3 integration sessions. Contrary to expectations, this treatment led to an abstinence rate of only 25% in a group of 20 patients. Subsequently, the model was adapted to take place in a residential group setting and as such substituted the individual sessions with 30 weekly hours of psychoeducation, group activities, guided imagery exercises along with breathing, meditation, yoga and cooking classes. The authors reported the results of 3 iterations of this model with each lasting respectively 1 week (35% 1-year abstinence rate, n=15), 2 weeks (60% 1-year abstinence rate, n=10) and 3 weeks (70% 1-year abstinence rate, n=15). In all 3 iterations, patients with a history of psychedelic use were excluded at screening (Kolp et al., 2006). In summary, this treatment format progressively increased the 1-year abstinence rates over 1 (35%), 2 (60%) and 3 (70%) weeks of treatment.

In a double-blind, active-placebo controlled study, 70 detoxified patients suffering from heroin addiction were randomised into two groups employing KPT (Krupitsky et al., 2007). Both groups received 10 hours of preparatory existential psychotherapy, 1 ketamine only infusion session (i.e., no other drugs were administered) and 5 more hours of integration psychotherapy. While one group received a high dose (2.0 mg/kg i.m.), the other received a low non-dissociative dose (0.20 mg/kg i.m.). Results showed improved abstinence, relapse rates, craving and anhedonia in the high dose group while both groups showed improvements in anxiety, depression, internal locus of control, understanding of the meaning and purpose in life and spiritual development. The abstinence rate was about 85% at the 1-month assessment, about 18% at the 24 months follow-up and remained significantly higher for the KPT group over all timepoints. A subsequent study suggested that increasing the number of both ketamine (2.0 mg/kg i.m.) and integration sessions from 1 to 2 may lead to better abstinence rates at the 1-year follow-up (Krupitsky et al., 2007).

KEP was also used in two case studies (a success and a failure) involving a 62-year-old female and a 46-year-old male patients diagnosed with life-threatening illnesses and suffering from death-related anxiety (Kolp et al., 2007). The authors' intention was to highlight how certain patient characteristics may modulate treatment efficacy. While the female patient reported remission

from panic attacks, discontinuation of morphine and lorazepam, increased feelings of comfort, the male patient did not resolve his death anxiety. This difference in clinical outcomes was attributed to the fact that while the woman was willing to discontinue benzodiazepine and decrease opiate use before the session, the man did not. They also pointed out that the woman never used psychedelics before while the man had an extensive history of psychotropic drug use. The authors of this paper seem to suggest that the efficacy of KEP is moderated by history of psychedelic use and they further hypothesise that the “novelty factor” associated with these substances may play a role in improving outcomes. Finally, they suggest that the concurrent use of other CNS depressants may diminish the patients’ response to ketamine and potentially cause amnesia of the experience thus hindering therapeutic response.

In summary, across the literature KET is delivered in different formats. It proposes at least 3 preparation sessions, 1 drug session and at least 1 integration session. When administered in residential settings, it may be complemented by other activities and may include an additional drug session. Existential psychotherapy is the most cited model associated with the treatment and principles of behavioural therapy were incorporated in its original conceptualisation. The role of therapists appears more directive compared with other models as clinicians are expected to actively work to establish positive expectations about the treatment, provide

personality-related aetiologies to explain AUD, and work to establish a structured therapeutic myth.

Medication-Assisted Psychotherapy

We identified 5 papers describing the efficacy of MAP in the context of a RCT (Ross et al., 2016; Belser et al., 2017; Swift et al., 2017; Malone et al., 2018; Agin-Liebes et al., 2020). MAP is a treatment model originally developed by Grof et al. (Grof et al., 1973; Grof and Halifax, 1978) to be used in palliative care settings but that has been applied in the treatment of other conditions as well. Lysergic Acid Diethylamide (LSD) or Dipropyltryptamine (DPT) was administered in combination with psychotherapy to treat depression, anxiety and pain, and address existential issues in patients suffering from life-threatening illnesses. More recently, the model was used in conjunction with psilocybin administration (Ross et al., 2016; Belser et al., 2017; Agin-Liebes et al., 2020).

In its original structure (Grof et al., 1973; Grof and Halifax, 1978), MAP proposes 6 to 12 hours of preparatory psychotherapy held over the period of 2 to 3 weeks focusing on the patients' present goals and issues instead of focusing on personal history and remote unresolved issues. Preparatory sessions are aimed at establishing rapport, working on family issues, addressing potential significant intrapsychic conflicts, confronting and accepting diagnosis, prognosis and death. The overarching goal of the therapeutic model is to facilitate patients in living their days in the fullest and most

meaningful way possible. Special attention is placed on preventing feelings of isolation and, therefore, the involvement of family members is encouraged. Once a good therapeutic relationship is formed and relevant issues are explored, patients are given more in-depth information concerning psychedelic sessions and the altered state of consciousness that they will experience. A session with the substance is then held by two trained facilitators in an appropriately furnished room where music can be played. Early accounts (Grof et al., 1973; Grof and Halifax, 1978) propose the use of family photographs to facilitate the resolution of relational problems and to promote the emergence of positive feelings.

More modern versions of MAP (Ross et al., 2016) encourage patients to bring items of personal and/or spiritual significance, to participate in acts (e.g., holding hands) aimed at conveying comfort and unity between the patient and the therapy team before the beginning of the session and to set their intentions towards finding relief from the psychological and existential suffering brought by cancer. During the course of the psychedelic experience, patients lie down wearing eye-shades and are invited to direct attention toward their internal experience. Therapists will remain present during the whole duration of the session and will offer nonverbal (e.g., holding hands, cradling, rocking) psychological and medical support when needed. During the final phases of the session, when the effects of the substance begin to subside, patients are encouraged to discuss their subjective experience in order to

consolidate its memory. This phase was compared to psycholytic therapy (Crocket et al., 1963; Leuner, 1967; Gasser, 1996; Majić et al., 2015; Ross et al., 2016), an approach in use in the '60s in which patients would take smaller doses of psychedelics to facilitate the emergence of material during psychotherapy sessions. This process constitutes the first step of the subsequent integration work. Relatives can be invited during the termination period of the drug session. Integrative sessions, usually three, are held after each drug session and are meant to consolidate the memory of the experience and promote the processing of the emerged material.

MAP was recently used in a crossover RCT involving patients suffering from life-threatening cancer (Ross et al., 2016). The trial design involved a single psilocybin (or niacin) session (0.3 mg/kg, p.o.), three 2-hour preparation sessions, three 2-hour integration sessions and targeted depression and anxiety levels as primary outcomes. Psychotherapeutic work integrated elements drawn from evidence-based psychotherapies addressed to patients with life-threatening illnesses such as supportive psychotherapy, cognitive-behavioural therapy, existentially oriented psychotherapies and psychodynamic psychotherapy. Results show that the treatment led to significant improvements in demoralisation and hopelessness, spiritual well-being and quality of life. These changes occurred rapidly after the psilocybin sessions and were maintained at the 6.5 month follow-up. At that time, patients showed lower existential distress and better attitudes toward death. Response rates for

depression were about 80% for the psilocybin group and between 20% and 30% (depending on the outcome measure) for the niacin group at the 1-day post session timepoint. Remission rates at the same timepoint were between 80% and 85% for the psilocybin group and between 20% and 30% for the niacin group. At the 7-week post session timepoint response rates were between 70% and 83% for the psilocybin group and between 14% and 40% in the niacin group. Remission rates at this timepoint were between 70% and 80% for the psilocybin group and between 20% and 40% for the niacin group. Response rates at the 1-day post session timepoint for anxiety were about 75% in the psilocybin group and about 40% in the niacin group. At the 7-week post session timepoint response rates were 58% for the psilocybin group and 14% for the niacin group. At the 6.5 months follow up, after the crossing over, response rates varied between 60% and 80% for depression and between 60% and 75% for anxiety. Long-term follow up (4.5 years) analyses of a subsample of patients from the above-mentioned study revealed that response rates were 57% for anxiety and ranged between 57% and 79% for depression. Remission rates ranged between 50% and 79% (Belser et al., 2017; Agin-Liebes et al., 2020). An earlier single sample, pre-post study (Pahnke et al., 1969) tested the efficacy of this model (using LSD, between 200 µg and 500 µg p.o. or dipropyltryptamine, between 60 mg and 105 mg i.m.) on a group of 31 cancer patients. Results showed “dramatic improvement” in 20% of patients, “moderate improvement” in 41.9% and no improvement in 22.6%. A very similar model, albeit

labelled Psychedelic Peak Therapy (PPT), was described in a case series study (Kurland, 1985), which described the effects it had on 2 female patients suffering from breast cancer, 1 female patient suffering from pancreatic cancer and 1 female patient suffering from cancer to the uterine cervix. The authors reported improvements in all four patients in measures of mood, optimism and pain management.

In summary, MAP proposes 6-12 hours of preparation, 1 drug session held by two trained facilitators and 3 integration sessions. The therapeutic model is eclectic, unstructured and integrates elements from multiple and diverse theoretical frameworks.

MDMA-Assisted Psychotherapy

Our search identified 12 papers (one of which analysed the pooled results of 6 separate studies) describing the findings of investigations conducted on 6 separate samples (1 case series, 3 RCTs, 1 pooled analysis of 6 RCTs) that used MDMA-assisted psychotherapy for Post-Traumatic Stress Disorder (MDMA-AP) (Bouso et al., 2008; Mithoefer et al., 2011, 2013, 2018, 2019; Oehen et al., 2013; Ot'alora G et al., 2018; Barone et al., 2019; Jerome et al., 2020; Wolfson et al., 2020; Jardim et al., 2021; Mitchell et al., 2021). Furthermore, we identified two papers that were based on the same small-sample within-subject study applying the model in an observational study on Alcohol Use Disorder (AUD; Sessa et al., 2019, 2021).

MDMA-AP (Mithoefer, 2016) is a structured approach to PAT that was developed by the Multidisciplinary Association for Psychedelic Studies (MAPS). MDMA-AP is an attempt to harness the pharmacological effects of MDMA to enhance psychotherapy effectiveness and aims at reducing or eliminating symptoms and achieving better functioning and well-being (Mithoefer, 2016). More specifically, the premise is that the substance-induced reduction in fear, increased interpersonal trust and positive emotions toward oneself and others will facilitate a corrective re-experiencing of the traumatic event in the context of a caring and supportive therapeutic relationship.

This treatment is based on earlier contributions by authors who proposed the use of psychedelics in psychotherapeutic settings (Pahnke et al., 1970; Greer and Tolbert, 1998), decisively relies on both preparation and integration sessions and adopts a seemingly non-directive, non-judgmental and empathetic approach to therapy (Mithoefer, 2016). The fundamental idea entails recruiting the patient's "inner healing intelligence" - i.e., "a person's innate capacity to heal the wounds of trauma" (Mithoefer, 2016) - to facilitate the processing of trauma through direct confrontation, mind-body techniques and a mindful and accepting mindset toward the MDMA-elicited internal experiences (Mithoefer, 2016). Therapists are encouraged to adopt a "beginner's mind" - i.e., an attitude that considers "any experience as an opportunity to heal and develop trust in their own inner healing intelligence" - while

being receptive to potential hidden meanings and sources of insights emerging from the experience (Mithoefer, 2016).

To conduct MDMA-AP, therapists must undergo a specific training, should be proficient in administering treatments for PTSD, are encouraged to learn Holotropic Breathwork to gain experience with different states of consciousness, Internal Family Systems Therapy to learn how to work with multiple parts of the self, Sensorimotor Psychotherapy and/or mindfulness-based methods along with other breathing and bodywork techniques to help patients remain focused on the present experience and process trauma through their bodies (Mithoefer, 2016). Preliminary phases include the preparation of an appropriate physical setting and the adoption of mindsets and techniques that are thought to facilitate the therapeutic process on the therapists' part (Mithoefer, 2016).

The room in which the MDMA sessions will be held should be private, quiet, comfortable, well-furnished and allow for the presence of two therapists and music during the course of the experience (Mithoefer, 2016). Therapists are required to support patients through somatic manifestation of traumas, accept potential transpersonal experiences that may emerge during drug sessions and be ready to work with multiple parts of a patient's self. Such multiplicity is defined by the authors as a healthy phenomenon that "may be more pronounced in people who have experienced trauma" (Mithoefer, 2016). MDMA-AP places emphasis on preparation

sessions as a means to determine patient eligibility, establish a functional therapeutic alliance, gather information about personal and trauma history, enquire about expectations, address concerns and prepare patients for the subsequent phases of the treatment (Mithoefer, 2016). Clinical studies usually include 2 to 3 preparation sessions each lasting 60 to 90 minutes (Bahji et al., 2020) which focus on personal history, therapeutic alliance and preparation of patients for the psychedelic session (Mithoefer, 2016). The general aim is to establish a sense of safety and comfort, an attitude of curiosity toward inner experience and trust toward one's inner healing intelligence (Mithoefer, 2016).

Unless medical or psychological contraindications are present, patients will take part in one or more drug sessions several weeks apart. MDMA sessions, 1 to 3 in clinical studies (Bahji et al., 2020), last 6 to 8 hours and are facilitated by two co-therapists, preferably one female and one male (Mithoefer, 2016). Therapists are required to maintain an empathic presence and to seek a balanced attitude between keeping in mind the patients' intentions for the session and being open to the emergence of unexpected perceptions or memories, or ideas (Mithoefer, 2016). Therapeutic interventions are non-directive and encourage patients to adopt a similar attitude toward the experience (Mithoefer, 2016). In fact, they are advised to follow the spontaneous evolution of the experience and to trust their inner healing intelligence (Mithoefer, 2016). Painful memories, perceptions and ideas may emerge and, should therapists observe

the adoption of avoidant attitudes on the patients' part, they should encourage them to mindfully confront such material and advise them on techniques they can use to work through the emotional distress (Mithoefer, 2016). Regular check-ins with silent patients are recommended in order to learn about their psychological state and experience (Mithoefer, 2016). During the later part of the session, while the effects of the substance begin to subside, therapists are advised to ask whether the patient is willing to provide more details about their experience (Mithoefer, 2016). These may be further discussed during follow-up (integration) sessions (Mithoefer, 2016). Patients are accompanied until the end of the session and are helped in resolving any potential emotional or physical distress that may persist (Mithoefer, 2016). Once the session is over, patients may be offered to spend the night in the treatment facility where their mental and physical state will be monitored by the clinical staff (Mithoefer, 2016). They can invite a significant other in. The morning after the MDMA session, the first integration session takes place (Mithoefer, 2016).

Integrative sessions - 2 to 3 in clinical studies (Bahji et al., 2020) aim at integrating the experience in the patients' ongoing therapeutic process and everyday life and usually last 60 to 90 minutes (Mithoefer, 2016). MDMA-AP rests on the assumption that the effects of the treatment will continue to unfold between sessions and after the treatment program is complete (Mithoefer, 2016). Patients are therefore informed that new insights, improvements in

resilience, emotional well-being and relational skills may keep occurring (Mithoefer, 2016). Furthermore, should they experience psychological problems or suffering as a result of the MDMA-induced experience, integration sessions can be used to tackle such issues and define the therapeutic trajectory (Mithoefer, 2016). In this phase, therapists answer patients' questions, adopt a supportive and validating attitude towards the experience and encourage them to process new insights concerning their trauma, history, relationships and personal life (Mithoefer, 2016). The non-directive character of the therapy is maintained through the integration phase and while interpretations by the therapist are allowed, they "should be minimised" (Mithoefer, 2016). Integrative work begins the morning after the first MDMA session (Mithoefer, 2016). Patients are invited to discuss their experience in greater detail. Therapeutic work may be complemented by focused bodywork (e.g., "giving resistance for the participant to push against"; Mithoefer, 2016), breathing techniques and other approaches to facilitate the processing of the emerged material (e.g., trauma-related memories and physical sensations) through arousal regulation (Mithoefer, 2016). Before the closing of the treatment program, patients' potential concerns and questions must be addressed and the techniques and procedures that they found useful can be reviewed and consolidated.

MDMA-AP has been tested in several studies investigating its potential in the treatment of PTSD in various populations. A recent

review and meta-analysis reported high rates of clinical response (72%) and more than 2 times the probability of achieving remission in the experimental groups with large effect sizes in symptom reduction at long term follow-up (between 12 and 74 months; Bahji et al., 2020). A study which tested this model plus elements from third wave CBT and MET as a potential treatment for AUD reported that in a sample of 14 previously detoxified patients, an 8-week course of MDMA-AP led to a significant drop in average units consumed per week from baseline (130.6 units/week) to the 9 months follow up (18.7 units/week) in 11 patients (79%) with 9 patients (64%) who were completely abstinent (Sessa et al., 2021). Finally, MDMA-AP was used to treat anxiety associated with life-threatening illnesses in a sample of 18 patients in a randomised pilot study (Wolfson et al., 2020). While the MDMA-AP group reported greater reductions in anxiety, the difference failed to reach the significance threshold.

In summary, MDMA-AP proposes 2 to 3 preparation sessions, 1 to 3 drug sessions held by two facilitators (preferably a male and a female) and 2 to 3 integration sessions per drug session. The therapeutic model places emphasis on non-directiveness, provides suggestions that highlight the role of the inner healing intelligence (the construct considered responsible for clinical change by the authors), aims at establishing positive expectations about the treatment and enquires about those of patients, allows for therapist direction of the session in case avoidant tendencies are observed

and encourages interpretation and search for hidden meanings on the therapist side. Furthermore, bodywork techniques, mindfulness and sensorimotor psychotherapy are considered valuable tools to work through the physical manifestations of trauma. Given that the patients' psyche is conceptualised as made of several parts, elements from Internal Family Systems therapy are used throughout all phases of treatment.

Preparation, Support, Integration

Our search identified 7 papers describing the findings of 1 open-label feasibility study employing the PSI model to treat patients suffering from Treatment Resistant Depression (TRD) (Carhart-Harris et al., 2016, 2018a; Erritzoe et al., 2018; Mertens et al., 2020; Stroud et al., 2018; Watts et al., 2017; Roseman et al., 2018).

PSI (Carhart-Harris et al., 2018a) is a psilocybin-assisted model to treat TRD. The model is briefly outlined in two papers (Carhart-Harris et al., 2016; Stroud et al., 2018) describing the outcomes of an open-label feasibility study. It comprises one 4-hour preparation session aimed at building a trusting relationship and encouraging patients to talk about their personal history and their hypotheses concerning the origin of their depression. They receive information concerning psilocybin's psychological effects and take part in a drug-free simulation of the psychedelic session. The two dosing sessions (10 mg and 25 mg, p.o.) take place one week apart and are held in a pre-decorated room in which patients can lie supine

wearing eye shades and listen to music. Two psychiatrists supervise the session and adopt a non-directive approach. The aim is to facilitate an “uninterrupted journey” for patients while regularly performing check-ins to keep track of their physiological and psychological state. Once the first session is over, patients are taken back home by a close friend or a relative and are contacted via telephone the next day to evaluate their well-being and monitor for adverse effects. Two, 3 and 5 weeks after the second dosing session, email assessments of clinical progress are performed. One final follow-up is performed remotely 3 months after the last high-dose psilocybin session. In another description, the model also includes an integration session held the day after dosing in which patients are invited to talk about their experiences and are met with compassionate listening and occasional interpretations to promote and consolidate positive change (Carhart-Harris et al., 2018a; Stroud et al., 2018).

Results reported in the open-label TRD papers show improvements in severity of self-reported depressive and anxiety symptoms 1 week, 3 months (n=12) and 6 months (n=19) after dosing (Carhart-Harris et al., 2016, 2018a). Remission rates were 67% at 1 week and 42% at 3 months while response rates were 58% at 3 months and 31% at 6 months. The 6-month follow-up study also reported decreases in suicidality at 1 and 2 weeks post-treatment (Carhart-Harris et al., 2018a). Further evidence shows that psilocybin and PSI improve processing of emotional faces in TRD patients (Stroud

et al., 2018) and that clinical improvements seem to be predicted by the quality of the psychedelic experience (Roseman et al., 2018). Finally, the authors reported significant decreases in neuroticism and increases in extraversion and openness to experience (Erritzoe et al., 2018).

In summary, PSI proposes one 4-hour preparation session, 1 drug session held by two psychiatrists and 1 integration session. The theoretical model is broadly described as non-directive and the therapists take an active role during preparation in gathering the hypotheses that participants have concerning the origin of their depression. During the integration phase, therapists are required to offer compassionate listening as well as provide interpretations and facilitate the consolidation of positive change.

Trauma interventions using mindfulness-based extinction and reconsolidation

Our search identified 2 papers investigating the efficacy of TIMBER on a single sample in the context of a RCT (Pradhan et al., 2017, 2018). TIMBER is a psychotherapeutic model conceived to treat PTSD (Pradhan et al., 2017) through the application of the principles of extinction, reconsolidation and arousal regulation. It employs mindfulness techniques and was used to improve the stability of clinical gains that were obtained in a previous study employing ketamine as a therapeutic agent (Feder et al., 2014). TIMBER, in its short version, is administered in the course of a 60-

minutes period and begins with a 10-minute reactivation of traumatic memories (Pradhan et al., 2017). More specifically, patients are asked to recall a traumatic event through a pre-prepared personalised script with the objective of activating arousal responses for the following 2-3 minutes. The 40-minute infusion period with 0.5 mg/kg (R, S)-ketamine is then initiated and patients are asked to recall calming memories and to practice the STOPP (Stop, Three mindful breaths, Observe, Practice more, Proceed (Pradhan and Pinninti, 2016)) mindfulness procedure for 5 minutes to de-escalate emotions such as frustration, anger, anxiety and reduce impulsivity. The goal of this phase is to achieve a state referred to as mindfulness-based detached monitoring.

In a small placebo-controlled, cross-over study (Pradhan et al., 2017), 10 patients with chronic and refractory PTSD were randomised in two groups to receive TIMBER with ketamine (dose, i.v.) or placebo (saline solution). The first session of both programs was the infusion session followed by 11 non-infusion sessions of which two were held in the same week of the infusion while the rest took place on a weekly basis. The psychotherapeutic model for the remaining 9 sessions was the same as that detailed above. Findings showed that before cross-over 9 out of 10 participants reported improvements in PTSD symptoms, depression and anxiety measures independent of group allocation. No significant differences in the magnitude or duration of treatment effects were observed between the two groups. A subsequent extension of the

study including 10 additional patients demonstrated a statistically significant 108% increase in response duration (18 days on average) after TIMBER with ketamine compared to TIMBER with placebo (Pradhan et al., 2018).

Adapted Therapeutic Models

Brief supportive expressive group therapy

Our search identified 3 papers on 1 open-label study employing psychedelic-assisted SEGT to treat demoralisation in a sample of demoralised older long-term male AIDS survivors (Anderson et al., 2020; Agin-Liebes et al., 2021; Stauffer et al., 2021). SEGT is a model that was created in the context of palliative care (Classen et al., 1993) and was adapted for use with HIV-infected patients (Maldonado et al., 1996). As described in SEGT manual (Maldonado et al., 1996), the treatment aims at creating an environment of mutual support to contrast the feelings of isolation that are often a consequence of receiving this diagnosis (Maldonado et al., 1996). Patients are encouraged and helped in disclosing their condition to their loved ones and in learning how to ask for the support they need (Maldonado et al., 1996). This is especially relevant when it comes to intimate relationships and importance is placed into promoting conscious and safe sexual practices (Maldonado et al., 1996). Cultivating openness and expression of both positive and negative emotions is a primary goal of the treatment in order to relieve and encourage patients in their

personal journeys (Maldonado et al., 1996). Emphasis is given in integrating the changes in self and body image (Maldonado et al., 1996). In fact, patients may find themselves in the position of requiring help in everyday activities for the first time in their lives and such experience may be troubling for some (Maldonado et al., 1996). Furthermore, the onset of opportunistic infections and other related pathologies may lead to changes in appearance that may need therapeutic work to facilitate acceptance and adaptation (Maldonado et al., 1996). After the diagnosis, patients find themselves tackling new challenges in life and, to support them, SEGT strives to expand and improve their coping skills through the experience of their fellow group members and therapist contribution (Maldonado et al., 1996). The development of a life project is encouraged and exploration of life values is intended as a tool to help clarify personal goals (Maldonado et al., 1996). Self-hypnosis is taught as a way to manage pain, improve sleep quality and deal with stress (Maldonado et al., 1996). Given the central role that pharmacological therapy has in the management of the infection and the high risk of poor adherence to treatments, patients are encouraged to be actively involved with the medical staff to promote a good doctor-patient relationship (Maldonado et al., 1996). Finally, receiving the HIV diagnosis may be the first time in which patients are confronted with their own mortality and therapists are instructed to address death related issues, avoidance behaviours and patterns of thoughts to allow group members to explicitly talk about death (Maldonado et al., 1996). Throughout the duration of the

treatment, interaction between group members is actively pursued and the focus of the discussion is kept on personal and concrete issues related to HIV/AIDS in a climate of empathy and unconditional positive regard (Maldonado et al., 1996). SEGT sessions are 90 minutes long and are conducted by two co-therapists who have experience in working with patients with HIV (Maldonado et al., 1996).

SEGT was used as an adapted model in conjunction with psilocybin sessions in studies aimed at testing its effectiveness in treating demoralisation in male older long-term AIDS survivors (Anderson et al., 2020). This integration model included a 90-minute psychotherapy session held before group initiation in which patients received psychoeducation on group therapy and psilocybin. Patients underwent 12-15h of group psychotherapy over the course of 7 weeks and took part in 1 8-hour individual psilocybin session (0.30-0.36 mg/kg p.o.). Finally, a second 2-hour individual psychotherapy session was held the day after the psilocybin session. The self-hypnosis module of SEGT was replaced by breathing and mindfulness exercises with the intention of providing patients with techniques they could use during dosing sessions. Results showed clinically relevant change in demoralisation (Anderson et al., 2020) and significant reductions in self-reported attachment anxiety at the 3-month follow-up (Stauffer et al., 2021). Regarding response rates, 88.8% and 66.7% of participants achieved a 2-point improvement in demoralisation at treatment end

and follow-up respectively. Fifty percent and 33.3% of them more than halved their baseline demoralisation scores at treatment end and follow-up respectively. An interpretive phenomenological analysis conducted by the same authors (Agin-Liebes et al., 2021) suggested that patients felt freed from their avoidant tendencies, able to access and process painful and self-transcendent feelings. They also reported an increase in prosocial attitudes and positive emotion along improvements in meaning-making and post-traumatic growth.

In summary, psychedelic-assisted SEGT integrated the psychedelic preparation in the preliminary session normally devoted to psychoeducation on group therapy. The treatment includes 1 psilocybin session and a subsequent integrative session. SEGT emphasises the importance of tackling specific topics common to HIV-infected patients in group through direct confrontation with themes, emotions and practical issues in an atmosphere of openness and acceptance.

Cognitive Behavioural Therapy

Our search identified 7 papers about the efficacy of psychedelic-assisted CBT in tobacco dependence (4 papers: open-label study (Garcia-Romeu et al., 2014; Johnson et al., 2014, 2017; Noorani et al., 2018), opioid dependence (1 paper: case study (Ocker et al., 2020) and TRD (2 papers: 1 RCT (Wilkinson et al., 2021) and 1 open label study (Wilkinson et al., 2017)). CBT in conjunction with

psilocybin has been used to support opioid tapering (Ocker et al., 2020) and, in the form of the Quit For Life programme (QFL (Marks, 1993), to treat tobacco addiction (Garcia-Romeu et al., 2014; Johnson et al., 2017). Furthermore, it has been employed with ketamine to treat TRD (Wilkinson et al., 2017).

QFL is a self-help CBT-model designed to achieve smoking cessation in 7-10 days and provides patients with tools to prevent relapse (Marks, 1993). The program frames smoking as a “psychological addiction”, asserts that quitting can be achieved with a moderate amount of willpower, poses emphasis in increasing patients’ self-efficacy and offers 30 different CBT-based approaches to reach such a goal. QFL is administered in the form of a handbook, cards, charts and audio recordings containing a summary of the material, relaxation music and suggestions to promote abstinence. Once a date for actual cessation is set, the first phase of the treatment begins: reduction. At this stage, patients are encouraged to reduce smoking by 50% everyday and are expected to reach abstinence one week later. Relapse prevention is the second phase of the program and makes use of several techniques such as mental imagery, suggestion, meditation and relaxation while teaching how to deal with other smokers. The program was initially tested in a two-year follow-up study (Sykes and Marks, 2001; Marks and Sykes, 2002) and authors reported that about 28% of individuals achieved abstinence or significant

reductions in the QFL group while only about 6% did in the control group. The difference between groups was statistically significant.

In an open-label pilot study recruiting 15 nicotine-dependent smokers, Johnson et al. (2014) tested the effects of a 15-week treatment program which integrated QFL with psilocybin sessions (2014). To this aim, they structured a model in which participants first established a target quit date (TQD) 5 weeks from the beginning of treatment and then received 4 weekly QFL inspired sessions. Each session also conveyed information about psilocybin, contained a 10-minute relaxation exercise along with the smelling of a scented oil and a guided imagery exercise, two elements drawn from another manualised smoking cessation intervention (Zernig et al., 2008). The first psilocybin session took place in week 5, employed an oral 20 mg/70 kg dose and coincided with the TQD. Following the first administration, participants went on with the weekly QFL program and took part in a second 30 mg/70 kg psilocybin session at week 7. Participants who still had not quit by that time, were offered a third psilocybin session at week 13 (30 mg/70 Kg, unless the participants themselves wished to lower it) while weekly QFL sessions went on until week 15. During all psilocybin sessions participants were asked to state a previously elaborated motivational statement for smoking cessation. They lay on a couch while listening to music through headphones, received support from the research staff and were involved in a guided imagery exercise during the final phases of the session when the

effects of psilocybin were subsiding. Finally, they were asked to write down a description of their experience to be used for discussion in an integration session that was held the following day.

In summary, psychedelic-assisted CBT for smoking cessation proposes 4 QFL/preparation sessions which included relaxation, guided imagery and smelling scented oil, 2 or 3 drug sessions held by at least one staff member and 1 integration session per each drug session. At the 6-month follow up, the authors reported significant reductions in daily smoking compared to baseline and that 80% (12 out of 15) of participants showed 7-day point prevalence abstinence. At 12 and ≥ 16 -months post-treatment, 67% (10 of 15) and 60% (9 of 15) were confirmed abstinent respectively (Johnson et al., 2017). Subsequent qualitative analysis of participants' accounts revealed that they experienced insights concerning their reasons for smoking, increased feelings of interconnectedness, awe and curiosity and long-term positive changes in pro-social behaviour and aesthetic appreciation (Noorani et al., 2018). Abstainers scored higher on measures of psilocybin-occasioned mystical experiences (Garcia-Romeu et al., 2014).

Ketamine plus CBT for opioid tapering was used in a recent case-study in which a 55-year-old male patient suffering from complex regional pain syndrome treated with opioids for 12 years achieved abstinence after a 5-day ketamine infusion program while

continuing a psychotherapy initiated 3 years prior (Ocker et al., 2020). Infusion began at 0.09 mg/kg/h and was titrated twice daily in 0.09 mg/kg/h increments. On the last day the patient had the dose halved in the morning and then discontinued in the afternoon.

Another ketamine plus CBT intervention was used in a study aiming at extending the stability of the antidepressant effect of the substance (Wilkinson et al., 2017, 2021). To this aim, the authors recruited 48 TRD patients and treated them with 6 intravenous infusions of ketamine (0.5mg/kg over 40 minutes) during the course of 3 weeks. The 28 (58%) participants who showed an improvement greater than 50% in depression scores were classified as responders and randomly assigned to two groups: 14 weeks of CBT or treatment as usual (TAU; regular visits with physician). The Quick Inventory of Depressive Symptoms scores showed more sustained improvement in the CBT group compared to TAU while the Montgomery Åsberg Depression Rating Scale scores did not reveal effects.

The CBT used in this study was based on Beck's model and comprised psychoeducation, cognitive restructuring and behavioural activation. The model included no preparation sessions and no formal integration sessions. Once the infusion cycle was completed, patients were referred to certified CBT therapists.

Cognitive Behavioural Conjoint Therapy

Our search identified 3 papers on an observational study testing the efficacy of psychedelic-assisted CBCT in the treatment of couples in which one member suffered from PTSD (Wagner et al., 2019, 2021; Monson et al., 2020). CBCT (Monson and Fredman, 2012) is a treatment model for PTSD which, instead of focusing on patients alone, recruits their intimate partners in an attempt to improve treatment outcomes. In this context, PTSD is conceptualised as an interpersonal disorder given a) the evidence showing that symptom severity correlates with intimate relationship adjustment and aggression (Taft et al., 2011); b) that the construction of meaning after the traumatic experience is an interpersonal process (Monson et al., 2010); and c) that the functioning of the relationship itself and of the intimate partner influences PTSD severity (Bradley et al., 2005; Lambert et al., 2012; Shnaider et al., 2014). CBCT promotes the development of new skills in the dyad as a whole and considers the relationship itself the actual client of the treatment (Monson and Fredman, 2012).

The efficacy of CBCT was tested in military samples in both controlled and uncontrolled studies (Liebman et al., 2020). This 15-session program comprises three phases synthesised by the acronym R.E.S.U.M.E. Phase 1 (Rationale and Education) provides psychoeducation concerning PTSD and its relational consequences and aims at building a climate of physical and emotional safety through behavioural strategies intended to

increase positive affect and behaviours. Phase 2 (Satisfaction Enhancement and Undermining Avoidance) focuses on teaching and training communication skills and treating emotional numbing and behavioural avoidance. The goal is to promote the approaching of feared situations and increasingly engage the dyad in enjoyable activities. Finally, in phase 3 (Meaning Making and End of Therapy) the goal shifts to trauma related appraisals and its consequent current cognitions. The aim is to weaken factors that consolidate PTSD symptoms and relational problems. A recent review shows that CBCT leads to significant improvements in PTSD symptoms, comorbid conditions and relational satisfaction in both clinician and patient ratings (Liebman et al., 2020).

CBCT was recently used in an uncontrolled trial aimed at testing its effectiveness in six couples with the inclusion of two 6-hour MDMA sessions (Monson et al., 2020) conducted in accordance with the guidelines specified in an earlier work (Wagner et al., 2019). The first two sessions of the treatment covered the R and E sections and were held on day 1. The next day participants would go through two more sessions covering part of the S and U sections. During the same day they would take part in the first dosing session (75 mg MDMA; 90 minutes after administration, patients could decide whether they wished to take an optional supplemental half-dose). The rationale was that by that time the couple would have already developed the necessary skills to effectively communicate during the session and share their experience. The first MDMA session

was followed by an integration session on day 3 and over the subsequent 3 weeks participants would complete the S and U sections. The second MDMA session (100 mg plus an optional 50mg) would then be held on day 23, to take advantage of the increased focus on trauma processing that the S and U sections entail. The program then proceeded with an integration session and the completion of modules M and E. All MDMA sessions took place in a room where participants could lie on a reclining chair. They listened to music through headphones, wore eyeshades and were encouraged to “spend time inside”. Results showed significant and sustained improvements in clinician-assessed PTSD with almost all participants achieving remission at the 6-month follow up. Five patients out of 6 showed remission at post-treatment follow-up (1 and 6 months). Depression, emotion regulation, trauma-related beliefs along with patient and partner satisfaction also improved. Subsequent analyses revealed improvements in post-traumatic growth measures, relational support, social intimacy as well as greater well-being within the couple, improved psychosocial functioning and empathic concern (Wagner et al., 2021).

In summary, psychedelic-assisted CBCT relies on a structured treatment model, does not include formal preparation sessions and places 2 drug sessions once certain communication skills are sufficiently developed. The drug sessions involve both partners and are followed by an integration session each.

Human Relations Training Laboratory Group

Our search identified 1 paper testing the efficacy of combining a large dose of LSD with a Human Relations Training Laboratory (HRTL) group intervention in treating individuals suffering from AUD (Bowen et al., 1970). HRTL (Blake and Mouton, 1964) is a group training intervention built from the assumption that AUD patients struggle in dealing with everyday problems because of a lack of relational skills. The program therefore focuses on lectures on how to “increase effectiveness in groups” (Bowen et al., 1970), structured exercises and a rating system designed to assess progress. Patients were not attending any form of psychotherapy. The study (Bowen et al., 1970) described two experiments. In the first one a group of inpatients was assigned to a single LSD (500 µg, n = 41) session plus HRTL while a second one went through the HRTL program alone (n = 40). In the second experiment an additional group was included which went through a single LSD session (25 µg, n = ~22) plus HRTL. In this second experiment the 500 µg group comprised 22 patients and the HRTL only group 15. The LSD session took place during the first 3 weeks of the program in a room furnished informally with “potentially symbolic articles such as a flower, pictures and a two-sided mirror” where music chosen by the participant could be played. The session was preceded by “several group lectures to prepare patients” (Bowen et al., 1970) and during this preparation facilitators aimed at establishing positive expectations towards both the psychedelic

experience and the clinical outcomes (Bowen et al., 1970). Patients were also encouraged toward relaxing and “going along” with the experience and were discouraged toward trying to control it (Bowen et al., 1970). LSD sessions were held by nursing assistants who were instructed to give close attention to patients, provide “positive suggestions” regarding their “ability to gain from the experience” (Bowen et al., 1970). Results showed no significant differences between any of the groups (Bowen et al., 1970).

MDMA-assisted therapy and mindfulness for adult autistic individuals

Our search identified 1 RCT investigating the potential of MDMA-ATM in the treatment of social anxiety in adult autistic individuals (Danforth et al., 2018). The treatment program followed a protocol published a couple of years earlier (Danforth et al., 2016).

The rationale for the treatment was built on the basis of a) research mostly from the ‘60s and ‘70s indicating potential for clinical improvement b) a better understanding of the importance of set and setting in ensuring the safety of patients c) the copious anecdotal reports of MDMA-induced improvements in empathy, ease of communication, comfort in social settings, feelings of ease in one’s own body reported in online fora (for a review see Danforth et al., 2016) and d) evidence showing that practicing mindfulness skills has beneficial effects in social, emotional and cognitive areas of functioning of autistic individuals (Bögels et al., 2008; Spek et al., 2016)

2013). Concerning this latter point, the authors adapted the mindfulness skills training module from Dialectical Behaviour Therapy (DBT), an already established model of psychotherapy (Linehan, 2018)

The model is structured in three phases as seen in other approaches. More specifically, before the first MDMA session, participants take part in three 60 to 90-minute preparatory sessions (Danforth et al., 2018) aimed at building rapport, clarifying treatment structure, expected effect of the substance, at discussing relevant issues expressed by participants and practicing mindfulness. Furthermore, the training aims at providing patients with an enriched vocabulary useful to describe the psychedelic experience. Once the preparation phase is complete and before taking the MDMA, patients are involved in a guided progressive muscle relaxation exercise (McCallie et al., 2006) in a room furnished to facilitate feelings of comfort. Patients are then accompanied through the experience by two co-therapists (one male and one female) for the whole duration of the session. During its course, a variety of tasks are proposed including artistic activities, listening to music, writing, introspection and therapist interaction. Therapists should create and maintain a supportive and safe setting and discuss social challenges that patients may have. The MDMA session is followed by 4 non-drug sessions (after 1 day, 2 weeks, 1 month and 6 months respectively) during which details concerning the experience are gathered and discussed to facilitate the

integration of the experience in everyday life (Danforth et al., 2018). A subsequent MDMA session with corresponding integration sessions then follows. Subsequently, patients are be involved in daily telephone check-ins. In a randomised, double-blind, placebo-controlled pilot study, 12 patients were assigned either to a MDMA-ATM (n = 8) or to a placebo plus mindfulness skills training group (n = 4). Both conditions comprised 3 preparatory sessions, 2 drug sessions (75 mg MDMA for the first session and 100 mg MDMA for the second or 2 inactive placebo) and 3 integration sessions after each drug session. The MDMA-ATM led to significantly greater improvements in social anxiety scores at the 6-month follow up and response rates (MDMA = 75%; control = 50%) (Danforth et al., 2018).

In summary, this model proposes 3 preparation/mindfulness training sessions, 2 MDMA sessions held by 2 therapists (1 female and 1 male) each preceded by a relaxation exercise and followed by 4 integration sessions. The psychotherapeutic method is adapted from the DBT mindfulness module, an already established model (Linehan, 2018).

Motivational Enhancement Therapy

Our search identified 5 papers on 2 separate studies investigating the efficacy of psychedelic-assisted MET in the treatment of AUD: 1 pilot RCT (Dakwar et al., 2020; Rothberg et al., 2021) and 1 open-label study (Bogenschutz et al., 2015, 2018; Nielson et al., 2018).

MET is a brief treatment model devised to achieve change in problem drinkers and individuals suffering from other addictive disorders (Miller, 1994). MET is based on the principles of motivational interviewing (Miller and Rollnick, 1991) and on the transtheoretical model of change (Prochaska, 1992) which conceptualises the process of changing maladaptive behavioural patterns as a cycle comprising 6 stages, i.e., precontemplation, contemplation, determination, action, maintenance and relapse, each requiring specific therapeutic actions (Prochaska and DiClemente, 1985, 1994). It begins with an initial structured assessment, resolves in 4 sessions held in a 90-day window and considers the mobilisation of the clients' own resources as the primary mechanism for effective therapy. This model rests on earlier literature indicating that effective treatments for problem drinkers share some common principles (Orford, 1986): they provide feedback of personal risk or impairment, emphasise personal responsibility, give clear advice, provide alternative options for change, value an empathic attitude on the part of the therapist (as opposed to a more confrontational one) and promote clients' self-efficacy (Prochaska and DiClemente, 1985, 1994).

During precontemplation individuals are not considering change and are usually uninterested in initiating treatment. In contemplation, they begin to consider the problematic aspects of their behaviours and the costs/benefits of change. If correctly facilitated by the therapist, patients will reach the determination

stage in which a firm stand to take action is established. Once patients begin to modify the problem behaviour, they are considered to have reached the action stage. Should the new behaviour pattern persist, after 3 to 6 months patients are considered to have reached the maintenance stage. Relapse is considered another stage of this cycle and, should patients experience such slips, they will be accompanied through the cycle again. During the first treatment session (Miller, 1994), patients receive feedback from the initial assessment phase which addresses addictive behaviours, symptoms, decisional considerations and future plans. The second session takes place a week after the first one and is dedicated to build or strengthen patient motivation. The subsequent two sessions, held 4 and 10 weeks after the second one, focus on monitoring and encouraging change and its maintenance. Therapists are required to adopt 5 motivational principles in conducting sessions: express empathy, develop discrepancy, avoid argumentation, roll with resistance, support self-efficacy. More specifically, therapists should aim at building an empathic and collaborative relationship. In this frame, patients are considered the only ones who can decide to change and therapists as supportive consultants who listen rather than tell and build up rather than tear down. Since motivation is conceptualised as the result of increasing discrepancy between the current and desired state, therapists should help to develop such discrepancy in order to increase the chances of opening a discussion on change options. Argumentation is firmly discouraged

172

in order to avoid the strengthening of defensive coping strategies. Additionally, the focus is on the consequences of addictive behaviours (as opposed to diagnostic aspects) and on leading clients themselves to be the ones voicing the arguments for change. Since ambivalence is viewed as a normal part of the treatment of addictive behaviours, therapists are encouraged to “roll with” resistance. Finally, the belief that clients can change their addictive behaviour is crucial for therapeutic success, therefore therapists should directly adopt strategies to build and consolidate self-efficacy (Bandura, 1982).

MET was used in conjunction with psilocybin to treat AUD in a proof-of-concept study that recruited 10 patients (Bogenschutz et al., 2015). The intervention model spanned over the course of 12 weeks and employed a total of 7 MET sessions, 3 preparation sessions, 2 psilocybin sessions and 2 debriefing sessions. More specifically, screened patients were involved in 2 preparation and 2 MET sessions followed by the first psilocybin session (0.3 mg/kg, p.o.). Subsequently, patients took part in a debriefing session, 2 more MET sessions and in another preparation session before proceeding to the second dosing session. In this case the proposed dose was 0.4 mg/kg unless the participant was unwilling to increase it, experienced adverse effects during the first one or already achieved a complete mystical experience. In these cases the employed dose would have been equal to that of the first session. The treatment course ended after another debriefing session and 3

more MET sessions. Psilocybin sessions took place in a living room-like space where patients were asked to lie down on a couch while listening to music through headphones and wearing eyeshades. Results showed that drinking and heavy drinking days decreased across weeks 5 to 12 compared to both baseline and 4-week since treatment initiation. Improvements were maintained at the 36-week follow-up. No data on response/remission rates was provided. Qualitative analysis of patient accounts of psilocybin sessions (Bogenschutz et al., 2018) revealed themes related to mystical experiences, feelings of forgiveness, self-compassion, acceptance and love as well as experiences of catharsis, increased mindfulness and “spaciousness”. According to the authors, the emerged material was personally meaningful to the individuals and tended to frame drinking behaviours in a wider psychodynamic perspective.

In another recent randomised, active-placebo controlled trial that compared the efficacy of a single ketamine hydrochloride (2-minute 0.11-mg/kg bolus in saline followed by a 50-minute slow-drip intravenous infusion of 0.6mg/kg) or midazolam (a 2-minute saline bolus followed by a 50-minute slow-drip intravenous infusion of midazolam, 0.025 mg/kg) administration session combined with psychotherapy to treat AUD (Dakwar et al., 2020), MET was adapted as follows. During the course of 5 weeks, patients were involved in a course of weekly sessions. The initial session aimed at defining goals and elaborating a motivational statement related

to quitting drinking. During the following week, they took part in an infusion session and in an additional MET session. The other sessions were scheduled for the following 3 weeks. Results showed better outcomes in the ketamine group in terms of drinking days, heavy drinking days, proportion of abstinent participants, at the 21 days post-infusion time point. Telephone interviews with a subset of the complete sample (n=19) suggested greater rates of abstinence in the ketamine group (75%) compared to the control group (27%) at the 6 months follow-up. Additional analyses showed that the occurrence of mystical-type experiences seemed to play a role in mediating treatment efficacy (Rothberg et al., 2021).

In summary, the first adaptation (psilocybin) saw preparation and integration (debriefing) sessions interspersed in the course of a MET program with 1 preparation session and 1 debriefing session before and after each drug session. One extra preparation session was carried out at the beginning of treatment. The second adaptation (ketamine) used no formal preparation but included an MET motivational and goal-setting session before the infusion. Subsequently, 4 more MET sessions were administered.

Discussion

The aim of the present work was to review the current therapeutic approaches adopted in clinical research on PAT to highlight common practices as well as diverging aspects and identify issues

in need of development. While most of the evidence for the efficacy of PAT can be considered preliminary and the need for more placebo-controlled trials is clear, clinical outcomes in the investigated conditions (most of which are considered chronic and refractory to treatments) seem promising (i.e., reported response rates are between 57% and 88%; reported remission rates are between 18% and 85%), especially considering that improvements are clinically relevant, sustained, observed in a short window of time, with fewer drug administrations and talk-therapy sessions compared to more established therapeutic options. For instance, literature on the efficacy of antidepressants in individuals suffering from end-of-life depression shows no clear differences when compared with placebo (e.g., Ostuzzi et al., 2018). Regarding PTSD, the Committee on the Assessment of Ongoing Efforts in the Treatment of Posttraumatic Stress Disorder estimated that up to 50% of diagnosed patients can be classified as non-responders to first-line therapies (Institute of Medicine, 2014). Similar considerations on treatment resistance and risk of relapse can be made for TRD, heroin addiction and tobacco addiction (Krupitsky et al., 2002; Cahill et al., 2014; Carhart-Harris et al., 2018a). As apparent from the outcomes of the selection process (Figure 1), several studies were excluded because they did not provide descriptions of structured psychotherapeutic interventions. Most of these excluded studies did not report use of psychotherapy (e.g., several ayahuasca studies such as Palhano-Fontes et al., 2019 or the Grob et al., 2011 psilocybin study), provided only generic labels

(e.g., regular psychodynamic psychotherapy; Müller et al., 2020) to refer to it (see for instance Berlowitz et al., 2019 or Giovannetti et al., 2020) or referenced the Johnson (2008) paper which actually provides guidelines for safety in the context of psychedelic clinical research (see for instance Griffiths et al., 2016 or Davis et al., 2021). Regarding the final subset of included studies, despite the fact that proposed theoretical frameworks and treatment structures vary considerably, our review identified factors that are almost constant and still unresolved issues.

Preparation

A preparation phase (varying in duration from 2 to 10 hours) is almost always included in both adapted and ad-hoc models and its sessions are used for a variety of purposes. In summary, all but 9 reviewed studies (n=43) explicitly mentioned a preparation phase. Almost all approaches use it to establish therapeutic alliance (Kolp et al., 2006, 2006; Johnson et al., 2014; Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Danforth et al., 2016; Ross et al., 2016; Anderson et al., 2020; Dakwar et al., 2020; Jerome et al., 2020; Monson et al., 2020). In the case of TIMBER (Pradhan et al., 2017) and of a case report on ketamine plus CBT (Ocker et al., 2020), no details on preparation sessions were reported. In psilocybin plus CBT for smoking cessation (Johnson et al., 2014) and in the CBCT plus MDMA (Monson et al., 2020), no explicit mention of interventions to improve therapeutic alliance was made.

Preparation is almost always described as a setting to discuss issues relevant to the aims of the individual and the supposed therapeutic mechanism of the model. For instance, MAP recommends exploring the themes of diagnosis, prognosis and death while promoting connection with family members as a way to prevent isolation and cultivate meaningfulness (Grof and Halifax, 1978); KPT/KET, when applied to end-of-life anxiety, explores beliefs about death and the afterlife (Kolp et al., 2007); MDMA-AP reviews trauma history (Mithoefer, 2016); PSI and KPT/KET for TRD encourage patients to talk about their hypotheses concerning the origin of their depression, anxiety or addiction (Krupitsky and Grinenko, 1997; Carhart-Harris et al., 2016; Stroud et al., 2018); finally, all adapted approaches include a preliminary phase in which treatment rationale is explained and focus is placed on the aspects that need to be worked upon to achieve remission, well-being or improvement in social skills. Furthermore, approaches such as KPT/KET, MET and QFL also explore personal motives that led each patient to pursue treatment and may even require them to produce a motivational statement to be used during the psychedelic session(s) (Kolp et al., 2007, 2007; Johnson et al., 2014; Bogenschutz et al., 2015; Dakwar et al., 2020).

This phase has a lot in common with the concept of setting clear intentions that is central to the set and setting theory (Hartogsohn, 2017; Carhart-Harris et al., 2018b) and, while most approaches tend to assume a non-directive stance toward the themes to be

178

discussed and the intentions and expectations to be set, there seems to be an exception in which therapist input plays a more central role. More on the directiveness end of the spectrum, in fact, we find KPT/KET whose preparatory sessions explicitly aim at structuring a therapeutic myth with considerable therapist input (Krupitsky and Grinenko, 1997). More specifically, positive expectations toward outcomes are established and patients are told that they will experience insights, that the causes of their addiction are unconscious in nature and related to their personality and that such causes will manifest themselves during the psychedelic session in symbolic form. Similar interventions, albeit described as less directive, can be found in the MDMA-AP treatment manual (Mithoefer, 2016). The authors, in fact, explicitly ask patients to trust their inner healing intelligence during the therapeutic process therefore assuming its “existence”, function and relevance. In both cases, whether such interventions are carried out with the aim of informing about an underlying process or to provide therapeutic suggestions to increase expectancy effects and, ultimately, therapeutic outcome is not explicitly addressed. This issue is especially relevant if we consider that psychedelics seem to increase suggestibility and, therefore, make patients more sensitive to the environment’s influence, therapist included. Furthermore, we point out that most papers describing ad-hoc and adapted therapeutic approaches with the exception of KPT/KET and MDMA-AP, only provide brief descriptions of the information and suggestions provided during the preparation phase and therefore

don't allow for an assessment of its potential suggestive effects. For instance, therapists should decide what aspect(s) should be discussed and therefore made salient in the preparation phases - be it the present symptoms, cognitions, behaviours, aspects related to conditioning processes, supposed causes, intrapsychic dynamics, existential issues or other clinically relevant themes. These considerations should stimulate clinicians and researchers alike to investigate the effects that such therapeutic strategies may have on outcomes and the most effective ways to frame PAT since the early preparation phases, to maximise effectiveness. In the case of CBCT (Monson et al., 2020) and MDMA-ATM (Danforth et al., 2016), preparation sessions are also used to train participants in acquiring skills that may be useful to go through the psychedelic experience and therapy in general.

Drug sessions

Drug sessions last between 45 minutes (i.e., ketamine sessions) and 8 hours (i.e., psilocybin sessions), are always supervised by 1 or 2 clinicians, are often held in rooms that are decorated to resemble a living room-like environment rather than a medical office, often make use of music and eyeshades and, in some cases, contain objects of personal significance to the participant. Before the onset of the effects, intentions are often reiterated and participants are often encouraged to shift their attention inward. Based on the descriptions provided in the articles, when it comes

to therapeutic stances during dosing sessions we noticed a continuum between two polarities. The first is the non-directive one (Grof and Halifax, 1978; Johnson et al., 2014; Bogenschutz et al., 2015; Carhart-Harris et al., 2016), in which therapists only aim at keeping the participants' attention inward and provide verbal and nonverbal support during challenging moments. These interventions include touching, rocking and holding hands as well as suggestions to use previously learned self-regulation techniques such as breathing and imagery exercises. It is the case of MAP, PSI, MDMA-ATM, psychedelic-assisted CBT, MDMA-assisted CBCT and psilocybin-assisted MET (Grof and Halifax, 1978; Johnson et al., 2014; Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Danforth et al., 2016; Monson et al., 2020). Moving toward more directive approaches, therapists in MDMA-AP are encouraged to identify avoidance strategies, direct patients' attention toward the issues that are considered relevant for the treatment and support them through the process (Mithoefer, 2016). Therapists are also required to remain receptive to hidden meanings that the contents of the session may suggest, thus promoting an actively interpretive stance. As was already apparent in the preparation phase, KPT/KET seems to adopt an even more directive stance. According to the original description of the method, during ketamine infusions, patients should be exposed to psychotherapeutic influences aiming at promoting sobriety and adaptive personality change (Krupitsky and Grinenko, 1997). Furthermore, the fact that this model incorporates spiritual, religious

and/or transcendental elements to the therapy session may expose patients to the risk of incorporating the therapists' belief systems (Johnson, 2021). This issue is even more sensitive if we consider the increase in suggestibility that psychedelics seem to produce (Carhart-Harris et al., 2015). The same could be said for non-empirically verified notions concerning the action of psychedelics and the nature of constructs such as the mind, personality, the self and the specific conditions that patients may be suffering from (Johnson, 2021). Among those examined in this review, TIMBER is the most directive and structured one.

Integration

Integration is a part of all approaches except for TIMBER (Pradhan et al., 2017) and is usually described as a phase in which the insights gained during the psychedelic experience are processed and generalised to everyday life. MAP, MDMA-AP, KPT/KET and the psilocybin-assisted CBT model for smoking cessation consider the final phase of the drug session - in which the substance's effects are subsiding - as the beginning of the integration phase (Grof and Halifax, 1978; Krupitsky and Grinenko, 1997; Johnson et al., 2014; Mithoefer, 2016). Patients are encouraged to discuss their experience or to write down a report in an attempt to consolidate memories and promote integration to everyday life.

Most studies provide little information about the therapeutic stance held during the integration phase and here too we find coherence

with some of the aspects we discussed above. For instance, MDMA-AP suggests the treatment as an ongoing process that unravels beyond the drug sessions themselves, into the integration sessions and in the patients' everyday life (Mithoefer, 2016). As is the case with PSI, SEGT and KPT/KEP, MDMA-AP also allows for occasional therapist interpretations of the psychedelic experience that are aimed at consolidating change and generating meaning (Krupitsky and Grinenko, 1997; Carhart-Harris et al., 2016; Mithoefer, 2016; Anderson et al., 2020). The inclusion of existentially oriented psychotherapies also seems to recur in this phase, supposedly because of its focus on meaningfulness (Grof and Halifax, 1978; Krupitsky and Grinenko, 1997).

Directiveness, information, expectation and suggestion

Early PAT models emphasised the importance of non-directiveness and of letting the therapeutic frame and the contents of sessions define themselves during the course of preparation, drug sessions and integration (Grof and Halifax, 1978). This general direction was adopted by several more modern approaches and is apparent from both direct descriptions of the methods and the suggestion to integrate elements from therapeutic models derived from very different theoretical premises (e.g., supportive psychotherapy, cognitive-behavioural therapy, existentially oriented psychotherapies, psychodynamic psychotherapy, mindfulness-based treatments).

While this framing allows for considerable flexibility on the therapists' part, it also reveals that a clear picture of what may make PAT work is still missing. Since the first moments of preparation, patients are presented with information and suggestions concerning therapy that will establish specific expectations. This aspect should be thoroughly investigated, especially if we consider that expectations seem to play a relevant role in defining the effectiveness of clinical interventions (Muthukumaraswamy et al., 2021). In a more practical sense, therapists should know if, how and where they should orient the contents of the sessions and how to treat such materials once they surface. The studies mentioned in this review suggest that the focus could be placed on the supposed causes of suffering, present life, intrapsychic dynamics, existential issues, family issues and/or traumatic events.

Moving to the more interventionist contributions, some of them provide a structured model of the condition (e.g., lack self-regulation skills, maladaptive personality profiles), actively intervene to build a tailored therapeutic myth or suggest the presence of inner processes promoting healing that can act once patients surrender to the psychedelic experience. Considering the potential increase in suggestibility caused by psychedelic substances (Carhart-Harris et al., 2015), a better understanding of what works for whom is highly desirable and future research should focus on determining the general interventions that make PAT work and the specific adaptations that may be required for different patient populations.

More concisely, therapists should know what aspects to make salient during the continuous process that is the establishment of appropriate therapeutic sets and settings.

Another way to look at the issue may be framing it in terms of potentially enhanced learning (Banks et al., 2021) and cognitive flexibility (Kuypers et al., 2016) that could facilitate acquisition and extinction. In this framework, psychedelics may be used to optimise already established CBT strategies in order to improve response rates and stability of results. Among the common themes emerged from our review we should also mention meaning-making as an aim of PAT. Aspects related to meaning making seem to be associated with psychological well-being (Preller et al., 2017) and psychedelic sessions have been found to increase perceived meaningfulness (Kaelen et al., 2018). Future research should focus on investigating how to integrate the search for meaning in PAT, in terms of the economy of both the single sessions and the therapeutic journey as a whole. Furthermore, while most approaches seem to value rapport, research on the potential moderating effects that varying degrees of therapeutic alliance may have on clinical outcomes of PAT is still in need of development (Carhart-Harris et al., 2018b). Finally, except for one study regarding KET/KPT (Krupitsky et al., 2007), we found no studies directly addressing the effects of treatment duration, number of drug and drug-free sessions on both clinical improvement and its stability in time. This is another relevant area to focus upon in future research.

Conclusion

The present paper critically reviews the models of PAT framing to provide a comprehensive picture of current practices in clinical psychedelic research. While some structural aspects of PAT seem to recur in clinical studies, the therapeutic stance and theoretical frameworks seem far from being exhaustively defined. Considering that psychedelics seem to enhance sensitivity to the internal and external environment (i.e., suggestibility), future research should provide more details on how such environments are constructed in terms of suggestions, description of the mechanisms underlying conditions and treatments, setting of expectations, therapeutic models employed and quality of the therapeutic relationship. This review fills a gap in the current literature and provides a systematic way to think about psychotherapeutic framing of PAT. The concepts discussed above are relevant to future construction of studies, designing of training programs for aspiring psychedelic psychotherapists and are presented with the intention to contribute to the development and implementation of PAT in several fields of psychiatric, psychological and medical relevance.

References

Abramson, H. A. (1960). *The Use of LSD in Psychotherapy: Transactions*. Josiah Macy, Jr. Foundation.

*Agin-Liebes, G., Ekman, E., Anderson, B., Malloy, M., Haas, A., and Woolley, J. (2021). Participant Reports of Mindfulness, Posttraumatic Growth, and Social Connectedness in Psilocybin-Assisted Group Therapy: An Interpretive Phenomenological Analysis. *J. Humanist. Psychol.*, 002216782110229. Doi:10.1177/00221678211022949.

*Agin-Liebes, G. I., Malone, T., Yalch, M. M., Mennenga, S. E., Ponté, K. L., Guss, J., et al. (2020). Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *J. Psychopharmacol. (Oxf.)* 34, 155–166. Doi:10.1177/0269881119897615.

Andersen, K. A. A., Carhart-Harris, R., Nutt, D. J., and Erritzoe, D. (2021). Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatr. Scand.* 143, 101–118. Doi:10.1111/acps.13249.

*Anderson, B. T., Danforth, A., Daroff, P. R., Stauffer, C., Ekman, E., Agin-Liebes, G., et al. (2020). Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label

safety and feasibility pilot study. *EclinicalMedicine* 27, 100538. Doi:10.1016/j.eclinm.2020.100538.

Bahji, A., Forsyth, A., Groll, D., and Hawken, E. R. (2020). Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder: A systematic review and meta-analysis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 96, 109735. Doi:10.1016/j.pnpbp.2019.109735.

Bandura, A. (1982). Self-efficacy mechanism in human agency. *Am. Psychol.* 37, 122.

Banks, M. I., Zahid, Z., Jones, N. T., Sultan, Z. W., and Wenthur, C. J. (2021). Catalysts for change: the cellular neurobiology of psychedelics. *Mol. Biol. Cell* 32, 1135–1144. Doi:10.1091/mbc.E20-05-0340.

*Barone, W., Beck, J., Mitsunaga-Whitten, M., and Perl, P. (2019). Perceived Benefits of MDMA-Assisted Psychotherapy beyond Symptom Reduction: Qualitative Follow-Up Study of a Clinical Trial for Individuals with Treatment-Resistant PTSD. *J. Psychoactive Drugs* 51, 199–208. Doi:10.1080/02791072.2019.1580805.

*Belser, A. B., Agin-Liebes, G., Swift, T. C., Terrana, S., Devenot, N., Friedman, H. L., et al. (2017). Patient Experiences of Psilocybin-Assisted Psychotherapy: An Interpretative Phenomenological

Analysis. *J. Humanist. Psychol.* 57, 354–388.
Doi:10.1177/0022167817706884.

Berlowitz, I., Walt, H., Ghasarian, C., Mendive, F., & Martin-Soelch, C. (2019). Short-Term Treatment Effects of a Substance Use Disorder Therapy Involving Traditional Amazonian Medicine. *Journal of Psychoactive Drugs*, 51(4), 323–334.
<https://doi.org/10.1080/02791072.2019.1607956>

Blake, R., & Mouton, J. (1964). *The managerial grid: The key to leadership excellence*. Gulf Publishing Co, 350.

Bögels, S., Hoogstad, B., Dun, L. van, Schutter, S. de, and Restifo, K. (2008). Mindfulness Training for Adolescents with Externalizing Disorders and their Parents. *Behav. Cogn. Psychother.* 36, 193–209. Doi:10.1017/S1352465808004190.

*Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P., and Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *J. Psychopharmacol. (Oxf.)* 29, 289–299.
Doi:10.1177/0269881114565144.

*Bogenschutz, M. P., Podrebarac, S. K., Duane, J. H., Amegadzie, S. S., Malone, T. C., Owens, L. T., et al. (2018). Clinical Interpretations of Patient Experience in a Trial of Psilocybin-

Assisted Psychotherapy for Alcohol Use Disorder. *Front. Pharmacol.* 9, 100. Doi:10.3389/fphar.2018.00100.

*Bouso, J. C., Doblin, R., Farré, M., Alcázar, M. Á., and Gómez-Jarabo, G. (2008). MDMA-Assisted Psychotherapy Using Low Doses in a Small Sample of Women with Chronic Posttraumatic Stress Disorder. *J. Psychoactive Drugs* 40, 225–236. Doi:10.1080/02791072.2008.10400637.

*Bowen, W. T., Soskin, R. A., & Chotlos, J. W. (1970). Lysergic acid diethylamide as a variable in the hospital treatment of alcoholism. *J Nerv Ment Dis* 150 (2), 111-8. Doi: 10.1097/00005053-197002000-00003.

Bradley, R., Greene, J., Russ, E., Dutra, L., and Westen, D. (2005). A Multidimensional Meta-Analysis of Psychotherapy for PTSD. *Am. J. Psychiatry* 162, 214–227. Doi:10.1176/appi.ajp.162.2.214.

Cahill, K., Stevens, S., and Lancaster, T. (2014). Pharmacological Treatments for Smoking Cessation. *JAMA* 311, 193–194. Doi:10.1001/jama.2013.283787.

Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., et al. (2018a). Psilocybin with psychological support for treatment-resistant depression: six-month

follow-up. *Psychopharmacology (Berl.)* 235, 399–408.
Doi:10.1007/s00213-017-4771-x.

*Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., et al. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* 3, 619–627. Doi:10.1016/S2215-0366(16)30065-7.

Carhart-Harris, R. L., and Friston, K. J. (2019). REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacol. Rev.* 71, 316–344.
Doi:10.1124/pr.118.017160.

Carhart-Harris, R. L., Kaelen, M., Whalley, M. G., Bolstridge, M., Feilding, A., and Nutt, D. J. (2015). LSD enhances suggestibility in healthy volunteers. *Psychopharmacology (Berl.)* 232, 785–794.
Doi:10.1007/s00213-014-3714-z.

Carhart-Harris, R. L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., Branchi, I., et al. (2018b). Psychedelics and the essential importance of context. *J. Psychopharmacol. (Oxf.)* 32, 725–731.
Doi:10.1177/0269881118754710.

*Carhart-Harris, R., and Nutt, D. (2017). Serotonin and brain function: a tale of two receptors. *J. Psychopharmacol. (Oxf.)* 31, 1091–1120. Doi:10.1177/0269881117725915.

Classen, C., Diamond, S., Soleman, A., Fobair, P., Spira, J., and Spiegel, D. (1993). Brief supportive-expressive group therapy for women with primary breast cancer: A treatment manual. Eds Book Brief Support.-Expressive Group Ther. Women Prim. Breast Cancer Treat. Man. Psychosoc. Treat. Lab. Stanf. CA.

Crocket, R., Sandison, R. A., and Walk, A. (1963). Hallucinogenic drugs and their psychotherapeutic use. 1st ed. London: Royal Medico-Psychological Association.

*Dakwar, E., Levin, F., Hart, C. L., Basaraba, C., Choi, J., Pavlicova, M., et al. (2020). A Single Ketamine Infusion Combined With Motivational Enhancement Therapy for Alcohol Use Disorder: A Randomized Midazolam-Controlled Pilot Trial. *Am. J. Psychiatry* 177, 125–133. Doi:10.1176/appi.ajp.2019.19070684.

*Danforth, A. L., Grob, C. S., Struble, C., Feduccia, A. A., Walker, N., Jerome, L., et al. (2018). Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology (Berl.)* 235, 3137–3148. Doi:10.1007/s00213-018-5010-9.

Danforth, A. L., Struble, C. M., Yazar-Klosinski, B., and Grob, C. S. (2016). MDMA-assisted therapy: A new treatment model for social anxiety in autistic adults. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 64, 237–249. Doi:10.1016/j.pnpbp.2015.03.011.

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, 78(5), 481. <https://doi.org/10.1001/jamapsychiatry.2020.3285>

de Vos, C. M. H., Mason, N. L., and Kuypers, K. P. C. (2021). Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics. *Front. Psychiatry* 12, 724606. Doi:10.3389/fpsy.2021.724606.

*Erritzoe, D., Roseman, L., Nour, M. M., MacLean, K., Kaelen, M., Nutt, D. J., et al. (2018). Effects of psilocybin therapy on personality structure. *Acta Psychiatr. Scand.* 138, 368–378. Doi:10.1111/acps.12904.

Fanciullacci, M., Bene, E. D., Franchi, G., and Sicuteri, F. (1977). Phantom Limb Pain: Sub-Hallucinogenic Treatment With Lysergic Acid Diethylamide (LSD-25). *Headache J. Head Face Pain* 17, 118–119. Doi:10.1111/j.1526-4610.1977.hed1703118.x.

Feder, A., Parides, M. K., Murrough, J. W., Perez, A. M., Morgan, J. E., Saxena, S., et al. (2014). Efficacy of Intravenous Ketamine for Treatment of Chronic Posttraumatic Stress Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* 71, 681–688. Doi:10.1001/jamapsychiatry.2014.62.

Frank, J. D., and Frank, J. B. (1993). *Persuasion and Healing: A Comparative Study of Psychotherapy*. JHU Press.

*Garcia-Romeu, A., Griffiths, R. R., and Johnson, M. W. (2014). Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. *Curr. Drug Abuse Rev.* 7, 157–164. Doi:10.2174/1874473708666150107121331.

Gasser, P. (1996). Die psycholytische Psychotherapie in der Schweiz von 1988 bis 1993. *Arch. Suisses Neurol. Psychiatr.* 147, 59–66.

Giovannetti, C., Garcia Arce, S., Rush, B., & Mendive, F. (2020). Pilot Evaluation of a Residential Drug Addiction Treatment Combining Traditional Amazonian Medicine, Ayahuasca and Psychotherapy on Depression and Anxiety. *Journal of Psychoactive Drugs*, 52(5), 472–481. <https://doi.org/10.1080/02791072.2020.1789247>

Green, S. M., Roback, M. G., Kennedy, R. M., and Krauss, B. (2011). Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update. *Ann. Emerg. Med.* 57, 449–461. Doi:10.1016/j.annemergmed.2010.11.030.

Greer, G. R., and Tolbert, R. (1998). A Method of Conducting Therapeutic Sessions with MDMA. *J. Psychoactive Drugs* 30, 371–379. Doi:10.1080/02791072.1998.10399713.

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, 30(12), 1181–1197. <https://doi.org/10.1177/0269881116675513>

Grob, C. S., Danforth, A. L., Chopra, G. S., Hagerty, M., McKay, C. R., Halberstadt, A. L., & Greer, G. R. (2011). Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. *Archives of General Psychiatry*, 68(1), 71. <https://doi.org/10.1001/archgenpsychiatry.2010.116>

Grof, S., Goodman, L. E., Richards, W. A., and Kurland, A. A. (1973). LSD-assisted psychotherapy in patients with terminal cancer. *Int. Pharmacopsychiatry* 8, 129–144.

Grof, S., and Halifax, J. (1978). *The human encounter with death*. New York: E.P. Dutton.

Grof, S. (2016). *Realms of the human unconscious: Observations from LSD research*. Souvenir Press.

Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Sci. Policy Law* 3, 205032451668332. Doi:10.1177/2050324516683325.

Hutten, N. R. P. W., Mason, N. L., Dolder, P. C., Theunissen, E. L., Holze, F., Liechti, M. E., et al. (2021). Low Doses of LSD Acutely Increase BDNF Blood Plasma Levels in Healthy Volunteers. *ACS Pharmacol. Transl. Sci.* 4, 461–466. Doi:10.1021/acsptsci.0c00099.

Institute of Medicine (2014). *Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations: Final Assessment*. Washington, DC: The National Academies Press doi:10.17226/18724.

*Jardim, A. V., Jardim, D. V., Chaves, B. R., Steglich, M., Ot'alora G., M., Mithoefer, M. C., et al. (2021). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for victims of sexual abuse with severe post-

traumatic stress disorder: an open label pilot study in Brazil. *Braz. J. Psychiatry* 43, 181–185. Doi:10.1590/1516-4446-2020-0980.

*Jerome, L., Feduccia, A. A., Wang, J. B., Hamilton, S., Yazar-Klosinski, B., Emerson, A., et al. (2020). Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology (Berl.)* 237, 2485–2497. Doi:10.1007/s00213-020-05548-2.

Johnson, M., Richards, W., and Griffiths, R. (2008). Human hallucinogen research: guidelines for safety. *J. Psychopharmacol. (Oxf.)* 22, 603–620. Doi:10.1177/0269881108093587.

*Johnson, M. W., Garcia-Romeu, A., Cosimano, M. P., and Griffiths, R. R. (2014). Pilot study of the 5-HT 2A R agonist psilocybin in the treatment of tobacco addiction. *J. Psychopharmacol. (Oxf.)* 28, 983–992. Doi:10.1177/0269881114548296.

*Johnson, M. W., Garcia-Romeu, A., and Griffiths, R. R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. *Am. J. Drug Alcohol Abuse* 43, 55–60. Doi:10.3109/00952990.2016.1170135.

Johnson, M. W. (2021). *Consciousness, Religion, and Gurus: Pitfalls of Psychedelic Medicine*. ACS Pharmacology &

Translational Science, 4(2), 578–581.
<https://doi.org/10.1021/acsptsci.0c00198>

Kaelen, M., Giribaldi, B., Raine, J., Evans, L., Timmerman, C., Rodriguez, N., et al. (2018). The hidden therapist: evidence for a central role of music in psychedelic therapy. *Psychopharmacology (Berl.)* 235, 505–519. Doi:10.1007/s00213-017-4820-5.

Kast, E. (1967). Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide. *Psychiatr. Q.* 41, 646–657. Doi:10.1007/BF01575629.

*Kolp, E., Friedman, H. L., Young, M. S., and Krupitsky, E. (2006). Ketamine Enhanced Psychotherapy: Preliminary Clinical Observations on Its Effectiveness in Treating Alcoholism. *Humanist. Psychol.* 34, 399–422. Doi:10.1207/s15473333thp3404_7.

*Kolp, E., Young, M. S., Florida Mental Health Institute of University of South Florida, Friedman, H., University of Florida, Krupitsky, E., et al. (2007). Ketamine-Enhanced Psychotherapy: Preliminary Clinical Observations on its Effects in Treating Death Anxiety. *Int. J. Transpers. Stud.* 26, 1–17. Doi:10.24972/ijts.2007.26.1.1.

*Krupitsky, E., Burakov, A., Romanova, T., Dunaevsky, I., Strassman, R., and Grinenko, A. (2002). Ketamine psychotherapy

for heroin addiction: immediate effects and two-year follow-up. *J. Subst. Abuse Treat.* 23, 273–283. Doi:10.1016/S0740-5472(02)00275-1.

*Krupitsky, E. M., Burakov, A. M., Dunaevsky, I. V., Romanova, T. N., Slavina, T. Y., and Grinenko, A. Y. (2007). Single Versus Repeated Sessions of Ketamine-Assisted Psychotherapy for People with Heroin Dependence. *J. Psychoactive Drugs* 39, 13–19. Doi:10.1080/02791072.2007.10399860.

Krupitsky, E. M., Grineko, Y., Berkaliyev, T. N., Paley, I., and Tetrov, N. (1992). The Combination of Psychedelic and Aversive Approaches in Alcoholism Treatment: The Affective Contra-Attribution Method. *Alcohol. Treat. Q.*, 7.

*Krupitsky, E. M., and Grinenko, A. Y. (1997). Ketamine Psychedelic Therapy (KPT): A Review of the Results of Ten Years of Research. *J. Psychoactive Drugs* 29, 165–183. Doi:10.1080/02791072.1997.10400185.

*Kurland, A. A. (1985). LSD in the Supportive Care of the Terminally Ill Cancer Patient. *Journal of Psychoactive Drugs*, 17(4), 279–290. <https://doi.org/10.1080/02791072.1985.10524332>

Kuypers, K. P. C., Riba, J., de la Fuente Revenga, M., Barker, S., Theunissen, E. L., and Ramaekers, J. G. (2016). Ayahuasca

enhances creative divergent thinking while decreasing conventional convergent thinking. *Psychopharmacology (Berl.)* 233, 3395–3403. Doi:10.1007/s00213-016-4377-8.

Lambert, J. E., Engh, R., Hasbun, A., and Holzer, J. (2012). Impact of posttraumatic stress disorder on the relationship quality and psychological distress of intimate partners: A meta-analytic review. *J. Fam. Psychol.* 26, 729–737. Doi:10.1037/a0029341.

Leary, T. (1961). Drugs, set & suggestibility. In annual meeting of the American Psychological Association.

Leuner, H. (1967). Present state of psycholytic therapy and its possibilities. *Use LSD Psychother. Alcohol.* 101.

Liebman, R. E., Whitfield, K. M., Sijercic, I., Ennis, N., and Monson, C. M. (2020). Harnessing the Healing Power of Relationships in Trauma Recovery: a Systematic Review of Cognitive-Behavioral Conjoint Therapy for PTSD. *Curr. Treat. Options Psychiatry* 7, 203–220. Doi:10.1007/s40501-020-00211-1.

Linehan, M. M. (2018). *Cognitive-Behavioral Treatment of Borderline Personality Disorder*. Guilford Publications.

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., et al. (2018). Psychedelics Promote Structural and

Functional Neural Plasticity. *Cell Rep.* 23, 3170–3182.
Doi:10.1016/j.celrep.2018.05.022.

Majić, T., Schmidt, T. T., and Gallinat, J. (2015). Peak experiences and the afterglow phenomenon: When and how do therapeutic effects of hallucinogens depend on psychedelic experiences? *J. Psychopharmacol.* (Oxf.) 29, 241–253.
Doi:10.1177/0269881114568040.

Maldonado, J., Durán, R., and Koopman, C. (1996). Supportive-expressive group therapy for people with HIV infection: A primer.

*Malone, T. C., Mennenga, S. E., Guss, J., Podrebarac, S. K., Owens, L. T., Bossis, A. P., et al. (2018). Individual Experiences in Four Cancer Patients Following Psilocybin-Assisted Psychotherapy. *Front. Pharmacol.* 9, 256.
Doi:10.3389/fphar.2018.00256.

Marks, D. F. (1993). *The Quit for Life Programme: an Easier Way to Stop Smoking and Not Start Again*. Leicester: Blackwell Publishers.

Marks, D. F., and Sykes, C. M. (2002). Randomized controlled trial of cognitive behavioural therapy for smokers living in a deprived area of London: Outcome at one-year follow-up. *Psychol. Health Med.* 7, 17–24. Doi:10.1080/13548500120101513.

McCallie, M. S., Blum, C. M., and Hood, C. J. (2006). Progressive Muscle Relaxation. *J. Hum. Behav. Soc. Environ.* 13, 51–66. Doi:10.1300/J137v13n03_04.

*Mertens, L. J., Wall, M. B., Roseman, L., Demetriou, L., Nutt, D. J., and Carhart-Harris, R. L. (2020). Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. *J. Psychopharmacol. (Oxf.)* 34, 167–180. Doi:10.1177/0269881119895520.

Miller, W. R. (1994). *Motivational enhancement therapy manual: a clinical research guide for therapists treating individuals with alcohol abuse and dependence.* Diane Publishing Company.

Miller, W. R., and Rollnick, S. (1991). *Motivational interviewing: Preparing people to change addictive behavior.* New York, NY, US: The Guilford Press.

*Mitchell, J. M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., et al. (2021). MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat. Med.* 27, 1025–1033. Doi:10.1038/s41591-021-01336-3.

Mithoefer, M. C. (2016). *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder*. 75.

*Mithoefer, M. C., Feduccia, A. A., Jerome, L., Mithoefer, A., Wagner, M., Walsh, Z., et al. (2019). MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology (Berl.)* 236, 2735–2745.

*Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., et al. (2018). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry* 5, 486–497. Doi:10.1016/S2215-0366(18)30135-4.

*Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., and Doblin, R. (2011). The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J. Psychopharmacol. Oxf. Engl.* 25, 439–452. Doi:10.1177/0269881110378371.

*Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., Martin, S. F., Yazar-Klosinski, B., et al. (2013). Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3, 4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *J. Psychopharmacol. (Oxf.)* 27, 28–39.

Monson, C. M., and Fredman, S. J. (2012). Cognitive-Behavioral Conjoint Therapy for PTSD. 257.

Monson, C. M., Fredman, S. J., and Dekel, R. (2010). "Posttraumatic stress disorder in an interpersonal context," in *Interpersonal processes in the anxiety disorders: Implications for understanding psychopathology and treatment* (Washington, DC, US: American Psychological Association), 179–208. Doi:10.1037/12084-007.

*Monson, C. M., Wagner, A. C., Mithoefer, A. T., Liebman, R. E., Feduccia, A. A., Jerome, L., et al. (2020). MDMA-facilitated cognitive-behavioural conjoint therapy for posttraumatic stress disorder: an uncontrolled trial. *Eur. J. Psychotraumatology* 11, 1840123. Doi:10.1080/20008198.2020.1840123.

Müller, F., Mühlhauser, M., Holze, F., Lang, U. E., Walter, M., Liechti, M. E., & Borgwardt, S. (2020). Treatment of a Complex

Personality Disorder Using Repeated Doses of LSD—A Case Report on Significant Improvements in the Absence of Acute Drug Effects. *Frontiers in Psychiatry*, 11, 573953. <https://doi.org/10.3389/fpsy.2020.573953>

Muthukumaraswamy, S., Forsyth, A., and Lumley, T. (2021). Blinding and Expectancy Confounds in Psychedelic Randomised Controlled Trials. *PsyArXiv* doi:10.31234/osf.io/q2hzm.

*Nielson, E. M., May, D. G., Forcehimes, A. A., and Bogenschutz, M. P. (2018). The Psychedelic Debriefing in Alcohol Dependence Treatment: Illustrating Key Change Phenomena through Qualitative Content Analysis of Clinical Sessions. *Front. Pharmacol.* 9. Available at: <https://www.frontiersin.org/article/10.3389/fphar.2018.00132> [Accessed February 24, 2022].

*Noorani, T., Garcia-Romeu, A., Swift, T. C., Griffiths, R. R., and Johnson, M. W. (2018). Psychedelic therapy for smoking cessation: Qualitative analysis of participant accounts. *J. Psychopharmacol. (Oxf.)* 32, 756–769. Doi:10.1177/0269881118780612.

Nutt, D., Erritzoe, D., and Carhart-Harris, R. (2020). Psychedelic Psychiatry's Brave New World. *Cell* 181, 24–28. Doi:10.1016/j.cell.2020.03.020.

*Ocker, A. C., Shah, N. B., Schwenk, E. S., Witkowski, T. A., Cohen, M. J., and Viscusi, E. R. (2020). Ketamine and Cognitive Behavioral Therapy for Rapid Opioid Tapering With Sustained Opioid Abstinence: A Case Report and 1-Year Follow-up. *Pain Pract.* 20, 95–100. Doi:10.1111/papr.12829.

*Oehen, P., Traber, R., Widmer, V., and Schnyder, U. (2013). A randomized, controlled pilot study of MDMA (\pm 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *J. Psychopharmacol. (Oxf.)* 27, 40–52. Doi:10.1177/0269881112464827.

Orford, J. (1986). "Critical Conditions for Change in the Addictive Behaviours," in *Treating AbbehavioursBehaviors: Processes of Change Applied Clinical Psychology.*, eds. W. R. Miller and N. Heather (Boston, MA: Springer US), 91–108. doi:10.1007/978-1-4613-2191-0_5.

Ostuzzi, G., Matcham, F., Dauchy, S., Barbui, C., and Hotopf, M. (2018). Antidepressants for the treatment of depression in people with cancer. *Cochrane Database Syst. Rev.* doi:10.1002/14651858.CD011006.pub3.

*Ot'abora G, M., Grigsby, J., Poulter, B., Van Derveer III, J. W., Giron, S. G., Jerome, L., et al. (2018). 3, 4-

Methylenedioxyamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: a randomized phase 2 controlled trial. *J. Psychopharmacol. (Oxf.)* 32, 1295–1307.

*Pahnke, W. N., Kurland, A. A., Goodman, L. E., & Richards, W. A. (1969). LSD-assisted psychotherapy with terminal cancer patients. *Current psychiatric therapies*, 9, 144-152.

Pahnke, W. N., Kurland, A. A., Unger, S., Savage, C., and Grof, S. (1970). The experimental use of psychedelic (LSD) psychotherapy. *JAMA* 212, 1856–1863.

Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., Mota-Rolim, S. A., Osório, F. L., Sanches, R., dos Santos, R. G., Tófoli, L. F., de Oliveira Silveira, G., Yonamine, M., Riba, J., Santos, F. R., Silva-Junior, A. A., Alchieri, J. C., Galvão-Coelho, N. L., Lobão-Soares, B., ... Araújo, D. B. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: A randomized placebo-controlled trial. *Psychological Medicine*, 49(4), 655–663. <https://doi.org/10.1017/S0033291718001356>

*Pradhan, B., Mitrev, L., Moaddell, R., and Wainer, I. W. (2018). D-Serine is a potential biomarker for clinical response in treatment of post-traumatic stress disorder using (R, S)-ketamine infusion and TIMBER psychotherapy: A pilot study. *Biochim. Biophys. Acta BBA*

– Proteins Proteomics 1866, 831–839.
Doi:10.1016/j.bbapap.2018.03.006.

Pradhan, B., and Pinninti, N. R. (2016). “Yoga and Mindfulness-Based Cognitive Therapy for Psychosis (Y-MBCTp©): A Pilot Study on Its Efficacy as Brief Therapy,” in *Brief Interventions for Psychosis: A Clinical Compendium*, eds. B. Pradhan, N. Pinninti, and S. Rathod (Cham: Springer International Publishing), 55–87.
Doi:10.1007/978-3-319-30521-9_5.

*Pradhan, B., Wainer, I., Moaddel, R., Torjman, M., Goldberg, M., Sabia, M., et al. (2017). Trauma Interventions using Mindfulness Based Extinction and Reconsolidation (TIMBER) psychotherapy prolong the therapeutic effects of single ketamine infusion on post-traumatic stress disorder and comorbid depression: a pilot randomized, placebo-controlled, crossover clinical trial. *Asia Pac. J. Clin. Trials Nerv. Syst. Dis.* 2, 80. Doi:10.4103/2542-3932.211589.

Preller, K. H., Herdener, M., Pokorny, T., Planzer, A., Kraehenmann, R., Stämpfli, P., et al. (2017). The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. *Curr. Biol.* 27, 451–457.
Doi:10.1016/j.cub.2016.12.030.

Prochaska, J., and DiClemente, C. (1985). Processes and stages of change in smoking, weight control, and psychological distress. *Coping Subst. Abuse*, 319–345.

Prochaska, J. O. (1992). Stage of change in the modification of problem I. *Prog. Behav. Modif.*, 184–218.

Prochaska, J. O., and DiClemente, C. C. (1994). *The transtheoretical approach: Crossing traditional boundaries of therapy*. Krieger Publishing Company.

Richards, W. (2015). *Sacred Knowledge: Psychedelics and Religious Experiences*. Columbia University Press
doi:10.7312/rich17406.

*Roseman, L., Nutt, D. J., and Carhart-Harris, R. L. (2018). Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. *Front. Pharmacol.* 8, 974. doi:10.3389/fphar.2017.00974.

*Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., et al. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J. Psychopharmacol. (Oxf.)* 30, 1165–1180.
doi:10.1177/0269881116675512.

*Rothberg, R. L., Azhari, N., Haug, N. A., and Dakwar, E. (2021). Mystical-type experiences occasioned by ketamine mediate its impact on at-risk drinking: Results from a randomized, controlled trial. *J. Psychopharmacol. (Oxf.)* 35, 150–158. doi:10.1177/0269881120970879.

*Sessa, B., Higbed, L., O'Brien, S., Durant, C., Sakal, C., Titheradge, D., et al. (2021). First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *J. Psychopharmacol. (Oxf.)* 35, 375–383. doi:10.1177/0269881121991792.

*Sessa, B., Sakal, C., O'Brien, S., and Nutt, D. (2019). First study of safety and tolerability of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with alcohol use disorder: preliminary data on the first four participants. *BMJ Case Rep.* 12, E230109. doi:10.1136/bcr-2019-230109.

Shnaider, P., Pukay-Martin, N. D., Fredman, S. J., Macdonald, A., and Monson, C. M. (2014). Effects of Cognitive-Behavioral Conjoint Therapy for PTSD on Partners' Psychological Functioning: CBCT for PTSD and Partners. *J. Trauma. Stress* 27, 129–136. doi:10.1002/jts.21893.

Smith, C. M. (1958). A New Adjunct to the Treatment of Alcoholism: The Hallucinogenic Drugs. *Q. J. Stud. Alcohol* 19, 406–417. doi:10.15288/qjsa.1958.19.406.

Spek, A. A., van Ham, N. C., and Nyklíček, I. (2013). Mindfulness-based therapy in adults with an autism spectrum disorder: A randomized controlled trial. *Res. Dev. Disabil.* 34, 246–253. doi:10.1016/j.ridd.2012.08.009.

*Stauffer, C. S., Anderson, B. T., Ortigo, K. M., and Woolley, J. (2021). Psilocybin-Assisted Group Therapy and Attachment: Observed Reduction in Attachment Anxiety and Influences of Attachment Insecurity on the Psilocybin Experience. *ACS Pharmacol. Transl. Sci.* 4, 526–532. doi:10.1021/acspsci.0c00169.

*Stroud, J. B., Freeman, T. P., Leech, R., Hindocha, C., Lawn, W., Nutt, D. J., et al. (2018). Psilocybin with psychological support improves emotional face recognition in treatment-resistant depression. *Psychopharmacology (Berl.)* 235, 459–466. doi:10.1007/s00213-017-4754-y.

*Swift, T. C., Belser, A. B., Agin-Liebes, G., Devenot, N., Terrana, S., Friedman, H. L., et al. (2017). Cancer at the Dinner Table: Experiences of Psilocybin-Assisted Psychotherapy for the Treatment of Cancer-Related Distress. *J. Humanist. Psychol.* 57, 488–519. doi:10.1177/0022167817715966.

Sykes, C. M., and Marks, D. F. (2001). Effectiveness of a cognitive behaviour therapy self-help programme for smokers in London, UK. *Health Promot. Int.* 16, 255–260. doi:10.1093/heapro/16.3.255.

Taft, C. T., Watkins, L. E., Stafford, J., Street, A. E., and Monson, C. M. (2011). Posttraumatic stress disorder and intimate relationship problems: A meta-analysis. *J. Consult. Clin. Psychol.* 79, 22–33. doi:10.1037/a0022196.

*Wagner, A. C., Liebman, R. E., Mithoefer, A. T., Mithoefer, M. C., and Monson, C. M. (2021). Relational and Growth Outcomes Following Couples Therapy With MDMA for PTSD. *Front. Psychiatry* 12, 702838. doi:10.3389/fpsyt.2021.702838.

*Wagner, A. C., Mithoefer, M. C., Mithoefer, A. T., and Monson, C. M. (2019). Combining Cognitive-Behavioral Conjoint Therapy for PTSD with 3,4-Methylenedioxymethamphetamine (MDMA): A Case Example. *J. Psychoactive Drugs* 51, 166–173. doi:10.1080/02791072.2019.1589028.

*Watts, R., Day, C., Krzanowski, J., Nutt, D., and Carhart-Harris, R. (2017). Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression. *J. Humanist. Psychol.* 57, 520–564. doi:10.1177/0022167817709585.

Wheeler, S. W., and Dyer, N. L. (2020). A systematic review of psychedelic-assisted psychotherapy for mental health: An evaluation of the current wave of research and suggestions for the future. *Psychol. Conscious. Theory Res. Pract.* 7, 279–315. doi:10.1037/cns0000237.

*Wilkinson, S. T., Rhee, T. G., Joormann, J., Webler, R., Ortiz Lopez, M., Kitay, B., et al. (2021). Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. *Psychother. Psychosom.* 90, 318–327. doi:10.1159/000517074.

*Wilkinson, S. T., Wright, D., Fasula, M. K., Fenton, L., Griep, M., Ostroff, R. B., et al. (2017). Cognitive Behavior Therapy May Sustain Antidepressant Effects of Intravenous Ketamine in Treatment-Resistant Depression. *Psychother. Psychosom.* 86, 162–167. doi:10.1159/000457960.

*Wolfson, P. E., Andries, J., Feduccia, A. A., Jerome, L., Wang, J. B., Williams, E., et al. (2020). MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. *Sci. Rep.* 10, 20442. doi:10.1038/s41598-020-75706-1.

Wolfson, P., and Hartelius, G. (2016). *The ketamine papers: Science, therapy, and transformation*. Multidisciplinary Association for Psychedelic Studies.

Zernig, G., Wallner, R., Grohs, U., Kriechbaum, N., Kemmler, G., and Saria, A. (2008). A randomized trial of short psychotherapy versus sustained-release bupropion for smoking cessation. *Addiction* 103, 2024–2031. doi:10.1111/j.1360-0443.2008.02348.x.

* Studies included in the present review.

Chapter 5

The therapeutic process of a fibromyalgia patient after a psychedelic retreat: a single case, 6 months follow-up study

Cavarra M., Whitfield H., Watling R., Ramaekers J. G., Theunissen E. L., Kuypers K. P. C.

This study examines the effects of psychedelic-assisted psychotherapy (PAP) in a 36-year-old psychologist, "Adam", who was suffering from fibromyalgia (FM). It evaluates changes in depression, anxiety, stress, mindfulness, cognitive fusion, and psychological flexibility at baseline, 2 weeks, 3 months, and 6 months post-psychedelic retreat. Interpretative phenomenological analysis (IPA) of interviews conducted at the 2 weeks, 3 months and 6 months time points explores Adam's retreat experiences, treatment outcomes, and integration sessions' effects. Results show decreased depression, anxiety, stress, and cognitive fusion, along with enhanced psychological flexibility and mindfulness. Adam gained a sustained feeling of inner guidance and connection with others, enacted lifestyle changes, perceived spiritual growth,

FM pain relief, and increased awareness. He could acknowledge suppressed trauma and better address emotional needs. The study underscores PAP's benefits for FM and mental health, suggesting its role in facilitating meaning-making and value-driven actions. However, limitations include potential bias from retrospective accounts, concurrent experiences' influence, and lifestyle changes. This case contributes to evidence supporting PAP in chronic pain management, demonstrating its promise in enhancing well-being and pain relief.

Introduction

Clinical applications of serotonergic psychedelics have recently been gaining momentum thanks to trials showing promising results in hard-to-treat conditions such as treatment-resistant depression (Carhart-Harris et al., 2016, 2018; Palhano-Fontes et al., 2019) and end-of-life anxiety (e.g. Ross, 2018). While recent research shows that they may have a therapeutic effect on their own (Reckweg et al., 2023), several authors maintain that clinical results are also dependent on the setting in which these drugs are taken (Hartogsohn, 2016), and the psychotherapeutic mechanisms that occur during and after the psychedelic experience (Grunder et al., 2023). For these reasons and to guarantee patient safety, most clinical trials have been carried out with the addition of

psychological support or psychotherapeutic interventions (Johnson et al., 2008). This integrated model is usually referred to as psychedelic-assisted psychotherapy (PAP) and usually includes preliminary non-drug sessions (preparation), one or more drug sessions, and subsequent non-drug sessions (integration) (Cavarra et al., 2022). Psychedelics show an anti-inflammatory effect (Castellanos et al., 2020), promote neuroplasticity (de Vos et al., 2021), and act mainly upon the 5-HT_{2A} receptor which, together with the 5-HT_{3A} receptor, is involved in nociception (Zia et al., 2023). In other words, psychedelics may act on the neurological pathways responsible for pain perception, and the development of hyperalgesia and allodynia. Based on this evidence concerning their biological mechanism of action, proposals have been recently made to test their effectiveness in the treatment of chronic pain conditions (Castellanos et al., 2020).

Research on the analgesic effects of psychedelics commenced prior to the onset of the war on drugs era (Reiff et al., 2020). Subsequently, evidence supporting their effectiveness in addressing various forms of pain, including neuropathic, ischemic, and cancer-related pain, has accumulated (Grof et al., 1973; Kast & Collins, 1963). These substances were also investigated in the context of life-threatening illnesses (Kast, 1967) and phantom limb pain (Fanciullacci et al., 1977) and showed promising results. Modern survey studies show that people with chronic pain report relief from using psychedelics (Bonnelle et al., 2022; Cavarra et al.,

2023), and recent retrospective studies showed psychedelics may benefit individuals experiencing cluster headaches, even at low, non-hallucinogenic doses (Schindler et al., 2015; Sewell et al., 2006). Furthermore, a randomised controlled trial involving healthy volunteers demonstrated that a non-hallucinogenic dose of LSD could enhance pain tolerance and reduce unpleasantness to a degree comparable to oxycodone or morphine (Ramaekers et al., 2021). Finally, an exploratory study (Schindler et al., 2021) employing psilocybin showed that it may be able to reduce migraine frequency even at sub or mildly hallucinogenic doses.

Fibromyalgia (FM) is a painful condition that causes widespread pain and fatigue. It can cause significant distress (Chinn et al., 2016; Wolfe et al., 2018) especially considering it is often associated with conditions such as depression (Alciati et al., 2012; Gelonch et al., 2018) and anxiety disorders (Wolfe et al., 2018). People living with FM demonstrate a heightened sensitivity to pain and various stimuli, indicating potential dysfunctions in ascending and descending pathways that impede inhibitory functions and facilitate pain signalling (Lorenz et al., 1996; Nijs et al., 2014; Smith et al., 2011). A range of evidence underscores diverse contributing factors, including neuroinflammation (Littlejohn, 2015), deficiencies in vitamins (Costantini et al., 2013; Jesus et al., 2013; Regland et al., 2015; Sakarya et al., 2011), autoimmune reactions (Applbaum & Lichtbroun, 2019), dysregulated gut-microbiome (Clos-Garcia et al., 2019), impaired neuromuscular efficiency (Casale, Boccia, et

218

al., 2019; Lima et al., 2020), neuroendocrine dysregulation (Pednekar et al., 2019), and psychological factors like trauma, and psychological stress (Casale et al., 2019).

Considering the evidence discussed above and the need for better treatment options for fibromyalgia patients, the present study will report on an Interpretative Phenomenological Analysis (IPA) of interview contents conducted with an FM patient throughout a PAP program which included a preparation phase, two psychedelic experiences during a four-day retreat, and five integration sessions. Interviews were conducted two weeks, three months, and six months after the retreat. Quantitative data regarding depression, anxiety, stress, psychological flexibility, mindfulness skills, and cognitive fusion were also collected at baseline and at each subsequent time point. The participant chose three issues as the target of the experience: improving FM symptoms, communicating with his unconscious mind, and gaining insight into his feelings of lack of support in close relationships. The present study aims at: a) monitoring the perception of the therapeutic effects of the psychedelic retreat; b) monitoring the reported changes in the three issues presented by the patient and c) monitoring the self-reported effects of integration sessions on the issues he focused on.

Methods

The patient

Adam (pseudonym) is a 36-year-old male clinical psychologist suffering from FM. The condition was diagnosed about four years before the retreat. Symptoms included recurrent pain and burning sensations in his hands, arms, knees, back, and shoulders accompanied by fatigue. Adam worked in the public healthcare system for 11 years before switching to a private company shortly before the retreat. The job change was motivated in part by the impact the condition had on his capacity to sustain the demands of the public healthcare system. About one year before the retreat, he went through a romantic breakup with his fiancé and the separation was followed by the sale of their house and the relocation to a new one. Concerning the potential causes or contributing factors of his FM, Adam mentioned that the condition may be, at least in part, psychogenic and that the intensity of its symptoms was influenced by the degrees of stress he experiences in his everyday life.

As reported during interviews, Adam signed up for the retreat intending to improve FM symptoms, communicate with his unconscious mind, and gain insight into his perceived lack of received support in close relationships. For a more detailed patient description, refer to Supplementary Material S1.

Intervention

The retreat lasted four and a half consecutive days and comprised two psychedelic journeys. Before arriving, retreat attendees journaled on prompts provided by the therapeutic team (e.g., what is missing in your life?) to begin the process of opening awareness to what may be difficult to feel. For a full list of these questions, see Supplementary materials S2.1. Each journey included preparation and integration exercises to take advantage of any new perspectives or increased psychological flexibility. Between the two ceremonies, one day was used to deepen the processes that the first journey had opened, thus aiming for greater openness during the second journey.

Preparation and integration were conducted based on the Acceptance and Commitment Therapy (ACT) framework adapted for psychedelic therapy (Whitfield, 2021). They included several activities such as intention setting, mindfulness meditation, breathwork, parts work (such as asking patients to attribute inner voices an age to learn when they appeared in the patient's life and giving them compassion they did not get at that time), shame work (to voice the most avoided self-evaluations), and group bonding exercises. The final retreat day included values exploration and how these might be expressed coherently through four domains of life (see Supplementary material S6). For a more detailed description, see Supplementary material S2.

Ceremonies were held in a group setting comprising 14 participants and four facilitators. Participants self-administered psilocybin in the form of a tea: psilocybin-containing truffles were put into hot water with lemon and ginger. Each tea serving was obtained by 30 g of truffles for the first ceremony and 60 g for the second one.

The psychotherapy process

The retreat

Adam hoped that by going through the first ceremony he could have “unlocked the [FM] problem”. During the first ceremony, in terms of psychedelic phenomenology, Adam experienced morphing visuals, an altered sense of time and space, and a loss of sense of identity. He re-experienced a traumatic event that occurred when he was 19 years old: he fell from the mast of a sailing boat, broke his collarbone, hit his head, and was hospitalised as a consequence. Adam was surprised to experience this as, while he was aware that the incident occurred, he reported having no memories of the fall itself. During this experience, he repeatedly told himself that the accident actually happened, apologised to himself for letting it happen, and promised himself it would never happen again. The experience was accompanied by feelings of calmness and comfort and was described as very profound. After the first ceremony, Adam reported an improvement in pain: “The pain was gone more or less. It kind of came up a little bit here and there in the first journey”.

Before the second ceremony, Adam felt more apprehensive because of the higher dose (60 g) he was supposed to take and because he noticed that during the first ceremony, several participants went through challenging experiences. Nonetheless, he felt more willing to ask for help if needed. During the second ceremony, he went through a challenging experience. More specifically, he felt that the universe was indifferent to him and anyone else. He felt “caught in irrelevance”, thought of himself as just waiting to die, and felt apathetic and sad. After receiving support from facilitators, Adam felt a pervasive feeling of “universal love”, “bliss”, “peace” and realised that everyone, himself included, was worthy of love. The feelings of irrelevance were also reframed as follows: “You don’t need to try so hard because it’s irrelevant”. His pain levels were low during the second ceremony.

The feelings of universal love persisted also on the subsequent retreat day during which Adam felt more connected with the other retreat participants, with nature, and with the universe. The improvement in pain levels persisted for four days following the end of the retreat. For additional details on the retreat experience, refer to Supplementary material S3.

Integration therapy sessions

Adam approached the integration sessions with the expectation of revisiting the psychedelic journeys (inspired by traumatic incident reduction (TIR)) and working on the “practical side of actions”

(ACT). Starting two weeks after the end of the retreat, Adam participated in five weekly integration therapy sessions, aimed at deepening and consolidating change. Sessions were led within an ACT framework in a one-on-one video-call setting, aimed at facilitating value-based action in everyday life, and employed a repetitive imaginal review of the psychedelic experience (TIR) to revisit the psychedelic experiences and to give more opportunity to make sense of the positive aspects (emotional contact with values) and the challenging aspects (willingness to experience traumatic memories or accommodate aversive emotions). This progressed to an imaginal re-experiencing of other related memories, intending to loosen and expand awareness of any rigid avoidance patterns or 'exiled parts' (old avoidant personality structures). Adam was surprised by the resurfacing of an apparent childhood traumatic memory that was revisited during the first integration sessions. Two further childhood memories were addressed in the third and fourth integration sessions. He also reported that there was not enough time to go through the second psychedelic experience. For a more detailed description of the contents of each integration session, see Supplementary materials S5 and S6.

Interviews and measures

The interviews

After having consented to participate in the study, Adam took part in three semi-structured interviews at three time points: two weeks (T1), three months (T2), and six months (T3) after the retreat. During the T1 interview, general anamnestic information about the patient and his diagnosis was gathered before interviewing him about the areas relevant to the present study. Across all time points, he was asked the following questions: “How does the effect of the psychedelic retreat seem to you now?”, “Has the psychedelic therapy had any effect, positive or negative, on your issues?”. At T2 and T3 he was also asked about the potential effects of integration sessions that started after T1. The content of the sessions was recorded and transcribed to be used as material for the IPA.

Interpretative phenomenological analysis

IPA (Larkin, 2021) is a qualitative research method widely used in scientific psychology to explore and understand the subjective experiences of individuals within a specific context. IPA focuses on how participants make sense of their experiences and aims to provide an in-depth, interpretative understanding of their lived experiences. The interview transcripts were used as material for the IPA. This allowed us to uncover themes and patterns emerging from the patient’s experience, perspectives, emotions, and attributed meanings.

Quantitative measures

At T0 and across all time points, Adam completed questionnaires aimed at assessing his levels of depression, anxiety, and stress (DASS 21; Lovibond & Lovibond, 1995), mindfulness (FFMQ-15; Baer et al., 2006), psychological flexibility (comPACT; Francis et al., 2016) and cognitive fusion (CFQ; (Gillanders et al., 2014). For a detailed description of the questionnaires, refer to Supplementary material S4.

Clinical material

Quantitative measures

Compared to T0, Adam reported improvements in all DASS 21 scales T3 (Figure 1). Depression levels increased past the mild and up to the moderate threshold scores at T1 before decreasing to mild at T2 and finally reaching 0 at T3. Anxiety scores were already low at T0, remained constant at T1, decreased to zero at T2, and remained stable until T3. Stress remained stable at T1, and increased at T2 surpassing the 'mild' threshold, before dropping to 0 at T3.

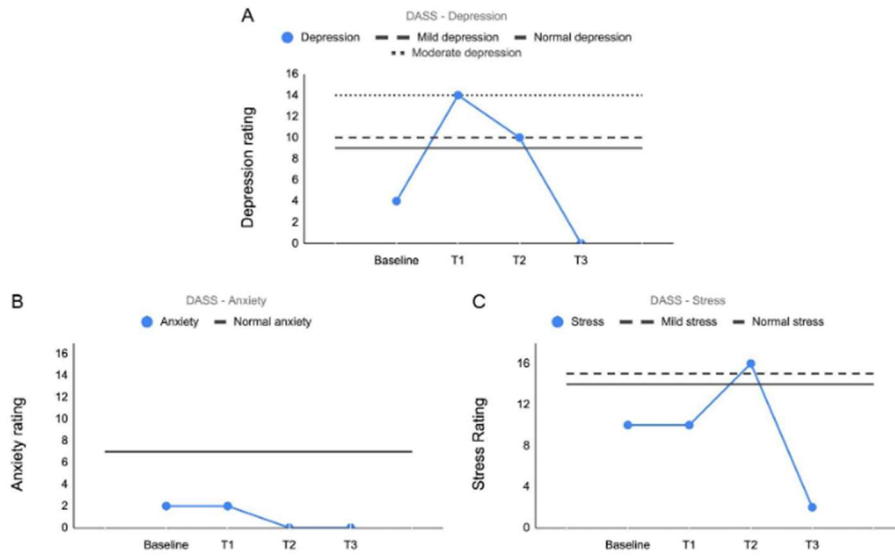


Figure 1. DASS 21 depression (A), anxiety (B), and stress (C) scores and cutoffs across all time points: T0, T1 (2 weeks), T2 (3 months), T3 (6 months).

The scores on the FFMQ questionnaire are shown in Figure 2. Between T0 and T1 the Observe scale increased; it decreased at T2 and reverted to T1 levels at T3. The Describe scale showed an immediate increase at T1 and remained stable across the other two time points. The Non-judgement scale score remained constant from T0 to T1, decreased at T2, and increased at T3 to one point higher than T0. Comparing T0 and T3 the Acting with awareness and Non-reactivity scale scores did not change even though the former increased at T2 before reverting to baseline levels and the

latter decreased at T1, increased above baseline levels at T2 and reverted back to baseline levels at T3.

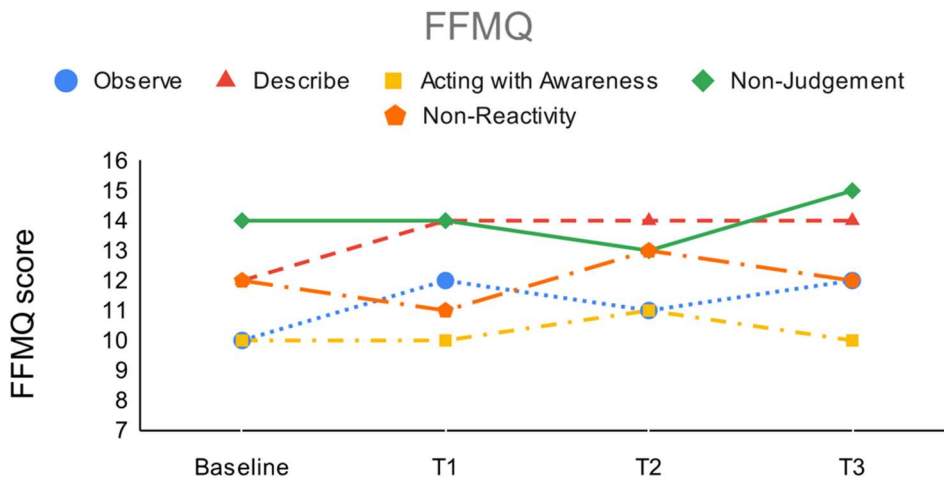


Figure 2. FFMQ scores across all time points: T0, T1 (2 weeks), T2 (3 months), T3 (6 months).

The Openness to experience scale of the CompACT (Figure 3) remained constant at T1, decreased at T2, and increased above T0 levels at T3. The valued action scale remained constant at T1, decreased by one point at T2, and increased above baseline levels at T3. The Behavioral awareness scale decreased at T1 and then increased across T2 and T3 remaining below baseline levels.

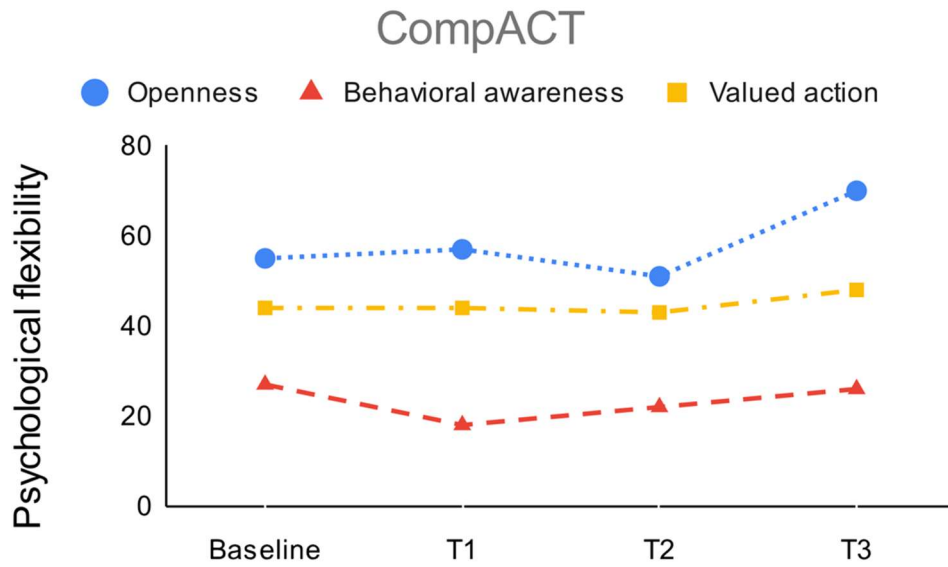


Figure 3. CompACT scores across all time points: T0, T1 (2 weeks), T2 (3 months), T3 (6 months).

Finally, the CFQ decreased at T1 and gradually decreased across T2 until reaching levels lower than baseline at T3.

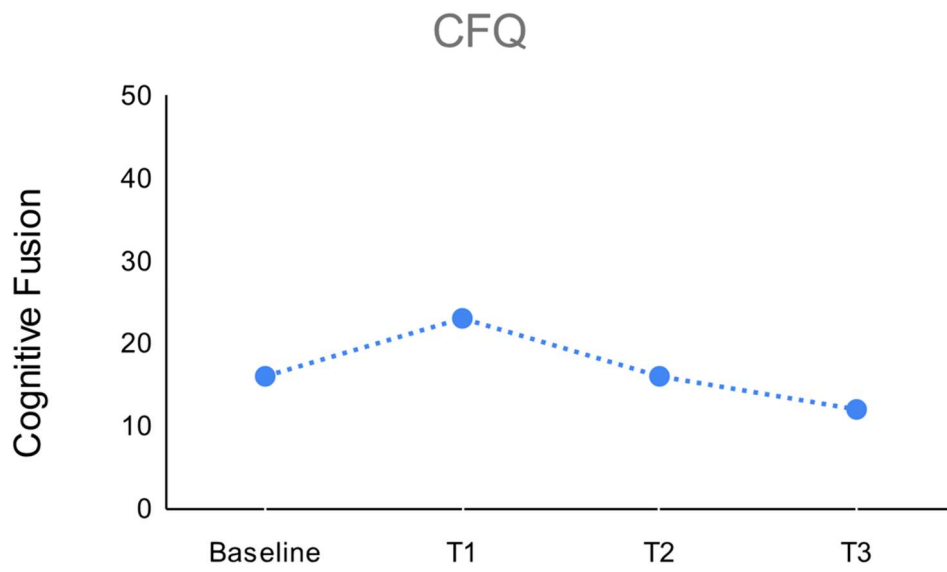


Figure 4. CFQ scores across all time points: T0, T1 (2 weeks), T2 (3 months), T3 (6 months).

Interpretative phenomenological analysis

The detailed results of the IPA are reported in Supplementary material S5. Below we report a summary of the main findings related to each research question.

Table 1. Summary of interview themes

Questions	T1 (post retreat) 2 weeks	T2 (post integration) 3 months	T3 (follow up) 6 months
How does the effect of the psychedelic retreat seem to you now?	<ul style="list-style-type: none"> - Inner guidance - Universal love - Hard to return to routine because of pain and fatigue 	<ul style="list-style-type: none"> - Inner guidance - Life changed 	<ul style="list-style-type: none"> - Increased feelings of connection to others and spiritual side - Life changed
Has the psychedelic therapy had any effect, positive or negative, on your issues?	<ul style="list-style-type: none"> - FM symptoms reappear - Insights: make small changes, it's all about love. - Trauma acknowledgment - Inner guidance 	<ul style="list-style-type: none"> - FM caused and/or aggravated by repressed emotions - Mindful attitude towards pain and acceptance - FM necessary to justify life changes - Stronger connection with the unconscious mind - Insight: current perceived lack of support in relationships has its roots in childhood 	<ul style="list-style-type: none"> - Pain improved - Definite answer on FM cause and triggers - Stronger connection with the unconscious mind - More clarity on relational needs

		dyslexia-related distress - Insight: perceived lack of support triggered by work-related dynamics Acceptance of his need of support, connection, and intimacy	
Did the integration sessions help you to do anything differently in your life?		- More aware and open towards his needs - Reduced avoidance - New meaning to traumatic experience	- More open towards his needs

Q1. How does the effect of the psychedelic retreat seem to you now?

At T1 Adam reported that since the retreat he felt a greater degree of “inner guidance” that allowed him to more easily enact lifestyle changes and to escape circular thoughts concerning FM that usually left him confused about what actions to take. Still, pain and fatigue, which reappeared after a couple of days in which he was feeling better, made going back into his work routine hard.

At T2, Adam still reports feeling guided and that his “whole life changed” after the retreat and he felt that the retreat itself could have been the cause or the catalyst for such change. More

specifically, he reduced his alcohol intake, left for a sabbatical, and felt less “worried and anxious”.

Finally, at T3, Adam reported that the retreat led to increased feelings of connection to others and his spiritual side and that the retreat “changed his life on a fundamental level”. For a more detailed discussion on the IPA, refer to Supplemental material S5.

Q2. Has the psychedelic therapy had any effect, positive or negative, on your issues?

When asked about the effect of psychedelic therapy on his issues at T1, Adam reports that the retreat led him to two meaningful insights. First, he could feel better by enacting small changes in his life as opposed to changing his “whole life in all these big ways”. Some of the changes he mentioned were related to listening more to his body and stopping pushing through pain and fatigue. Secondly, the retreat made him feel reassured as he realised that “it’s all about love, so it’s all going to be fine”. He attributes to the inner guidance mentioned earlier the fact that he was able to enact life changes in areas that he felt affected FM symptom severity such as: taking a break from work, exercising with moderation, practising mindfulness, getting therapy, applying for a new job and reducing alcohol intake. Finally, the psychedelic retreat allowed him to acknowledge past trauma: “[The psychedelic experience has] shown me that there’s something I need to think about, I need to work on, there’s trauma there”.

Before therapy, Adam was already considering a psychogenic hypothesis of FM or that psychological factors were contributing to it. Following therapy at T2, Adam expressed a stronger belief that his FM might be linked to suppressed emotions and traumatic memories, one of which emerged during the first ceremony followed by four others during integration. As a consequence, he adopted a more accepting and mindful approach towards these factors. Furthermore, he characterised FM as essential in justifying lifestyle changes that he would not have made solely due to psychological distress.

Regarding his feelings of unsatisfactory relational support, Adam realised that they may be rooted in the dyslexia-related distress he experienced as a child and the fact that he felt dependent on his parents' help to succeed in school. In his narrative, as an adult, he reacted by striving toward independence and self-sufficiency, disregarding the need of support that was then triggered by work-related dynamics (e.g., lack of appropriate supervision and contact with clients with no social support) and by the emotional distance experienced in his previous romantic relationship. As a result of the PAP, he felt more accepting of his needs for support, connection, and intimacy.

Finally, at T3, Adam reported an improvement in pain levels and expressed that the retreat "sped up [his] healing". This allowed him to resume exercising more intensely. Pain is now described as "very

different” and “more manageable”. He felt he was “finding answers” and progressively dispelling confusion. For a more detailed discussion on the IPA, refer to Supplemental material S5.

Q3. Did the integration sessions help you to do anything differently in your life?

Two weeks after the end of the retreat, Adam started attending integration sessions. At T2, he reported that the sessions helped him feel more open towards his needs (“my exiled parts”). Among these he mentioned the need to be in nature more, to “be much slower” and to reconsider his adherence to societal expectations. Integration also helped him be more “aware”, “conscious” and “present”. The ACT component of integration was reportedly helpful in acknowledging alcohol use as a strategy to avoid loneliness and in enacting behaviours to expand his social network (“finding people hanging out”). Also, he attributed new meaning to the accident: the climbing of the mast was an attempt to avoid boredom. At T3 Adam reported that integration was helpful in increasing his feelings of openness towards his needs and improving his connection with his unconscious mind, especially as a consequence of supposed suppressed memory that he recovered during the sessions. Finally, Adam felt that he could have used more integration sessions to process the material that emerged during the course of therapy. For more detailed discussion on the IPA, refer to Supplemental material S5. For more detailed information about the contents of each integration session refer to Supplementary material S6.

Discussion

This study reported on the therapeutic process of Adam, a man living with FM, who enrolled in a PAP program consisting of a preparation phase, two psychedelic experiences in the context of a four-and-a-half-day retreat, and five integration sessions. The patient completed self-reported measures of depression, anxiety, stress, mindfulness skills, cognitive fusion and psychological flexibility at baseline and at 3 subsequent time points following the retreat: T1 (2 weeks after), T2 (3 months after) and T3 (six months after).

Across all time points following the retreat, Adam was also asked two questions: “How does the effect of the psychedelic retreat seem to you now?” and “Has the psychedelic therapy had any effect, positive or negative, on your issues?”. An IPA conducted on the first question revealed that the retreat experience left him with a stable sense of inner guidance that helped him enact lifestyle changes and alleviate confusion and circular thoughts regarding FM, its causes, and the actions he needed to take to address it. He reported that the two psychedelic experiences either caused or catalysed a general life change both in terms of professional choices, adoption of healthier habits, and better emotional well-being. The retreat also left him with stronger feelings of connection to others and his spiritual side.

In response to the second question, Adam identified three main target issues for the PAP, i.e., to improve FM symptoms, communicate with his unconscious mind and gain insight into his perceived lack of support in close relationships. Adam reported reduced FM pain during ceremonies and, although the pain returned to pre-retreat levels about four days after the retreat, it eventually decreased 6 months later, after integration therapy and other self-care practice including a vipassana retreat and other psychedelic experiences. Adam attributed this decrease in part to PAP that made the pain reportedly more manageable as he became more accepting and mindful of it. As a consequence of the insights he experienced during ceremonies (i.e., he could enact small life changes as opposed to changing his whole life and an experience of universal love), he felt reassured (“it’s all going to be fine”) and more able to enact lifestyle changes that he felt contributed to relieve FM symptoms intensity. These changes were also discussed during integration sessions (see Supplementary material S6) aiming at choosing those that aligned with his values, goals and resources. Regarding his intention to communicate with his unconscious mind, Adam felt that such communication improved as a consequence of PAP. More specifically, the fact that he re-experienced a traumatic memory during the ceremony and another four traumatic episodes during integration sessions. These latter strengthened his pre-existing hypothesis that FM was, at least in part, psychogenic in nature and related to suppressed emotion and trauma. FM was reframed as a necessary factor to justify such

changes that he felt he would not have allowed himself to alter due to psychological distress alone. The cause of the third issue, the perceived lack of support in close relationships, was attributed in part to the distress he experienced as a child struggling with dyslexia and to his reactive attempt, as an adult, to strive towards self-sufficiency pushing through his needs for support and intimacy. These feelings of lack of support were then triggered later, in his adult life, by events and dynamics happening in both his romantic and professional life. As a consequence of this realisation, Adam reported having become more accepting of such needs.

At T2 and T3 Adam was asked a third question that was also the target of IPA: “Did the integration sessions help you to do anything differently in your life?”. He reported that integration made him more “present” and more aware of dysfunctional avoidance tendencies (e.g., alcohol to alleviate loneliness) and more able to more functionally respond to the feelings at the root of such tendencies (e.g., engaging in social situations). As mentioned earlier, integration was also reported as helpful in improving his communication with his implicit, unconscious mind as it was the setting in which he recovered supposedly suppressed traumatic childhood memories.

On a more general note, Adam reported that PAP felt helpful and highly meaningful at all time points.

By analysing the results of the questionnaires and the IPA side by side at T1 (post-retreat/pre-integration), Adam reported greater inner guidance and a lingering feeling of universal love, while measures potentially related to these themes worsened or remained constant. More specifically, measures of unpleasant emotional states (DASS 21) remained constant (anxiety and stress) or increased (depression); Behavioural awareness (CompACT) decreased, and Acting with awareness (FFMQ) remained constant; Finally, Non-reactivity decreased. The measures that improved at this time point are the Observe and Describe subscales potentially indicating increased awareness of internal states, their causes, and the external world which may have led to better clarity regarding his emotional and existential needs. Also, cognitive fusion scores (CFQ) improved, showing that Adam was better able to not identify with his thoughts and feelings. In this light, the worsening of Behavioural awareness and valued action (CompACT), and the unchanged Acting with awareness (FFMQ) scales at T1, may represent another facet of increased awareness or, in other words, a sign that Adam realised the need to more appropriately direct his behaviour to fulfill his emotional and existential needs. The increase in depression scores may be related to the resurfacing of trauma and the resurgence of FM symptoms shortly after the end of the retreat.

In terms of unpleasant emotional states, at T2 (post-integration sessions) Adam reports a reduction in depression scores (from

moderate to mild), a small reduction in anxiety, and an increase in stress (from normal to mild) that, on the qualitative side, correspond to life changes reportedly brought by the increased feeling of inner guidance. This emphasis on action and reduced avoidance is also reflected by the increase in Non-reactivity and Acting with awareness scales (FFMQ), and the decrease in cognitive fusion (CFQ). The reduction in depression scores may also be associated with the increased accepting attitude Adam felt toward pain and his needs for support, connection, and intimacy which were also the focus of integration sessions.

At T3 (six months follow-up) several measures showed improvement compared to T0, more specifically: depression, anxiety, stress, valued action, Behavioural awareness, Non-judgement, Observe, Describe, and cognitive fusion. At this point, Adam also reports improvements in pain, the feeling of having received clear answers related to the causes and triggers of FM pain, and having developed a stronger connection with his unconscious mind being more open and accepting of his needs for support. Finally, this case study shows a continuing improvement in symptoms and psychological flexibility processes between T2 and T3 in terms of Depression, Stress, Openness to Experience, Behavioural Awareness, Valued Action, Cognitive Fusion, and a sustained reduction in Anxiety. Considering that relapse at six months follow-up is common (Carhart-Harris et al., 2018; Nutt et al.,

2020), case details of when a new trajectory of symptom improvement is sustained may be of note.

Limitations

While the present study offers a very granular perspective on the experience and perceived therapeutic effects of a patient undergoing PAP, it also suffers from some limitations typical of single-participant retrospective designs that may limit the generalisability of the results. The IPA was conducted through a retrospective account of the retreat and this may have constituted a source of bias. However, the inclusion of quantitative measures partially mitigates the risk allowing for comparisons between baseline scores and scores at the other time points. Generalisability of results may also be limited by the fact that Adam, especially between T2 and T3 declared having engaged in several other psychedelic and non-psychedelic experiences (e.g., mindfulness retreat) that may have contributed to the reported improvements. However, engaging in these activities may also be a result of the insights gained throughout therapy. On a similar note, the extended break from work he took may be responsible to a certain degree for such improvements and may raise concerns about the long-term sustainability of this choice. On the other hand, these lifestyle changes may be interpreted as one of the beneficial effects of PAP, which allowed him to validate his needs and act upon the new awareness and values that emerged during the psychedelic

experience, thus improving his mental health and sense of well-being in the long run which may favour better long-term functioning and life satisfaction.

Conclusion

In conclusion, the study identifies three distinct phases of the PAP and their effects on Adam. The first phase, increased awareness (T1), led to enhanced inner guidance, a sustained feeling of universal love, and improved self-reported introspective abilities. However, this phase also brought temporary heightened suffering, possibly due to increased awareness of the gap between the current and desired state.

During the acceptance and action phase (T2) Adam reported an improvement in mood, anxiety, and avoidant tendencies, as he made lifestyle changes inspired by an inner guiding principle. He also expanded his awareness of the influence of multiple traumatic memories on his fibromyalgia pain and planned new valued actions for the future. This phase enabled increases in mindfulness, acceptance of fibromyalgia pain, and intimacy needs.

The consolidation phase (T3) reported further enhanced well-being, including improved fibromyalgia pain, positive emotional states, acceptance, and connection to others, to his unconscious mind, and his spiritual side. Future research should explore PAP's effects in

controlled studies focusing on chronic pain conditions, addressing potential contributing and confounding factors (e.g., participants engaging in multiple psychedelic and non-psychedelic experiences, placebo effects, group influences, unreliable doses, and self-selection and the effects of processing of related traumatic memories) and examining long-term outcomes. This study suggests that FM patients may benefit from extended integration periods, achieved through additional trauma-focused integration sessions or increased spacing between psychedelic experiences to enhance and sustain therapeutic gains.

Ethical approval

This study was reviewed by the Psychology Research Ethics Committee of Regent's University - London.

References

Alciati, A., Sgiarovello, P., Atzeni, F., & Sarzi-Puttini, P. (2012). Psychiatric problems in fibromyalgia: Clinical and neurobiological links between mood disorders and fibromyalgia. *Reumatismo*, 64(4), Article 4. <https://doi.org/10.4081/reumatismo.2012.268>

Applbaum, E., & Lichtbroun, A. (2019). Novel Sjögren's autoantibodies found in fibromyalgia patients with sicca and/or xerostomia. *Autoimmunity Reviews*, 18(2), 199–202. <https://doi.org/10.1016/j.autrev.2018.09.004>

Baer, R. A., Smith, G. T., Hopkins, J., Krietemeyer, J., & Toney, L. (2006). Using Self-Report Assessment Methods to Explore Facets of Mindfulness. *Assessment*, 13(1), 27–45. <https://doi.org/10.1177/1073191105283504>

Bonnelle, V., Smith, W. J., Mason, N. L., Cavarra, M., Kryskow, P., Kuypers, K. P. C., Ramaekers, J. G., & Feilding, A. (2022). Analgesic potential of macrodoses and microdoses of classical psychedelics in chronic pain sufferers: A population survey. *British Journal of Pain*, 13.

Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., & Nutt, D. J. (2018). Psilocybin with psychological support for
244

treatment-resistant depression: Six-month follow-up.
Psychopharmacology, 235(2), 399–408.
<https://doi.org/10.1007/s00213-017-4771-x>

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *The Lancet Psychiatry*, 3(7), 619–627. [https://doi.org/10.1016/S2215-0366\(16\)30065-7](https://doi.org/10.1016/S2215-0366(16)30065-7)

Casale, R., Boccia, G., Symeonidou, Z., Atzeni, F., Batticciotto, A., Salaffi, F., Sarzi-Puttini, P., Brustio, P. R., & Rainoldi, A. (2019). Neuromuscular efficiency in fibromyalgia is improved by hyperbaric oxygen therapy: Looking inside muscles by means of surface electromyography. *Clinical and Experimental Rheumatology*, 6.

Casale, R., Sarzi-Puttini, P., Botto, R., Alciati, A., Batticciotto, A., Marotto, D., & Torta, R. (2019). Review Fibromyalgia and the concept of resilience. *Clinical and Experimental Rheumatology*, 9.

Castellanos, J. P., Woolley, C., Bruno, K. A., Zeidan, F., Halberstadt, A., & Furnish, T. (2020). Chronic pain and psychedelics: A review and proposed mechanism of action.

Regional Anesthesia & Pain Medicine, 45(7), 486–494.
<https://doi.org/10.1136/rapm-2020-101273>

Cavarra, M., Falzone, A., Ramaekers, J. G., Kuypers, K. P. C., & Mento, C. (2022). Psychedelic-Assisted Psychotherapy—A Systematic Review of Associated Psychological Interventions. *Frontiers in Psychology*, 13.
<https://www.frontiersin.org/article/10.3389/fpsyg.2022.887255>

Cavarra, M., Mason, N. L., Kuypers, K. P. C., Bonnelle, V., Smith, W. J., Feilding, A., Kryskow, P., & Ramaekers, J. G. (2023). Potential analgesic effects of psychedelics on select chronic pain conditions: A survey study. *European Journal of Pain*, n/a(n/a).
<https://doi.org/10.1002/ejp.2171>

Chinn, S., Caldwell, W., & Gritsenko, K. (2016). Fibromyalgia Pathogenesis and Treatment Options Update. *Current Pain and Headache Reports*, 20(4), 25. <https://doi.org/10.1007/s11916-016-0556-x>

Clos-Garcia, M., Andrés-Marin, N., Fernández-Eulate, G., Abecia, L., Lavín, J. L., van Liempd, S., Cabrera, D., Royo, F., Valero, A., Errazquin, N., Vega, M. C. G., Govillard, L., Tackett, M. R., Tejada, G., González, E., Anguita, J., Bujanda, L., Orcasitas, A. M. C., Aransay, A. M., ... Falcón-Pérez, J. M. (2019). Gut microbiome and serum metabolome analyses identify molecular biomarkers and

altered glutamate metabolism in fibromyalgia. *EBioMedicine*, 46, 499–511. <https://doi.org/10.1016/j.ebiom.2019.07.031>

Costantini, A., Giorgi, R., D'Agostino, S., & Pala, M. I. (2013). High-dose thiamine improves the symptoms of Friedreich's ataxia. *Case Reports*, 2013, bcr2013009424. <https://doi.org/10.1136/bcr-2013-009424>

Crawford, J. R., & Henry, J. D. (2003). The Depression Anxiety Stress Scales (DASS): Normative data and latent structure in a large non-clinical sample. *British Journal of Clinical Psychology*, 42(2), 111–131. <https://doi.org/10.1348/014466503321903544>

de Vos, C. M. H., Mason, N. L., & Kuypers, K. P. C. (2021). Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics. *Frontiers in Psychiatry*, 12, 724606. <https://doi.org/10.3389/fpsy.2021.724606>

Donati, M. A., Berrocal, C., Bernini, O., Gori, C., & Primi, C. (2021). Measuring cognitive fusion through the Cognitive Fusion Questionnaire-7: Measurement invariance across non-clinical and clinical psychological samples. *PLOS ONE*, 16(2), e0246434. <https://doi.org/10.1371/journal.pone.0246434>

Fanciullacci, M., Bene, E. D., Franchi, G., & Sicuteri, F. (1977). Phantom Limb Pain: Sub-Hallucinogenic Treatment With Lysergic

Acid Diethylamide (LSD-25). *Headache: The Journal of Head and Face Pain*, 17(3), 118–119. <https://doi.org/10.1111/j.1526-4610.1977.hed1703118.x>

Francis, A. W., Dawson, D. L., & Golijani-Moghaddam, N. (2016). The development and validation of the Comprehensive assessment of Acceptance and Commitment Therapy processes (CompACT). *Journal of Contextual Behavioral Science*, 5(3), 134–145. <https://doi.org/10.1016/j.jcbs.2016.05.003>

Gelonch, O., Garolera, M., Valls, J., Castellà, G., Varela, O., Rosselló, L., & Pifarre, J. (2018). The effect of depressive symptoms on cognition in patients with fibromyalgia. *PLOS ONE*, 13(7), e0200057. <https://doi.org/10.1371/journal.pone.0200057>

Gillanders, D. T., Bolderston, H., Bond, F. W., Dempster, M., Flaxman, P. E., Campbell, L., Kerr, S., Tansey, L., Noel, P., Ferenbach, C., Masley, S., Roach, L., Lloyd, J., May, L., Clarke, S., & Remington, B. (2014). The Development and Initial Validation of the Cognitive Fusion Questionnaire. *Behavior Therapy*, 45(1), 83–101. <https://doi.org/10.1016/j.beth.2013.09.001>

Grof, S., Goodman, L. E., Richards, W. A., & Kurland, A. A. (1973). LSD-Assisted Psychotherapy in Patients with Terminal Cancer. *International Pharmacopsychiatry*, 8(3), 129–144. <https://doi.org/10.1159/000467984>

Gründer, G., Brand, M., Mertens, L. J., Jungaberle, H., Kärtner, L., Scharf, D. J., Spangemacher, M., & Wolff, M. (2023). Treatment with psychedelics is psychotherapy: Beyond reductionism. *The Lancet Psychiatry*, 0(0). [https://doi.org/10.1016/S2215-0366\(23\)00363-2](https://doi.org/10.1016/S2215-0366(23)00363-2)

Hartogsohn, I. (2016). Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. *Journal of Psychopharmacology (Oxford, England)*, 30(12), 1259–1267. <https://doi.org/10.1177/0269881116677852>

Hartogsohn, I. (2018). The Meaning-Enhancing Properties of Psychedelics and Their Mediator Role in Psychedelic Therapy, Spirituality, and Creativity. *Frontiers in Neuroscience*, 12. <https://www.frontiersin.org/articles/10.3389/fnins.2018.00129>

Jesus, C. A. S., Feder, D., & Peres, M. F. P. (2013). The Role of Vitamin D in Pathophysiology and Treatment of Fibromyalgia. *Current Pain and Headache Reports*, 17(8), 355. <https://doi.org/10.1007/s11916-013-0355-6>

Johnson, M. W., Richards, W., & Griffiths, R. R. (2008). Human hallucinogen research: Guidelines for safety. *Journal of Psychopharmacology*, 22(6), 603–620. <https://doi.org/10.1177/0269881108093587>

Kast, E. C. (1967). Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide. *The Psychiatric Quarterly*, 41(4), 646–657. <https://doi.org/10.1007/BF01575629>

Kast, E. C., & Collins, V. J. (1963). Study of Lysergic Acid Diethylamide as an Analgesic Agent. *Anesthesia and Analgesia*, 43(3), 285–291.

Larkin, M. (2021). Interpretative Phenomenological Analysis: Theory, Method and Research. 1–100.

Lima, L. O. de, Zicarelli, C. A. M., Matsumura, A. S., Moroti-Perugini, L. R., Teixeira, D. de C., Fernandes, K. B. P., Perrucini, P. D. de O., & Poli-Frederico, R. C. (2020). Lower limb muscle strength and serotonin receptor gene polymorphism as factors associated in women with fibromyalgia. *Advances in Rheumatology*, 59. <https://doi.org/10.1186/s42358-019-0101-9>

Littlejohn, G. (2015). Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. *Nature Reviews. Rheumatology*, 11(11), 639–648. <https://doi.org/10.1038/nrrheum.2015.100>

Lorenz, J., Grasedyck, K., & Bromm, B. (1996). Middle and long latency somatosensory evoked potentials after painful laser stimulation in patients with fibromyalgia syndrome.

Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 100(2), 165–168. [https://doi.org/10.1016/0013-4694\(95\)00259-6](https://doi.org/10.1016/0013-4694(95)00259-6)

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy*, 33(3), 335–343. [https://doi.org/10.1016/0005-7967\(94\)00075-U](https://doi.org/10.1016/0005-7967(94)00075-U)

Nijs, J., Malfliet, A., Ickmans, K., Baert, I., & Meeus, M. (2014). Treatment of central sensitization in patients with ‘unexplained’ chronic pain: An update. *Expert Opinion on Pharmacotherapy*, 15(12), 1671–1683. <https://doi.org/10.1517/14656566.2014.925446>

Oei, T. P. S., Sawang, S., Goh, Y. W., & Mukhtar, F. (2013). Using the Depression Anxiety Stress Scale 21 (DASS-21) across cultures. *International Journal of Psychology*, 48(6), 1018–1029. <https://doi.org/10.1080/00207594.2012.755535>

Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., Mota-Rolim, S. A., Osório, F. L., Sanches, R., dos Santos, R. G., Tófoli, L. F., de Oliveira Silveira, G., Yonamine, M., Riba, J., Santos, F. R., Silva-Junior, A. A., Alchieri, J. C., Galvão-Coelho, N. L., Lobão-Soares, B., ... Araújo, D. B. (2019).

Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: A randomized placebo-controlled trial. *Psychological Medicine*, 49(4), 655–663. <https://doi.org/10.1017/S0033291718001356>

Pednekar, D. D., Amin, Md. R., Azgomi, H. F., Aschbacher, K., Crofford, L. J., & Faghieh, R. T. (2019). A System Theoretic Investigation of Cortisol Dysregulation in Fibromyalgia Patients with Chronic Fatigue. 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 6896–6901. <https://doi.org/10.1109/EMBC.2019.8857427>

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., Liechti, M. E., Feilding, A., & Kuypers, K. P. C. (2021). A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of Psychopharmacology*, 35(4), 398–405. <https://doi.org/10.1177/0269881120940937>

Reckweg, J. T., Leeuwen, C. J., Amelsvoort, T., Theunissen, E., Mason, N. L., Paci, R., Terwey, T., & Ramaekers, J. G. (2023). A Phase 1/2 Trial to Assess Safety and Efficacy of a Vaporized 5-Methoxy-N,N-Dimethyltryptamine Formulation (GH001) in Patients with Treatment-Resistant Depression. *Frontiers in Psychiatry*, 14. <https://doi.org/10.3389/fpsy.2023.1133414>

Regland, B., Forsmark, S., Halaouate, L., Matousek, M., Peilot, B., Zachrisson, O., & Gottfries, C.-G. (2015). Response to Vitamin B12 and Folic Acid in Myalgic Encephalomyelitis and Fibromyalgia. *PLOS ONE*, 10(4), e0124648. <https://doi.org/10.1371/journal.pone.0124648>

Reiff, C. M., Richman, E. E., Nemeroff, C. B., Carpenter, L. L., Widge, A. S., Rodriguez, C. I., Kalin, N. H., McDonald, W. M., & the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research. (2020). Psychedelics and Psychedelic-Assisted Psychotherapy. *The American Journal of Psychiatry*, 177(5), 391–410. <https://doi.org/10.1176/appi.ajp.2019.19010035>

Ross, S. (2018). Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress. *International Review of Psychiatry*, 30(4), 317–330. <https://doi.org/10.1080/09540261.2018.1482261>

Sakarya, S. T., Akyol, Y., Bedir, A., & Canturk, F. (2011). The relationship between serum antioxidant vitamins, magnesium levels, and clinical parameters in patients with primary fibromyalgia syndrome. *Clinical Rheumatology*, 30(8), 1039–1043. <https://doi.org/10.1007/s10067-011-1697-2>

Schindler, E. A. D., Gottschalk, C. H., Weil, M. J., Shapiro, R. E., Wright, D. A., & Sewell, R. A. (2015). Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters Medication Use Survey. *Journal of Psychoactive Drugs*, 47(5), 372–381. <https://doi.org/10.1080/02791072.2015.1107664>

Schindler, E. A. D., Sewell, R. A., Gottschalk, C. H., Luddy, C., Flynn, L. T., Lindsey, H., Pittman, B. P., Cozzi, N. V., & D'Souza, D. C. (2021). Exploratory Controlled Study of the Migraine-Suppressing Effects of Psilocybin. *Neurotherapeutics*, 18(1), 534–543. <https://doi.org/10.1007/s13311-020-00962-y>

Sewell, R. A., Halpern, J. H., & Pope, H. G. (2006). Response of cluster headache to psilocybin and LSD. *Neurology*, 66(12), 1920–1922. <https://doi.org/10.1212/01.wnl.0000219761.05466.43>

Smith, H. S., Harris, R. E., & Clauw, D. J. (2011). Fibromyalgia. In *Essentials of Pain Medicine E-book* (pp. 345–350). Elsevier Health Sciences.

Whitfield, H. (2021). A Spectrum of Selves reinforced in multilevel coherence: A Contextual Behavioural response to the challenges of psychedelic-assisted therapy development. <https://www.frontiersin.org/articles/10.3389/fpsy.2021.727572/full>

Wolfe, F., Walitt, B., Perrot, S., Rasker, J. J., & Häuser, W. (2018). Fibromyalgia diagnosis and biased assessment: Sex, prevalence and bias. *PLOS ONE*, 13(9), e0203755. <https://doi.org/10.1371/journal.pone.0203755>

Wolgast, M. (2014). What Does the Acceptance and Action Questionnaire (AAQ-II) Really Measure? *Behavior Therapy*, 45(6), 831–839. <https://doi.org/10.1016/j.beth.2014.07.002>

Zia, F. Z., Baumann, M. H., Belouin, S. J., Dworkin, R. H., Ghauri, M. H., Hendricks, P. S., Henningfield, J. E., Lanier, R. K., Ross, S., & Berger, A. (2023). Are psychedelic medicines the reset for chronic pain? Preliminary findings and research needs. *Neuropharmacology*, 233, 109528. <https://doi.org/10.1016/j.neuropharm.2023.109528>

Supplementary materials

S1. Detailed patient description

As typical for FM, Adam's symptoms appeared and subsided cyclically and the patient hypothesised that their worsening may result from periods of higher stress at work, values-based conflicts with and lack of support from his supervisor at his earlier workplace, emotional fatigue due to his "tendency to absorb others' emotions", suppressing his personal needs of support and care in an intimate relationship, not "listening to his unconscious mind" and ignoring his physical sensations of tiredness and pain. Other potential precipitating factors he identified were excessive physical exercise, alcohol, and caffeine use. Finally, among the causes of, or contributing factors to, the onset of the symptoms, Adam thought that potential old traumas were contributing to the onset of his FM symptoms.

FM made him feel overwhelmed and not present in his everyday life and he reported that the uncertainty regarding the cause of the disease was a source of confusion and emotional suffering. Among the actions he took to seek relief from his symptoms before the retreat, he mentioned attempting to push through the pain and fatigue at first and then taking days off work, psychotherapy to work on past traumas, mindfulness, yoga, reduced exercise, and reduced alcohol and caffeine use. He had one previous experience

with psychedelic mushrooms during his university years in a recreational context and was referred to the psychedelic retreat by a colleague.

S2. List of retreat activities and description

The retreat and its activities were designed to enable the participants to access their deeper personality structures and the barriers to change these may engender.

- Self-as-context meditation (allowing a changing sense of self).
- Mindful walks.
- Breathwork.
- Intention setting.
- Reverse compass of ACT - noticing experiential avoidance as an indicator for what might need to be addressed.
- Internal Family Systems with modelling clay - representing critical and fearful parts of self.
- Authentic relating with ACT principles of cognitive defusion and functional analysis
- Shame work
- Values and behaviour change work
- Spectrum of Selves work (Whitfield, 2021) to understand what different parts of self are doing and enabling a more present compassionate self to choose a new path in life through the domains of self-care, relationships, community and environment.

S2.1 Pre-retreat journaling questions

- Are there potential challenges that you have held yourself back from?
- When do you turn away from your feelings or your inner experience? (what are you not willing to feel?)
- What do you do that gets in the way of what you want? (why do you do that?)
- What fears do your comfort zones shelter you from?
- What do you need help with?
- What are you curious about?
- What would you like to understand more and learn about?
- What are you grateful for?

S3. Additional details on retreat experience

Before the ceremonies Adam reported feelings of uncertainty, and apprehension but also excitement, interest, and hopefulness. After the first round of preparation, he reported feeling openness, and safety regarding both fellow retreatgoers and facilitators. The experience was described as moving, powerful, profoundly beautiful, amazing, challenging, scary, ineffable and unexpected.

During his hospital stay following the fall from the mast 17 years before, he reported to have gone in and out of consciousness for one week; he reported re-experiencing this flickering sense of consciousness and identity during the ceremony. He reported feeling emotionally dissociated from the scene while he was experiencing it and having seen several hands coming towards him that he was not able to hold while falling.

After asking for help during the challenging experience he encountered in the second ceremony, he received support multiple times from the facilitators who reminded him of his intentions, of things that mattered to him including his significant others, challenged him to come out of such a “spiritual trap” and invited him to focus on his breath. This prompted him to focus on his pain, to inquire FM about its needs, and to show love towards it. After this he accessed the feelings of universal love described in the main paper.

S4. Questionnaires

CompACT

CompACT (Francis et al., 2016) is a measure of ACT psychological flexibility processes using 23 items in three subscales: Openness to experience, Behavioural awareness, and Valued action. These latter three scales offer a broader picture of psychological flexibility, as understood in terms of the six ACT processes, and performed well for internal consistency. The compACT was developed following criticism that the AAQ2 (Wolgast, 2014) may conflate distress outcome variables with ACT processes (see Francis et al., 2016, p.135).

Depression Anxiety and Stress Scales

The Depression Anxiety and Stress Scales (DASS 21) (Lovibond & Lovibond, 1995) measured psychological stress anxiety and depression as three subscales of 7 items, each scored with self-report through 4-point Likert scales. The scales have shown high reliability and validity across settings (Crawford & Henry, 2003; Oei et al., 2013), and correlate with the Beck Depression Inventory (0.74) and the Beck Anxiety Inventory (0.81) (Lovibond & Lovibond, 1995). Each scale has cutoff scores to determine the severity of unpleasant emotional states: normal, mild, moderate, severe, extremely severe.

Cognitive Fusion Questionnaire

The Cognitive Fusion Questionnaire (CFQ) (Gillanders et al., 2014) is a seven-item single scale (CFQ-7) measure of Cognitive fusion or 'identification with thoughts' applicable to different contexts. The higher the score, the more the person experiences such identification. This is one of the six core processes in ACT and fundamental to progress in any mindfulness approach. Its psychometric properties have been investigated across different countries and socio-cultural contexts, showing it to have high internal consistency and adequate test-retest stability with both clinical and non-clinical populations (Donati et al., 2021).

Five Facets Mindfulness Questionnaire 15

The Five Facets Mindfulness Questionnaire 15 (Baer et al., 2006) employs 15 items to measure mindfulness using five sub-constructs of mindfulness. Namely propensities to 1) be non-reactive to inner experiences, e.g. "I perceive my feelings and emotions without having to react to them"; 2) observe or attend to one's internal and external experiences, e.g. "I notice the smells and aromas of things"; 3) attend to a current activity with or without "automatic pilot", e.g. "I find myself doing things without paying attention"; 4) label observed experiences with words, e.g. "I'm good at finding words to describe my feelings" and 5) be non-judging of experience - accepting inner experiences without evaluation, e.g. "I tell myself I shouldn't be feeling the way I'm feeling". These five are

abbreviated to Non-reactivity, Observe, Acting with awareness,
Describe and Non-Judgement.

S5. Detailed IPA report

First interview - two weeks after the retreat

1. How does the effect of the psychedelic retreat seem to you now?

Inner guidance - Adam reported to feel a greater degree of “inner guidance” that helped him plan and enact lifestyle changes. He felt more clarity about “where I need to be going and what I need to be doing.” This description was provided in contrast with his experience before the retreat in which he described himself as more prone to circular thoughts about the causes of his FM and more confused about the actions to take. He also reported that while he felt that before the retreat his general attitude towards various areas of life was about “trying hard”, after the retreat “this kind of striving had been sort of turned off” or became less prominent.

Universal love - Adam felt that the experience of universal love lingered in the days following the retreat accompanied by feelings of bliss, reassurance, and gratitude. The patient also reported increased pleasure as well as a stronger connection to himself, nature, and his significant others. While during the first days, he felt that this state would accompany him in a stable way, he noticed that it was gradually fading with the passing of time.

Returning to routine - Adam reported that while he felt more creative at work, it was hard to reintegrate, and felt disappointed

since the pain and fatigue started to come back on the fourth day after the retreat and were impacting his job performance.

2. Has the psychedelic therapy had any effect, positive or negative, on your issues?

FM Symptoms

FM symptoms reappear - During the first four days after the end of the retreat Adam reported that while a part of him was hoping that the relief in symptomatology he experienced could have been stable, another part of him “knew that [...] fibro was still there”. Since the fourth day after the end of the retreat, Adam experienced a resurgence in pain and fatigue symptoms which left him disappointed and confused: “My fibro came back as the experience kind of went down”.

Insights - Adam reported new insights and feelings that those that he experienced during the retreat were still valid and active. More specifically, he realised that he did not need to change his “whole life in all these big ways”, that he should listen to his body more attentively, and should not “push through” the pain and fatigue as “it really does not matter [...], it’s all love so it’s all going to be fine. [...] Don’t worry”.

Trauma acknowledgment - Furthermore, he feels that acknowledging the trauma he experienced when he fell from the mast added “a bit of the puzzle that [he] hadn’t noticed. [The psychedelic experience has] shown me that there’s something I need to think about, I need to work on, there’s trauma there”.

Inner guidance - As a consequence of these realisations, as reported by the patient, the feelings of uncertainty were gone and he became more committed to engage in actions to improve his FM symptoms such as take a break from work, focus on his new relationship, seek therapy when the symptoms reappear, exercise with more moderation, sign up to an upcoming mindfulness retreat, apply for a psychotherapist position in a centre providing psychedelic-assisted psychotherapy, reduce his drinking. Concerning this last point, he felt guilty for having resumed drinking after the retreat. Adam reported having a plan, in contrast to the feeling of confusion and being overwhelmed he experienced before the retreat. As per his narrative, these were lifestyle changes he was already considering before and the retreat gave him “[...] more evidence that I need to do these things. And what I do and don't need to do”.

Second interview - three months after the retreat

1. How does the effect of the psychedelic retreat seem to you now?

Inner guidance - Adam reported that he was still feeling the clarity and sense of direction that he described during the previous interview and added that mushrooms “gave [him] a map, but it didn't get me to the destination.”

Life changed - Adam reported that his life changed since the previous interview and he was not sure “if it's because of the

psychedelics or they were a catalyst or both”. Among the lifestyle changes he enacted, he reported leaving for a sabbatical that he intended to spend travelling and the effort to reduce his alcohol intake. Concerning this last aspect, he also reported that he became more compassionate towards himself when he drank more than intended. He also reported feeling less worried and anxious about considering and enacting lifestyle changes.

2. Has the psychedelic therapy had any effect, positive or negative, on your issues?

FM Symptoms

Psychogenic cause of FM - three months after the end of the retreat, Adam reported to be more committed to exploring the possibility that his FM may be the result of or be aggravated by repressed emotion.

Pain acceptance and mindful attitude - Moving from the psychogenic hypothesis, he was prompted to feel more accepting of the pain and adopted a more mindful attitude towards it. More specifically, he feels more able to “just let it [the pain] be” if it appears during working hours. He also reported being more able to listen to his body and the pain, “not judging it as a negative thing”, to “talk to it” and inquire about its needs.

FM necessary to justify lifestyle changes - Adam also built new meaning around FM as he felt that it was the result of “a part of [his] mind [...] trying to protect itself”. More specifically, he feels that physical health is a stronger reason, compared to psychological health, to justify the lifestyle changes he needed to reduce the perceived weight of responsibilities and engage in pleasurable activities: “the fibromyalgia has given me the permission to be more selfish than I would normally be”. Finally, he now feels able to show love for his FM.

Communication with his unconscious mind

Trauma re-experiencing - Adam felt a stronger connection to his unconscious mind due to the first ceremony's focus on the forgotten fall experience. Moreover, he interpreted this event as a sign that the traumatic experience is meaningfully linked to his FM. Another sign of this connection is that he feels more in contact with his needs, his “neglected parts”.

Lack of support in close relationships

Insight on potential remote causes - Adam shared that as a child he suffered from dyslexia and before receiving the diagnosis and proper support he hypothesised having endured a period of struggle while attempting to keep up with school demands. His parents eventually got him the help he needed and Adam describes this phase of his life as a period in which he needed the support of others to succeed. More specifically, he attributes his success to

his parents' "structure" and their ability to keep him "on the train tracks".

Insight on potential triggers - Adam feels that this sensitivity to feelings of lack of support was triggered by being in contact with his clients from public healthcare job who endured situations of familial and social neglect, by the inability of his supervisor to properly advise him due to theoretical differences in their clinical approach and the fact that his former fiancée was "very much in her own world". To these challenges he responded by pushing toward self-reliance, an attitude he says he may have "absorbed" from his fiancée.

Acceptance of his need for support - As a consequence of these insights, Adam feels more accepting of his need for emotional intimacy, connection, and support in close relationships.

3. Did the Integration sessions help you to do anything differently in your life?

Re-experiencing and acknowledgment of trauma - In the first integration session, working with a TIR-informed procedure of Repetitive Imaginal Re-experiencing Of the Psychedelic Experience (RIROPE) and related traumatic memories, Adam felt that his mind was unexpectedly "steering itself" and "being sidetracked" to the point that he thought that he was "doing therapy wrong". He also experienced uncommon physical sensations such

as his left eye being pulled, and the feeling of a dark figure in the room accompanied by headaches. This experience eventually led him to what he reported as a potential recovered memory in which he recalled being delivered to a house as a child where two girls performed oral sex on him. He also reported that years ago his older siblings reported remembering them “being sexually abused as a group of kids” but later denied that. This experience left Adam feeling uncomfortable and asking himself whether these memories were “real or not” but also open to exploring their meaning. Adam also reported that acknowledging this potential suppressed memory and the trauma caused by the fall incident were helpful to him.

Presence and openness - Adam reported that the integration sessions helped him feel more open toward his needs (“my exiled parts”). Among these he mentioned the need to be in nature more, to “be much slower” and to reconsider his adherence to societal expectations. Integration also helped him be more “aware”, “conscious” and “present”.

Reduced avoidance - Discussing the ACT practices aimed at identifying barriers to change and ACT based on personal values, Adam reported that integration was helpful in recognising alcohol as a way to avoid unpleasant emotional states such as loneliness and in committing to resolving that emotion by “finding people hanging out”. He also hypothesised that overly intense exercise may have had an avoidance function. Finally, he reported giving

new meaning to the fall: it was the attempt to avoid boredom that led him to climb the mast in the first place.

Third interview - six months after the retreat

1. How does the effect of the psychedelic retreat seem to you now?

Life changed - Adam reported that the retreat was a “surprising”, “hugely powerful” experience that “changed his life on a fundamental level” and brought “lots of insights”.

Increased feelings of connection - Adam reported that he felt connected to the other retreat participants. He was temporarily living with one of them and helping him renovate his house. He also felt more open to the possibility of something existing beyond the physical world, more connected to his spiritual side.

Causes and maintenance factors of changes - Adam engaged in several other activities that according to him may have contributed to support his change that may have been prompted or encouraged by the retreat experience. More specifically, going on a sabbatical, attending a mindfulness retreat, a float tank session, internal family systems (IFS) therapy, kambo ceremonies, and other psychedelic sessions, namely: DMT, LSD, and mushrooms. He also mentioned that being part of the “psychedelic world” played a part in improving his condition along with choosing to prioritise his healing and cultivating his spiritual side.

2. Has the psychedelic therapy had any effect, positive or negative, on your issues?

FM Symptoms

Pain improved - Adam feels that the therapy caused his pain to improve and “sped up [his] healing”. He resumed exercising to an intensity that he thought he would not be able to sustain anymore. Pain perception also changed. He describes it as “very different” and “more manageable” and feels like he is making “real progress”.

FM cause and triggers - Adam feels he has a better understanding of the causes and triggers of FM. He feels like he is “finding answers” and “edges” related to FM as opposed to the doubts and frustrations he had before. He also reported feeling committed to understanding its connection to the head injury he got from the fall, to his work stress, and to his relationships. More specifically, he feels that FM may have been caused and/or exacerbated by the suppression of the fall trauma and by the attitude of his old fiancée who triggered in him feelings of unworthiness, helplessness, and weakness. Concerning this last point, Adam thinks that the mushrooms presented him with an experience of universal love as a response to those feelings. Adam feels to have received a “definite answer” that reduced the feelings of confusion he had before the retreat.

Communication with his unconscious mind

The unconscious mind and the exiles - Adam feels that thanks to psychedelic therapy, his connection with the unconscious mind has improved. At the moment he prefers to refer to it as his “exiled parts”, as he feels that they are not properly unconscious. He feels more capable of accepting parts of himself that he previously judged weak or unacceptable such as those which represented the need for greater support in relationships.

Lack of support in close relationships

More sensitive than he thought - Adam reports to having realised that he is more sensitive than he previously thought. The lack of support in his relationship reportedly impacted him more than he realised: a “death by 1000 cuts” that put into question his “manliness”, sense of “power”, “strength” and “stability”. Adam feels that he has more clarity on his relational needs and considers now kindness and the ability to support as a fundamental characteristic of his potential partners.

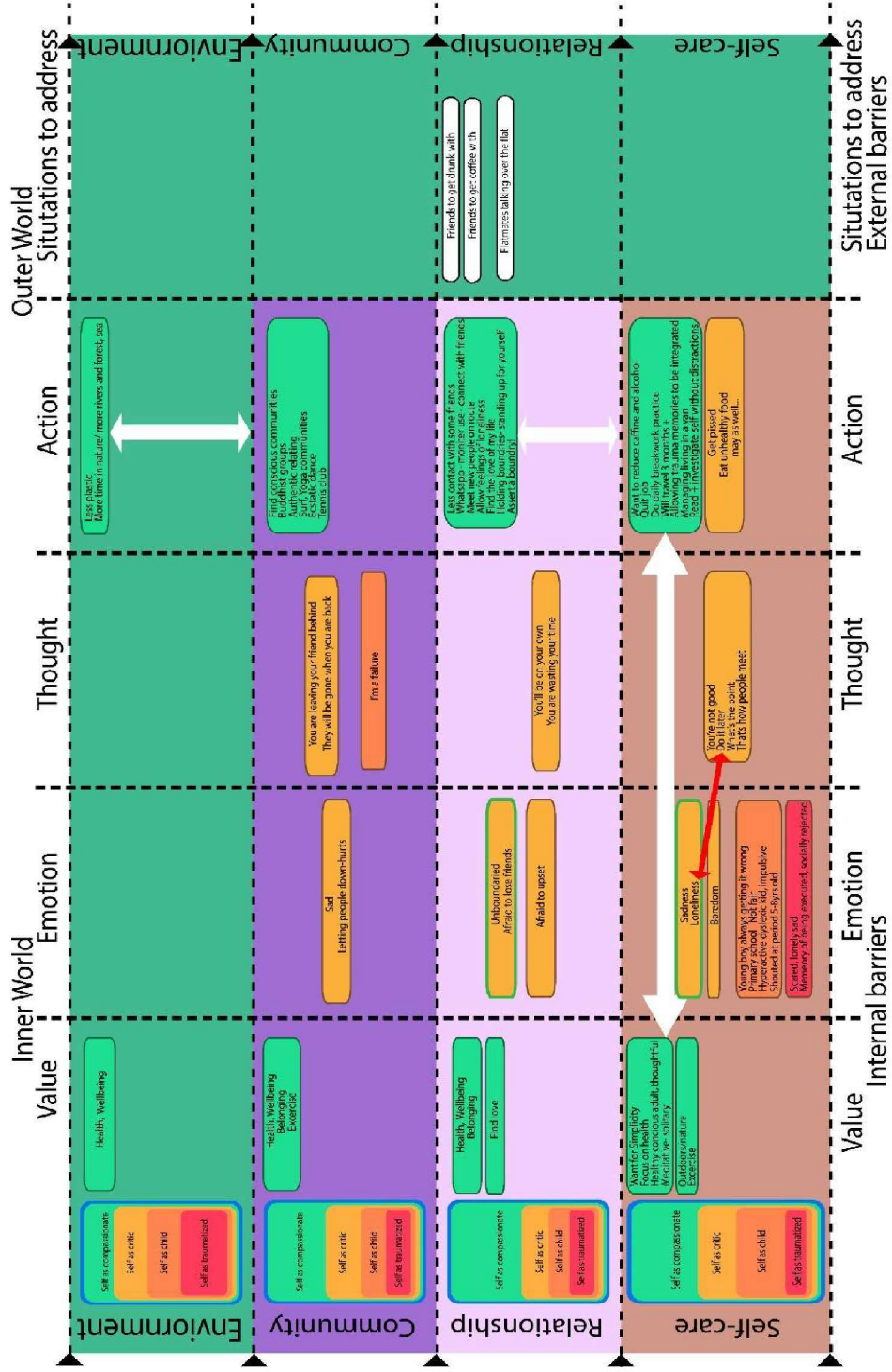
3. Did the Integration sessions help you to do anything differently in your life?

Increased openness - Integration was helpful in improving his connection to his unconscious mind and his feelings of openness.

S6. Content of integration sessions and multilevel values and action chart

Session 1	Session 2	Session 3	Session 4	Session 5
<p>ACT framed TIR (to increase willingness, presence, values awareness) on first psychedelic journey: falling from the mast.</p> <p>After increasingly feeling the fear and thoughts from the fall, another incident that may have been very early childhood trauma containing sexual abuse.</p> <p>Intention to ask his siblings about the recovered memory of a childhood</p>	<p>"My sibling agreed with my memories" (childhood sexual trauma).</p> <p>Reported having taken part to more psilocybin experiences and a mindfulness retreat.</p> <p>"I see futility in pushing myself to heal - I'm stressing myself".</p> <p>"I realise I have frozen memory of falling off the mast."</p> <p>Tension of trying not to fall is the same tension in the nerve down my</p>	<p>IFS Parts work: An anxious fearful part wants to hide "Don't hurt me".</p> <p>I tried acupuncture. "The pain is there a little bit still."</p> <p>TIR on falling then going to hospital. "Echoes of pain in the head as I get closer to the ground"</p> <p>Tingling in head and hands. Somatic awareness increases.</p> <p>Review another memory of getting stuck behind a tree</p>	<p>Handed in my notice. Feeling freer & elated. Started drinking again.</p> <p>Fibro getting better since I quit my job. Did partswork homework. Superhero part is called Maximus. When they fight I get frustrated.</p> <p>Spreadsheet work done on alignment between life domains (see S6)</p> <p>I want people to like me. I want to be included.</p> <p>Defusion Tichener technique repeating: "I want people to like me." [I'm getting younger as I say this]</p>	<p>I've had to break it off with the girl I was dating.</p> <p>Review multilevel spreadsheet and Integration checklist questions to Q7.</p> <p>Values clarified: Decisiveness, progression, creativity, health.</p> <p>Actions that express these: Seek conscious community, Do breathwork, train dog, cook more and eat healthy, weekly exercise.</p> <p>Environmental barriers to enacting these identified.</p>

<p>sexual trauma.</p>	<p>neck. "My nerves still frozen in tightness of bracing for impact".</p> <p>TIR on falling off the mast. Result: "A piece of the jigsaw has been found."</p>	<p>and needing a ladder.</p> <p>"I processed more memory".</p> <p>Parts work on a part that wants to be big and strong versus a compassionate part.</p> <p>Homework to voice what the different parts say in a spreadsheet.</p>	<p>I want girls to like me</p> <p>TIR on childhood humiliation regarding a girl, and being rejected as a friend.</p> <p>Memory of playing with a girl.</p> <p>Topic of social exclusion and being unwanted by females is still painful.</p> <p>Homework is to list possible compassionate self actions for better health.</p>	<p>Hedonistic teenage part can be a barrier.</p> <p>Compassionate part can encourage the desired behaviour change.</p> <p>Defining and listing of emotions, thoughts, feelings, sensations that can be a barrier.</p>
-----------------------	---	---	---	---



Chapter 6

Psychedelic therapies to treat mental pain

Mauro Cavarra, Kim P. C. Kuypers, Eef L. Theunissen, Johannes G. Ramaekers, Carmela Mento

The present chapter delves into the potential of psychedelic therapies for treating mental pain (MP). It begins by defining and understanding MP, highlighting its significant implications for mental health, particularly its strong association with suicide ideation and attempts. The chapter then explores the resurgence of psychedelic research, focusing on the therapeutic potentials of psychedelics in treating various mental health disorders, including depression, PTSD, and substance abuse. It discusses different forms of psychedelic-assisted psychotherapy (PAP), their effectiveness, and the overlap between the conditions associated with MP and those targeted in PAP studies. The chapter emphasises the importance of considering individual and contextual factors, set and setting, in the effectiveness of PAP. The concluding sections describe the potential therapeutic mechanisms of psychedelics, suggesting their role in emotion regulation, identity formation, and behaviour patterns.

Under review as book chapter in:

Mento, C., et al. (2024). Mental pain: a focus on diagnosis and treatment in clinical psychology and psychiatry, Nova.

Definition, causes, and mental health implications of mental pain

Mental pain (MP) as a construct gained attention for its ability to explain the intense psychological suffering that individuals experience in response to various types of stressors (Shneidman, 1993). Shneidman (1993) coined the term "psychological pain" to refer to the intense emotional distress that arises when an individual's psychological needs are unfulfilled. This type of pain has been characterised as a deep ache or throbbing in the psyche, causing hurt, anguish, soreness, and gnawing feelings (Ryan & Deci, 2000; Shneidman, 1993). Recent qualitative studies focusing on reports by patients, clinicians, and caregivers describe it as an unbearable, torture-like experience (Chevance et al., 2020).

Just as its physical counterpart, the experience of MP recruits brain regions such as the insula and anterior cingulate cortex (Meerwijk et al., 2013) and involves the opioid μ -receptor system (Nummenmaa & Tuominen, 2018). Social isolation or conflicts in relationships (Joiner et al., 2009), the loss of a loved one (Shneidman, 1993), traumatic experiences like physical or sexual abuse (Briere & Scott, 2015), as well as mental health conditions such as depression (Conejero et al., 2018; Joiner et al., 2009), anxiety (Joiner et al., 2009), PTSD (Tossani, 2013), problematic substance use (Dangel et al., 2018; Dangel & Webb, 2018), and

physical ailments such as migraines (Cosci et al., 2021) are some examples of circumstances that can give rise to MP.

The construct has significant implications for mental health, as it is strongly associated with suicide ideation and suicide attempts (Verrocchio et al., 2016). Studies have shown that MP is a better predictor of suicide ideation and attempts than depression or hopelessness (Joiner et al., 2009; Van Orden et al., 2008). Furthermore, it has been found to mediate the relationship between various risk factors, such as thwarted belongingness (i.e., a painful psychological state caused by feeling that one's need for connection and belonging is not met) (Van Orden et al., 2012), perceived burdensomeness, acquired capability (i.e., an individual's acquired tolerance or ability to engage in self-harm or suicidal behavior) (Van Orden et al., 2008), and suicide ideation and attempts (Joiner et al., 2009; Van Orden et al., 2008).

No specific treatment has been defined for MP per se as, given its transdiagnostic character (i.e., it can be present in several mental health conditions), research has focused on therapeutic avenues that could target the underlying diagnoses such as depression, substance abuse, PTSD. Currently supported treatments for these conditions typically include a combination of pharmacological, behavioural and psychosocial interventions (Dunlop et al., 2012; Gaynes, 2009; McGovern & Carroll, 2003). These conditions have also been the target of recent clinical studies that have tested the

therapeutic potential of psychedelic-assisted psychotherapy (PAP), as we will discuss in the following sections.

The second wave of psychedelic research

Psychedelics are a class of psychoactive substances that acutely alter perception, cognition, and mood, inducing profound changes in consciousness and even mystical or transcendent experiences (Griffiths et al., 2008; Nichols, 2016). These substances - including LSD, psilocybin, mescaline, and DMT - typically exert their effects by binding to 5-HT₂ serotonin receptors in the brain (Vollenweider & Kometer, 2010). Studies have proposed that psychedelics could affect brain networks related to self-referential processing (Carhart-Harris & Friston, 2019), emotion regulation (Mertens et al., 2020), and cognitive flexibility (Davis et al., 2020). Additionally, psychedelics may promote neuroplasticity (de Vos et al., 2021; Ly et al., 2018) and potentially be used as a therapy for various mental health disorders (Nutt et al., 2020).

The first wave of research on the potential therapeutic effects of psychedelics such as LSD and psilocybin came about around the 1960s and their effects were tested in a variety of clinical conditions including alcohol dependence (Bowen et al., 1970; Kurland et al., 1967; Smart et al., 1966; Smith, 1958; Tomsovic & Edwards, 1970), neuroses (Abramson, 1960), physical pain (Kast & Collins, 1963)

and life-threatening illnesses (Grof et al., 1973; Kast, 1967; Kurland et al., 1972, p. 72; Pahnke et al., 1970).

Despite the encouraging early results, their use was prohibited mainly in the 1970s due to concerns over their safety, supposed potential for abuse, and a stigmatizing political climate (Nutt, 2015). This cultural environment significantly impacted research as regulations made it increasingly hard to conduct studies on this class of substances (Nutt, 2015). In recent years, a resurgence of interest in the therapeutic potential of these substances has sparked what is known as the psychedelic renaissance (Sessa, 2012). Between the 1990s and through the 2010s, in fact, the number of publications consistently increased across a wide range of areas including psychopharmacology (Kometer et al., 2012; Passie et al., 2002; Preller et al., 2017; Valle et al., 2016; Vollenweider et al., 1998), neuroimaging (Carhart-Harris et al., 2012; Muthukumaraswamy et al., 2021; Riba et al., 2004; Vollenweider, 1997), creativity (Kuypers et al., 2016), and clinical research on conditions such as life-threatening illnesses (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), addictions (Bogenschutz et al., 2015; Johnson et al., 2014), depression (Carhart-Harris et al., 2016) and other psychopathological conditions and symptoms (Uthaug et al., 2018, 2019). It should also be mentioned that other classes of substances that produce profound alterations in consciousness while not relying on serotonergic receptors have been receiving increasing

284

attention. More specifically, several studies were published investigating the effects of MDMA-assisted psychotherapy (Smith et al., 2022) in the treatment of conditions such as PTSD, as well as examining the effect of ketamine infusions (Murrough et al., 2013) and ketamine-assisted psychotherapy (Drozdz et al., 2022) for depression. As a result of this research, advocacy efforts to legalize these drugs for medical use have been intensifying (Nutt, 2015).

Psychedelic-assisted psychotherapy for mental pain

Psychedelic-assisted psychotherapy (PAP) is a label used to refer to clinical interventions that integrate a psychotherapeutic intervention with one or more psychedelic sessions (Cavarra et al., 2022). Currently, there is no definitive agreement on the optimal structure of psychotherapeutic interventions in this context (McNamee et al., 2023) and the evidence supporting the necessity of psychotherapy is limited and based on preliminary research (Johnson et al., 2008). Furthermore, a recent paper suggests that psychedelic pharmacotherapy alone may lead to significant clinical improvements (Reckweg et al., 2023). Still, several models of PAP (Psychotherapeutic Assisted Psychotherapy) have been put forth (Cavarra et al., 2022). Most models include a preparation phase,

one or more sessions in which a psychedelic substance is administered, followed by one or more integration sessions. During preparation, themes relevant to the therapeutic process are discussed and patients are informed about the effects they can experience during the dosing session. During integration, patients discuss the experience and potential insights they gained from the psychedelic experience(s) and work with the therapist or facilitator to integrate them into everyday life (Cavarra et al., 2022).

There is a substantial overlap between the conditions with which MP is usually associated and those targeted in clinical studies investigating the therapeutic potential of PAP. In the following sections we will provide an overview of such studies on depression, PTSD and substance abuse highlighting the potential therapeutic role that psychedelics may have in treating MP. As we will discuss, there are reasons to believe that the therapeutic mechanisms underlying PAP action may specifically target neurobiological and psychological factors responsible for MP.

Depression

The effects of psychedelic-assisted psychotherapy on treatment-resistant depression (TRD) were tested in an open-label feasibility study (Carhart-Harris et al., 2016) which employed a treatment program named Preparation, Support, Integration (PSI). PSI entails a 4-hour preparation phase in which therapists aim to build a functional therapeutic relationship, gathering patients' personal

history and hypotheses concerning the origin of their depression and preparing them for the psychedelic session (Carhart-Harris et al., 2016; Stroud et al., 2018). Patients went through 2 supervised psilocybin sessions (10 mg and 25 mg) separated by one week. In this model, therapists are encouraged to facilitate an “uninterrupted journey” and to regularly monitor the patients’ state during the whole session (Carhart-Harris et al., 2016; Stroud et al., 2018). After each psilocybin session, participants took part in an integration session in which they are encouraged to talk about their psychedelic experience and are helped to consolidate positive changes in their daily lives (Carhart-Harris et al., 2016; Stroud et al., 2018). Results showed antidepressant effects that were maintained at the 3 (Carhart-Harris et al., 2016) and 6 months (Stroud et al., 2018) follow-up.

More recently, the effectiveness of psilocybin-assisted psychotherapy for TRD delivered within an acceptance and commitment therapy (ACT) frame was tested in an RCT comparing psilocybin to escitalopram (Carhart-Harris et al., 2021) in a sample of 59 patients who also received psychological support in both conditions. Both groups reported reductions in depressive symptoms, but the between-group difference in the primary measure of depression (i.e., Quick Inventory of Depressive Symptomatology–Self-Report score) was not significant (Carhart-Harris et al., 2021). Secondary measures such as the Beck Depression Inventory 1A, the Hamilton Depression Scale and the

Montgomery and Åsberg Depression Rating Scale tended to favor psilocybin (Carhart-Harris et al., 2021).

TRD was also the target of studies which tested the effectiveness of both ketamine infusions alone (Marcantoni et al., 2020) and ketamine-assisted psychotherapy (Joneborg et al., 2022). While ketamine infusions alone showed rapid and strong antidepressant effects, their duration tended to diminish over the course of the week following treatment (Marcantoni et al., 2020). This finding led researchers to test whether combining infusions with psychotherapy may yield better results. To this aim, Wilkinson et al. (2017) recruited a sample of TRD patients and included them in an open-label trial of cognitive-behavioral therapy (CBT) plus ketamine infusions to test whether the addition of psychotherapy may prolong the antidepressant effects. More specifically, participants underwent 4 ketamine infusions (0.5 mg/kg) over the course of 2 weeks while concurrently receiving CBT twice a week. Once the infusion cycle was completed, patients remained in a weekly CBT program for 8 additional weeks. Results showed more stable antidepressant effects (12 weeks after the last ketamine infusion) compared to previous studies (Wilkinson et al., 2017). Most patients ended up relapsing and most of them did so at the end of the CBT treatment cycle (Wilkinson et al., 2017). A subsequent study by the same authors (Wilkinson et al., 2021) compared the effects of a ketamine plus CBT program with ketamine plus treatment as usual (TAU). Results showed greater improvement in depressive

288

symptomatology of the former group compared to the latter (Wilkinson et al., 2021).

PAP was also tested in depression associated with life-threatening illnesses (LTI). Early research attempts were carried out during the first wave of psychedelic research when LSD was used to improve depression and pain in patients affected by LTI. Kast et al. (1967), in an open-label, single-session design showed that LSD (100 µg) by itself could lead to reduced pain up to 12 weeks after administration. Subsequently, Grof et al., (1973) ran an open-label study in which patients suffering from an LTI received a single LSD-assisted psychotherapy session preceded by a preparation phase aimed at developing rapport, processing intrapsychic conflicts, confronting the diagnosis, prognosis and death. Patients also received information about the effects of LSD before taking part in the psychedelic session. They were administered 200 µg to 500 µg of LSD in a supervised setting and after the psychedelic session they took part in integration sessions. Results showed improved depression, anxiety, fear of death and ratings of isolation, along with a reduction in pain (Grof et al., 1973). More recent, placebo-controlled studies confirmed these early results (Gasser et al., 2014; Griffiths et al., 2016, p. 16; Grob et al., 2011; Ross et al., 2016).

Depressed patients often struggle with MP and a body of evidence seems to indicate that such experience is sustained by rigid and

dysfunctional cognitive functioning (Conejero et al., 2018). More specifically, studies show that measures of MP such as the Orbach & Mikulincer Mental Pain scale (Casanova et al., 2021) are associated with dysfunctional cognitions about oneself, one's environment and social network (Orbach et al., 2003). Such beliefs seem to play a role in turning previously non-aversive stimuli into aversive ones, further deteriorating the individuals' well-being and mental health and increasing their feelings of self-estrangement and disconnection (Conejero et al., 2018).

Thematic analyses of reports by TRD patients who underwent PAP seem to suggest that psychedelics specifically act upon some of the mechanisms sustaining MP (Watts et al., 2017). In fact, patients report improvements in beliefs related to themselves such as increased self-worth, confidence, personal strength and resilience (Watts et al., 2017). Furthermore, from a state in which they felt stuck in repetitive rumination, they reported to have reached a state of openness, clarity and mental agility (Watts et al., 2017). Also, PAP seems to promote greater feelings of connection on several levels relevant to MP in depressed patients, such as connection to oneself (both in terms of physical senses and sense of self), to close family and friends, to others and - in some cases - to the whole world and to spiritual principles (Watts et al., 2017). Additionally, patients also report discovering (or re-discovering) personally relevant values (Watts et al., 2017). This contributes to increasing the sense of meaning in their life (Preller et al., 2017), a dimension

that is severely impaired in depressed patients struggling with MP (Orbach et al., 2003). Finally, we must mention that depression is often comorbid with other conditions that are associated with MP. For this reason, the points raised in this section may be also relevant for the conditions we will shortly discuss, namely PTSD and substance use disorders.

PTSD

The majority of studies investigating the role of PAP in the treatment of PTSD focus on MDMA-assisted psychotherapy (MDMA-AP) (Mithoefer, 2016). MDMA-AP aims at using the MDMA-induced reduction of fear, increased personal trust, and positive emotions to facilitate the processing of traumatic events in the context of a supportive psychotherapeutic setting (Mithoefer, 2016). The treatment entails a preparation phase lasting 2 to 3 sessions, which pursues objectives similar to those described above. Uniquely, MDMA-AP instructs patients to trust their “inner healing intelligence” through the course of the psychedelic experience to facilitate the therapeutic process. Typically, MDMA therapy involves one to three sessions with a dosage range of 75 to 125 mg. Subsequently, patients undergo two to three integration sessions intended to reinforce any insights they may have encountered during the drug sessions and to apply them to their daily lives (Mithoefer, 2016). Pooled analyses of 4 phase 2 RCTs show reduced PTSD symptoms compared to control groups with a large

effect size (Mithoefer et al., 2019). As a consequence of these results, the Food and Drug Administration granted MDMA-AP the status of breakthrough therapy for PTSD (Burge, 2020), a designation reserved to promising experimental treatments that expedites their development (Commissioner, 2018).

Other approaches tested for their effectiveness in treating PTSD involve the use of 2 forms of ketamine-assisted psychotherapy: The Trauma Interventions using Mindfulness-Based Extinction and Reconsolidation (TIMBER) and ketamine infusions plus exposure therapy. TIMBER is a therapeutic approach that incorporates the principles of extinction, reconsolidation, and mindfulness-based emotion regulation to alleviate PTSD symptoms (Pradhan et al., 2017). In the context of an RCT (Pradhan et al., 2017), the effectiveness and stability of clinical gains of TIMBER plus a single ketamine infusion (0.5 mg/kg) were compared to that of TIMBER plus placebo in a small sample (5 individuals per group) of treatment-resistant PTSD patients. Participants were offered 2 additional non-drug TIMBER sessions in the same week of the infusion and 9 subsequent weekly sessions (Pradhan et al., 2017). While no significant difference was observed in terms of symptom reduction between the two groups, a follow-up study including 10 additional patients reported a more sustained duration in the group that received the ketamine infusions (Pradhan et al., 2018). The effects of adding a ketamine infusion to already established treatments for chronic PTSD were also investigated in a proof-of-

292

concept study involving a small sample (n = 12) of veterans (Shiroma et al., 2020). Patients were involved in a prolonged exposure (PE) program starting the day after the infusion (0.5 mg/kg), including 3 to 10 psychotherapy sessions (Shiroma et al., 2020). The 10 patients who completed the treatment showed improvements in PTSD symptoms at the 4-month follow-up (Shiroma et al., 2020).

Research on PTSD points out that avoidance and numbing play an important role in sustaining and worsening the burden of the condition (Badour et al., 2012) and the resulting degrees of MP (Tossani, 2013). The above-cited clinical trials showed that PAP (and more specifically MDMA-AP) seems to specifically target the avoidance component of the disorder (K. W. Smith et al., 2022), suggesting that this therapeutic avenue may constitute a valid response when attempting to reduce the burden of MP in PTSD patients.

Substance abuse

Two different forms of psilocybin-assisted psychotherapy were tested as potential treatments for substance abuse (Bogenschutz et al., 2015; Johnson et al., 2008). More specifically, a 15-week integrated program including 2 to 3 psilocybin sessions (20-30mg/70kg) in the context of a quit-for-life (QFL) program (a CBT-derived approach) was administered to 15 smokers in an open-label feasibility study (Johnson et al., 2014). Psychotherapy included

preparation and integration sessions, a relaxation exercise, an imagery exercise and smelling scented oils alongside weekly QFL sessions for the duration of the program (Johnson et al., 2014). Abstinent participants at the 6, 12, and ≥ 16 -month follow-up were 80%, 67%, and 60%, respectively (Johnson et al., 2014). PAP was also tested by Bogenschutz et al. (2015) in 10 patients suffering from alcohol use disorder (AUD). Participants received 2 psilocybin sessions (0.3-0.4mg/kg) in the context of a 12-week motivational enhancement therapy (MET) program (Miller, 1994). MET is a brief treatment model developed specifically to achieve behavioral change in patients suffering from substance abuse issues (Miller & Rollnick, 1991). Alongside the MET program, and the psilocybin sessions, the authors included 3 preparation sessions and 2 debriefing sessions (Bogenschutz et al., 2015). Heavy drinking days decreased during the program and improvements were maintained at the 36-week follow-up (Bogenschutz et al., 2015). In a more recent double-blind RCT, the same authors tested the effects of two psilocybin sessions (25-40 mg/70kg) plus a psychotherapeutic approach integrating MET and CBT with a sample of alcohol use disorder (AUD) patients. The control group received an antihistamine (diphenhydramine, 50-100 mg) alongside the same psychotherapy program (Bogenschutz et al., 2022). Diphenhydramine was chosen under the assumption that its subjective effects (Preston et al., 1992) could possibly be mistaken for psilocybin by psychedelic-naive participants (Bogenschutz et al., 2022). After 12 weeks of treatment, the percentage of drinking days

decreased significantly compared to the control condition (Bogenschutz et al., 2022).

A 5-week MET program was also tested in conjunction with a ketamine infusion (0.6mg/kg) in a controlled trial (Dakwar et al., 2020). Effectiveness was tested against a control group receiving MET plus a benzodiazepine (midazolam, 0.025 mg/kg); the ketamine group had a reduced number of drinking days, heavy drinking days and proportion of abstinent participants 21 days after the infusion compared to the control group (Dakwar et al., 2020). At the 6-month follow-up, results suggested greater rates of abstinence in the ketamine group (Dakwar et al., 2020). An RCT evaluated the efficacy of a ketamine infusion as part of a ketamine-assisted psychotherapy (KAP) program for the treatment of 70 individuals with heroin addiction. The study compared the effectiveness of high (2 mg/kg) versus low doses (0.2 mg/g) of ketamine (Krupitsky et al., 2002). The infusion was preceded by 10 preparation sessions and followed by 5 integration sessions (Krupitsky et al., 2002). Results showed increased abstinence rates in the high-dose group compared to the low-dose group one at the 24-month follow-up as well as lower cravings in the high-dose group (Krupitsky et al., 2002). A later study by the same authors suggested that multiple ketamine sessions may increase adherence to the treatment program and long-term abstinence rates (1 year) (Krupitsky et al., 2007). An RCT conducted in a 5-day inpatient setting examined the efficacy of a single infusion of

ketamine (0.5 mg/kg) in combination with mindfulness-based relapse prevention (MBRP) for treating cocaine dependence. The study compared this approach with MBRP plus a midazolam infusion (0.025 mg/kg) (Dakwar et al., 2019). During their inpatient stay, the 55 participants received daily MBRP sessions while, after discharge, they received 2 sessions per week for 4 weeks (Dakwar et al., 2019). Results showed higher rates of abstinence in the high-dose group following treatment and at the 6-month follow-up compared to the midazolam group (Dakwar et al., 2019).

The role of MP in substance abuse can be understood in the self-medication hypothesis (SMH) framework (Khantzian, 1997). According to the SMH, substance abuse is the result of an effort to attenuate aversive emotional states (Khantzian, 1997) described by some authors as “emotionally struggling to affirm one’s meaningful existence” (Webb et al., 2015). Such states are therefore believed to be a critical causal factor for the development of problematic substance use, may increase the amount of perceived MP and in turn trigger more substance use (Dangel & Webb, 2018). Finally, the degree of MP in these patients seems to be inversely associated with their capacity to forgive themselves for past actions (Webb et al., 2015). In this context, forgiveness is conceptualised as a “the framing of a perceived transgression such that one’s responses [...] are transformed from negative to neutral or positive. The [...] object of forgiveness may be oneself, another person or persons, or a situation that one views as being beyond anyone’s

control” (Thompson et al., 2005). The capacity for self-forgiveness may be relevant to patients with problematic substance abuse issues as it may allow them to accept past actions, preventing them from experiencing unpleasant emotions such as guilt when thinking back to those times and thus reducing the burden of MP (Dangel & Webb, 2018).

As we will discuss more in detail in the following section (8.4 Therapeutic mechanisms), properly prepared psychedelic experiences are often rated among the most meaningful in a person’s life (Griffiths et al., 2008) and the resulting improvement in well-being has been reported to be lasting for several weeks after the experience itself (Majić et al., 2015). PAP also seems to promote acceptance of unpleasant emotions which may be relevant in relation to the disposition to accept and forgive oneself while engaging in the therapeutic journey (Watts et al., 2017).

In conclusion, PAP may constitute a specific response to the lack of meaning and inability to forgive oneself that substance abuse patients often report. In fact, these two factors seem to play a substantial role in increasing MP and psychedelic experiences seem to respond to the need for meaning while increasing the ability to forgive oneself. For these reasons, PAP may constitute a promising candidate to target and reduce the burden of MP on patients suffering from problematic substance use.

Therapeutic mechanisms

While the causal pathways underlying the therapeutic effects of psychedelics are not fully understood, existing evidence points to psychological and neurobiological mechanisms that could explain them.

Neuroimaging data shows that psychedelics seem to modulate the activities of areas involved in (interpersonal) emotion regulation (Carhart-Harris et al., 2017; Roseman et al., 2018), identity and the sustaining of habitual behaviors and thought patterns (Carhart-Harris et al., 2012, 2013; Palhano-Fontes et al., 2015; Roseman et al., 2014; Scheidegger et al., 2012; Tagliazucchi et al., 2016). The studies mentioned previously regarding the impact of PSI on TRD demonstrated that patients exhibited lower amygdala activation in the absence of emotionally charged stimuli after treatment (Carhart-Harris et al., 2017). Conversely, patients showed increased amygdala activation when exposed to images of emotional and neutral faces following treatment (Roseman et al., 2018).

Psychedelics seem to modulate the activity of the default mode network (DMN), which is believed to be the neurobiological basis of the sense of self, and is involved in processes such as rumination and mind wandering (Carhart-Harris & Friston, 2010). The DMN is

perturbed as a consequence of the administration of several psychedelic substances (as well as MDMA and ketamine) (Carhart-Harris et al., 2012, 2013; Mason, Kuypers, Müller, et al., 2020; Palhano-Fontes et al., 2015; Roseman et al., 2014; Scheidegger et al., 2012; Swanson, 2018; Tagliazucchi et al., 2016; Tolle et al., 2023). Functional connectivity (FC) is decreased acutely (Gattuso et al., 2023; Lebedev et al., 2015; Mason, Kuypers, Reckweg, et al., 2020; Tagliazucchi et al., 2016) and is increased the day after administration in a PAP setting (Carhart-Harris et al., 2017). This constellation of events seems to mirror the participants' subjective experience both during the psychedelic session and in the following days. More specifically, TRD patients report feeling more able to approach and confront painful and previously avoided emotional content (i.e., increased amygdala activation as a consequence of emotion-laden stimuli) (Carhart-Harris et al., 2017), they may go through experiences of ego dissolution (i.e., decreased FC in the DMN) and insights that end up reshaping their perception of themselves and their life (i.e., increased FC in the DMN).

The picture emerging from fMRI data, paired with evidence showing increased neuroplasticity (de Vos et al., 2021; Ly et al., 2018), cognitive flexibility (Kuypers et al., 2016; Majić et al., 2015) and suggestibility (Carhart-Harris et al., 2015) as a consequence of psychedelic intake led some researchers to refer to these drugs as psychoplastogens (Ly et al., 2018). These considerations provide new depth to theories that were proposed during the first wave of

research in the field. More specifically, one of the long-standing beliefs is that individual variables (personality, preparation, expectation and intention) and contextual factors (the physical, social, and cultural environment surrounding the psychedelic experience) are important modulators of the quality of the experience as well as of clinical outcomes (Hartogsohn, 2016). This is known as the set and setting theory, one of the earliest models used to describe the action of psychedelics (Zinberg, 1984).

Perhaps most relevant to MP and its relation to suicide risk is the fact that peak psychedelic experiences within the context of PAP are considered highly meaningful on a personal and/or spiritual level for the participants involved (Preller et al., 2017). Some studies even report that such experiences are considered among the most meaningful in an individual's life (Griffiths et al., 2008). Considering that perception of meaning in life has been considered an important mediator between psychological suffering and suicide ideation and attempts (Costanza et al., 2020; Lew et al., 2020; Marco et al., 2016), the meaning-enhancing properties of psychedelics (Hartogsohn, 2018) may constitute a powerful tool to help patients resolve their suicidality. Current evidence on the effects of psychedelics on suicidality is mixed (Zeifman et al., 2019) and, considering the heterogeneity of designs and measurements adopted in existing literature (Zeifman et al., 2021), more focused research is needed to ascertain what their actual effects may be.

Conclusion

While MP has not yet been directly investigated in any of the existing clinical trials investigating the effectiveness of PAP, this family of treatments seems to lead to improvements in conditions that are commonly associated with it, namely: depression, PTSD, and substance abuse. Furthermore, specific effects of PAP seem to be particularly suited to treat MP in the above-cited conditions, namely: the loosening of rigid thought patterns related to the self, the environment and others; the enhancement of feelings of connection and meaning in life; the reduction of avoidance tendencies; the increased capacity to face and accept unpleasant emotions.

References

Abramson, H. A. (1960). *The Use of LSD in Psychotherapy: Transactions*. Josiah Macy, Jr. Foundation.

Badour, C. L., Blonigen, D. M., Boden, M. T., Feldner, M. T., & Bonn-Miller, M. O. (2012). A longitudinal test of the bi-directional relations between avoidance coping and PTSD severity during and after PTSD treatment. *Behaviour Research and Therapy*, 50(10), 610–616. <https://doi.org/10.1016/j.brat.2012.06.006>

Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Psychopharmacology*, 29(3), 289–299. <https://doi.org/10.1177/0269881114565144>

Bogenschutz, M. P., Ross, S., Bhatt, S., Baron, T., Forcehimes, A. A., Laska, E., Mennenga, S. E., O'Donnell, K., Owens, L. T., Podrebarac, S., Rotrosen, J., Tonigan, J. S., & Worth, L. (2022). Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, 79(10), 953–962. <https://doi.org/10.1001/jamapsychiatry.2022.2096>

Bowen, W. T., Soskin, R. A., & Chotlos, J. W. (1970). Lysergic acid diethylamide as a variable in the hospital treatment of alcoholism. *Journal of Nervous and Mental Disease*, 150(2), 111–118. <https://doi.org/10.1097/00005053-197002000-00003>

Briere, J., & Scott, C. (2015). Complex Trauma in Adolescents and Adults: Effects and Treatment. *Psychiatric Clinics*, 38(3), 515–527. <https://doi.org/10.1016/j.psc.2015.05.004>

Burge, B. (2020, January 17). FDA Agrees to Expanded Access Program for MDMA-Assisted Therapy for PTSD. Multidisciplinary Association for Psychedelic Studies - MAPS. <https://maps.org/news/media/press-release-fda-agrees-to-expanded-access-program-for-mdma-assisted-psychotherapy-for-ptsd/>

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *The Lancet Psychiatry*, 3(7), 619–627. [https://doi.org/10.1016/S2215-0366\(16\)30065-7](https://doi.org/10.1016/S2215-0366(16)30065-7)

Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., Tyacke, R. J., Leech, R., Malizia, A. L., Murphy,

K., Hobden, P., Evans, J., Feilding, A., Wise, R. G., & Nutt, D. J. (2012). Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences*, 109(6), 2138–2143. <https://doi.org/10.1073/pnas.1119598109>

Carhart-Harris, R. L., & Friston, K. J. (2010). The default-mode, ego-functions and free-energy: A neurobiological account of Freudian ideas. *Brain*, 133(4), 1265–1283. <https://doi.org/10.1093/brain/awq010>

Carhart-Harris, R. L., & Friston, K. J. (2019). REBUS and the Anarchic Brain: Toward a Unified Model of the Brain Action of Psychedelics. *Pharmacological Reviews*, 71(3), 316–344. <https://doi.org/10.1124/pr.118.017160>

Carhart-Harris, R. L., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. *New England Journal of Medicine*, 384(15), 1402–1411. <https://doi.org/10.1056/NEJMoa2032994>

Carhart-Harris, R. L., Kaelen, M., Whalley, M. G., Bolstridge, M., Feilding, A., & Nutt, D. J. (2015). LSD enhances suggestibility in healthy volunteers. *Psychopharmacology*, 232(4), 785–794. <https://doi.org/10.1007/s00213-014-3714-z>

Carhart-Harris, R. L., Leech, R., Erritzoe, D., Williams, T. M., Stone, J. M., Evans, J., Sharp, D. J., Feilding, A., Wise, R. G., & Nutt, D. J. (2013). Functional Connectivity Measures After Psilocybin Inform a Novel Hypothesis of Early Psychosis. *Schizophrenia Bulletin*, 39(6), 1343–1351. <https://doi.org/10.1093/schbul/sbs117>

Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H. V., & Nutt, D. J. (2017). Psilocybin for treatment-resistant depression: FMRI-measured brain mechanisms. *Scientific Reports*, 7(1), 13187. <https://doi.org/10.1038/s41598-017-13282-7>

Casanova, M. P., Nelson, M. C., Pickering, M. A., Appleby, K. M., Grindley, E. J., Larkins, L. W., & Baker, R. T. (2021). Measuring psychological pain: Psychometric analysis of the Orbach and Mikulincer Mental Pain Scale. *Measurement Instruments for the Social Sciences*, 3(1), 7. <https://doi.org/10.1186/s42409-021-00025-8>

Cavarra, M., Falzone, A., Ramaekers, J. G., Kuypers, K. P. C., & Mento, C. (2022). Psychedelic-Assisted Psychotherapy—A Systematic Review of Associated Psychological Interventions. *Frontiers in Psychology*, 13. <https://www.frontiersin.org/article/10.3389/fpsyg.2022.887255>

Chevance, A., Ravaud, P., Tomlinson, A., Berre, C. L., Teufer, B., Touboul, S., Fried, E. I., Gartlehner, G., Cipriani, A., & Tran, V. T. (2020). Identifying outcomes for depression that matter to patients, informal caregivers, and health-care professionals: Qualitative content analysis of a large international online survey. *The Lancet Psychiatry*, 7(8), 692–702. [https://doi.org/10.1016/S2215-0366\(20\)30191-7](https://doi.org/10.1016/S2215-0366(20)30191-7)

Commissioner, O. of the. (2018). Breakthrough Therapy. FDA. <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy>

Conejero, I., Olié, E., Calati, R., Ducasse, D., & Courtet, P. (2018). Psychological Pain, Depression, and Suicide: Recent Evidences and Future Directions. *Current Psychiatry Reports*, 20(5), 33. <https://doi.org/10.1007/s11920-018-0893-z>

Cosci, F., Svicher, A., Mansueto, G., Benemei, S., Chiarugi, A., Cesaris, F. D., Guidi, J., & Zipfel, S. (2021). Mental pain and pain-proneness in patients with migraine: Results from the PAINMIG cohort-study. *CNS Spectrums*, 26(5), 491–500. <https://doi.org/10.1017/S1092852920001480>

Costanza, A., Baertschi, M., Richard-Lepouriel, H., Weber, K., Pompili, M., & Canuto, A. (2020). The Presence and the Search Constructs of Meaning in Life in Suicidal Patients Attending a

Psychiatric Emergency Department. *Frontiers in Psychiatry*, 11.
<https://www.frontiersin.org/articles/10.3389/fpsy.2020.00327>

Dakwar, E., Levin, F., Hart, C. L., Basaraba, C., Choi, J., Pavlicova, M., & Nunes, E. V. (2020). A Single Ketamine Infusion Combined With Motivational Enhancement Therapy for Alcohol Use Disorder: A Randomized Midazolam-Controlled Pilot Trial. *American Journal of Psychiatry*, 177(2), 125–133.
<https://doi.org/10.1176/appi.ajp.2019.19070684>

Dakwar, E., Nunes, E. V., Hart, C. L., Foltin, R. W., Mathew, S. J., Carpenter, K. M., Choi, C. J. “Jean”, Basaraba, C. N., Pavlicova, M., & Levin, F. R. (2019). A Single Ketamine Infusion Combined With Mindfulness-Based Behavioral Modification to Treat Cocaine Dependence: A Randomized Clinical Trial. *American Journal of Psychiatry*, 176(11), 923–930.
<https://doi.org/10.1176/appi.ajp.2019.18101123>

Dangel, T., McBee, M. T., & Webb, J. R. (2018). An Analysis of the Psychache Scale in College Student Problematic Drinkers. *Addictive Disorders & Their Treatment*, 17(3), 147–154.
<https://doi.org/10.1097/ADT.0000000000000135>

Dangel, T., & Webb, J. R. (2018). Forgiveness and substance use problems among college students: Psychache, depressive symptoms, and hopelessness as mediators. *Journal of Substance*

Use, 23(6), 618–625.
<https://doi.org/10.1080/14659891.2018.1489003>

Davis, A. K., Barrett, F. S., & Griffiths, R. R. (2020). Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *Journal of Contextual Behavioral Science*, 15, 39–45.
<https://doi.org/10.1016/j.jcbs.2019.11.004>

de Vos, C. M. H., Mason, N. L., & Kuypers, K. P. C. (2021). Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics. *Frontiers in Psychiatry*, 12, 724606. <https://doi.org/10.3389/fpsy.2021.724606>

Drozd, S. J., Goel, A., McGarr, M. W., Katz, J., Ritvo, P., Mattina, G. F., Bhat, V., Diep, C., & Ladha, K. S. (2022). Ketamine Assisted Psychotherapy: A Systematic Narrative Review of the Literature. *Journal of Pain Research*, 15, 1691–1706.
<https://doi.org/10.2147/JPR.S360733>

Dunlop, B., Mansson, E., & Gerardi, M. (2012). Pharmacological Innovations for Posttraumatic Stress Disorder and Medication-Enhanced Psychotherapy. *Current Pharmaceutical Design*, 18(35), 5645–5658. <https://doi.org/10.2174/138161212803530899>

Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., & Brenneisen, R. (2014). Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated With Life-threatening Diseases. *Journal of Nervous & Mental Disease*, 202(7), 513–520. <https://doi.org/10.1097/NMD.0000000000000113>

Gattuso, J. J., Perkins, D., Ruffell, S., Lawrence, A. J., Hoyer, D., Jacobson, L. H., Timmermann, C., Castle, D., Rossell, S. L., Downey, L. A., Pagni, B. A., Galvão-Coelho, N. L., Nutt, D., & Sarris, J. (2023). Default Mode Network Modulation by Psychedelics: A Systematic Review. *International Journal of Neuropsychopharmacology*, 26(3), 155–188. <https://doi.org/10.1093/ijnp/pyac074>

Gaynes, B. N. (2009). Identifying difficult-to-treat depression: Differential diagnosis, subtypes, and comorbidities. *The Journal of Clinical Psychiatry*, 70 Suppl 6, 10–15. <https://doi.org/10.4088/JCP.8133su1c.02>

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of*

Psychopharmacology, 30(12), 1181–1197.
<https://doi.org/10.1177/0269881116675513>

Griffiths, R. R., Richards, W., Johnson, M. W., McCann, U., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology*, 22(6), 621–632. <https://doi.org/10.1177/0269881108094300>

Grob, C. S., Danforth, A. L., Chopra, G. S., Hagerty, M., McKay, C. R., Halberstadt, A. L., & Greer, G. R. (2011). Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. *Archives of General Psychiatry*, 68(1), 71. <https://doi.org/10.1001/archgenpsychiatry.2010.116>

Grof, S., Goodman, L. E., Richards, W. A., & Kurland, A. A. (1973). LSD-Assisted Psychotherapy in Patients with Terminal Cancer. *International Pharmacopsychiatry*, 8(3), 129–144. <https://doi.org/10.1159/000467984>

Hartogsohn, I. (2016). Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. *Journal of Psychopharmacology (Oxford, England)*, 30(12), 1259–1267. <https://doi.org/10.1177/0269881116677852>

Hartogsohn, I. (2018). The Meaning-Enhancing Properties of Psychedelics and Their Mediator Role in Psychedelic Therapy, Spirituality, and Creativity. *Frontiers in Neuroscience*, 12. <https://www.frontiersin.org/articles/10.3389/fnins.2018.00129>

Johnson, M. W., Garcia-Romeu, A., Cosimano, M. P., & Griffiths, R. R. (2014). Pilot study of the 5-HT 2A R agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology*, 28(11), 983–992. <https://doi.org/10.1177/0269881114548296>

Johnson, M. W., Richards, W., & Griffiths, R. R. (2008). Human hallucinogen research: Guidelines for safety. *Journal of Psychopharmacology*, 22(6), 603–620. <https://doi.org/10.1177/0269881108093587>

Joiner, T. E., Van Orden, K. A., Witte, T. K., & Rudd, M. D. (2009). *The interpersonal theory of suicide: Guidance for working with suicidal clients* (pp. x, 246). American Psychological Association. <https://doi.org/10.1037/11869-000>

Joneborg, I., Lee, Y., Di Vincenzo, J. D., Ceban, F., Meshkat, S., Lui, L. M. W., Fancy, F., Rosenblat, J. D., & McIntyre, R. S. (2022). Active mechanisms of ketamine-assisted psychotherapy: A systematic review. *Journal of Affective Disorders*, 315, 105–112. <https://doi.org/10.1016/j.jad.2022.07.030>

Kast, E. C. (1967). Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide. *The Psychiatric Quarterly*, 41(4), 646–657. <https://doi.org/10.1007/BF01575629>

Kast, E. C., & Collins, V. J. (1963). Study of Lysergic Acid Diethylamide as an Analgesic Agent. *Anesthesia and Analgesia*, 43(3), 285–291.

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. *Harvard Review of Psychiatry*, 4(5), 231–244. <https://doi.org/10.3109/10673229709030550>

Kometer, M., Schmidt, A., Bachmann, R., Studerus, E., Seifritz, E., & Vollenweider, F. X. (2012). Psilocybin Biases Facial Recognition, Goal-Directed Behavior, and Mood State Toward Positive Relative to Negative Emotions Through Different Serotonergic Subreceptors. *Biological Psychiatry*, 72(11), 898–906. <https://doi.org/10.1016/j.biopsych.2012.04.005>

Krupitsky, E. M., Burakov, A. M., Dunaevsky, I. V., Romanova, T. N., Slavina, T. Y., & Grinenko, A. Y. (2007). Single Versus Repeated Sessions of Ketamine-Assisted Psychotherapy for People with Heroin Dependence. *Journal of Psychoactive Drugs*, 39(1), 13–19. <https://doi.org/10.1080/02791072.2007.10399860>

Krupitsky, E. M., Burakov, A., Romanova, T., Dunaevsky, I., Strassman, R., & Grinenko, A. (2002). Ketamine psychotherapy for heroin addiction: Immediate effects and two-year follow-up. *Journal of Substance Abuse Treatment*, 23(4), 273–283. [https://doi.org/10.1016/S0740-5472\(02\)00275-1](https://doi.org/10.1016/S0740-5472(02)00275-1)

Kurland, A. A., Grof, S., Pahnke, W. N., & Goodman, L. E. (1972). Psychedelic drug assisted psychotherapy in patients with terminal cancer. *Journal of Thanatology*, 2(1–2), 644–691.

Kurland, A. A., Unger, S., Shaffer, J. W., & Savage, C. (1967). Psychedelic Therapy Utilizing LSD in the Treatment of the Alcoholic Patient: A Preliminary Report. *American Journal of Psychiatry*, 123(10), 1202–1209. <https://doi.org/10.1176/ajp.123.10.1202>

Kuypers, K. P. C., Riba, J., de la Fuente Revenga, M., Barker, S., Theunissen, E. L., & Ramaekers, J. G. (2016). Ayahuasca enhances creative divergent thinking while decreasing conventional convergent thinking. *Psychopharmacology*, 233(18), 3395–3403. <https://doi.org/10.1007/s00213-016-4377-8>

Lebedev, A. V., Lövdén, M., Rosenthal, G., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2015). Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. *Human Brain Mapping*, 36(8), 3137–3153. <https://doi.org/10.1002/hbm.22833>

Lew, B., Chistopolskaya, K., Osman, A., Huen, J. M. Y., Abu Talib, M., & Leung, A. N. M. (2020). Meaning in life as a protective factor against suicidal tendencies in Chinese University students. *BMC Psychiatry*, 20(1), 73. <https://doi.org/10.1186/s12888-020-02485-4>

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Soltanzadeh Zarandi, S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics Promote Structural and Functional Neural Plasticity. *Cell Reports*, 23(11), 3170–3182. <https://doi.org/10.1016/j.celrep.2018.05.022>

Majić, T., Schmidt, T. T., & Gallinat, J. (2015). Peak experiences and the afterglow phenomenon: When and how do therapeutic effects of hallucinogens depend on psychedelic experiences? *Journal of Psychopharmacology*, 29(3), 241–253. <https://doi.org/10.1177/0269881114568040>

Marcantoni, W. S., Akoumba, B. S., Wassef, M., Mayrand, J., Lai, H., Richard-Devantoy, S., & Beauchamp, S. (2020). A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009 – January 2019. *Journal of Affective Disorders*, 277, 831–841. <https://doi.org/10.1016/j.jad.2020.09.007>

Marco, J. H., Pérez, S., & García-Alandete, J. (2016). Meaning in Life Buffers the Association Between Risk Factors for Suicide and Hopelessness in Participants With Mental Disorders. *Journal of Clinical Psychology, 72*(7), 689–700. <https://doi.org/10.1002/jclp.22285>

Mason, N. L., Kuypers, K. P. C., Müller, F., Reckweg, J., Tse, D. H. Y., Toennes, S. W., Hutten, N. R. P. W., Jansen, J. F. A., Stiers, P., Feilding, A., & Ramaekers, J. G. (2020). Me, myself, bye: Regional alterations in glutamate and the experience of ego dissolution with psilocybin. *Neuropsychopharmacology, 45*(12), Article 12. <https://doi.org/10.1038/s41386-020-0718-8>

Mason, N. L., Kuypers, K., Reckweg, J., Tse, D., Muller, F., Toennes, S., Feilding, A., & Ramaekers, J. (2020). Acute effects of psilocybin on glutamate concentration levels, functional connectivity and subjective state. *European Neuropsychopharmacology, 31*, S64–S65. <https://doi.org/10.1016/j.euroneuro.2019.12.087>

McGovern, M. P., & Carroll, K. M. (2003). Evidence-based practices for substance use disorders. *The Psychiatric Clinics of North America, 26*(4), 991–1010.

McNamee, S., Devenot, N., & Buisson, M. (2023). Studying Harms Is Key to Improving Psychedelic-Assisted Therapy—Participants

Call for Changes to Research Landscape. *JAMA Psychiatry*, 80(5), 411–412. <https://doi.org/10.1001/jamapsychiatry.2023.0099>

Meerwijk, E. L., Ford, J. M., & Weiss, S. J. (2013). Brain regions associated with psychological pain: Implications for a neural network and its relationship to physical pain. *Brain Imaging and Behavior*, 7(1), 1–14. <https://doi.org/10.1007/s11682-012-9179-y>

Mertens, L. J., Wall, M. B., Roseman, L., Demetriou, L., Nutt, D. J., & Carhart-Harris, R. L. (2020). Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. *Journal of Psychopharmacology*, 34(2), 167–180. <https://doi.org/10.1177/0269881119895520>

Miller, W. R. (1994). *Motivational enhancement therapy manual: A clinical research guide for therapists treating individuals with alcohol abuse and dependence*. Diane Publishing Company.

Miller, W. R., & Rollnick, S. (1991). *Motivational interviewing: Preparing people to change addictive behavior* (pp. xvii, 348). The Guilford Press.

Mithoefer, M. C. (2016). *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder*. Multidisciplinary Association for Psychedelic Studies.

<https://maps.org/research-archive/mdma/MDMA-Assisted-Psychotherapy-Treatment-Manual-Version7-19Aug15-FINAL.pdf>

Mithoefer, M. C., Feduccia, A. A., Jerome, L., Mithoefer, A., Wagner, M., Walsh, Z., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Doblin, R. (2019). MDMA-assisted psychotherapy for treatment of PTSD: Study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology*, 236(9), 2735–2745.

Murrough, J. W., Perez, A. M., Pillemer, S., Stern, J., Parides, M. K., Rot, M. aan het, Collins, K. A., Mathew, S. J., Charney, D. S., & Iosifescu, D. V. (2013). Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression. *Biological Psychiatry*, 74(4), 250–256. <https://doi.org/10.1016/j.biopsych.2012.06.022>

Muthukumaraswamy, S., Forsyth, A., & Lumley, T. (2021). Blinding and Expectancy Confounds in Psychedelic Randomised Controlled Trials. <https://doi.org/10.31234/osf.io/q2hzm>

Nichols, D. E. (2016). Psychedelics. *Pharmacological Reviews*, 68(2), 264–355. <https://doi.org/10.1124/pr.115.011478>

Nummenmaa, L., & Tuominen, L. (2018). Opioid system and human emotions. *British Journal of Pharmacology*, 175(14), 2737–2749. <https://doi.org/10.1111/bph.13812>

Nutt, D. (2015). Illegal Drugs Laws: Clearing a 50-Year-Old Obstacle to Research. *PLOS Biology*, 13(1), e1002047. <https://doi.org/10.1371/journal.pbio.1002047>

Nutt, D., Erritzoe, D., & Carhart-Harris, R. (2020). Psychedelic Psychiatry's Brave New World. *Cell*, 181(1), 24–28. <https://doi.org/10.1016/j.cell.2020.03.020>

Orbach, I., Mikulincer, M., Gilboa-Schechtman, E., & Sirota, P. (2003). Mental Pain and Its Relationship to Suicidality and Life Meaning. *Suicide and Life-Threatening Behavior*, 33(3), 231–241. <https://doi.org/10.1521/suli.33.3.231.23213>

Pahnke, W. N., Kurland, A. A., Unger, S., Savage, C., Wolf, S., & Goodman, L. E. (1970). Psychedelic Therapy (Utilizing LSD) with Cancer Patients. *Journal of Psychedelic Drugs*, 3(1), 63–75. <https://doi.org/10.1080/02791072.1970.10471363>

Palhano-Fontes, F., Andrade, K. C., Tofoli, L. F., Santos, A. C., Crippa, J. A. S., Hallak, J. E. C., Ribeiro, S., & Araujo, D. B. de. (2015). The Psychedelic State Induced by Ayahuasca Modulates the Activity and Connectivity of the Default Mode Network. *PLOS*

ONE, 10(2), e0118143.
<https://doi.org/10.1371/journal.pone.0118143>

Passie, T., Seifert, J., Schneider, U., & Emrich, H. M. (2002). The pharmacology of psilocybin. *Addiction Biology*, 7(4).
<https://doi.org/10.1080/1355621021000005937>

Pradhan, B., Mitrev, L., Moaddell, R., & Wainer, I. W. (2018). d - Serine is a potential biomarker for clinical response in treatment of post-traumatic stress disorder using (R , S)-ketamine infusion and TIMBER psychotherapy: A pilot study. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics*, 1866(7), 831–839.
<https://doi.org/10.1016/j.bbapap.2018.03.006>

Pradhan, B., Wainer, I., Moaddel, R., Torjman, M., Goldberg, M., Sabia, M., Parikh, T., & Pumariega, A. (2017). Trauma Interventions using Mindfulness Based Extinction and Reconsolidation (TIMBER) psychotherapy prolong the therapeutic effects of single ketamine infusion on post-traumatic stress disorder and comorbid depression: A pilot randomized, placebo-controlled, crossover clinical trial. *Asia Pacific Journal of Clinical Trials: Nervous System Diseases*, 2(3), 80.

Preller, K. H., Herdener, M., Pokorny, T., Planzer, A., Kraehenmann, R., Stämpfli, P., Liechti, M. E., Seifritz, E., & Vollenweider, F. X. (2017). The Fabric of Meaning and Subjective

Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. *Current Biology*, 27(3), 451–457. <https://doi.org/10.1016/j.cub.2016.12.030>

Preston, K. L., Wolf, B., Guarino, J. J., & Griffiths, R. R. (1992). Subjective and behavioral effects of diphenhydramine, lorazepam and methocarbamol: Evaluation of abuse liability. *The Journal of Pharmacology and Experimental Therapeutics*, 262(2), 707–720.

Reckweg, J. T., Leeuwen, C. J., Amelsvoort, T., Theunissen, E., Mason, N. L., Paci, R., Terwey, T., & Ramaekers, J. G. (2023). A Phase 1/2 Trial to Assess Safety and Efficacy of a Vaporized 5-Methoxy-N,N-Dimethyltryptamine Formulation (GH001) in Patients with Treatment-Resistant Depression. *Frontiers in Psychiatry*, 14. <https://doi.org/10.3389/fpsy.2023.1133414>

Riba, J., Anderer, P., Jané, F., Saletu, B., & Barbanoj, M. J. (2004). Effects of the South American Psychoactive Beverage Ayahuasca on Regional Brain Electrical Activity in Humans: A Functional Neuroimaging Study Using Low-Resolution Electromagnetic Tomography. *Neuropsychobiology*, 50(1), 89–101. <https://doi.org/10.1159/000077946>

Roseman, L., Demetriou, L., Wall, M. B., Nutt, D. J., & Carhart-Harris, R. L. (2018). Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression.

Neuropharmacology, 142, 263–269.
<https://doi.org/10.1016/j.neuropharm.2017.12.041>

Roseman, L., Leech, R., Feilding, A., Nutt, D. J., & Carhart-Harris, R. L. (2014). The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. *Frontiers in Human Neuroscience*, 8. <https://www.frontiersin.org/articles/10.3389/fnhum.2014.00204>

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology*, 30(12), 1165–1180. <https://doi.org/10.1177/0269881116675512>

Ryan, R. M., & Deci, E. L. (2000). The Darker and Brighter Sides of Human Existence: Basic Psychological Needs as a Unifying Concept. *Psychological Inquiry*, 11(4), 319–338. https://doi.org/10.1207/S15327965PLI1104_03

Scheidegger, M., Walter, M., Lehmann, M., Metzger, C., Grimm, S., Boeker, H., Boesiger, P., Henning, A., & Seifritz, E. (2012). Ketamine Decreases Resting State Functional Network Connectivity in Healthy Subjects: Implications for Antidepressant

Drug Action. PLOS ONE, 7(9), e44799.
<https://doi.org/10.1371/journal.pone.0044799>

Sessa, B. (2012). *The psychedelic renaissance: Reassessing the role of psychedelic drugs in 21st century psychiatry and society* (pp. xi, 237). Muswell Hill Press.

Shiroma, P. R., Thuras, P., Wels, J., Albott, C. S., Erbes, C., Tye, S., & Lim, K. O. (2020). A randomized, double-blind, active placebo-controlled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. *Translational Psychiatry*, 10(1), 206.
<https://doi.org/10.1038/s41398-020-00897-0>

Shneidman, E. S. (1993). *Suicide as Psychache: A Clinical Approach to Self-destructive Behavior*. Jason Aronson.

Smart, R. G., Storm, T., Baker, E. F. W., & Solursh, L. (1966). A Controlled Study of Lysergide in the Treatment of Alcoholism. I. The Effects on Drinking Behavior. *Quarterly Journal of Studies on Alcohol*, 27(3), 469–482. <https://doi.org/10.15288/qjsa.1966.27.469>

Smith, C. M. (1958). A New Adjunct to the Treatment of Alcoholism: The Hallucinogenic Drugs. *Quarterly Journal of Studies on Alcohol*, 19(3), 406–417. <https://doi.org/10.15288/qjsa.1958.19.406>

Smith, K. W., Sicignano, D. J., Hernandez, A. V., & White, C. M. (2022). MDMA-Assisted Psychotherapy for Treatment of Posttraumatic Stress Disorder: A Systematic Review With Meta-Analysis. *The Journal of Clinical Pharmacology*, 62(4), 463–471. <https://doi.org/10.1002/jcph.1995>

Stroud, J. B., Freeman, T. P., Leech, R., Hindocha, C., Lawn, W., Nutt, D. J., Curran, H. V., & Carhart-Harris, R. L. (2018). Psilocybin with psychological support improves emotional face recognition in treatment-resistant depression. *Psychopharmacology*, 235(2), 459–466. <https://doi.org/10.1007/s00213-017-4754-y>

Swanson, L. R. (2018). Unifying Theories of Psychedelic Drug Effects. *Frontiers in Pharmacology*, 9. <https://www.frontiersin.org/articles/10.3389/fphar.2018.00172>

Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S. D., Murphy, K., Laufs, H., Leech, R., McGonigle, J., Crossley, N., Bullmore, E., Williams, T., Bolstridge, M., Feilding, A., Nutt, D. J., & Carhart-Harris, R. (2016). Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution. *Current Biology*, 26(8), 1043–1050. <https://doi.org/10.1016/j.cub.2016.02.010>

Thompson, L. Y., Snyder, C. R., Hoffman, L., Michael, S. T., Rasmussen, H. N., Billings, L. S., Heinze, L., Neufeld, J. E., Shorey,

H. S., Roberts, J. C., & Roberts, D. E. (2005). Dispositional Forgiveness of Self, Others, and Situations. *Journal of Personality*, 73(2), 313–360. <https://doi.org/10.1111/j.1467-6494.2005.00311.x>

Tolle, H. M., Farah, J. C., Mallaroni, P., Mason, N. L., Ramaekers, J. G., & Amico, E. (2023). The unique neural signature of your trip: Functional connectome fingerprints of subjective psilocybin experience (p. 2023.03.20.532894). *bioRxiv*. <https://doi.org/10.1101/2023.03.20.532894>

Tomsovic, M., & Edwards, R. V. (1970). Lysergide Treatment of Schizophrenic and Nonschizophrenic Alcoholics; A Controlled Evaluation. *Quarterly Journal of Studies on Alcohol*, 31(4), 932–949. <https://doi.org/10.15288/qjsa.1970.31.932>

Tossani, E. (2013). The Concept of Mental Pain. *Psychotherapy and Psychosomatics*, 82(2), 67–73. <https://doi.org/10.1159/000343003>

Uthaug, M. V., Lancelotta, R., van Oorsouw, K., Kuypers, K. P. C., Mason, N., Rak, J., Šuláková, A., Jurok, R., Maryška, M., Kuchař, M., Páleníček, T., Riba, J., & Ramaekers, J. G. (2019). A single inhalation of vapor from dried toad secretion containing 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in a naturalistic setting is related to sustained enhancement of satisfaction with life, mindfulness-related capacities, and a decrement of

psychopathological symptoms. *Psychopharmacology*, 236(9), 2653–2666. <https://doi.org/10.1007/s00213-019-05236-w>

Uthaug, M. V., van Oorsouw, K., Kuypers, K. P. C., van Boxtel, M., Broers, N. J., Mason, N. L., Toennes, S. W., Riba, J., & Ramaekers, J. G. (2018). Sub-acute and long-term effects of ayahuasca on affect and cognitive thinking style and their association with ego dissolution. *Psychopharmacology*, 235(10), 2979–2989. <https://doi.org/10.1007/s00213-018-4988-3>

Valle, M., Maqueda, A. E., Rabella, M., Rodríguez-Pujadas, A., Antonijoan, R. M., Romero, S., Alonso, J. F., Mañanas, M. À., Barker, S., Friedlander, P., Feilding, A., & Riba, J. (2016). Inhibition of alpha oscillations through serotonin-2A receptor activation underlies the visual effects of ayahuasca in humans. *European Neuropsychopharmacology*, 26(7), 1161–1175. <https://doi.org/10.1016/j.euroneuro.2016.03.012>

Van Orden, K. A., Cukrowicz, K. C., Witte, T. K., & Joiner Jr., T. E. (2012). Thwarted belongingness and perceived burdensomeness: Construct validity and psychometric properties of the Interpersonal Needs Questionnaire. *Psychological Assessment*, 24, 197–215. <https://doi.org/10.1037/a0025358>

Van Orden, K. A., Witte, T. K., Gordon, K. H., Bender, T. W., & Joiner Jr., T. E. (2008). Suicidal desire and the capability for suicide:

Tests of the interpersonal-psychological theory of suicidal behavior among adults. *Journal of Consulting and Clinical Psychology*, 76, 72–83. <https://doi.org/10.1037/0022-006X.76.1.72>

Verrocchio, M. C., Carrozzino, D., Marchetti, D., Andreasson, K., Fulcheri, M., & Bech, P. (2016). Mental Pain and Suicide: A Systematic Review of the Literature. *Frontiers in Psychiatry*, 7. <https://www.frontiersin.org/articles/10.3389/fpsy.2016.00108>

Vollenweider, F. (1997). Positron Emission Tomography and Fluorodeoxyglucose Studies of Metabolic Hyperfrontality and Psychopathology in the Psilocybin Model of Psychosis. *Neuropsychopharmacology*, 16(5), 357–372. [https://doi.org/10.1016/S0893-133X\(96\)00246-1](https://doi.org/10.1016/S0893-133X(96)00246-1)

Vollenweider, F. X., & Komater, M. (2010). The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. *Nature Reviews Neuroscience*, 11(9), 642–651. <https://doi.org/10.1038/nrn2884>

Vollenweider, F. X., Vollenweider-Scherpenhuyzen, M. F. I., Bäbler, A., Vogel, H., & Hell, D. (1998). Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *NeuroReport*, 9(17), 3897.

Watts, R., Day, C., Krzanowski, J., Nutt, D., & Carhart-Harris, R. (2017). Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression. *Journal of Humanistic Psychology*, 57(5), 520–564. <https://doi.org/10.1177/0022167817709585>

Webb, J. R., Hirsch, J. K., & Toussaint, L. (2015). Forgiveness as a positive psychotherapy for addiction and suicide: Theory, research, and practice. *Spirituality in Clinical Practice*, 2, 48–60. <https://doi.org/10.1037/scp0000054>

Wilkinson, S. T., Rhee, T. G., Joormann, J., Webler, R., Ortiz Lopez, M., Kitay, B., Fasula, M., Elder, C., Fenton, L., & Sanacora, G. (2021). Cognitive Behavioral Therapy to Sustain the Antidepressant Effects of Ketamine in Treatment-Resistant Depression: A Randomized Clinical Trial. *Psychotherapy and Psychosomatics*, 90(5), 318–327. <https://doi.org/10.1159/000517074>

Wilkinson, S. T., Wright, D., Fasula, M. K., Fenton, L., Griep, M., Ostroff, R. B., & Sanacora, G. (2017). Cognitive Behavior Therapy May Sustain Antidepressant Effects of Intravenous Ketamine in Treatment-Resistant Depression. *Psychotherapy and Psychosomatics*, 86(3), 162–167. <https://doi.org/10.1159/000457960>

Zeifman, R. J., Palhano-Fontes, F., Hallak, J., Arcoverde, E., Maia-Oliveira, J. P., & Araujo, D. B. (2019). The Impact of Ayahuasca on Suicidality: Results From a Randomized Controlled Trial. *Frontiers in Pharmacology*, 10, 1325. <https://doi.org/10.3389/fphar.2019.01325>

Zeifman, R. J., Singhal, N., Breslow, L., & Weissman, C. R. (2021). On the Relationship between Classic Psychedelics and Suicidality: A Systematic Review. *ACS Pharmacology & Translational Science*, 4(2), 436–451. <https://doi.org/10.1021/acspsci.1c00024>

Zinberg, N. E. (1984). *Drug, set, and setting: The basis for controlled intoxicant use*. New Haven: Yale University Press. <http://archive.org/details/drugsetsettingba0000zinb>

Chapter 7

Discussion

This dissertation aims to expand our understanding of the potential for psychedelics to function as pain-relieving agents. The studies we presented contribute to filling current gaps in the literature, such as the dearth of information regarding the naturalistic use of psychedelics in chronic pain conditions like fibromyalgia, arthritis, and tension-type headache; the potential effects of psychedelic microdosing schedules to improve pain tolerance; and the potential effects of integrating psychedelics and psychotherapy to achieve pain relief. Furthermore, given the relevance of PAP in current clinical psychedelic research, we presented a review of current PAP models that could potentially be used in the treatment of chronic pain and proposed mental pain as a potential target of psychedelic therapies.

The potential of psychedelic microdosing in the treatment of chronic pain

Data from our survey study presented in **Chapter 2**, our RCT on LSD microdosing (**Chapter 3**), previous research from our lab (Ramaekers et al., 2021; Bonnelle et al., 2022), and early psychedelic research on pain (Kast and Collins, 1963; Kast, 1967;

Kurland et al., 1972; Grof et al., 1973; Kurland, 1985; Fanciullacci et al., 1977) offers support for the use of psychedelic microdoses as analgesic agents. More specifically, our survey data show that in FM and arthritis, psychedelic microdoses led to a comparable degree of pain relief as conventional medication, and their reported effect was even greater than conventional medication in migraine and TTH. While analgesic effects of psychedelics were already suggested by previous survey literature on cluster headache (Sewell et al., 2006; Schindler et al., 2015; Di Lorenzo et al., 2016; Andersson et al., 2017) and a qualitative study with migraine and cluster headache patients (Andersson et al., 2017), our survey is the first to focus on in FM, arthritis, and TTH. Furthermore, results from our RCT provide marginal evidence that base LSD (15 µg) may improve pain tolerance and reduce pain unpleasantness produced by acute painful stimuli. This result, together with the finding that 20 µg of LSD improved pain tolerance and ratings of unpleasantness (Ramaekers et al., 2021), suggests that improvements can be obtained by the use of small doses of psychedelics alone, without the addition of any psychological intervention. If these results are confirmed in patient populations, it will mean that psychedelics can be used for pain management in the context of what we call a pure *analgesic model*, which is a therapeutic route in which the administration of a certain drug is sufficient to obtain a certain degree of relief. The research on this application is still in its infancy and there are still several questions that need to be answered.

For instance, while a single small LSD dose seemed to have the potential to bring about analgesic effects (**Chapter 3**; Ramaekers et al., 2021), our RCT provides no support for the effectiveness of repeated dosing, known as microdosing (**Chapter 3**). This result may in part have been caused by the unexpectedly high proportion of pain-resistant participants in our sample and would need to be investigated further in both non-clinical and clinical populations. If this lack of support for microdosing is confirmed, this would mean that the applicability of small doses of psychedelics to treat chronic pain would be greatly reduced as they may offer only temporary relief to pain. On the other hand, should future clinical trials show that repeated administration of small, non-hallucinogenic doses (i.e., within a microdosing schedule) of psychedelics can bring stable relief from pain, we may be discovering a novel compound to remedy chronic pain that would be compatible with everyday functioning. Replication should ideally be carried out through designs that could control for potential confounding/contributing factors such as expectation (measured before treatment), dose, dosing schedule, the context of administration, previous experience with psychedelics, interaction with other drugs or psychological treatments, and personality features. Ideally, such research would also include the measurement of biomarkers that are relevant to understanding the mechanisms of analgesic effects. Concerning this last point, several authors have suggested that the interaction of psychedelics with descending serotonergic pathways and their neuroplastic and anti-inflammatory effects may hold promise to

remedy the abnormal functioning of pain-modulating networks that are thought to be responsible for the transition from acute pain to chronic pain and the development of hyperalgesia and allodynia (Castellanos et al., 2020; Zia et al., 2023; Goel et al., 2023).

The potential of full psychedelic doses in the treatment of chronic pain

Before the present work, evidence from clinical research on the therapeutic potential of full psychedelic doses in the treatment of chronic pain was still limited to several open-label case series studies (Kurland, 1985; Grof et al., 1973; Kast, 1967; Kurland et al., 1972) and an RCT (Kast and Collins, 1963) conducted during the first wave of psychedelic research. Taken together, the results seem to indicate that psychedelics alone or in combination with psychological support or psychotherapy can lead to improvements in pain levels and emotional well-being in patients suffering from life-threatening illnesses. Our survey data (**Chapter 2**) and case study (**Chapter 5**) represent a continuation of these efforts and show support for the use of psychedelics in the treatment of chronic pain. Both studies report improvements in pain relief in participants and are complementary in terms of their perspectives. More specifically, our survey showed that (full) psychedelic doses were considered more effective than both microdosing and conventional medication by survey respondents. Our case study, on the other hand, focused on the experience of a patient in a retreat-based PAP

332

program, revealing that the psychedelic sessions were highly meaningful and aligned with therapeutic goals and that the integration sessions were perceived as beneficial.

The most parsimonious explanation of the larger analgesic effects of full doses points to the fact that higher doses may increase the neuroplastic and anti-inflammatory effects of psychedelics (Castellanos et al., 2020; Zia et al., 2023; Goel et al., 2023), again in the context of a purely analgesic model. However, most clinical research on psychedelic therapies is carried out within a PAP theoretical framework (**Chapter 4**) and, to our knowledge, no study has yet compared the effectiveness of a psychedelic ‘chemotherapy’ (Pahnke et al., 1970) model to that of a PAP model (**Chapter 4**) in any clinical condition. This means that currently, we can not rule out the possibility that other factors typically associated with full dose use (e.g., preparation and integration activities, setting of administration, insights, the psychedelic-induced effects such transpersonal experiences, age regression, feelings of connection with others) and their interaction with individual characteristics (such as personality traits, psychiatric history, previous psychedelic experience) may play a role in achieving clinically relevant results. Theoretically, this view is grounded in set and setting theory (Hartogsohn, 2017) and has received partial support by evidence indicating that certain extra-pharmacological elements of both set (e.g., levels of openness, clear intentions, absorption, state of surrender, acceptance) and setting (e.g., music, meditation, and

spiritual practices, nature settings) contribute to the quality of the experience (Haijen et al., 2018; Gandy, 2022). The latter is in turn associated with better outcomes in terms of psychological well-being as, for instance, individuals who go through mystical experiences seem to benefit from the experience more compared to those who do not (Haijen et al., 2018; Ko et al., 2022). Another reason to consider the addition of psychotherapeutic or behavioural interventions to psychedelic sessions is that chronic pain, like most mental health conditions, is currently considered a bio-psycho-social phenomenon (Treede et al., 2019). This view is supported by evidence from neurobiological and psychological research showing that emotional well-being and perceived pain intensity are linked (Lumley et al., 2011). More specifically, psycho-social factors such as pain catastrophizing, pain-related anxiety and fear, social rejection, insecure attachment, and unpleasant emotions are positively associated with pain intensity, and maladjustment and contribute to triggering, worsening, or maintaining pain (Lumley et al., 2011). These psychosocial factors are typically treated through psychotherapy (Williams et al., 2020). Neural correlates of these factors and their association with pain have been identified in the so-called medial pain pathway (Vogt & Sikes, 2000) which is responsible for the emotional component of pain and is involved in the development of hyperalgesia, allodynia, and spontaneous bouts of pain (Lumley et al., 2011). In terms of the effectiveness of psychotherapy in the treatment of chronic pain, recent systematic reviews showed that CBT had a positive effect on pain relief (albeit

334

small or very small) in a variety of conditions compared to active controls (Williams et al., 2020), that hypnosis seems to bring greater relief compared to interventions such as attention-control, physical therapy, and education (Thompson et al., 2019), and that mindfulness approaches may be valuable in reducing pain compared to a wide range of control conditions (Hilton et al., 2017). It must also be pointed out that these results are often obtained with patients who are already following a pharmacological treatment plan for chronic pain, suggesting that combining drug therapy and psychotherapy may be a promising route to implement PAP for chronic pain (Williams et al., 2020; Thompson et al., 2019; Hilton et al., 2017).

How will future PAP for pain look like?

While there is not yet scientific evidence for the effectiveness of a PAP model in treating chronic pain, there are theoretical reasons to believe that it may hold clinical value. Therefore, it may be interesting to consider how psychological interventions in psychedelic therapies may be implemented. Our review of PAP (**Chapter 4**) reveals that most models follow a three-stage structure, including preparation, psychedelic, and integration sessions as suggested by previously published guidelines (Johnson et al., 2008). If we extend the same rationale to the treatment of chronic pain, preparation will likely include discussing pain and the issues related to it (i.e., impact on functioning,

emotional reactions, coping mechanisms, potential catastrophizing, prognosis, etc.) and setting intentions towards the reduction of pain. Following this, the therapeutic path can vary based on: a) the facilitator's level of direction, b) the focus on addressing pain versus other psychological issues, aiming for enhanced emotional and relational well-being to alleviate pain intensity, and c) the setting, (e.g., retreat-based, traditional psychotherapy format, individual, group). Starting from the least directive approach in the directiveness vs non-directiveness continuum, we could imagine a full *non-directive PAP* (NDPAP). In such a model, after pain-related issues are discussed in the preparation phase and an intention related to treatment of chronic pain is formulated, the patient would be invited to the psychedelic session, advised to shift their attention inward, and encouraged to mentally surrender to the experience regardless of what content it may bring and of how closely it is related to pain. The integration sessions would then focus on the content of the experience, aiming at consolidating the insights patients may have experienced, and providing minimal or no interpretation from the therapist. NDPAP would carry the advantage of minimising the risk of potentially introducing therapists' beliefs, hypotheses, and suggestions (Johnson, 2021) while patients are in a suggestible and vulnerable state (Carhart-Harris et al., 2015).

In conditions like PTSD, where it is expected that patients may display avoidant tendencies toward talking about or confronting the main issues they are struggling with, a more directive approach may

be preferable to keep the focus on the therapeutic target, such as the index trauma. In MDMA-assisted psychotherapy for PTSD, for instance, therapists are instructed to lead patients to confront their index trauma through imaginative trauma exposure (Mithoefer et al., 2016). In such a directive, *pain-focused PAP* (PFPAP) approach, patients about to begin their psychedelic session would be encouraged to focus on their pain or on the body part that is usually in pain. Previous research has shown that clear intentions are associated with greater chances of having a mystical-type experience and with greater improvements in well-being (Haijen et al., 2018; Russ et al., 2019). Focusing attention on pain may also increase the likelihood that the potential insights (Preller et al., 2017) of psychedelics will meaningfully revolve around chronic pain and chronic pain-related aspects (e.g., pain-related emotions, pain-related avoidance, tendency to catastrophize, maladjustment issues). While this approach may carry the risk of increasing perceived pain as a consequence of focusing attention on it during the psychedelic session, this risk may be offset by the purely pharmacological analgesic effects of psychedelics.

Should future studies support the analgesic effects of psychedelics (**Chapter 2; Chapter 3; Chapter 5**; Ramaekers et al., 2021; Bonnelle et al., 2022), reliable guidelines for therapists and facilitators would need to be developed. These guidelines would aim to strike a balance between leveraging the potential therapeutic benefits of directing attention toward pain and ensuring the

intervention's manageability and endurance. Ideally, patients should maintain a manageable level of pain while actively addressing it, a state achievable through practices such as mindfulness (Hilton et al., 2017), hypnosis, or self-hypnosis (Thompson et al., 2019), all known for their efficacy in mitigating the perception of pain. Also in PFPAP, patients would then discuss the experience in the integration sessions.

Finally, a third possible approach could aim at supporting patients in dealing with factors associated with chronic pain instead of pain itself. This *supportive PAP for chronic pain* (SPCP) would target pain-related psychosocial factors and mental health issues (Lumley et al., 2011) to improve psychological and social well-being, coping strategies, and general adjustment to life with chronic pain. Just as PFPAP, this approach would have directive components as, instead of targeting pain itself during the psychedelic session, patients will be encouraged to confront issues related to pain. In practice, this would mean that the therapist would exert a certain degree of directiveness to shift the focus of the session on said areas especially in case the patient's thought processes would circle around pain as often happens in case of high catastrophizing tendencies. This approach would probably be the first choice in case the analgesic effects of psychedelics will be disconfirmed by future research as patients with chronic pain could still benefit from the positive effects on mental health and well-being that psychedelics produce (**Chapter 4**).

Finally, as stated in our review (**Chapter 4**) and reported by other authors (Brennan and Belser, 2022), there is no current consensus concerning what training a facilitator/therapist would require to be effective and which professionals should be allowed to lead such therapies. Current clinical research employs a variety of health and mental health professionals including psychotherapists, psychiatrists, MDs, nurses, counsellors, and ill-defined facilitators who often went through PAP training programs of variable duration and scope (**Chapter 5**). Usually, each patient is attended by the same member(s) of the clinical staff along all three phases of treatment, implying that continuity is favoured in the context of PAP (**Chapter 5**). Intuitively, highly skilled clinicians such as psychiatrists or psychotherapists seem preferable especially when treating severe conditions or conditions that are associated with impulsivity, aggression, or self-harm. This would however represent a challenge for the scalability and sustainability of interventions and potentially limit the dissemination of PAP. Another possibility would be to employ psychiatrists or psychotherapists in the preparation and integration sessions, i.e., the therapeutic phases that are more directly dealing with classical psychotherapeutic themes (e.g., intrapsychic conflicts, relational dynamics, trauma) and that require more specialised training. Less skilled facilitators may be employed to lead the drug session(s) as, according to most PAP approaches (**Chapter 5**), during psychedelic experiences the role of clinical personnel is almost entirely supportive. More specifically, facilitators of drug sessions are often instructed to help patients

keep their attention inward (possibly toward the target issue), provide reassurance, and practical support (e.g., restroom use), and encourage a generally open attitude toward the contents of the experience.

Future research should investigate the effect of facilitator training on treatment outcomes and help to define the optimal profile of a PAP practitioner to maximise patient safety and treatment outcomes.

To retreat or not to retreat?

Another open question regarding PAP for chronic pain concerns duration, frequency, and setting of the intervention. This issue is still to be directly addressed by clinical psychedelic research as a whole, as most of the PAP clinical trials employ a limited number of psychedelic sessions in the three-stage/phase structure (**Chapter 4**). As is the case for the patient whose therapeutic process we described in **Chapter 5**, most guided, full-dose, psychedelic experiences are currently carried out in retreat settings where patients spend a limited amount of time in a retreat centre, going through one or multiple psychedelic experiences that may or may not be accompanied by preparation and or integration activities. This intervention structure addresses practical concerns due to the global illegality of psychedelics, and lacks supporting research indicating improved outcomes in this setting. An alternative model of therapy may look more similar to “traditional” psychotherapy, in

which patients are usually admitted to a long-term treatment plan with regular sessions for months or years. While no study has yet compared these two treatment structures in terms of outcomes, safety, and sustainability, our case study (**Chapter 5**) shows that more extensive integration programs may be beneficial to further personal development and pursue better mental health and well-being.

Another way in which retreat-based interventions differ from practices currently adopted in clinical trials is that the former are usually delivered in group settings (**Chapter 5**) while the latter almost exclusively adopt individual sessions in all three phases of PAP (**Chapter 4**). While the individual treatment model is gathering evidence of effectiveness in modern research (**Chapter 5**), the considerable amount of resources it requires may pose a challenge in terms of the scalability and sustainability of the intervention. Furthermore, the traditional use of psychedelics in ceremonial settings is often experienced in groups and the group itself is considered to be a factor conducive to spiritual insight, therapeutic outcome, and setting safety (Labate, 2016; Labate & Cavnar, 2014). While no study has currently been published in which outcomes between these two treatment modalities are compared, open-label studies, looking primarily at the safety and feasibility of such a group intervention yielded encouraging results (Anderson et al., 2020; Lewis et al., 2023). The interventions were tolerated with limited (Anderson et al., 2020) or no adverse events (Anderson et

al., 2020; Lewis et al., 2023). Furthermore, all participants showed some form of improvement ranging from clinically significant to full remission in variables such as demoralisation in AIDS survivors (Anderson et al., 2020) and depression in individuals with cancer (Lewis et al., 2023).

In summary, the optimal duration, frequency, psychotherapeutic models, and setting of PAP are still to be identified and future research will have to compare different treatment structures, ideally in the context of RCTs. This issue remains open for interventions targeting mental health issues and PAP for chronic pain alike.

Safety of full-dose use and repeated use of psychedelics

In case future research finds evidence to support PAP for chronic pain, multiple therapy cycles may be necessary to achieve clinically relevant results. This would then raise the issue of the safety of repeated dosing. Based on a recent systematic review (Dos Santos et al., 2018), a single dose or a few doses of psychedelics such as psilocybin and LSD are generally considered to be physiologically safe when administered in controlled settings. Their use can be associated with few transient and moderate adverse reactions (i.e., anxiety- and psychotic-like reactions, transient and moderate increases in systolic and diastolic blood pressure, headaches, nausea, vomiting) (Dos Santos et al., 2018). Further evidence is needed to establish whether a potential increase in the number of psychedelic sessions would still be safe and tolerable. Current

342

safety concerns revolve around three main areas: a) the development of Hallucinogenic Persisting Perception Disorder (HPPD), b) the cardiovascular risk associated with the psychedelic-induced 5-HT_{2B} receptor activation, and c) patient selection.

HPPD is a condition characterised by the re-emergence of perceptual symptoms experienced during acute hallucinogen intoxication following drug cessation (Ford et al., 2022). The disorder is associated with a broad spectrum of visual phenomena, including visual snow, floaters, palinopsia, photophobia, nyctalopia, and other visual disturbances (American Psychiatric Association, 2013). HPPD can be triggered by the use of various substances, including classic psychedelics such as LSD and psilocybin, as well as entactogens like MDMA, and cannabinoids (Ford et al., 2022). The underlying pathophysiology of HPPD is poorly understood, and the disorder is considered rare (about 1 in 50.000 cases), with symptoms that may be intermittent or constant (Ford et al., 2022). Ophthalmic and neurologic investigations in HPPD cases are typically normal, and the majority of patients may experience ongoing symptoms (Ford et al., 2022). Research on the condition is still limited and a deeper understanding of it is necessary to ensure the safety of patients.

The activation of the 5-HT_{2B} receptor by psychedelics has raised safety concerns, particularly concerning potential cardiac complications (Wsól, 2023; Malcom and Thomas, 2022). Research

has indicated that the induction of serotonergic 5-HT_{2B} receptor activation can lead to serious cardiovascular issues, including the risk of heart valve disease and significant prolongation of the QT interval, which may occur at high doses. This risk should also be carefully considered in terms of prolonged exposure to psychedelic substances like when microdosing. While serotonergic psychedelics have shown therapeutic potential (**Chapter 4**), their impact on the cardiovascular system, particularly through 5-HT_{2B} receptor activation, requires comprehensive assessment to determine the safety and minimise potential risks, especially in the context of long-term psychedelic therapies. The exact determination of the cardiovascular safety of psychedelic medicines, including the long-term effects, remains an area that necessitates continued medical research and scientific exploration to ensure the safe and effective use of these substances in clinical settings (Tagen et al., 2023; Benjamin and Kelan; 2022).

When it comes to screening and inclusion/exclusion criteria for PAP, most studies choose to exclude patients with a (family) history of schizophrenia or psychotic disorders, or bipolar disorders to avoid the risk of precipitating psychotic or manic episodes (Johnson et al., 2008; Bosch et al., 2022). Recently though, a non-randomised controlled trial of 15 individuals with bipolar type II depression who received a single dose of synthetic psilocybin with psychotherapy was published (Aaronson et al., 2023). The study found that most participants met remission criteria on the

Montgomery-Åsberg Depression Rating Scale at 3 weeks post-dose, and most remained in remission 12 weeks post-dose with no increase in mania/hypomania symptoms and no significant adverse events. The study suggests that psilocybin is effective and safe in treating bipolar type II disorder and supports further study of psychedelics in this population.

In summary, while psychedelics are usually considered both psychologically and physiologically safe when administered under controlled conditions and to appropriately screened participants, more research is needed to better understand and prevent occurrences of HPPD and cardiac complications.

Where to go from here?

Considering the above-discussed results in the context of the wider literature on psychedelic treatments for chronic pain, it is evident that more experimental research is needed to test the analgesic effects of psychedelics. Ideally, future studies would be built as randomised, double-blind, placebo-controlled clinical studies, recruiting a sample of chronic pain patients and controlling for confounding/contributing factors.

Our lab is planning to run such a study in 2024 with a sample of FM patients included in a within-subjects design aiming at determining the analgesic effects of 2 doses of psilocybin (5 mg and 10 mg)

against an inactive placebo. The study will measure changes in both FM-related pain and acute pain tolerance and will control for the effect of several variables such as mood, treatment expectancy (Mooney et al., 2014), patients' perceived treatment credibility (Mooney et al., 2014), and personality traits such as openness and self-transcendence (Bouso et al., 2018).

Our study will fill a notable gap in knowledge about the effects of psychedelic therapies on pain. Currently, no randomised, double-blind, placebo controlled trial has investigated the effectiveness of any psychedelic therapy on fibromyalgia, a severely invalidating condition that only partially responds to current therapies (Mascarenhas et al., 2021). Furthermore, the research will look into the potential analgesic mechanisms underlying psychedelic action in fibromyalgia patients. More specifically, evidence points to peripheral neuro-inflammation (Littlejohn, 2015), as a cause of the disorder and psychedelics have demonstrated anti-inflammatory properties in existing research (Flanagan and Nichols, 2018). Moreover, pain seems to become chronic because of structural and functional changes in the nervous system that ultimately lead to abnormal signalling (Kuner and Flor, 2017) and the neuroplasticity-promoting effects of psilocybin may promote the disruption of these established pathways and potentially lead to analgesia (Castellanos et al., 2020). For these reasons, we will collect multiple blood sample over the course of the study day to determine concentrations of biomarkers of inflammation and neuroplasticity

(BDNF). Finally, the addition of the recorded hypnotic induction, a technique that is effective in reducing levels of perceived pain (Thompson et al., 2019), will allow us to test whether a combined intervention (psilocybin plus hypnosis) is able to produce greater analgesia in fibromyalgia patients.

In summary, the trial will test the effectiveness of psilocybin in treating fibromyalgia pain, will expand our knowledge on its potential therapeutic mechanisms and on the analgesic effects of a combined psycho-pharmacological intervention.

Impact: the potential societal impact of psychedelic therapy for chronic pain

Are psychedelic therapies effective in treating pain? The studies included in this dissertation suggest that psychedelic therapy may constitute a novel, safe, and effective treatment.

Chronic pain affects approximately 20% of the population (Goldberg & McGee, 2011) and has a significant impact on society, resulting in years lost to disability and high costs for individuals, families, and healthcare systems (Zia et al., 2023). Pharmacological treatments such as nonsteroidal anti-inflammatory drugs, opioids, anticonvulsants, and antidepressants are currently prescribed, but a considerable portion of patients do not experience substantial benefits (Johannes et al., 2010). While opioids can

provide relief, they carry numerous undesirable effects, have a high potential for addiction, are linked to a heightened occurrence of severe adverse events and overdose, and may potentially induce opioid-induced hyperalgesia (Coussens et al., 2019; Els et al., 2017; Nijs et al., 2014; Zia et al., 2023).

Public interest in the possibility of using various forms of psychedelic therapies to treat pain has been growing in recent years (Andersson et al., 2017; Soussan & Kjellgren, 2016). Such interest is in part due to a rediscovery by Western research of the beneficial effects that these treatments showed in patients suffering from chronic mental health conditions (**Chapter 4**).

In summary, the studies included in this dissertation show that people who were suffering from fibromyalgia, arthritis, migraine, and tension-type headache and who used psychedelics reported significant improvements in their pain levels with both full and small doses. Also, such improvements were equal to or better than that achieved with conventional medication. We also showed that a single, low dose of LSD may be able to improve pain tolerance and decrease feelings of unpleasantness caused by a painful stimulus in healthy volunteers and that taking part in a psychedelic-assisted psychotherapy program may lead to improvements in pain levels and psychological well-being. Finally, we propose that psychedelic therapies may be valuable in treating mental pain, a distressing

experience that is associated with suicide risk and that is present in several mental health conditions.

If confirmed effective in treating chronic pain, psychedelic therapy could provide a much-needed alternative to traditional pain management approaches, potentially reducing the need for opioids and other pain medications. In the form of a pure pharmacotherapy regimen utilising repeated, small, non-psychedelic doses, psychedelic therapy could offer several advantages. The side effect profile of such substances is more favourable compared to conventional treatments and, when appropriately dosed, would ideally have minimal impact on daily functioning (**Chapter 3**; Ramaekers et al., 2021). This treatment model may allow individuals to self-manage their therapy, potentially leading to increased patient engagement and adherence to the treatment plan (Damush et al., 2016), ultimately contributing to improved outcomes. In the form of psychedelic-assisted psychotherapy, the pharmacologically driven analgesic effects could be integrated with psychotherapeutic treatment, thus offering a setting where psychological factors associated with pain intensity can be addressed (Lumley et al., 2011). Emotional well-being is associated with both perceived pain intensity and daily functioning in chronic pain patients (Lumley et al., 2011). Psychedelic-assisted psychotherapy may leverage the therapeutic mechanisms activated by these substances (i.e., increased neuroplasticity, anti-inflammatory action, 5-HT_{2A}, and 5-HT₃ agonism, increased

suggestibility, increased psychological flexibility) (Castellanos et al., 2020; Zia et al., 2023; Carhart-Harris et al., 2015; Kuypers et al., 2016) to ideally achieve better pain management in terms of pain relief, psychological well-being, stability of therapeutic outcomes and daily functioning.

In conclusion, should the results presented here receive support from future studies, psychedelic therapies would allow a considerable portion of the population that is currently suffering from chronic pain to be able to achieve pain-free lives or lower pain levels. This would promote a more satisfying life in several areas. Painless individuals are more willing to engage with the world in terms of contact with loved ones, professional challenges, pursuit of interests, and personal development. Furthermore, given the many similarities and shared causal factors between physical and mental pain, our work may contribute to sparking research into this field and potentially reduce the burden of suicidality and self-harming tendencies for individuals, families, and wider communities.

References

Aaronson, S. T., van der Vaart, A., Miller, T., LaPratt, J., Swartz, K., Shoultz, A., Lauterbach, M., Sackeim, H. A., & Suppes, T. (2023). Single-Dose Synthetic Psilocybin With Psychotherapy for Treatment-Resistant Bipolar Type II Major Depressive Episodes: A Nonrandomized Controlled Trial. *JAMA Psychiatry*. <https://doi.org/10.1001/jamapsychiatry.2023.4685>

Anderson, B. T., Danforth, A., Daroff, P. R., Stauffer, C., Ekman, E., Agin-Liebes, G., Trope, A., Boden, M. T., Dilley, P. J., Mitchell, J., & Woolley, J. (2020). Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. *EClinicalMedicine*, 27, 100538. <https://doi.org/10.1016/j.eclinm.2020.100538>

Andersson, M., Persson, M., & Kjellgren, A. (2017). Psychoactive substances as a last resort—A qualitative study of self-treatment of migraine and cluster headaches. *Harm Reduction Journal*, 14(1), 60. <https://doi.org/10.1186/s12954-017-0186-6>

Association, A. P. (2013). *Diagnostic and Statistical Manual of Mental Disorders (5th edition)*. American Psychiatric Association Publishing.

Bonnelle, V., Smith, W. J., Mason, N. L., Cavarra, M., Kryskow, P., Kuypers, K. P. C., Ramaekers, J. G., & Feilding, A. (2022).

Analgesic potential of macrodoses and microdoses of classical psychedelics in chronic pain sufferers: A population survey. *British Journal of Pain*, 13.

Bosch, O. G., Halm, S., & Seifritz, E. (2022). Psychedelics in the treatment of unipolar and bipolar depression. *International Journal of Bipolar Disorders*, 10, 18. <https://doi.org/10.1186/s40345-022-00265-5>

Bouso, J. C., dos Santos, R. G., Alcázar-Córcoles, M. Á., & Hallak, J. E. C. (2018). Serotonergic psychedelics and personality: A systematic review of contemporary research. *Neuroscience & Biobehavioral Reviews*, 87, 118–132. <https://doi.org/10.1016/j.neubiorev.2018.02.004>

Brennan, W., & Belser, A. B. (2022). Models of Psychedelic-Assisted Psychotherapy: A Contemporary Assessment and an Introduction to EMBARK, a Transdiagnostic, Trans-Drug Model. *Frontiers in Psychology*, 13. <https://www.frontiersin.org/articles/10.3389/fpsyg.2022.866018>

Carhart-Harris, R. L., Kaelen, M., Whalley, M. G., Bolstridge, M., Feilding, A., & Nutt, D. J. (2015). LSD enhances suggestibility in

healthy volunteers. *Psychopharmacology*, 232(4), 785–794.
<https://doi.org/10.1007/s00213-014-3714-z>

Castellanos, J. P., Woolley, C., Bruno, K. A., Zeidan, F., Halberstadt, A., & Furnish, T. (2020). Chronic pain and psychedelics: A review and proposed mechanism of action. *Regional Anesthesia & Pain Medicine*, 45(7), 486–494.
<https://doi.org/10.1136/rapm-2020-101273>

Cavnar, C., & Labate, B. (2016). *Peyote: History, Tradition, Politics, and Conservation (Illustrated edition)*. Bloomsbury 3PL.

Damush, T. m., Kroenke, K., Bair, M. j., Wu, J., Tu, W., Krebs, E. e., & Poleshuck, E. (2016). Pain self-management training increases self-efficacy, self-management behaviours and pain and depression outcomes. *European Journal of Pain*, 20(7), 1070–1078. <https://doi.org/10.1002/ejp.830>

Di Lorenzo, C., Coppola, G., Di Lorenzo, G., Bracaglia, M., Rossi, P., & Pierelli, F. (2016). The use of illicit drugs as self-medication in the treatment of cluster headache: Results from an Italian online survey. *Cephalalgia*, 36(2), 194–198.
<https://doi.org/10.1177/0333102415583145>

dos Santos, R. G., Bouso, J. C., Alcázar-Córcoles, M. Á., & Hallak, J. E. C. (2018). Efficacy, tolerability, and safety of serotonergic

psychedelics for the management of mood, anxiety, and substance-use disorders: A systematic review of systematic reviews. *Expert Review of Clinical Pharmacology*, 11(9), 889–902. <https://doi.org/10.1080/17512433.2018.1511424>

Fanciullacci, M., Bene, E. D., Franchi, G., & Sicuteri, F. (1977). Phantom Limb Pain: Sub-Hallucinogenic Treatment With Lysergic Acid Diethylamide (LSD-25). *Headache: The Journal of Head and Face Pain*, 17(3), 118–119. <https://doi.org/10.1111/j.1526-4610.1977.hed1703118.x>

Flanagan, T. W., & Nichols, C. D. (2018). Psychedelics as anti-inflammatory agents. *International Review of Psychiatry*, 30(4), 363–375. <https://doi.org/10.1080/09540261.2018.1481827>

Gandy, S. (2022). Predictors and potentiators of psychedelic-occasioned mystical experiences. *Journal of Psychedelic Studies*, 6(1), 31–47. <https://doi.org/10.1556/2054.2022.00198>

Goel, A., Rai, Y., Sivadas, S., Diep, C., Clarke, H., Shanthanna, H., & Ladha, K. S. (2023). Use of Psychedelics for Pain: A Scoping Review. *Anesthesiology*, 139(4), 523–536. <https://doi.org/10.1097/ALN.0000000000004673>

Grof, S., Goodman, L. E., Richards, W. A., & Kurland, A. A. (1973). LSD-Assisted Psychotherapy in Patients with Terminal Cancer.

International Pharmacopsychiatry, 8(3), 129–144.
<https://doi.org/10.1159/000467984>

Haijen, E. C. H. M., Kaelen, M., Roseman, L., Timmermann, C., Kettner, H., Russ, S., Nutt, D., Daws, R. E., Hampshire, A. D. G., Lorenz, R., & Carhart-Harris, R. L. (2018). Predicting Responses to Psychedelics: A Prospective Study. *Frontiers in Pharmacology*, 9, 897. <https://doi.org/10.3389/fphar.2018.00897>

Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law*, 3, 205032451668332. <https://doi.org/10.1177/2050324516683325>

Hilton, L., Hempel, S., Ewing, B. A., Apaydin, E., Xenakis, L., Newberry, S., Colaiaco, B., Maher, A. R., Shanman, R. M., Sorbero, M. E., & Maglione, M. A. (2017). Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. *Annals of Behavioral Medicine*, 51(2), 199–213. <https://doi.org/10.1007/s12160-016-9844-2>

Hutten, N. R. P. W., Mason, N. L., Dolder, P. C., Theunissen, E. L., Holze, F., Liechti, M. E., et al. (2021). Low Doses of LSD Acutely Increase BDNF Blood Plasma Levels in Healthy Volunteers. *ACS Pharmacol. Transl. Sci.* 4, 461–466. Doi:10.1021/acsptsci.0c00099.

Johnson, M. W. (2021). Consciousness, Religion, and Gurus: Pitfalls of Psychedelic Medicine. *ACS Pharmacology & Translational Science*, 4(2), 578–581. <https://doi.org/10.1021/acsptsci.0c00198>

Johnson, M. W., Richards, W., & Griffiths, R. R. (2008). Human hallucinogen research: Guidelines for safety. *Journal of Psychopharmacology*, 22(6), 603–620. <https://doi.org/10.1177/0269881108093587>

Kast, E. C. (1967). Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide. *The Psychiatric Quarterly*, 41(4), 646–657. <https://doi.org/10.1007/BF01575629>

Kast, E. C., & Collins, V. J. (1963). Study of Lysergic Acid Diethylamide as an Analgesic Agent. *Anesthesia and Analgesia*, 43(3), 285–291.

Ko, K., Knight, G., Rucker, J. J., & Cleare, A. J. (2022). Psychedelics, Mystical Experience, and Therapeutic Efficacy: A Systematic Review. *Frontiers in Psychiatry*, 13. <https://www.frontiersin.org/articles/10.3389/fpsy.2022.917199>

Kuner, R., & Flor, H. (2017). Structural plasticity and reorganisation in chronic pain. *Nature Reviews Neuroscience*, 18(1), Article 1. <https://doi.org/10.1038/nrn.2016.162>

Kurland, A. A. (1985). LSD in the Supportive Care of the Terminally Ill Cancer Patient. *Journal of Psychoactive Drugs*, 17(4), 279–290. <https://doi.org/10.1080/02791072.1985.10524332>

Kurland, A. A., Grof, S., Pahnke, W. N., & Goodman, L. E. (1972). Psychedelic drug assisted psychotherapy in patients with terminal cancer. *Journal of Thanatology*, 2(1–2), 644–691.

Kuypers, K. P. C., Riba, J., de la Fuente Revenga, M., Barker, S., Theunissen, E. L., & Ramaekers, J. G. (2016). Ayahuasca enhances creative divergent thinking while decreasing conventional convergent thinking. *Psychopharmacology*, 233(18), 3395–3403. <https://doi.org/10.1007/s00213-016-4377-8>

Labate, B. C., Cavnar, C., Labate, B. C., & Cavnar, C. (Eds.). (2014). *Ayahuasca Shamanism in the Amazon and Beyond*. Oxford University Press.

Lewis, B. R., Garland, E. L., Byrne, K., Durns, T., Hendrick, J., Beck, A., & Thielking, P. (2023). HOPE: A Pilot Study of Psilocybin Enhanced Group Psychotherapy in Patients With Cancer. *Journal of Pain and Symptom Management*, 66(3), 258–269. <https://doi.org/10.1016/j.jpainsymman.2023.06.006>

Littlejohn, G. (2015). Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. *Nature Reviews*.

Rheumatology, 11(11), 639–648.
<https://doi.org/10.1038/nrrheum.2015.100>

Lumley, M. A., Cohen, J. L., Borszcz, G. S., Cano, A., Radcliffe, A. M., Porter, L. S., Schubiner, H., & Keefe, F. J. (2011). Pain and emotion: A biopsychosocial review of recent research. *Journal of Clinical Psychology*, 67(9), 942–968.
<https://doi.org/10.1002/jclp.20816>

Malcolm, B., & Thomas, K. (2022). Serotonin toxicity of serotonergic psychedelics. *Psychopharmacology*, 239(6), 1881–1891.
<https://doi.org/10.1007/s00213-021-05876-x>

Mascarenhas, R. O., Souza, M. B., Oliveira, M. X., Lacerda, A. C., Mendonça, V. A., Henschke, N., & Oliveira, V. C. (2021). Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. *JAMA Internal Medicine*, 181(1), 104–112.
<https://doi.org/10.1001/jamainternmed.2020.5651>

Mayer, E. A., & Saper, C. B. (2000). *The Biological Basis for Mind Body Interactions*. Elsevier.

Mithoefer, M. C. (2016). *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder*. Multidisciplinary Association for Psychedelic Studies.

<https://maps.org/research-archive/mdma/MDMA-Assisted-Psychotherapy-Treatment-Manual-Version7-19Aug15-FINAL.pdf>

Mooney, T. K., Gibbons, M. B. C., Gallop, R., Mack, R. A., & Crits-Christoph, P. (2014). Psychotherapy credibility ratings: Patient predictors of credibility and the relation of credibility to therapy outcome. *Psychotherapy Research: Journal of the Society for Psychotherapy Research*, 24(5), 565–577. <https://doi.org/10.1080/10503307.2013.847988>

Pahnke, W. N., Kurland, A. A., Unger, S., Savage, C., & Grof, S. (1970). The Experimental Use of Psychedelic (LSD) Psychotherapy. *JAMA*, 212(11), 1856–1863. <https://doi.org/10.1001/jama.1970.03170240060010>

Preller, K. H., Herdener, M., Pokorny, T., Planzer, A., Kraehenmann, R., Stämpfli, P., Liechti, M. E., Seifritz, E., & Vollenweider, F. X. (2017). The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. *Current Biology*, 27(3), 451–457. <https://doi.org/10.1016/j.cub.2016.12.030>

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., Liechti, M. E., Feilding, A., & Kuypers, K. P. C. (2021). A low dose of lysergic acid diethylamide decreases pain

perception in healthy volunteers. *Journal of Psychopharmacology*, 35(4), 398–405. <https://doi.org/10.1177/0269881120940937>

Russ, S. L., Carhart-Harris, R. L., Maruyama, G., & Elliott, M. S. (2019). States and traits related to the quality and consequences of psychedelic experiences. *Psychology of Consciousness: Theory, Research, and Practice*, 6(1), 1–21. <https://doi.org/10.1037/cns0000169>

Schindler, E. A. D., Gottschalk, C. H., Weil, M. J., Shapiro, R. E., Wright, D. A., & Sewell, R. A. (2015). Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters Medication Use Survey. *Journal of Psychoactive Drugs*, 47(5), 372–381. <https://doi.org/10.1080/02791072.2015.1107664>

Schlag, A. K., Aday, J., Salam, I., Neill, J. C., & Nutt, D. J. (2022). Adverse effects of psychedelics: From anecdotes and misinformation to systematic science. *Journal of Psychopharmacology (Oxford, England)*, 36(3), 258–272. <https://doi.org/10.1177/02698811211069100>

Sewell, R. A., Halpern, J. H., & Pope, H. G. (2006). Response of cluster headache to psilocybin and LSD. *Neurology*, 66(12), 1920–1922. <https://doi.org/10.1212/01.wnl.0000219761.05466.43>

Tagen, M., Mantuani, D., van Heerden, L., Holstein, A., Klumpers, L. E., & Knowles, R. (2023). The risk of chronic psychedelic and MDMA microdosing for valvular heart disease. *Journal of Psychopharmacology*, 37(9), 876–890. <https://doi.org/10.1177/02698811231190865>

Thompson, T., Terhune, D. B., Oram, C., Sharangparni, J., Rouf, R., Solmi, M., Veronese, N., & Stubbs, B. (2019). The effectiveness of hypnosis for pain relief: A systematic review and meta-analysis of 85 controlled experimental trials. *Neuroscience and Biobehavioral Reviews*, 99, 298–310. <https://doi.org/10.1016/j.neubiorev.2019.02.013>

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Korwisi, B., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., ... Wang, S.-J. (2019). Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *PAIN*, 160(1), 19. <https://doi.org/10.1097/j.pain.0000000000001384>

Williams, A. C. de C., Fisher, E., Hearn, L., & Eccleston, C. (2020). Psychological therapies for the management of chronic pain (excluding headache) in adults. *The Cochrane Database of*

Systematic Reviews, 2020(8).
<https://doi.org/10.1002/14651858.CD007407.pub4>

Wsól, A. (2023). Cardiovascular safety of psychedelic medicine: Current status and future directions. *Pharmacological Reports*, 75(6), 1362–1380. <https://doi.org/10.1007/s43440-023-00539-4>

Zia, F. Z., Baumann, M. H., Belouin, S. J., Dworkin, R. H., Ghauri, M. H., Hendricks, P. S., Henningfield, J. E., Lanier, R. K., Ross, S., & Berger, A. (2023). Are psychedelic medicines the reset for chronic pain? Preliminary findings and research needs. *Neuropharmacology*, 233, 109528. <https://doi.org/10.1016/j.neuropharm.2023.109528>

Summary

The recent resurgence of interest in the analgesic potential of psychedelics has been driven by qualitative and survey studies, which have shown that individuals suffering from chronic pain conditions, such as cluster headaches, reported improvements when using both high and low, non-hallucinogenic doses of psychedelics like LSD and psilocybin. More recent survey studies have further supported these findings, demonstrating similar benefits in samples of people living with chronic pain. Additionally, case studies have indicated that psychedelics may help manage pain in conditions such as phantom limb pain, fibromyalgia, chronic fatigue, and cluster headaches. These findings suggest that psychedelics have the potential to serve as effective pain-relieving agents, offering a promising alternative for individuals struggling with chronic pain.

In **Chapter 2** we present the results of a survey study aiming at assessing the reported effects of psychedelics in people suffering from chronic pain conditions. The survey inquired about their psychedelic use and the relief levels achieved with conventional treatments, full psychedelic doses, and microdoses. Data related to five conditions (fibromyalgia, arthritis, migraine, tension-type headache, and sciatica) were analysed. The results showed that, except for sciatica, volunteers reported that psychedelics led to better pain relief compared to conventional medication in all

examined conditions. Specifically, full doses performed better than conventional medication, and microdoses led to significantly better relief in migraines and comparable relief in the remaining three conditions. The implications for future research are discussed, and the conclusion drawn is that full doses and microdoses may hold value in the treatment of some specific chronic pain conditions.

In **Chapter 3** we present a randomised, placebo-controlled study to investigate the potential analgesic effects of LSD microdosing in a sample of healthy participants. The participants received 15 µg of LSD or a placebo over four administrations, and pain tolerance was assessed using the Cold Pressor Task. Self-reported painfulness, unpleasantness, and stress were also recorded during the study. After removing a portion of participants who displayed plateau pain tolerance at baseline and throughout treatment, marginal but significant effects of LSD were found on measures of pain tolerance and unpleasantness, as indicated by Treatment x Test day interactions. The study concluded that a small LSD dose may produce marginal analgesic effects, and it is recommended to conduct further research with larger samples and higher microdoses to better understand LSD's analgesic effects and its potential application in clinical setting.

In **Chapter 4** we present a review of clinical studies on psychedelics that used and described a structured associated psychotherapeutic intervention. The aim of this review was to construct a picture of the

current models of psychedelic-assisted psychotherapy (PAP) used in clinical research and to report on their clinical outcomes. The review describes ad-hoc and adapted therapeutic methods, common principles, points of divergence, and potential future directions in PAP. It discusses the role of the therapeutic stance, degree of directiveness, and potential suggestive effects of information provided to patients as important factors to consider in the development and implementation of effective PAP models.

In **Chapter 5** we present a comprehensive case analysis of a 36-year-old male clinical psychologist suffering from fibromyalgia who participated in a psychedelic-assisted therapy program. We collected quantitative measures at baseline and three subsequent time points: 2 weeks, 3 months, and 6 months after a psychedelic retreat. Interpretative phenomenological analysis (IPA) was conducted on the transcripts of semi-structured interviews conducted 2 weeks, 3, and 6 months after the retreat. The findings revealed improvements in mental health, with decreased levels of depression, anxiety, stress, and cognitive fusion, and improved psychological flexibility and mindfulness skills. The retreat sessions also provided relief from fibromyalgia pain, and integration sessions helped him feel more aware and present, acknowledge suppressed trauma, and reportedly enabled him to address his emotional needs. The study's findings highlight the potential therapeutic benefits of psychedelic-assisted psychotherapy in addressing fibromyalgia and improving mental health outcomes.

In **Chapter 6** we propose psychedelic-assisted psychotherapy as a potential treatment for mental pain. In fact, there is a substantial overlap between the conditions with which mental pain is usually associated and those that were targeted in clinical studies investigating the therapeutic potential of psychedelic-assisted psychotherapy. In the chapter we provide an overview of such studies on depression, PTSD and substance abuse highlighting the potential therapeutic role that psychedelics may have in treating mental pain. Additionally we argue that the therapeutic mechanisms underlying psychedelic-assisted psychotherapy may specifically target neurobiological and psychological factors responsible for mental pain.

Finally, in **Chapter 7**, the results of the above mentioned studies are discussed in the wider context of psychedelic research. More specifically, we highlight the unique possibilities that different forms of psychedelic therapies may offer patients. Namely, we describe how a purely analgesic model (i.e., a model that only relies on pharmacological effects of psychedelics) versus various forms of psychedelic-assisted psychotherapies for chronic pain would look like. Furthermore, we discuss the implications of using different settings to host psychedelic-assisted psychotherapy (i.e., retreat based treatments vs “traditional” psychotherapeutic sessions, group vs. individual settings), and address issues related to the safety of psychedelic and repeated use of them. Finally, we mention future directions for psychedelic pain research.

Samenvatting

De recente opleving van interesse in het pijnstillende potentieel van psychedelica wordt gedreven door kwalitatieve studies en vragenlijstonderzoeken. Deze studies hebben aangetoond dat individuen die lijden aan chronische pijncondities, zoals clusterhoofdpijnen, verbeteringen rapporteerden bij het gebruik van zowel hoge als lage, niet-hallucinogene doses van psychedelica zoals LSD en psilocybine. Recenter vragenlijstonderzoek heeft deze bevindingen verder ondersteund en toont vergelijkbare voordelen in steekproeven van mensen die leven met chronische pijn. Daarnaast hebben casestudies aangetoond dat psychedelica kunnen helpen bij het beheersen van pijn bij aandoeningen zoals fantoomledemaatpijn, fibromyalgie, chronische vermoeidheid en clusterhoofdpijnen. Deze bevindingen suggereren dat psychedelica potentieel kunnen dienen als effectieve pijnstillende middelen, en bieden een veelbelovend alternatief voor individuen die worstelen met chronische pijn.

In **Hoofdstuk 2** presenteren we de resultaten van een vragenlijstonderzoek dat gericht is op het beoordelen van de gerapporteerde effecten van psychedelica bij mensen met chronische pijncondities. De vragenlijst vroeg naar hun gebruik van psychedelica en de verlichtingsniveaus die bereikt werden met conventionele behandelingen en psychedelica in hoge en lage doseringen ('microdosing'). Data gerelateerd aan vijf

aandoeningen (fibromyalgie, artritis, migraine, spanningshoofdpijn en ischias) werden geanalyseerd. De resultaten toonden aan dat in alle onderzochte condities, behalve ischias, vrijwilligers meldden dat psychedelica leidden tot betere pijnverlichting vergeleken met conventionele medicatie. Specifiek gaven hoge doseringen betere resultaten dan conventionele medicatie, en leidden microdoseringen tot significant betere verlichting bij migraine en vergelijkbare verlichting bij de overige drie aandoeningen. De implicaties voor toekomstig onderzoek worden besproken, en de conclusie is dat zowel het nemen van hoge doseringen psychedelica alsook microdoseringen waardevol kunnen zijn in de behandeling van sommige specifieke chronische pijncondities.

In **Hoofdstuk 3** presenteren we een gerandomiseerde, placebogecontroleerde, tussengroepsstudie om de potentiële pijnstillende effecten van LSD in lage, herhaalde doseringen ('microdosereren') te onderzoeken bij een groep gezonde deelnemers. De deelnemers ontvingen vier keer 15 µg LSD of een placebo. Na inname van het middel werd pijntolerantie beoordeeld met behulp van de 'Koude Druk Test'. Ook werden zelfgerapporteerde pijnintensiteit, onaangenaamheid en stress geregistreerd tijdens de studie. Na het verwijderen van een aantal deelnemers die bij aanvang en gedurende de behandeling een plateau in pijntolerantie vertoonden, werden marginale maar significante effecten van LSD gevonden op maten van pijntolerantie en onaangenaamheid, zoals aangegeven door interacties tussen

368

behandeling en testdag. De studie concludeerde dat een kleine dosis LSD marginale pijnstillende effecten kan produceren, en het wordt aanbevolen om verder onderzoek uit te voeren met grotere steekproeven en hogere microdoseringen (bvb. 20 mcg) om de pijnstillende effecten van LSD beter te begrijpen en de potentiële toepassing ervan in een klinische setting te onderzoeken.

In **Hoofdstuk 4** presenteren we een overzicht van klinische studies met psychedelica die een gestructureerde psychotherapeutische interventie gebruikten en beschreven. Het doel van deze review was om een beeld te schetsen van de huidige modellen van psychedelisch-ondersteunde psychotherapie (PAP) die in klinisch onderzoek worden gebruikt en om te rapporteren over hun klinische uitkomsten. De review beschrijft ad-hoc en aangepaste therapeutische methoden, gemeenschappelijke principes, punten van divergentie en potentiële toekomstige richtingen in PAP. Het bespreekt de rol van de therapeutische houding, de mate van directiviteit, en de potentiële suggestieve effecten van de informatie die aan patiënten wordt verstrekt, als belangrijke factoren om te overwegen bij de ontwikkeling en implementatie van effectieve PAP-modellen.

In **Hoofdstuk 5** presenteren we een uitgebreide casus-analyse van een 36-jarige mannelijke klinisch psycholoog die leed aan fibromyalgie en deelnam aan een psychedelisch retraite waar hij een programma voor psychedelisch-ondersteunde therapie volgde.

We verzamelden kwantitatieve metingen bij voor de deelname aan de therapie en op drie daaropvolgende tijdstippen: 2 weken, 3 maanden en 6 maanden na een psychedelisch retraite waarbij truffels met psilocybine genuttigd werden. Interpretatieve fenomenologische analyse (IPA) werd uitgevoerd op de transcripten van semi-gestructureerde interviews die 2 weken, 3 en 6 maanden na de retraite werden gehouden. De bevindingen toonden verbeteringen in zijn mentale gezondheid, een afname van symptomen van depressie, angst en stress en 'cognitieve fusie', en verbeterde psychologische flexibiliteit en mindfulness vaardigheden. De retraite sessies waar truffels met psilocybine genuttigd werden boden ook verlichting van de pijn van fibromyalgie, en integratie sessies die daarop volgden hielpen hem zich meer bewust en aanwezig te voelen, onderdrukte trauma's te erkennen en naar verluidt stelde het hem in staat zijn emotionele behoeften aan te pakken. De bevindingen van de studie benadrukken de potentiële therapeutische voordelen van psychedelisch-ondersteunde psychotherapie bij het aanpakken van fibromyalgie en het verbeteren van de uitkomsten van de mentale gezondheid.

In **Hoofdstuk 6** stellen we psychedelisch-ondersteunde psychotherapie voor als een mogelijke behandeling voor mentale pijn. Er is namelijk een aanzienlijke overlap tussen de aandoeningen waarmee mentale pijn doorgaans wordt geassocieerd en die welke zijn onderzocht in klinische studies naar

370

het therapeutische potentieel van psychedelisch-ondersteunde psychotherapie. In het hoofdstuk bieden we een overzicht van dergelijke studies naar depressie, PTSS en middelenmisbruik, waarbij we de mogelijke therapeutische rol benadrukken die psychedelica kunnen spelen bij de behandeling van mentale pijn. Daarnaast betogen we dat de therapeutische mechanismen die ten grondslag liggen aan psychedelisch-ondersteunde psychotherapie specifiek neurobiologische en psychologische factoren kunnen aanpakken die verantwoordelijk zijn voor mentale pijn.

Tot slot worden in **Hoofdstuk 7** de resultaten van de eerdergenoemde studies besproken in de bredere context van psychedelisch onderzoek. Meer specifiek belichten we de unieke mogelijkheden die verschillende vormen van psychedelische therapieën patiënten kunnen bieden. We beschrijven hoe een puur analgetisch model (d.w.z. een model dat uitsluitend gebaseerd is op de farmacologische effecten van psychedelica) eruit zou zien in vergelijking met verschillende vormen van psychedelisch-ondersteunde psychotherapieën voor chronische pijn. Verder bespreken we de implicaties van het gebruik van verschillende settings voor het uitvoeren van psychedelisch-ondersteunde psychotherapie (bijvoorbeeld retraite-gebaseerde behandelingen versus "traditionele" psychotherapeutische sessies, groeps- versus individuele instellingen) en kwesties die gerelateerd zijn aan de veiligheid van psychedelica en het herhaaldelijk gebruik ervan. Tot

slot vermelden we toekomstige richtingen voor onderzoek naar psychedelica en pijn.

Acknowledgments

This PhD journey would not have been possible without the exceptional group of people who guided, supervised, supported, and encouraged me every step of the way. First and foremost, I would like to thank my supervisory team.

Jan, I want to thank you for the direct, pragmatic, and goal-oriented feedback you provided throughout our time working together. You taught me, through your guidance and example, how to identify and focus on what truly mattered. I became better at keeping the momentum going in the complex process of research, from design to testing to writing. Your lightheartedness, love of life, and great musical taste enriched our time together and showed me that it's possible to be passionate, diligent, and productive in academia while still cultivating a rich and fun personality. It is truly inspiring.

Kim, your warm, driven, and passionate energy holds a special place in my heart. In you, I see an example of courage, determination, intelligence, and kindness that I have rarely encountered elsewhere. I cannot emphasise enough how grateful I am that you considered my proposal at the beginning of this PhD journey. Even now, I sometimes reflect on that first online meeting we had. The way you took me seriously, despite my being an outsider to the research world, made a lasting impression on me and convinced me that you were the right person to learn from and work with. Your meticulousness, rigour, and approachability form a precious combination that helped me build confidence in both my research and organisational skills, and for this, I will be forever grateful. During the years we worked together, I saw you interact with people in different roles—standing your ground, offering support when needed, providing guidance, warning of perils, celebrating successes, and maintaining a compassionate attitude, even in the face of shortcomings. Recently, during our short and dense Californian days, I had the opportunity to spend more time with you and further

appreciate your humour, perseverance, and humanity. I felt proud and privileged to be there with you, and I hope we can continue building in our next project and beyond. Thank you from the bottom of my heart.

Eef, you have been a constant source of support throughout these PhD years, and I have deeply appreciated your warmth and joyful presence. I am especially grateful for your writing suggestions, precise feedback, help in navigating ethical committees, and, of course, your amazing marmalade!

Prof. **Carmela Mento**, I am grateful to you for providing the means that enabled me to begin and complete my PhD journey. Our time together helped me stay focused on the bigger picture, remain true to my ambitions, and never forget that I had one foot firmly planted in my homeland.

Prof. **Francesco Parisi**, these PhD years have been filled with our engaging conversations about psychedelics, consciousness, and deeper themes related to roots, belonging, and shared humanity. I have always appreciated your fresh perspective on the mind's alterations, to the point that the phrase "media pharmacology" has become a meme that lives rent-free in my mind. I am deeply grateful for the time we spent together, beyond the purely academic discussions, and I will cherish the memories we created that summer night in Tono. In other words: Cisco, thank you for tending to the fire :)

I would like to express my gratitude to the members of the assessment committee—Prof. Dr. **Arjan Blokland**, Prof. Dr. **Kees Kramers**, Prof. Dr. **Ivan Formica**, Prof. **Madelon Peters**, and Dr. **Monique van Velzen**—for accepting to evaluate my dissertation and for being part of the promotion committee for the public defence.

Prof. **Alessandra Falzone**, you have supported and guided me since the earliest days of my PhD, when this research idea was still in its infancy and its future

uncertain. Your unwavering commitment to ensuring that all the necessary resources were in place so that I could safely and successfully complete this journey will never be forgotten. Without your help, none of this would have been possible.

Johannes, unfortunately, I couldn't find a way to serenade you in these pages. I'm sorry—I know you were expecting me to play guitar and sing your praises before the end of my PhD, but alas, I must confess, I failed. Despite all the effort you put into teaching me how to manage test days, handle blood draws, ice buckets, buggy tasks, lab shipments, labels, and even cope with scathing padel defeats, I must disappoint you. Thank you sincerely for always being available to help, offer advice, and joke about the most outrageous things in life :D.

Natasha, your welcoming and caring attitude was precious in helping me integrate into this wonderful workgroup, and for that, I am very grateful. When I think back to my early days in the department and in Maastricht, I often recall our first bouldering session, where you introduced me to part of the team and Bram (hi Bram!). It felt warm and familiar, and that played a big part in helping me settle into my new life. In you, I see an example of creativity and dedication, and your genuine interest and curiosity continue to inspire me. Lastly, thank you for introducing me to your amazing country—our U.S. trip was a literally awesome. I hope we can stay office mates for the next 100 years!

Jessica, thank you for all the chats about love, life and all the rest that matters that we had. Many of those memories hold a special place in my heart.

Zeus, thank you for the constant encouragement and the good times we spent together :)

Prof. **Pietro Perconti**, you were among the first to learn about this project and you enthusiastically encouraged me to go on. While we only met once, I am grateful for your support.

Prof. **Rosa Angela Fabio**, even before the start of this PhD, you have always been an ally to me. Thanks to you, I gained a better understanding of how to navigate the academic world, improve my scientific writing, and had a listening ear for all my questions. Beyond our professional relationship, I am grateful to have met such a sensitive and kind human being who never hesitates to stand up for what she believes is right.

René, thank you for our beautiful friendship and all the things you taught me. Now that some road is behind us and way more is ahead I want to thank you for being a pristine space where to play with light and darkness, for your wide perspective, for your sharp intellect, for being the ally, the accomplice, the adversary.

Laura, over the past four years, I have often reflected on what brought about this significant change in my life. Your presence has been an essential ingredient in this delicate alchemy. Thank you for reigniting my spark, for reconnecting me with my most creative and lively self, and for your unwavering faith, trust, and support. Now that so much has changed, whenever I find myself thinking, “Who would have thought I’d end up here?” I know exactly who that is—it’s you.

Everything begins and ends with family, and I cannot express how privileged I feel to have been born to my mother and father, and raised alongside my sister and brother. **Dad**, you taught me strength, perseverance, and cared about my future through thick and thin—whether I was sweet or harsh, wavering or stubborn. You were always there for me, always believing in me, and always loving me. **Mom**, you are the most exceptional woman I’ve ever met. You have always been able to reach me and show me the way. I admire your clarity in

focusing on what truly matters and letting the rest sort itself out. I know that my ability to connect with and understand people comes mostly from you and the lessons you taught me. Thank you, Mom, for everything you did that I could see, and for all that remains unseen. **Alice**, my incredible sister, whose strength I can only hope to achieve one day. Thank you for paving the way, for loving me since my first days, for being part of my fondest childhood memories, for being the memory keeper of this family, and for keeping grandpa's spirit alive in all our hearts. **Francesco** (see, I didn't call you Ninni), words fail me when I think about how much you mean to me. You always knew, and you always believed in me. I truly couldn't have made it without you. I am grateful for the "*we'll see in two years*" look you give me when I resist and you know you're right, for never giving up on me despite my stubbornness, for your honesty and willingness to disagree and persuade me. Thank you for all the nights and days we've shared, and for all those yet to come. You are my strength, my pride, my unwavering ally, my secret weapon.

