

Critique of the Royal Australian and New Zealand College of Psychiatrists Psychedelic Therapy Clinical Memorandum, Dated May 2020

Victor Chiruta¹ ✉ Paulina K Zemla², Pixie Miller³, Dr Nicola Santarossa⁴ and John A Hannan⁵

¹School of Health Sciences, University of South Australia, 101 Currie St, Adelaide, SA 5001, AU; Independent Food & Therapeutic Authority, M/134 Great Western Hwy, Blaxland, NSW 2774, AU; Mind Medicine Australia, 1/10 Dorcas St, South Melbourne, VIC 3205, AU

²Faculty of Social Sciences, University of Wollongong, Northfields Ave, Wollongong, NSW 2522, AU; Independent Food & Therapeutic Authority, M/134 Great Western Hwy, Blaxland, NSW 2774, AU; Mind Medicine Australia, 1/10 Dorcas St, South Melbourne, VIC 3205, AU

³School of Health and Human Sciences, Southern Cross University, Military Rd, East Lismore, NSW 2480, AU; Mind Medicine Australia, 1/10 Dorcas St, South Melbourne, VIC 3205, AU

⁴College of Medicine and Dentistry, James Cook University, 1 James Cook Dr, Douglas, QLD 4911, AU; Faculty of Health and Behavioural Sciences, University of Queensland, St Lucia, QLD 4072, AU; Mind Medicine Australia, 1/10 Dorcas St, South Melbourne, VIC 3205, AU

⁵School of Psychology, University of Queensland, Sir Fred Schonell Dr, St Lucia, QLD 4072, AU; Mind Medicine Australia, 1/10 Dorcas St, South Melbourne, VIC 3205, AU

✉ **Corresponding Author:** Victor Chiruta, **E-mail:** victor@zkqgroup.com.au

ARTICLE INFORMATION

Received: 01 November 2021

Accepted: 25 November 2021

Published: 31 December 2021

DOI: 10.32996/jmhs.2021.2.2.18

KEYWORDS

Psychedelic medicine, MDMA, psilocybin, TGA, psychedelic therapy, psychotherapy, RANZCP

ABSTRACT

Objective: In its Clinical Memorandum on the *Therapeutic Use of Psychedelic Substances*, May 2020, the Royal Australian and New Zealand College of Psychiatrists (RANZCP) currently positions itself against medically controlled patient access to 3,4-methylenedioxyamphetamine (MDMA) and psilocybin in therapeutic settings. This paper will analyse the validity of the arguments used by RANZCP in their memorandum. **Methods:** In order to evaluate if certain claims made by RANZCP in its CM are factual, every reference in the clinical memorandum (CM) was checked against the original publications used by RANZCP to justify its position. In addition, scientific search engines, Government websites, institutional websites, Australian and New Zealand legislation were searched for pertinent and up-to-date information. **Results:** The authors have found no scientific or medical evidence from the last 70 years to suggest that either psilocybin or MDMA, when administered as an adjunct to therapy in a controlled clinical setting, are linked to either mental illness or negative health outcomes. On the contrary, MDMA and psilocybin have been shown to be safe, non-toxic, non-addictive, and efficacious when administered in a medically-controlled clinical environment. All associated risks are apparent in an uncontrolled setting. **Conclusion:** The RANZCP's position is based on outdated, irrelevant, misinterpreted, and misinformed evidence. With recent media hype around the efficacy of these medicines when used as an adjunct to therapy, there is an intrinsic risk of self-medication or underground therapy. This means that any medical discussion must also consider the ethical responsibilities and social duties associated with these substances.

1. Introduction

In Australia, there are currently public submissions from the charitable organization Mind Medicine Australia (MMA) to have the Australian medical regulatory body reschedule MDMA and psilocybin from Schedule 9 (S9) prohibited substances to Schedule 8

(S8) controlled medicines (MMA, 2020b). MDMA is a chemical sometimes present in ecstasy, and psilocybin (in its natural form) is a compound found in most species of psychedelic mushrooms. This rescheduling would allow for controlled patient access - restricted to medically controlled clinical environments – for Australians suffering from Treatment-Resistant Depression (TRD) and Treatment-Resistant Post-Traumatic Stress Disorder (TR-PTSD). As the RANZCP Clinical Memorandum rightly relays, these therapies have been classified as ‘breakthrough designated therapies’ by the US Food and Drug Administration (FDA). FDA breakthrough designated therapies mean that clinical trials may be fast-tracked, and patients in the community can access breakthrough therapies under compassionate grounds during Phase 3 trials.

Even though the RANZCP CM is now 1.5 years dated, the TGA relied heavily on the CM as clinical evidence for their interim decision not to grant State and Territory access under compassionate use to patients for MDMA and psilocybin-assisted psychotherapies.²

2. Key Points

The RANZCP released a CM in May 2020 titled *Therapeutic Use Of Psychedelic Substances*. The CM concludes in its key message that psychedelic-assisted psychotherapy should remain research only, without patients outside of research trials having access to psychedelic therapy: "*Research into medicines containing psychedelic substances should only occur under research trial conditions that include oversight by an institutional research ethics committee*". Even though RANZCP considers it premature for Australia to provide access to these therapies in non-research settings, the Australian Federal Government, as well as governments in Canada, Israel, Switzerland, and the US have already permitted patients access to MDMA or psilocybin therapeutically.

In Australia, if a patient receives Federal approval for compassionate use of a S9, the Australian States and Territories have no legal provisions for prescribing a S9 for therapeutic use to patients. Further to this, some Australian States and Territories do not have any legal provisions for the scientific research of a S9. The RANZCP is of the position that Australia should not, at the present time, approve the use of medically supervised psychedelic-assisted psychotherapy in a clinical environment. This position is based on evidence provided in the CM. However, the CM contains referencing errors, misinformation, irrelevant data, and incomplete research. This paper will scientifically analyze and academically evaluate the evidence provided in the CM.

- RANZCP rely on legality to classify MDMA as ‘not technically a psychedelic,’ when, in actuality, MDMA is a psychedelic when classifying its pharmacology, chemistry, therapeutic outcome, and application in psychedelic-assisted psychotherapy.
- RANZCP classify all psychedelics as ‘illicit’ in Australia and New Zealand. This is erroneous, as psychedelics are already used in psychotherapy (ketamine, ibogaine), approved for use in therapeutic applications (ibotenic acid, harmala alkaloids, methysergide), or are constituents of approved medicines or ingredients in medicines (ibotenic acid, *N,N*-DMT, NMT, 5-MeO-DMT, methysergide, *peganum harmala*, harmala alkaloids).
- RANZCP cite references where apparently systematic reviews show that MDMA and psilocybin use can cause psychosis. However, our review of the references disproves their claim, as none of their evidence actually mentions MDMA or psilocybin as causing psychosis. However, there was one recorded case of MDMA contributing to psychosis when polyabused with cannabis and LSD.
- RANZCP severely underplays the impressive amount of research conducted over many decades into psychedelic clinical application, as well as the analysis of much larger quantities of participants than RANZCP suggest, who have undergone MDMA therapy and clinical trials, with successful outcomes.
- RANZCP state that the scientific community do not understand the neuromechanisms of MDMA and psilocybin. Yet there are decades of literature demonstrating the neuropsychopharmacology, somatic pharmacodynamics, and fMRI data of these substances.
- RANZCP state that no country has regulated psychedelic therapy. However, we will show that many countries and Jurisdictions have regulated and use psychedelic therapy.

3. Methodology

Every reference in the CM was checked against the original publications. In addition, the search engines Google Scholar, PubMed, ScienceDirect, the MAPS website, the TGA website, and relevant Australian and New Zealand legislation were searched for pertinent and up-to-date information. Relevant legislation included the *Poisons Standard February 2021, Therapeutic Goods (Permissible Ingredients) Determination (No. 4) 2020* (Cth), *Therapeutic Goods Act 1989* (Cth), and *Misuse of Drugs Act 1975* (NZ).

² <https://www.tga.gov.au/resources/publication/scheduling-decisions-interim/notice-interim-decisions-proposed-amendments-poisons-standard-acms-accs-and-joint-acms-accs-meetings-november-2020/24-psilocybin>, <https://www.tga.gov.au/resources/publication/scheduling-decisions-interim/notice-interim-decisions-proposed-amendments-poisons-standard-acms-accs-and-joint-acms-accs-meetings-november-2020/25-n-dimethyl-34-methylenedioxyphenylethylamine-mdma>

4. Psychedelics and Their Regulation

There is confusion in the CM about what a psychedelic is. The CM states that MDMA is “not technically a psychedelic”:

“Though technically not a psychedelic, MDMA is included as it is similar to psychedelics with regard to legal impediments to research and potential therapeutic methods”.

In fact, “legal impediments” and “potential therapeutic methods” are far from the only factors that might legitimise MDMA’s designation as a psychedelic. MDMA is both pharmacologically and structurally a resemblance to other psychedelics. In the scientific literature, MDMA’s effects on the central nervous system (CNS) are described as psychedelic (Nutt, 2019; Steele et al., 1994). MDMA has highly complex pharmacodynamics, mostly as a monoamine releaser and serotonin transporter, although a target is the serotonin subtype-2A receptor (5-HT_{2A}) (Amoroso, 2015). 5-HT_{2A} is the classic serotonergic psychedelic receptor (Jalal, 2018; Moreno et al., 2011). Another target of MDMA is the dopamine type-2 receptor (D₂) (Amoroso, 2015). D₂ is one of the main targets of the classic psychedelic lysergic acid diethylamide (LSD) (Giacomelli et al., 1998; Seeman et al., 2009) and the very potent natural psychedelic salvinorin A (Seeman et al., 2009). MDMA is further described in some scientific literature as a psychedelic phenylethylamine substituted amphetamine (Schmidt, 1987; Trachsel, 2012). In the literature, many phenylethylamines with a substituted amphetamine are classified as psychedelics, e.g. 3,4-methylenedioxyamphetamine (MDA) (Baggott et al., 2019), 2,5-dimethoxy-4-methylamphetamine (DOM) (Eckler et al., 2003), and 2,5-dimethoxy-4-bromophenylamine (2C-B) (Papaseit et al., 2018). MDA is viewed as a classic psychedelic and is MDMA’s main hepatic metabolite. It is therefore reductive to claim that MDMA is “not technically a psychedelic”.

Furthermore, the CM proffers contradictory statements about the regulatory frameworks for the medical use of psychedelic substances in Australia and New Zealand. One of its key claims is that:

“Psychedelic substances are illicit and are not registered for any use by the Therapeutic Goods Administration (TGA) in Australia or Medsafe in New Zealand. They cannot be prescribed or administered outside of properly approved research trials”.

The RANZCP state that the CM is educational material written for psychiatrists. However, using the word ‘illicit’ as a blanket descriptor for psychedelic substances is unscientific and misleading. It is important for psychiatrists to be aware of restrictions surrounding potential candidates for medical research or expanded access. The term ‘illicit’ is an inappropriate descriptor given that several psychedelic substances are legal when used in medically-controlled environments with proper approvals but illegal when used recreationally. Examples include ketamine, ibotenic acid, harmala alkaloids, ibogaine, and methysergide. In Australia, ‘illicit’ drugs, from a medical perspective, would fall under Schedule 10 (S10) of the *Poisons Standard* (Cth), which lists drugs of such danger to public health as to warrant a full prohibition on the sale, supply and use. As this review will illuminate, the phrase ‘psychedelic substances’ covers several classes of drugs, which are subject to different controls in Australia and New Zealand — ranging from research only, controlled prescription, uncontrolled prescription, or as unregulated substances. An example of an ‘illicit’ psychedelic is the plant *Acorus calamus*, which is prohibited in Australia for human therapeutic use under S10 of the *Poisons Standard* (Cth).

4.1 Medically Regulated Psychedelics in Australia and NZ

This section is to provide information on the therapeutic use of psychedelic medicine in Australia and New Zealand. Although the focal scope of the CM is MDMA and psilocybin, the RANZCP make generalized comments on the prohibition of all psychedelics in medicine, however, several psychedelics are approved for therapeutic use in Australia and New Zealand.

4.1.1 MDMA

MDMA has been classified as a B1 controlled drug in New Zealand by Medsafe since 2005 (NZ, 2005). B1 is the category of controlled medicines, including controlled prescription medicines morphine, methadone, medicinal cannabis, and amphetamine (NZ, 1975). This means that with the approval of the regulator, MDMA is technically available for prescription in New Zealand by doctors (*Controlled Drugs*, 2019). However, the authors are unaware of any MDMA applications or approvals in New Zealand. Nevertheless, MDMA is available as a B1 controlled drug. In Australia, MDMA is Federally classified as a S9 substance in the *Poison Standards* (Cth). This means that MDMA can be legally made available for use in research, and doctors can only access this medicine for patients with appropriate approval under the TGA’s Special Access Scheme-B (SAS-B) or its Authorized Prescriber Scheme (APS) (Cth, 1989). Even though MDMA is Federally scheduled as a prohibited substance, several patients with otherwise treatment-resistant mental health conditions have been approved to receive MDMA therapeutically under SAS-B (MMA, 2020a). The authors are unaware of any doctors with APS status to prescribe MDMA. The complication in Australia comes at the State level. Victoria provides for access through a permit system, whilst NSW and WA prohibit the therapeutic use of MDMA, when a patient has Federal TGA approval.

4.1.2 Ketamine

The next medicine to evaluate is ketamine. The RANZCP note in its CM that ketamine has its own RANZCP clinical memorandum (RANZCP, 2020). Ketamine is described in multiple scientific literary papers as a psychedelic (Bowdle et al., 1998; Kolp et al., 2014; Krupitsky & Grinenko, 1997; Lim, 2003). Between the years 1985 and 1995, ketamine was studied successfully in over 1,000 participants for its use in psychedelic-assisted psychotherapy (Krupitsky & Grinenko, 1997). Ketamine has recently gained application once again for use in psychedelic-assisted psychotherapy (Kolp et al., 2014). The TGA has approved the psychedelic ketamine (ingredient ID: 70736) and its enantiomer esketamine (ingredient ID: 114417) for use in medicine in Australia. There are currently 13 approved medicines listed on the Australian Register of Therapeutic Goods (ARTG) containing ketamine (TGA, 2020).

4.1.3 Ibotenic Acid and Muscimol

Another interesting group of psychedelic compounds are the GABAergic isoxazoles from the psychedelic variants of the *Amanita spp.* The psychedelic mushroom *Amanita muscaria* has rich historical entheogenic use in traditional and indigenous cultures all over the world (Falandysz et al., 2020; Feeney, 2010; Ott, 1996; Trutmann, 2012). The *Amanita spp.* are Federally not scheduled in the *Poison Standards* (Cth) in Australia, nor in the *Misuse of Drugs Act 1975* (NZ) in New Zealand. However, *Amanita spp.* are prohibited for use in food in both countries in the *Food Standards Australia New Zealand Act 1991* (Cth). The primary psychedelic compounds in the mushroom are ibotenic acid and muscimol. Ibotenic acid is a prodrug for muscimol. Ibotenic acid is not scheduled in Australia, nor New Zealand. In Australia, ibotenic acid (ingredient ID: 105657) has been approved for use in therapeutic biological devices by the TGA. Muscimol is classified as a S9 substance in Australia, but unscheduled in New Zealand.

4.1.4 Harmala (Ayahuasca) Alkaloids

Harmala alkaloids have become renowned for their application in the South American Ayahuasca tea (Callaway et al., 1996). Harmala alkaloids are the compounds in the Ayahuasca vine (*Banisteriopsis caapi*) that activate the *N,N*-dimethyltryptamine (DMT) in the Ayahuasca tea. Harmala alkaloids are Federally S9 substances but unscheduled if used in herbs or preparations for therapeutic use in certain conditions. The TGA prescribes a protocol for the therapeutic use of harmala alkaloids. Further to this, the psychedelic plant *Peganum harmala* (ingredient ID: 83330) has been approved by the TGA for use in medicine. *Peganum harmala* is used as a substitute for *Banisteriopsis caapi* in the Ayahuasca tea (Kaasik et al., 2020). *Peganum harmala* has a rich history of entheogenic and spiritual use (Mina et al., 2015; Moloudizargari et al., 2013).

4.1.6 Ibogaine

In Australia in the *Poison Standards* (Cth), the powerful psychedelic ibogaine and its metabolite noribogaine are Schedule 4 (S4; prescription only) without prescription controls and in New Zealand are classified for a prescription without restrictions or controls (Medsafe, 2020). The scheduling of ibogaine in Australia and New Zealand occurred in 2010. The National Drugs and Poisons Schedule Committee (NDPSC) made the recommendation to the TGA based on the rescheduling reasons provided by the New Zealand Medicines Classification Committee (MCC) in 2009 (NDPSC, 2010):

- i. The need for supervision of the substances' use in the management/treatment of addiction to limit attempts at self-treatment and prevent recreational use as a "party pill" (although noting that the documented experience is usually not pleasant);
- ii. The need to control the import and supply of ibogaine, its metabolite or products containing each or both of the substances;
- iii. Data suggesting that the number of deaths due to ibogaine were lower than those associated with methadone; and
- iv. The opinion that although ibogaine's appeal as a recreational drug was low, there were dangers in ad hoc use as self-medication for drug addiction following potential media interest.

Significantly, if we take into consideration the above, the RANZCP's position on the use of psychedelics in therapy directly contradicts the reasons the NDPSC, TGA, and MCC had for scheduling ibogaine. It may be taken, that if the above Committee points are considered for the current psychedelics in MMA's submissions (MDMA and psilocybin), the proposed rescheduling is likely to be approved.

4.1.5 DMT

In regard to DMT, DMT is federally a S9 substance in Australia and is a Class A controlled drug in New Zealand. However, the TGA has approved a handful of DMT-containing plants for use in medicine.

The ARTG lists one medicine containing *Acacia longifolia* (ARTG ID: 176056). The medicine is listed for wellbeing and contains the equivalent of 500 mg of *Acacia longifolia* per mL. According to Lim 2014, there would be 1-1.5 mg of DMT per mL of the Australian approved medicine (Lim, 2014).

Table 1. DMT-containing plants approved for use in medicines by TGA in Australia

Plant	Approved medical ingredient ID	Psychedelic	Amount
<i>Acacia longifolia</i>	86827	DMT	0.2-0.3% (Lim, 2014)
<i>Phalaris arundinacea</i>	87004	DMT NMT 5-MeO-DMT 5-MeO-NMT β -Carbolines	0.2-0.7% (Østrem, 1987; Woods & Clark, 1971)
<i>Mucuna pruriens</i>	83253	DMT Bufotenine	Unspecified (Kavitha & Thangamani, 2014)

NMT	<i>N</i> -Methyltryptamine
5-MeO-DMT	5-Methoxy- <i>N,N</i> -dimethyltryptamine
5-MeO-NMT	5-Methoxy- <i>N</i> -methyltryptamine
β -Carbolines	Harmala alkaloid family
Bufotenine	5-Hydroxy-dimethyltryptamine (5-OH-DMT)

6. Patterns of Use in Medically-Controlled Environments for Psychedelics

6.1 Media Interest

There is increasing media interest in the use of MDMA and psilocybin as an adjunct to therapy for the treatment of the common mental health conditions listed in Table 3, such as depression, PTSD, General Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), and addiction. Particularly in the last two years, MDMA and psilocybin have gained much attention as potential 'cures' for these disorders on mainstream Australian media (ABC (Malcom & Bedi, 2018), 7NEWS (Daoud, 2020), The Sydney Morning Herald (McCauley, 2020), and 60 minutes (Abo, 2020; Taylor, 2020)). The FDA has granted both MDMA and psilocybin-assisted therapies 'breakthrough therapy' status in the US (Feduccia et al., 2019; Nichols, 2020), which the RANZCP CM itself acknowledges. However there are other Government approvals that the CM does not recognise. For instance, the FDA has opened an 'expanded access scheme' for treating PTSD with MDMA (Brewerton et al., 2020), the Israeli Ministry of Health has embraced the treatment of PTSD with MDMA under 'compassionate use' (MAPS, 2019b) – the RANZCP acknowledge Israel, and compassionate MDMA therapy has been conducted in Switzerland (Sessa et al., 2019). The state of Oregon in the US has legalized psilocybin therapy (*Oregon Measure 109, Psilocybin Mushroom Services Program Initiative (2020)*, 2020), whilst Canada has approved for patients to use psilocybin-assisted psychotherapy for depression and end-of-life anxiety (Carpenter, 2020; Semley, 2020). The Honourable Canadian Health Minister has granted patients suffering from anxiety associated with terminal illness lawful access to psilocybin therapeutically under section 56(1) of the *Controlled Drugs and Substances Act* (Wood et al., 2019). Psychedelic-assisted psychotherapy clinics have opened up in Toronto (*Psychedelic therapies that bring you to life*, 2020), New York City, Los Angeles, Chicago, with a psilocybin microdose dispensary for therapeutic use opened in Canada (*Access to microdoses of psilocybe mushrooms for therapeutic purposes*, 2020). This list is by no means exhaustive for MDMA and psilocybin (let alone other psychedelics). A lengthy paper on the international regulatory coverage of different psychedelic patterns of use in medically-controlled environments could be written.

It becomes apparent to re-articulate that the TGA has granted patients special access use of MDMA and psilocybin in Australia under SAS-B. However, States prohibit patient access to S9s even with Federal approval. This, in fact, is more restrictive than in other countries, since current laws within Australia prohibit even compassionate use or expanded access to MDMA and psilocybin. However as noted, MDMA and psilocybin are still not medically available in places where compassionate use is permitted.

6.2 Regulatory Interest

According to the NDPSC, TGA, and MCC, given the increasing public awareness of uses around the world of the psychedelic substance ibogaine, there is an increased risk of self-medication if there is not an accessible route through the medical system (NDPSC, 2010). The RANZCP has not only expressed the simplistic opinion in its CM that psychedelics are 'illicit' in Australia and New Zealand, but the CM also states that:

"Currently psychedelic therapy is not regulated for use in any country."

This statement is misleading because, whilst there are no psychedelic-specific indications for the medical use of psychedelic substances, MDMA and psilocybin are accessible by doctors for their patients under expanded access schemes and regulatory provisions in a number of International Jurisdictions. The authors understand, expanded access is not medical approval. However, stating that psychedelic therapy is not regulated for use in any country is misleading. The CM contradicts itself by listing some instances of legal allowance, but their references are, even then, evasively meagre, and so, misleading. In the case of ibogaine, it is

available in Australia and New Zealand through prescription, also through clinics in Canada (IbogaSoul, 2020; *Sacred Soul Therapy • Squamish, Vancouver, BC, Canada, 2021*; *Specializing in opiate addiction detox, 2020*), Mexico (*Ibogaine Treatment Center Mexico, 2020*; *We are the World's Foremost Experts in Medically-based Ibogaine Treatment, 2020*), Gabon (*Iboga Retreat Gabon, West Africa, 2019*), South Africa (Underwood, 2020), Costa Rica (*Boutique Hotel & Retreat Center, 2020*) and the Bahamas (*The Avante Ibogaine Treatment Centre, 2020*). Ayahuasca is also being medically administered as part of therapy for the rehabilitation of violent and sexual offenders in Brazilian jails (Rocha & Rossi, 2019; Romero, 2015).

7. Safety Profile of Medicinal MDMA and Psilocybin

7.1 Medicinal MDMA

The dangers of self-medication constitute a critical part of the discourse on uncontrolled unsupervised use versus controlled and medically-supervised psychedelic treatments. With MDMA use, morbidity and mortality have only occurred in uncontrolled non-clinical settings (Sessa et al., 2019). All serious adverse effects in a clinical setting have been rare and non-life-threatening (MAPS, 2019a).. The risks of self-medication was one of the key arguments behind the scheduling of ibogaine in Australia and New Zealand.

RANZCP state in its CM in relation to MDMA that:

“Clinical trials have demonstrated safety profile; for example, 760 individuals have participated in the MAPS’ MDMA trials with only one serious adverse event reported [17] relating to tachycardia and increased blood pressure.”

This statement is in reference to what appears to be an outdated MAPS MDMA poster (MAPS, n.d.). The CM states in its referencing that the poster was published in 2019 (reference [17]) (RANZCP, 2020). However, the poster has no publication date. A small referencing error has been made by RANZCP. The poster states, ‘over 780 human subjects’, not ‘760 individuals’ (MAPS, n.d.). On page 54 of a 2013 Investigator’s Brochure publication, MAPS states, ‘as of November 2012, 811 participants have received MDMA in trials’ (MAPS, 2013). This coincides with the poster publication of the number of MDMA trial participants. Although the poster did not show on its face when it was published, the American Counselling Association (ACA) made reference to an archived version of the poster in 2018 (ACA, 2018). It is logical to assume the release date of the poster is older than the archived version of the poster that the ACA cite, considering the poster does not cite the original source it is based off. Regardless, a public poster is not scientific evidence that should be used when arguing against the profound social, medical, and economic impact of the medical rescheduling of MDMA. The RANZCP clearly did not fact check the poster against the original scientific data and incorrectly represents that this data is recent. The relevant scientific publication should be cited when discussing drugs and medicines’ regulation and medical impact. The RANZCP is of the opinion 760 individuals have participated in MDMA studies. However, MAPS, which is sponsoring the current Phase 3 trials of MDMA, have reported much larger numbers.

MAPS report that since post-prohibition in 1987, 3,347 people have participated in MDMA studies around the world (Table 2). This is in comparison to the 760 participants reported by the RANZCP. With only one serious unexpected adverse event reported in the last 30 years of clinical trials, the significance of serious unexpected adverse events falls from 0.13% to less than 0.03%.

Several sources have published that thousands of participants undertook MDMA-assisted psychotherapy until prohibition in 1987 (MAPS, 2013, 2016, 2017, 2018a, 2019a, 2020b; Passie, 2018), with MAPS publishing there were an estimated 500,000 doses administered to patients in these early psychotherapy sessions (MAPS, 2020b). An evaluation of pre-prohibition studies published in the Drug Science, Policy and Law journal states that early psychotherapeutic use of MDMA was without complication (Passie, 2018). It would appear that RANZCP is basing its position on 2013 rather than 2020 data (and have excluded all pre-prohibition data about safety). RANZCP’s substantive understatement of data is further evidenced by its statement in the CM that, *“Since 2006, there have been several pilot trials and randomized controlled trials using psychedelics in various non-psychotic psychiatric disorders”*. Between 2009 until May 2020 (the CM publication), over 34 completed trials for MDMA alone have been published on www.clinicaltrials.gov, with over 50 completed psychedelic-medicine trials in total. The trials are reported in Table 3. MAPS report there are approximately 78 MDMA clinical trials completed to this date (MAPS, 2020b, 2021). Considering the vast number of completed psychedelic drugs studied in trials since 2006, Table 3 only collates data from 2009 (Table 3 is by no means exhaustive, excluding the hundreds of completed clinical ketamine studies and completed psychedelic clinical studies pre-prohibition).

Table 2. MAPS reported trial participants who have received MDMA

Year	# of participants	Source
Pre-1987 (pre-prohibition)	≈ 500,000 doses of MDMA administered to patients globally	Investigator’s Brochure 2020, p. 56 (MAPS, 2020b)
2000-2012	811 cumulative	Investigator’s Brochure 2013, p. 54 (MAPS, 2013)

until 2015	1,180 cumulative	Investigator's Brochure 2016, p. 92 (MAPS, 2016)
until 2016	1,280 cumulative	Investigator's Brochure 2017, p. 133 (MAPS, 2017)
until 2018	> 1,500 cumulative	Investigator's Brochure 2018, p. 127 (MAPS, 2018a)
until April 2020	1,431 (non-MAPS sponsored) 279 (MAPS sponsored) 1,710 cumulative	Investigator's Brochure 2020, p. 14 (MAPS, 2020b)
until October 2020	1,434 (non-MAPS sponsored) 341 (MAPS Sponsored) 1,775 cumulative	Investigator's Brochure 2021, p. 54 (MAPS, 2021)

The RANZCP's restrictive stance on using MDMA as part of therapy is based on incomplete analysis and misinterpreted information. Furthermore, the above reference to 'several' completed psychedelic trials is clearly misleading, when there have been over 50 completed trials since 2009, and many others before that. MAPS report that 1,775 participants have participated in MDMA trials (as of August 2020 – excluding 2021) and approximately 500,000 administered doses pre-prohibition. This equates to over 40 years worth of data. MDMA was first synthesized in 1912 by Merck (Passie et al., 2002) and has thorough toxicology studies and safety data (both short-term and long-term).

MDMA, as part of the recreational drug ecstasy, has a reputation for being associated with overdoses and deaths at dance parties (Armenian et al., 2013). In assessing the safety of MDMA, important distinctions need to be made between medicinal MDMA and the street-drug ecstasy (MMA, 2020a):

- i. Ecstasy may only contain a minimal amount of MDMA if any at all;
- ii. Ecstasy may contain other ingredients unknown, thus being dangerous;
- iii. Dosage of ecstasy cannot be regulated;
- iv. Ecstasy use is uncontrolled;
- v. Ecstasy users do not undergo any testing to ensure that they are fit to consume.

Medicinal MDMA is administered in a medically-controlled clinical setting. It is pharmaceutical grade, the dosage is known, patients are properly screened, the use of the medicine is regulated, the medicine is administered only by trained health professionals, and patients receive ongoing psychological support. Understanding the distinction between the two types of substances (recreational ecstasy and medical-grade MDMA) is fundamental when examining the safety evidence for MDMA. The lethal dose of MDMA in humans is estimated to be 10-20 mg/kg (Jerome et al., 2013). The largest dose used in clinical studies is 1-2 mg/kg (MAPS, 2018b). The maximum therapeutic dose for MDMA is a safety factor of 5-20 when compared with the lethal dose. Paracetamol is described in the scientific literature as having a safety factor of 10 from the lethal dose when compared to its maximum therapeutic dose (Wong, 2002).

According to the *International Journal of Drug Policy*, in Australia, between the years 2000 to 2018, 243 deaths in recreational environments involved drug toxicity where MDMA was present (Roxburgh & Lappin, 2020). However, only 14 deaths between 2000 and 2018 occurred solely due to MDMA toxicity (i.e. multiple drugs weren't detected). In its CM under the heading Risks and side effects, the RANZCP make the following observation:

"Frequent high dose MDMA can be neurotoxic (damaging to the nervous system) [16]".

Although this statement is true in a recreational setting, it has no relevance to the medical use of MDMA in controlled environments. More appropriately, this statement should be in a section called Risks and adverse effects of recreational use, misuse and abuse. The RANZCP has omitted the following information:

- i. Morbidity and mortality of MDMA use has only occurred in uncontrolled non-clinical settings (Sessa et al., 2019);
- ii. All serious adverse effects of MDMA in a clinical setting have been rare and non-life-threatening (MAPS, 2019a);
- iii. Early psychotherapeutic use of MDMA was without complication (Passie, 2018);
- iv. MDMA administered therapeutically in a controlled environment does not produce dependence (Kalant, 2001);
- v. Therapeutic treatment with MDMA has not been shown to increase illicit drug use (Sessa et al., 2019).

7.2 Psilocybin

Psilocybin is of concurrent importance to MDMA in the ethos of psychedelic-medicines as a way of changing the current mental health treatment paradigm in Australia. The RANZCP has published in the *Australian and New Zealand Journal of Psychiatry* that many Australians with key mental illnesses are not getting well (Jorm, 2014). Moreover, some mental health medicines (such as antidepressants) can have serious and debilitating side-effects (Cartwright et al., 2016). The RANZCP state in its CM that it is not satisfied with the safety profile of psychedelics in psychiatric use. But psychedelics range from hundreds of different compounds and plants. The CM makes no mention of the toxicology or safety data of medicinal psilocybin. Under Risks and side effects in the CM, RANZCP make the following statement, "*Psychedelics, when misused, can cause psychosis (hallucinogen induced psychotic disorder) as well as Hallucinogen Persisting Perception Disorder (HPPD). [18, 19] This is a potential long-term risk factor following psychedelic therapy, though this has not been investigated in research trials*". The key terminology here is 'when misused'. Again, this statement should be in a section called Risks and adverse effects of recreational use, misuse and abuse. This should not cloud any potential risks associated with controlled medical use.

When the references used by RANZCP in the CM for HPPD and psychosis (in the CM [18, 19]) are cross-checked, the authors in both articles do not state that psilocybin or MDMA are associated with HPPD or psychosis (Martinotti et al., 2018; Murrie et al., 2020). In reference [18] to the CM, the cited paper reports that cannabis, cannabis co-administered with MDMA, LSD, cannabis co-administered with LSD, phencyclidine (PCP), and risperidone are associated with HPPD (Martinotti et al., 2018). In reference [19] to the CM, the paper concludes that the most common cause of drug-induced psychosis is alcohol (Murrie et al., 2020). From the meta-analysis' study inclusions in the paper, out of 40,783 individuals with psychosis, only 208 cases were associated with hallucinogens used in a recreational setting. Although the authors included psilocybin and MDMA amongst many other hallucinogens in the keyword search, they do not specify what type of hallucinogens are associated with psychosis. 208 out of 40,783 equates to 0.5%. The other 99.5% of psychosis cases in the meta-analysis were associated with alcohol, cannabis, amphetamines, opioids, sedatives, a mix of drugs, or an unknown cause. It is of particular significance that every one of the 0.5% of cases of hallucinogen-induced psychosis in the meta-analysis occurred in an uncontrolled setting.

A population study published in the *Journal of Psychopharmacology* was conducted across a cohort of 135,000 individuals. The study found no link between psychedelic use and psychosis (Johansen & Krebs, 2015). The researchers concluded, individuals who had taken psychedelics were not at increased risk of developing mental health problems, including schizophrenia, psychosis, depression, anxiety disorders, and suicide attempts. However, a self-reporting study at Johns Hopkins University involving 1,993 individuals completing an online survey about their single most psychologically difficult or challenging experience after consuming psilocybin-containing mushrooms. In an uncontrolled setting, the survey revealed that 0.15% of participants reported a suicide attempt and 0.15% self-reported enduring psychosis (Carbonaro et al., 2016). Nevertheless, if used within a controlled setting, psilocybin has been shown to have little to no adverse reactions (Carhart-Harris et al., 2018; Strassman, 1984). Early therapeutic use of the pharmaceutical psilocybin (Indocybin®, developed by Sandoz) was without complication (Passie et al., 2002). In more recent trials, there have been no significant adverse events with psilocybin administration in a controlled setting (Dos Santos et al., 2018).

The toxicity of psilocybin and psilocybin-containing mushrooms is very low (Gable, 2004). The lethal dose of psilocybin is extrapolated to 6 g in humans. This is 300 times the typical therapeutic dose of 20 mg. It would be quite bizarre to consume 300 cups of coffee, doses of Panadol, pints of beer, or even daily multi-vitamins. The *Japanese Journal of Legal Medicine* and the *Proceedings of the Western Pharmacology Society* have published that fatal intoxication due to ingesting psilocybin-containing mushrooms is extremely rare (Gonmori & Yoshioka, 2002; McCawley et al., 1962). A review on the harm potential of psilocybin-containing mushrooms published in the scientific journal *Regulatory Toxicology and Pharmacology* found only two deaths due to direct overdosing internationally since 1960 (van Amsterdam et al., 2011). For comparison, the ABS reported that within Australia during the year 2016 only, there were 276 deaths from antidepressants and 663 deaths from anti-anxiety medication (ABS, 2018). The lethal toxicity of fresh psilocybin-containing mushrooms in humans is 17 kg (van Amsterdam et al., 2011). It would be highly unusual and very challenging to consume 17 kg of mushrooms in one sitting.

Table 3. A non-exhaustive list of completed psychedelic studies from 2009 till May 2020

#	Year complete	Psychedelic substance	Condition or illness	Reference
1	2020		PTSD	https://clinicaltrials.gov/ct2/show/NCT03537014
2	2020		PTSD	https://clinicaltrials.gov/ct2/show/NCT03485287
3	2020		GAD	https://clinicaltrials.gov/ct2/show/NCT02427568
4	2019		SAD in Autistic Adults	https://clinicaltrials.gov/ct2/show/NCT02008396
6	2019		PTSD	https://clinicaltrials.gov/ct2/show/NCT02876172
6	2019		Substance-Related Disorders	https://clinicaltrials.gov/ct2/show/NCT01148342
7	2019		Mood, Performance	https://clinicaltrials.gov/ct2/show/NCT02033707
8	2018		PTSD	https://clinicaltrials.gov/ct2/show/NCT01689740
9	2018		PTSD	https://clinicaltrials.gov/ct2/show/NCT01793610
10	2018		Effects on Emotional and Social Memories	https://clinicaltrials.gov/ct2/show/NCT03050541
11	2018		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT01270672
12	2018		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT01386177
13	2018		PTSD	https://clinicaltrials.gov/ct2/show/NCT01211405
14	2018		GAD	https://clinicaltrials.gov/ct2/show/NCT02954562
15	2018		Emotion Processing	https://clinicaltrials.gov/ct2/show/NCT03019822
16	2018		Social Cognition	https://clinicaltrials.gov/ct2/show/NCT01616407
17	2017		PTSD	https://clinicaltrials.gov/ct2/show/NCT00353938
18	2017	MDMA	PTSD	https://clinicaltrials.gov/ct2/show/NCT01958593
19	2017		PTSD	https://clinicaltrials.gov/ct2/show/NCT02102802
20	2017		PTSD	https://clinicaltrials.gov/ct2/show/NCT01458327
21	2016		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT01951508
22	2016		Emotional Effects	https://clinicaltrials.gov/ct2/show/NCT01465685
23	2016		Substance-Related Disorders	https://clinicaltrials.gov/ct2/show/NCT01771874
24	2015		PTSD	https://clinicaltrials.gov/ct2/show/NCT00090064
25	2014		Drug Addiction	https://clinicaltrials.gov/ct2/show/NCT01849419
26	2014		Amphetamine-Related Disorders	https://clinicaltrials.gov/ct2/show/NCT02232789
27	2013		MDMA Discontinuation Syndrome	https://clinicaltrials.gov/ct2/show/NCT01053403
28	2013		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT01136278
29	2013		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT00990067
30	2013		Mechanism of Action	https://clinicaltrials.gov/ct2/show/NCT00838305
31	2013		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT00886886
32	2011		Pharmacokinetics	https://clinicaltrials.gov/ct2/show/NCT01447472
33	2011		Hangover	https://clinicaltrials.gov/ct2/show/NCT01400204
34	2009		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT00895804
35	2020		Distress, Depression, Grief	https://clinicaltrials.gov/ct2/show/NCT02950467
36	2020		Healthy	https://clinicaltrials.gov/ct2/show/NCT02163707
37	2019		Persisting Effects	https://clinicaltrials.gov/ct2/show/NCT02971605
38	2019		Healthy	https://clinicaltrials.gov/ct2/show/NCT02145091
7	2019	Psilocybin	Mood, Performance	https://clinicaltrials.gov/ct2/show/NCT02033707
39	2018		Depression, GAD, Cancer	https://clinicaltrials.gov/ct2/show/NCT00465595
40	2016		Healthy	https://clinicaltrials.gov/ct2/show/NCT00802282
41	2014		Pharmacology, Therapeutic Uses	https://clinicaltrials.gov/ct2/show/NCT01988311
42	2013		GAD	https://clinicaltrials.gov/ct2/show/NCT00302744
43	2019		Treatment-Resistant Depression	https://doi.org/10.1017/S0033291718001356
44	2019	Ayahuasca	Major Depression Disorder (MDD)	https://doi.org/10.3389/fpsyg.2019.0123
45	2017		MDD	https://clinicaltrials.gov/ct2/show/NCT02914769
46	2020		Microdose	https://clinicaltrials.gov/ct2/show/NCT04421105
16	2018		Emotion Processing	https://clinicaltrials.gov/ct2/show/NCT03019822
47	2019		Healthy	https://clinicaltrials.gov/ct2/show/NCT03321136
8	2019		Mood, Performance	https://clinicaltrials.gov/ct2/show/NCT02033707
48	2016	LSD	Healthy	https://clinicaltrials.gov/ct2/show/NCT01878942
49	2016		Personal Meaning	https://clinicaltrials.gov/ct2/show/NCT02451072
50	2015		Healthy	https://clinicaltrials.gov/ct2/show/NCT02308969
51	2014		GAD	https://clinicaltrials.gov/ct2/show/NCT00920387
8	2019	Mescaline	Mood, Performance	https://clinicaltrials.gov/ct2/show/NCT02033707
52	2013	MDA	Healthy	https://clinicaltrials.gov/ct2/show/NCT00823407

7.3 Risk of self-medication

As previously discussed, there is a huge international surge of interest in MDMA and psilocybin use in therapy. According to the NDPS, TGA, and MCC, this media interest will be intrinsically linked to an increased risk of self-medication (NDPS, 2010). Considering the extremely low toxicity of psilocybin-containing mushroom and the ease of access to ecstasy pills, attempts at self-medication of psilocybin and MDMA in an uncontrolled setting is where dangers and risks can transpire. Just like with ibogaine, there is an urgent need to regulate the use of these medicines in medically controlled environments to help prevent the hazards of self-medication from occurring.

8. How MDMA and psilocybin work in the brain

Another statement from the RANZCP CM severely downplays the current knowledge on psychedelics:

"Much about the neuroscience of psychedelics remains unknown, although there are theories that they heighten emotional responses and encourage people to confront their disorder actively, which can prompt enduring shifts in mind-set".

The neuroscience of psilocybin and MDMA has been heavily researched. This topic is beyond the scope of this review and is a lengthy and complex topic. This paper will briefly point out some key studies behind the neuroscience of psilocybin and MDMA for the RANZCP to further investigate. For psilocybin, see the following references (Carhart-Harris et al., 2017; Maple et al., 2015; Moya & Powell, 2018; Nichols et al., 2017; Ray, 2010; Yu et al., 2008). There are brain-imaging fMRI data to explain the therapeutic actions of psilocybin through changes of brain network dynamics in Functional Connectivity and the Default Mode Network (Carhart-Harris et al., 2017). The neuropharmacology of MDMA is very well documented throughout the academic literature. The following references study the neuroscientific relationship between MDMA-assisted psychotherapy and treating PTSD (Amoroso & Workman, 2016; Bremner et al., 2005; Carhart-Harris et al., 2014; Doss et al., 2018; Feduccia & Mithoefer, 2018; Thal & Lommen, 2018). What remains unknown are the mechanisms and reasons conditioning the 'mystical experience' associated with positive therapeutic outcomes is created in the brain (Griffiths et al., 2008; Griffiths et al., 2011) – a topic that borders on the nature of human consciousness, which we are barely at the beginning of understanding.

9. The need for further research

The RANZCP note in its CM that:

"Further research is required to assess the efficacy, safety and effectiveness of psychedelic therapies to inform future potential use in psychiatric practices. Research into the clinical use of psychedelic substances should only occur under research trial conditions that include oversight by an institutional research ethics committee and careful monitoring and reporting of efficacy and safety outcomes."

Trials to date suggest remission rates for TRD and TR-PTSD are between 60-80% for both psilocybin and MDMA when used as an adjunct to therapy (Agin-Liebman et al., 2020; MAPS, 2020a). As previously mentioned, both therapies have been awarded 'breakthrough therapy' status by the FDA (Feduccia et al., 2019; Nichols, 2020), with the first MDMA Phase 3 trial successfully complete (MAPS, 2020a). Given the high incidence of depression and PTSD in Australia (Mills et al., 2011) and associated high levels of suicide (ABS, 2018; Qi et al., 2012), there needs to be substantiated reasons for insisting that these therapies should not be made available on a case-by-case basis for patients through experienced medical practitioners. The incomplete and outdated safety and efficacy data in the RANZCP CM does not support withholding these therapies. It is a truism to state that a particular medicine associated with a treatment for a particular mental illness would benefit from further research. However, a lack of understanding of mechanisms of action has not stopped other medicines from being used. There are many commonly prescribed pharmaceuticals with the unknown therapeutic mechanism of action, such as paracetamol (Toussaint et al., 2010), lithium (Hedya et al., 2020), general anaesthetic (Mashour et al., 2005; Pavel et al., 2020), and modafinil (Gerrard & Malcolm, 2007). For example, the exact way in which lithium helps stabilize mood is unknown (Jakobsson et al., 2017; Oruch et al., 2014; Risby et al., 1991; Treiser et al., 1981); however, its use is not questioned. Further, toxicity is a known long-term consequence of lithium, yet it continues to be prescribed (Hedya et al., 2020).

There is significant data on the safety, efficacy and effectiveness of psilocybin and MDMA-assisted therapies to support the use by medical specialists as part of therapy with case-specific regulatory approvals, such as in Canada, Switzerland, Israel, and the US. The RANZCP further says that, *"The treatments can be expensive, and the short timeframes of application (1-2 sessions) suggested by early research put limits on the potential profitability of psychedelic therapies; as a result, there are few pharmaceutical companies supporting research"*. For the reasons given in this paper, the above reference to 'early research' is misleading. In addition, the cost of treatment is relative. A lifetime of taking antidepressants can be far more costly for an individual than a short treatment that generates remission.

10. Discussion

The RANZCP suggest there are many unknown factors, short and long-term side-effects of using psychedelics in medically controlled environments as an aid in psychotherapy (RANZCP, 2020). They further state that there is only some evidence that psychedelics may have therapeutic potential. However, thousands of patients had received MDMA in psychotherapy from the 1960s until prohibition in 1986 (Passie, 2018). The first clinical study for MDMA in psychotherapy occurred in 1984 (Downing, 1986). The FDA began approving clinical trials for treating PTSD with MDMA in 2000 (Doblin, 2002). The first post-prohibition clinical trial was completed in 2001, and the first MDMA phase 3 trial was successfully completed in 2020 (MAPS, 2020a). There is over 30 years of recent data and over 20 years of pre-prohibition data to assess the efficacy and safety of MDMA. Psilocybin has received regulatory approval for therapeutic use in the state of Oregon, US (*Oregon Measure 109, Psilocybin Mushroom Services Program Initiative (2020)*, 2020) and is being administered medically to patients in Canada under compassionate use (Carpenter, 2020; Semley, 2020; Wood et al., 2019). Furthermore, reviews of all the studies indicate that both MDMA and psilocybin are safe, non-toxic, and non-addictive when used in a medically-controlled environment.

In a non-medical environment in Australia and the UK, controlled medicines buprenorphine, methadone, fentanyl, cannabis, ketamine, amphetamines, prescription medicines, anabolic steroids, benzodiazepines; and unscheduled drugs tobacco and alcohol cause significantly more harm to the user and society than either MDMA or psilocybin (Bonomo et al., 2019; Nutt et al., 2010). Regulating MDMA and psilocybin under strict medical guidelines and supervision will further mitigate associated risks with self-medication.

11. Conclusion

With the recent positive media coverage of the efficacy of MDMA and psilocybin when used as an adjunct to psychotherapy, there is an intrinsic risk of self-medication or underground therapy. This means that any medical discussion must also survey the ethical responsibilities and social duties associated with these substances. MDMA and psilocybin are easy to access either naturally (in the case of psilocybin-containing mushrooms, which grow in many parts of Australia) or through the Dark Web. This is a significant risk factor for use in an uncontrolled setting.

The RANZCP, which represents psychiatrists in Australia, is an influential organization with a vision of improving:

"...the mental health of communities through high-quality psychiatric care, education, leadership and advocacy", with values that include "collaboration, excellence, integrity, compassion and innovation."

The RANZCP should, therefore, as a matter of urgency, review and update its CM and its conclusions, keeping with the factual position in relation to the medical use of these substances.

There needs to be a clear regulatory avenue for suffering Australians who have exhausted conventional means of treatment in Australia to have controlled medical access to MDMA and psilocybin-assisted psychotherapies. A thoroughly researched and objective clinical memorandum is required from RANZCP, the institutional representative of psychiatry in Australia and New Zealand.

The authors suggest the RANZCP conduct future research to answer the following questions:

1. What is the precise research that the RANZCP believes needs to be undertaken to allow compassionate use of MDMA and psilocybin on a case-by-case basis, and why?
2. How does that RANZCP envisage that this research will be funded in a timely manner?
3. What is the timeframe anticipated by RANZCP before these therapies are made available to Australians suffering from key treatment-resistant mental illnesses?
4. Further, how can this time lag be justified?

This research was limited to psychedelic medicines in the scope of the RANZCP CM.

Conflicts of interest: All the authors are members of the organization Mind Medicine Australia (MMA). Victor Chiruta is Chair of the Independent Food and Therapeutic Authority (IFTA), www.ifta.org.au. Paulina Zemla is co-founder of IFTA. IFTA is an organizational member of the Public Health Association of Australia and is a TGA agent. Victor Chiruta was the main researcher and writer for the applications to the TGA to have MDMA and psilocybin rescheduled from S9 prohibited drugs to S8 controlled medicines.

Funding: The Article Processing Charge (APC) was funded by IFTA. There is no other funding to declare.

ORCID: Victor Chiruta: <https://orcid.org/0000-0002-3947-7741>

Acknowledgements: The authors would like to acknowledge Dr Gabrielle Dixon Ritchie for her support with editing the paper for disability support to Victor Chiruta, Peter Hunt AM (Chair of MMA) for his suggestions in this review, and Robert Renshaw for assisting as a disability scribe for Victor Chiruta.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers.

References

- [1] Abo, S. (2020). *Revolutionary drug trials could see ecstasy used as prescription medicine for those living with PTSD and mental illness*. Retrieved Dec 2020 from <https://9now.nine.com.au/60-minutes/revolutionary-mdma-trial-changing-lives-of-those-with-mental-illness-60-minutes/6e9f2a9d-e88c-49b5-9654-a2636fec7db9>
- [2] ABS. (2018). *3303.0 – Causes of Death, Australia, 2016*. Australian Government Retrieved from <https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3303.0Main+Features62016?OpenDocument>
- [3] ACA. (2018). *Psychedelic Assisted Treatments - Testing the Waters*. ACA. Retrieved Dec 2020 from <https://fusion.counseling.org/news/aca-blogs/aca-member-blogs/aca-member-blogs/2018/06/22/psychedelic-assisted-treatments---testing-the-waters>
- [4] *Access to microdoses of psilocybe mushrooms for therapeutic purposes*. (2020). Medicinal Mushroom Dispensary. Retrieved Dec 2020 from <https://mushroomdispensary.com>
- [5] Agin-Liebes, G. I., Malone, T., Yalch, M. M., Mennenga, S. E., Ponte, K. L., Guss, J., Bossis, A. P., Grigsby, J., Fischer, S., & Ross, S. (2020). Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *J Psychopharmacol*, *34*(2), 155-166. <https://doi.org/10.1177/0269881119897615>
- [6] Amoroso, T. (2015). The Psychopharmacology of +/-3,4 Methylendioxyamphetamine and its Role in the Treatment of Posttraumatic Stress Disorder. *J Psychoactive Drugs*, *47*(5), 337-344. <https://doi.org/10.1080/02791072.2015.1094156>
- [7] Amoroso, T., & Workman, M. (2016). Treating posttraumatic stress disorder with MDMA-assisted psychotherapy: A preliminary meta-analysis and comparison to prolonged exposure therapy. *J Psychopharmacol*, *30*(7), 595-600. <https://doi.org/10.1177/0269881116642542>
- [8] Armenian, P., Mamantov, T. M., Tsutaoka, B. T., Gerona, R. R., Silman, E. F., Wu, A. H., & Olson, K. R. (2013). Multiple MDMA (Ecstasy) overdoses at a rave event: a case series. *J Intensive Care Med*, *28*(4), 252-258. <https://doi.org/10.1177/0885066612445982>
- [9] *The Avante Ibogaine Treatment Centre*. (2020). The Avante Institute. Retrieved Dec 2020 from <https://avanteibogaine.com>
- [10] Baggott, M. J., Garrison, K. J., Coyle, J. R., Galloway, G. P., Barnes, A. J., Huestis, M. A., & Mendelson, J. E. (2019). Effects of the Psychedelic Amphetamine MDA (3,4-Methylendioxyamphetamine) in Healthy Volunteers. *J Psychoactive Drugs*, *51*(2), 108-117. <https://doi.org/10.1080/02791072.2019.1593560>
- [11] Bonomo, Y., Norman, A., Biondo, S., Bruno, R., Daglish, M., Dawe, S., Egerton-Warburton, D., Karro, J., Kim, C., Lenton, S., Lubman, D. I., Pastor, A., Rundle, J., Ryan, J., Gordon, P., Sharry, P., Nutt, D., & Castle, D. (2019). The Australian drug harms ranking study. *J Psychopharmacol*, *33*(7), 759-768. <https://doi.org/10.1177/0269881119841569>
- [12] *Boutique Hotel & Retreat Center*. (2020). Costa Rica Yoga Spa. Retrieved Dec 2020 from <https://www.costaricayogaspa.com>
- [13] Bowdle, T. A., Radant, A. D., Cowley, D. S., Kharasch, E. D., Strassman, R. J., & Roy-Byrne, P. P. (1998). Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. *Anesthesiology*, *88*(1), 82-88. <https://doi.org/10.1097/0000542-199801000-00015>
- [14] Bremner, J. D., Vermetten, E., Schmahl, C., Vaccarino, V., Vythilingam, M., Afzal, N., Grillon, C., & Charney, D. S. (2005). Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual abuse-related post-traumatic stress disorder. *Psychol Med*, *35*(6), 791-806. <https://doi.org/10.1017/s0033291704003290>
- [15] Brewerton, T. D., Lafrance, A., & Mithoefer, M. C. (2020). The potential use of N-methyl-3,4-methylendioxyamphetamine (MDMA) assisted psychotherapy in the treatment of eating disorders comorbid with PTSD. *Med Hypotheses*, 110367. <https://doi.org/10.1016/j.mehy.2020.110367>
- [16] Callaway, J. C., Raymon, L. P., Hearn, W. L., McKenna, D. J., Grob, C. S., Brito, G. S., & Mash, D. C. (1996). Quantitation of N,N-dimethyltryptamine and harmala alkaloids in human plasma after oral dosing with ayahuasca. *J Anal Toxicol*, *20*(6), 492-497. <https://doi.org/10.1093/jat/20.6.492>
- [17] Carbonaro, T. M., Bradstreet, M. P., Barrett, F. S., MacLean, K. A., Jesse, R., Johnson, M. W., & Griffiths, R. R. (2016). A survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *J Psychopharmacol*, *30*(12), 1268-1278. <https://doi.org/10.1177/0269881116662634>
- [18] 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 (Berl)*, *235*(2), 399-408. <https://doi.org/10.1007/s00213-017-4771-x>
- [19] 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. *Sci Rep*, *7*(1), 13187. <https://doi.org/10.1038/s41598-017-13282-7>
- [20] Carhart-Harris, R. L., Wall, M. B., Erritzoe, D., Kaelen, M., Ferguson, B., De Meer, I., Tanner, M., Bloomfield, M., Williams, T. M., Bolstridge, M., Stewart, L., Morgan, C. J., Newbould, R. D., Feilding, A., Curran, H. V., & Nutt, D. J. (2014). The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *Int J Neuropsychopharmacol*, *17*(4), 527-540. <https://doi.org/10.1017/S1461145713001405>

- [21] Carpenter, D. (2020). *Four Terminally Ill Canadians Gain Legal Right To Use Magic Mushrooms For End-Of-Life Distress*. Forbes. Retrieved Dec 2020 from <https://www.forbes.com/sites/davidcarpenter/2020/08/08/four-terminally-ill-canadians-gain-legal-right-to-use-magic-mushrooms-for-end-of-life-distress/?sh=7623533d2bdf>
- [22] Cartwright, C., Gibson, K., Read, J., Cowan, O., & Dehar, T. (2016). Long-term antidepressant use: patient perspectives of benefits and adverse effects. *Patient Prefer Adherence*, 19, 1401-1407. <https://doi.org/10.2147/PPA.S110632>
- [23] *Controlled Drugs*. (2019). Ministry of Health. Retrieved Dec 2020 from <https://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/controlled-drugs>
- [24] *Therapeutic Goods Act 1989*, (1989). <https://www.legislation.gov.au/Details/C2020C00267>
- [25] *Australia New Zealand Food Standards Code - Schedule 23 - Prohibited plants and fungi*, (2015).
- [26] *Therapeutic Goods (Permissible Ingredients) Determination (No. 4) 2020*, (2020). <https://www.legislation.gov.au/Details/F2020L00666>
- [27] *Poisons Standard February 2021*, (2021). <https://www.legislation.gov.au/Details/F2020L01716>
- [28] Daoud, E. (2020). *Mind Medicine Australia urges psychedelic drugs for mental health treatment during COVID-19*. 7NEWS. Retrieved Dec 2020 from <https://7news.com.au/lifestyle/health-wellbeing/mind-medicine-australia-urges-psychedelic-drugs-for-mental-health-treatment-during-covid-19-c-977749>
- [29] Doblin, R. (2002). A clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): partnering with the FDA. *J Psychoactive Drugs*, 34(2), 185-194. <https://doi.org/10.1080/02791072.2002.10399952>
- [30] Dos Santos, R. G., Bouso, J. C., Alcazar-Corcoles, M. A., & 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 Rev Clin Pharmacol*, 11(9), 889-902. <https://doi.org/10.1080/17512433.2018.1511424>
- [31] Doss, M. K., Weafer, J., Gallo, D. A., & de Wit, H. (2018). MDMA Impairs Both the Encoding and Retrieval of Emotional Recollections. *Neuropsychopharmacology*, 43(4), 791-800. <https://doi.org/10.1038/npp.2017.171>
- [32] Downing, J. (1986). The psychological and physiological effects of MDMA on normal volunteers. *J Psychoactive Drugs*, 18(4), 335-340. <https://doi.org/10.1080/02791072.1986.10472366>
- [33] Eckler, J. R., Chang-Fong, J., Rabin, R. A., Smith, C., Teitler, M., Glennon, R. A., & Winter, J. C. (2003). Behavioural characterization of 2-O-desmethyl and 5-O-desmethyl metabolites of the phenylethylamine hallucinogen DOM. *Pharmacol Biochem Behav*, 75(4), 845-852. [https://doi.org/10.1016/s0091-3057\(03\)00159-x](https://doi.org/10.1016/s0091-3057(03)00159-x)
- [34] Falandysz, J., Hanć, A., Barańkiewicz, D., Zhang, J., & Treu, R. (2020). Metallic and metalloid elements in various developmental stages of *Amanita muscaria* (L.) Lam. *Fungal Biology*, 124(3-4), 174-182. <https://doi.org/10.1016/j.funbio.2020.01.008>
- [35] Feduccia, A. A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2019). Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline. *Front Psychiatry*, 10, 650. <https://doi.org/10.3389/fpsy.2019.00650>
- [36] Feduccia, A. A., & Mithoefer, M. C. (2018). MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear underlying extinction mechanisms? *Prog Neuropsychopharmacol Biol Psychiatry*, 84(Pt A), 221-228. <https://doi.org/10.1016/j.pnpbp.2018.03.003>
- [37] Feeney, K. (2010). Revisiting Wasson's Soma: exploring the effects of preparation on the chemistry of *Amanita muscaria*. *J Psychoactive Drugs*, 42(4), 499-506. <https://doi.org/10.1080/02791072.2010.10400712>
- [38] Gable, R. S. (2004). Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction*, 99(6), 686-696. <https://doi.org/10.1111/j.1360-0443.2004.00744.x>
- [39] Gerrard, P., & Malcolm, R. (2007). Mechanisms of modafinil: A review of current research. *Neuropsychiatr Dis Treat*, 3(3), 349-364. <https://www.ncbi.nlm.nih.gov/pubmed/19300566>
- [40] Giacomelli, S., Palmery, M., Romanelli, L., Cheng, C. Y., & Silvestrini, B. (1998). Lysergic acid diethylamide (LSD) is a partial agonist of D2 dopaminergic receptors, and it potentiates dopamine-mediated prolactin secretion in lactotrophs in vitro. *Life Sci*, 63(3), 215-222. [https://doi.org/10.1016/s0024-3205\(98\)00262-8](https://doi.org/10.1016/s0024-3205(98)00262-8)
- [41] Gonmori, K., & Yoshioka, N. (2002). A fatal case of mushroom poisoning by hallucinogenic species. *Jpn J Legal Med*, 56(1), P-15.
- [42] Griffiths, R., Richards, W., Johnson, M., McCann, U., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol*, 22(6), 621-632. <https://doi.org/10.1177/0269881108094300>
- [43] Griffiths, R. R., Johnson, M. W., Richards, W. A., Richards, B. D., McCann, U., & Jesse, R. (2011). Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology (Berl)*, 218(4), 649-665. <https://doi.org/10.1007/s00213-011-2358-5>
- [44] Hedy, S. A., Avula, A., & Swoboda, H. D. (2020). Lithium Toxicity. In *StatPearls*. <https://www.ncbi.nlm.nih.gov/pubmed/29763168>
- [45] *Iboga Retreat Gabon, West Africa*. (2019). Bwiti Healing. Retrieved Jan 2021 from <http://bwitihealing.com/africa-retreat/>
- [46] *Ibogaine Treatment Center Mexico*. (2020). IbogaQuest. Retrieved Jan 2021 from <https://ibogaquest.com>
- [47] IbogaSoul. (2020). *IbogaSoul is proud to operate in the exquisite beauty of West Vancouver, British Columbia, Canada*. Ibogasoul Shamanic Healing LTD. <http://ibogasoul.com/contact/>
- [48] Jakobsson, E., Arguello-Miranda, O., Chiu, S. W., Fazal, Z., Kruczek, J., Nunez-Corrales, S., Pandit, S., & Pritchett, L. (2017). Towards a Unified Understanding of Lithium Action in Basic Biology and its Significance for Applied Biology. *J Membr Biol*, 250(6), 587-604. <https://doi.org/10.1007/s00232-017-9998-2>
- [49] Jalal, B. (2018). The neuropharmacology of sleep paralysis hallucinations: serotonin 2A activation and a novel therapeutic drug. *Psychopharmacology (Berl)*, 235(11), 3083-3091. <https://doi.org/10.1007/s00213-018-5042-1>
- [50] Jerome, L., Schuster, S., & Yazar-Klosinski, B. B. (2013). Can MDMA play a role in the treatment of substance abuse? *Curr Drug Abuse Rev*, 6(1), 54-62. <https://doi.org/10.2174/18744737112059990005>
- [51] Johansen, P. O., & Krebs, T. S. (2015). Psychedelics not linked to mental health problems or suicidal behaviour: a population study. *J Psychopharmacol*, 29(3), 270-279. <https://doi.org/10.1177/0269881114568039>

- [52] Jorm, A. F. (2014). Why hasn't the mental health of Australians improved? The need for a national prevention strategy. *Aust N Z J Psychiatry*, 48(9), 795-801. <https://doi.org/10.1177/0004867414546387>
- [53] Kaasik, H., Souza, R. C. Z., Zandonadi, F. S., Tofoli, L. F., & Sussulini, A. (2020). Chemical Composition of Traditional and Analog Ayahuasca. *J Psychoactive Drugs*, 1-11. <https://doi.org/10.1080/02791072.2020.1815911>
- [54] Kalant, H. (2001). The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *CMAJ*, 165(7), 917-928. <https://www.ncbi.nlm.nih.gov/pubmed/11599334>
- [55] Kavitha, C., & Thangamani, C. (2014). Amazing bean "Mucuna pruriens": A comprehensive review. *J Med Plants Res*, 8(2), 138-143. <https://doi.org/10.5897/JMPR2013.5036>
- [56] Kolp, E., Friedman, H. L., Krupitsky, E., Jansen, K., Sylvester, M., Young, M. S., & Kolp, A. (2014). Ketamine Psychedelic Psychotherapy: Focus on its Pharmacology, Phenomenology, and Clinical Applications. *Int J Transpers*, 33(2), Article 8. <https://doi.org/10.24972/ijts.2014.33.2.84>
- [57] Krupitsky, E. M., & Grinenko, A. Y. (1997). Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs*, 29(2), 165-183. <https://doi.org/10.1080/02791072.1997.10400185>
- [58] Lim, D. K. (2003). Ketamine associated psychedelic effects and dependence. *Singapore Med J*, 44(1), 31-34. <https://www.ncbi.nlm.nih.gov/pubmed/12762561>
- [59] Lim, T. (2014). *Acacia longifolia*. In *Edible Medicinal And Non-Medicinal Plants: Volume 7, Flowers* (Vol. 7, pp. 738-742). Springer Science.
- [60] Malcom, L., & Bedi, G. (2018). *MDMA—its potential therapeutic use podcast extra*. ABC. Retrieved Dec 2020 from <https://www.abc.net.au/radionational/programs/allinthemind/mdma-and-its-potential-therapeutic-use—a-podcast-extra/10200140>
- [61] Maple, A. M., Zhao, X., Elizalde, D. I., McBride, A. K., & Gallitano, A. L. (2015). Htr2a Expression Responds Rapidly to Environmental Stimuli in an Egr3-Dependent Manner. *ACS Chem Neurosci*, 6(7), 1137-1142. <https://doi.org/10.1021/acschemneuro.5b00031>
- [62] MAPS. (2013). *Investigator's Brochure*. https://maps.org/research-archive/mdma/MDMA_FINAL%20IB-edition-7_1Aug13.pdf
- [63] MAPS. (2016). *Investigator's Brochure*. https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/MDMA_IB_FINAL_30Mar2016_Linked.pdf
- [64] MAPS. (2017). *Investigator's Brochure*. https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/MDMA_IB_9thEd_FINAL_21MAY2017+linked+TOC+gray+table+shading.pdf
- [65] MAPS. (2018a). *Investigator's Brochure*. https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/MDMA_2018_MDMA_Investigators_Brochure_Edition10_10JUL2018.pdf
- [66] MAPS. (2018b). *Protocol MAPP1 IND #063384*. https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/mdma/mapp1/FINAL+MAPP1+Public+Protocol+A4V1_+22MAY2020.pdf
- [67] MAPS. (2019a). *Investigator's Brochure*. <https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/mdma/MDMA-Investigator-Brochure-IB-11thEdition-MAPS-2019-07-10.pdf>
- [68] MAPS. (2019b). *Israel Approves Compassionate Use of MDMA-Assisted Psychotherapy for PTSD*. MAPS. Retrieved Dec 2020 from <https://maps.org/research/mdma/ptsd/phase3/timeline/7631-israel-approves-compassionate-use-of-mdma-assisted-psychotherapy-for-ptsd>
- [69] MAPS. (2020a). *Development Safety Update Report 3,4-methylenedioxymethamphetamine (MDMA)*. <https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/mdma/Development-Safety-Update-Report-on-MDMA-DSUR-11DEC2020.pdf>
- [70] MAPS. (2020b). *Investigator's Brochure*. <https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/MDMA+IB+12th+Edition+Final+17AUG2020.pdf>
- [71] MAPS. (2021). *Investigator's Brochure*. <https://maps.org/wp-content/uploads/2015/10/MDMAIB13thEditionFinal22MAR2021.pdf>
- [72] MAPS. (n.d.). *Treating PTSD with MDMA- Assisted Psychotherapy*. MAPS. Retrieved Dec 2020 from <https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/PTSDandMDMA.png>
- [73] Martinotti, G., Santacrose, R., Pettorusso, M., Montemitto, C., Spano, M. C., Lorusso, M., di Giannantonio, M., & Lerner, A. G. (2018). Hallucinogen Persisting Perception Disorder: Etiology, Clinical Features, and Therapeutic Perspectives. *Brain Sci*, 8(3). <https://doi.org/10.3390/brainsci8030047>
- [74] Mashour, G. A., Forman, S. A., & Campagna, J. A. (2005). Mechanisms of general anesthesia: from molecules to mind. *Best Pract Res Clin Anaesthesiol*, 19(3), 349-364. <https://doi.org/10.1016/j.bpa.2005.01.004>
- [75] McCauley, D. (2020). *Regulator weighs push to legalize MDMA for mental health treatment*. The Sydney Morning Herald. Retrieved Dec 2020 from <<https://www.smh.com.au/politics/federal/regulator-weighs-push-to-legalise-mdma-for-mental-health-treatment-20200901-p55rch.html>
- [76] McCawley, E. L., Brummett, R. E., & Dana, G. W. (1962). Convulsions from psilocybe mushroom poisoning. *Proc West Pharmacol Soc*, 5, 27-33. <https://www.ncbi.nlm.nih.gov/pubmed/13932070>
- [77] Medsafe. (2020). *Classification Database*. New Zealand Medicines and Medical Devices Safety Authority. Retrieved Dec 2020 from <https://www.medsafe.govt.nz/profs/class/classintro.asp>
- [78] Mills, K. L., McFarlane, A. C., Slade, T., Creamer, M., Silove, D., Teesson, M., & Bryant, R. (2011). Assessing the prevalence of trauma exposure in epidemiological surveys. *Aust N Z J Psychiatry*, 45(5), 407-415. <https://doi.org/10.3109/00048674.2010.543654>
- [79] Mina, C. N., Farzaei, M. H., & Gholamreza, A. (2015). Medicinal properties of Peganum harmala L. in traditional Iranian medicine and modern phytotherapy: a review. *J Tradit Chin Med*, 35(1), 104-109. [https://doi.org/10.1016/s0254-6272\(15\)30016-9](https://doi.org/10.1016/s0254-6272(15)30016-9)
- [80] MMA. (2020a). *Application to Reschedule N,α-DIMETHYL-3,4(METHYLENEDIOXY)PHENYLETHYLAME (MDMA) from Schedule 9 to Schedule 8 of the Poisons Standard*. MMA. Retrieved Dec 2020 from <https://mindmedicineaustralia.org/wp-content/uploads/2020/08/Mind-Medicine-Australia-MDMA-Rescheduling-S9-to-S8-15-July-2020-FINAL.pdf>
- [81] MMA. (2020b). *TGA Rescheduling Submissions*. MMA. Retrieved Jan 2021 from <https://mindmedicineaustralia.org.au/tga/>
- [82] Moloudizargari, M., Mikaili, P., Aghajanshakeri, S., Asghari, M. H., & Shayegh, J. (2013). Pharmacological and therapeutic effects of Peganum harmala and its main alkaloids. *Pharmacogn Rev*, 7(14), 199-212. <https://doi.org/10.4103/0973-7847.120524>

- [83] Moreno, J. L., Holloway, T., Albizu, L., Sealfon, S. C., & Gonzalez-Maeso, J. (2011). Metabotropic glutamate mGlu2 receptor is necessary for the pharmacological and behavioral effects induced by hallucinogenic 5-HT_{2A} receptor agonists. *Neurosci Lett*, 493(3), 76-79. <https://doi.org/10.1016/j.neulet.2011.01.046>
- [84] Moya, E. A., & Powell, F. L. (2018). Serotonin and Adenosine G-protein Coupled Receptor Signaling for Ventilatory Acclimatization to Sustained Hypoxia. *Front Physiol*, 9, 860. <https://doi.org/10.3389/fphys.2018.00860>
- [85] Murrie, B., Lappin, J., Large, M., & Sara, G. (2020). The transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. *Schizophr Bull*, 46(3), 505-516. <https://doi.org/10.1093/schbul/sbz102>
- [86] NDPSC. (2010). *Record of Reasons 58th Meeting 16-17 February 2010*. TGA. Retrieved Dec 2020 from <https://www.tga.gov.au/sites/default/files/ndpsc-record-58.pdf>
- [87] Nichols, D. E. (2020). Psilocybin: from ancient magic to modern medicine. *J Antibiot (Tokyo)*, 73(10), 679-686. <https://doi.org/10.1038/s41429-020-0311-8>
- [88] Nichols, D. E., Johnson, M. W., & Nichols, C. D. (2017). Psychedelics as Medicines: An Emerging New Paradigm. *Clin Pharmacol Ther*, 101(2), 209-219. <https://doi.org/10.1002/cpt.557>
- [89] Nutt, D. (2019). Psychedelic drugs-a new era in psychiatry? *Dialogues Clin Neurosci*, 21(2), 139-147. <https://doi.org/10.31887/DCNS.2019.21.2/dnutt>
- [90] Nutt, D. J., King, L. A., Phillips, L. D., & Independent Scientific Committee on, D. (2010). Drug harms in the UK: a multicriteria decision analysis. *Lancet*, 376(9752), 1558-1565. [https://doi.org/10.1016/S0140-6736\(10\)61462-6](https://doi.org/10.1016/S0140-6736(10)61462-6)
- [91] *Misuse of Drugs Act 1975*. (1975). <https://www.legislation.govt.nz/act/public/1975/0116/latest/whole.html#DLM436586>
- [92] *Misuse of Drugs (Changes to Controlled Drugs) Orders 2005*, (2005). <https://www.legislation.govt.nz/regulation/public/2005/0175/latest/DLM335121.html>
- [93] *Oregon Measure 109, Psilocybin Mushroom Services Program Initiative (2020)*. (2020). BallotPedia. Retrieved Dec 2020 from [https://ballotpedia.org/Oregon_Measure_109_Psilocybin_Mushroom_Services_Program_Initiative_\(2020\)](https://ballotpedia.org/Oregon_Measure_109_Psilocybin_Mushroom_Services_Program_Initiative_(2020))
- [94] Oruch, R., Elderbi, M. A., Khattab, H. A., Pryme, I. F., & Lund, A. (2014). Lithium: a review of pharmacology, clinical uses, and toxicity. *Eur J Pharmacol*, 740, 464-473. <https://doi.org/10.1016/j.ejphar.2014.06.042>
- [95] Østrem, L. (1987). Studies on genetic variation in reed canarygrass, *Phalaris arundinacea* L. I. Alkaloid type and concentration. *Hereditas*, 707, 235-248. <https://doi.org/10.1111/j.1601-5223.1987.tb00290.x>
- [96] Ott, J. (1996). Entheogens II: on entheology and entheobotany. *J Psychoactive Drugs*, 28(2), 205-209. <https://doi.org/10.1080/02791072.1996.10524393>
- [97] Papaseit, E., Farre, M., Perez-Mana, C., Torrens, M., Ventura, M., Pujadas, M., de la Torre, R., & Gonzalez, D. (2018). Acute Pharmacological Effects of 2C-B in Humans: An Observational Study. *Front Pharmacol*, 9, 206. <https://doi.org/10.3389/fphar.2018.00206>
- [98] Passie, T. (2018). The early use of MDMA ('Ecstasy') in psychotherapy (1977–1985). *Drug Science, Law and Policy*, 4, 1-19. <https://doi.org/10.1177/2050324518767442>
- [99] Passie, T., Seifert, J., Schneider, U., & Emrich, H. M. (2002). The pharmacology of psilocybin. *Addict Biol*, 7(4), 357-364. <https://doi.org/10.1080/1355621021000005937>
- [100] Pavel, M. A., Petersen, E. N., Wang, H., Lerner, R. A., & Hansen, S. B. (2020). Studies on the mechanism of general anesthesia. *Proc Natl Acad Sci U S A*, 117(24), 13757-13766. <https://doi.org/10.1073/pnas.2004259117>
- [101] *Psychedelic therapies that bring you to life*. (2020). Field Trip Health Inc. Retrieved Dec 2020 from <https://www.fieldtriphealth.com>
- [102] Qi, X., Hu, W., Page, A., & Tong, S. (2012). Spatial clusters of suicide in Australia. *BMC Psychiatry*, 12(86). <https://doi.org/10.1186/1471-244X-12-86>
- [103] RANZCP. (2020). *Clinical Memorandum Therapeutic use of psychedelic substances, May 2020*. RANZCP. Retrieved Dec 2020 from https://www.ranzcp.org/files/resources/college_statements/clinical_memoranda/cm-therapeutic-use-of-psychedelics.aspx
- [104] Ray, T. S. (2010). Psychedelics and the human receptorome. *PLoS One*, 5(2), e9019. <https://doi.org/10.1371/journal.pone.0009019>
- [105] Risby, E. D., Hsiao, J. K., Manji, H. K., Bitran, J., Moses, F., Zhou, D. F., & Potter, W. Z. (1991). The mechanisms of action of lithium. II. Effects on adenylate cyclase activity and beta-adrenergic receptor binding in normal subjects. *Arch Gen Psychiatry*, 48(6), 513-524. <https://doi.org/10.1001/archpsyc.1991.01810300025004>
- [106] Rocha, J. M., & Rossi, G. N. (2019). *Meet the Person Serving Ayahuasca to Inmates in Brazil: An Interview with Edilsom Fernandes*. Khapi. Retrieved Dec 2020 from <https://kahpi.net/ayahuasca-prisoners-brazil-edilsom-fernades/>
- [107] Romero, R. (2015). *In Brazil, Some Inmates Get Therapy With Hallucinogenic Tea*. The New York Times. <https://www.nytimes.com/2015/03/29/world/americas/a-hallucinogenic-tea-time-for-some-brazilian-prisoners.html>
- [108] Roxburgh, A., & Lappin, J. (2020). MDMA-related deaths in Australia 2000 to 2018. *Int J Drug Policy*, 76, 102630. <https://doi.org/10.1016/j.drugpo.2019.102630>
- [109] *Sacred Soul Therapy • Squamish, Vancouver, BC, Canada*. (2021). Sacred Soul Therapy. Retrieved Jan 2021 from <http://sacredsoultherapy.ca>
- [110] Schmidt, C. J. (1987). Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *J Pharmacol Exp Ther*, 240(1), 1-7. <https://www.ncbi.nlm.nih.gov/pubmed/2433425>
- [111] Seeman, P., Guan, H. C., & Hirbec, H. (2009). Dopamine D₂High receptors stimulated by phencyclidines, lysergic acid diethylamide, salvinorin A, and modafinil. *Synapse*, 63(8), 698-704. <https://doi.org/10.1002/syn.20647>
- [112] Semley, J. (2020). *Canada Is Allowing People With Depression to Do Psychedelic Mushrooms*. Vice. Retrieved Dec 2020 from <https://www.vice.com/en/article/4adw4w/canada-is-allowing-people-with-depression-to-do-psychedelic-mushrooms>
- [113] Sessa, B., Higbed, L., & Nutt, D. (2019). A Review of 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy. *Front Psychiatry*, 10, 138. <https://doi.org/10.3389/fpsy.2019.00138>
- [114] *Specializing in opiate addiction detox*. (2020). Inner Realms Center. Retrieved Dec 2020 from <https://www.innerrealmscenter.com>
- [115] Steele, T. D., McCann, U. D., & Ricaurte, G. A. (1994). 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"): pharmacology and toxicology in animals and humans. *Addiction*, 89(5), 539-551. <https://doi.org/10.1111/j.1360-0443.1994.tb03330.x>

- [116] Strassman, R. J. (1984). Adverse reactions to psychedelic drugs. A review of the literature. *J Nerv Ment Dis*, 172(10), 577-595. <https://doi.org/10.1097/00005053-198410000-00001>
- [117] Taylor, S. (2020). Using MDMA to cure PTSD: How a revolutionary ecstasy trial saved the life of a former police officer traumatized by the Port Arthur massacre. 60 minutes. Retrieved Dec 2020 from <https://9now.nine.com.au/60-minutes/nick-watchorn-says-mdma-saved-his-life-after-post-traumatic-stress/de8472fb-7f95-45c5-9669-d9786eec5133>
- [118] TGA. (2020). ARTG Search. TGA. Retrieved Dec 2020 from http://tga-search.clients.funnelback.com/s/search.html?collection=tga-artg&profile=record&meta_i=176056
- [119] Thal, S. B., & Lommen, M. J. J. (2018). Current Perspective on MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder. *J Contemp Psychother*, 48(2), 99-108. <https://doi.org/10.1007/s10879-017-9379-2>
- [120] Toussaint, K., Yang, X. C., Zielinski, M. A., Reigle, K. L., Sacavage, S. D., Nagar, S., & Raffa, R. B. (2010). What do we (not) know about how paracetamol (acetaminophen) works? *J Clin Pharm Ther*, 35(6), 617-638. <https://doi.org/10.1111/j.1365-2710.2009.01143.x>
- [121] Trachsel, D. (2012). Fluorine in psychedelic phenethylamines. *Drug Test Anal*, 4(7-8), 577-590. <https://doi.org/10.1002/dta.413>
- [122] Treiser, S. L., Cascio, C. S., O'Donohue, T. L., Thoa, N. B., Jacobowitz, D. M., & Kellar, K. J. (1981). Lithium increases serotonin release and decreases serotonin receptors in the hippocampus. *Science*, 213(4515), 1529-1531. <https://doi.org/10.1126/science.6269180>
- [123] Trutmann, P. (2012). The Forgotten Mushrooms of Ancient Peru. In *Fungi and Mountains Publication Series* (pp. 1-33). Global Mountain Action.
- [124] Underwood, M. S. (2020). *At Magalies Wellness Centre, we facilitate journeys of transformation*. Magalies Wellness Centre. Retrieved Jan 2020 from <https://www.magalieswellnesscentre.com>
- [125] van Amsterdam, J., Opperhuizen, A., & van den Brink, W. (2011). Harm potential of magic mushroom use: a review. *Regul Toxicol Pharmacol*, 59(3), 423-429. <https://doi.org/10.1016/j.yrtph.2011.01.006>
- [126] *We are the World's Foremost Experts in Medically-based Ibogaine Treatment*. (2020). Clear Sky Recovery. Retrieved Jan 2021 from <https://clearskyibogaine.com>
- [127] Wong, S. K. (2002). Analysis of Drug Overdose in Teenagers. *Hong Kong Journal of Emergency Medicine*, 9, 144-149. <https://doi.org/10.1177/102490790200900305>
- [128] Wood, E., Christie, D., Maté, G., Kryskow, P., Walsh, Z., Browning, K., & Marr, J. (2019). *Email correspondence to the Honourable Canadian Health Minister*. Numinus Wellness Clinical Advisory Board. Retrieved Dec 2020 from <https://numinus.ca/dist/assets/docs/Health-Canada-Briefing-Note.pdf>
- [129] Woods, D., & Clark, K. (1971). Genetic Control And Seasonal Variation Of Some Alkaloids In Reed Canarygrass'. *Can J Plant Sci*, 51, 323-329. <https://doi.org/10.4141/cjps71-062>
- [130] Yu, B., Becnel, J., Zerfaoui, M., Rohatgi, R., Boulares, A. H., & Nichols, C. D. (2008). Serotonin 5-hydroxytryptamine(2A) receptor activation suppresses tumour necrosis factor-alpha-induced inflammation with extraordinary potency. *J Pharmacol Exp Ther*, 327(2), 316-323. <https://doi.org/10.1124/jpet.108.143461>