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Critique of the Royal Australian and New Zealand College of Psychiatrists psychedelic therapy clinical memorandum, dated May 2020

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Objective: The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has positioned itself against medically controlled patient access (at this current time) to 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin-assisted therapies in its Therapeutic Use of Psychedelic Substances Clinical Memorandum, May 2020. The main reason given by the RANZCP for its stance is safety concerns. This critique will argue that the RANZCP's position is based on outdated, irrelevant, misinterpreted, and misinformed evidence.

Methods: Every reference in the clinical memorandum (CM) was checked against the original publications used by RANZCP to justify its position. In addition, the search engines Google Scholar, PubMed, ScienceDirect, the Multidisciplinary Association for Psychedelic Therapies (MAPS) website, the Therapeutic Goods Administration (TGA) website, relevant Australian and New Zealand legislation were searched for pertinent and up-to-date-information.

Results: There is no scientific or medical evidence from the last 70 years to suggest that either psilocybin or MDMA when administered as an adjutant 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: With the recent positive media coverage of 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 purvey 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) and through the Dark Web. The RANZCP, which represents psychiatrists in Australia, is an influential organisation 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.

Keywords: psychedelic medicine, MDMA, psilocybin, TGA, psychedelic therapy, psychotherapy, RANZCP

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1. Introduction

In Australia, there are currently public submissions from the charitable organisation 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[1]. This rescheduling would allow for controlled patient access, restricted to medically controlled environments, for Australians suffering from treatment-resistant depression and treatment-resistant Post-Traumatic Stress Disorder (PTSD). These therapies are classified as breakthrough designated therapies by the US Food and Drug Administration (FDA). MDMA is a chemical sometimes present in ecstasy and psilocybin (in its natural form) is a compound found in a number of species of psychedelic mushrooms.

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 access to patients outside of research trials. The CM summary states[2],

> *"Research into medicines containing psychedelic substances should only occur under research trial conditions that include oversight by an institutional research ethics committee…"*

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 review will scientifically analyse and academically evaluate the evidence provided in the CM.

2. Methods

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*, *Therapeutic Goods Act 1989*, and *Misuse of Drugs Act 1975*.

3. Correction on psychedelics and their regulation

In the CM, there is a statement that MDMA is not a psychedelic[2],

> *"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."*

Further, the CM describes the current regulatory frameworks for psychedelics[2],

> *"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."*

There is confusion in the CM about what a psychedelic actually is. There are also contradictory statements about the regulatory frameworks for the medical use of psychedelic substances in Australia and New Zealand.

The RANZCP state that the CM is educational material written for psychiatrists. Using the word 'illicit' is unscientific and uninformative for psychiatrists. This is an inappropriate caveat given that a number of substances are legal when used in medically-controlled environments with proper approvals, but illegal when used recreationally. Examples include morphine, ketamine, and fentanyl. In Australia, 'illicit' drugs from a medical perspective, would fall under schedule 10 (S10) of the *Poisons Standard February 2021*[3], which lists drugs of such danger to public health as to warrant full prohibition on sale, supply and use. As this review will illuminate, the phrase 'psychedelic substances' covers several discrete substances which are subject to different controls in Australia and New Zealand. Ranging from research only, controlled prescription, uncontrolled prescription or as unregulated substances. The only exception is the psychedelic plant *Acorus calamus*, which is prohibited in Australia for human therapeutic use under S10 of the *Poisons Standard February 2021*.

3.1. MDMA

Starting with the RANZCP's statement on MDMA. MDMA is both pharmacologically and structurally a psychedelic. In the scientific literature, MDMA's effects on the central nervous system (CNS) are described as psychedelic[4, 5]. MDMA has highly complex pharmacodynamics, although a target is the serotonin subtype-2A receptor (5-HT_{2A})[6]. 5-HT_{2A} is the classic serotonergic psychedelic receptor[7, 8]. Another target of MDMA is the dopamine type-2 receptor (D_2)[6]. D_2 is one of the main targets of the classic psychedelic lysergic acid diethylamide (LSD)[9, 10] and the very potent natural psychedelic salvinorin A[9]. MDMA is further described in the scientific literature as a psychedelic phenylethylamine substituted amphetamine[11, 12]. In the literature, many phenylethylamines with a substituted amphetamine are classified as psychedelics, eg. 3,4-methylenedioxyamphetamine (MDA)[13], 2,5-dimethoxy-4-methylamphetamine (DOM)[14], and 2,5-dimethoxy-4-bromophenylamine (2C-B)[15].

MDMA has been classified as a B1 controlled drug in New Zealand by Medsafe since 2005[16]. B1 is the category of controlled medicines, which includes substances such as morphine, methadone, medicinal cannabis, and amphetamine[17]. This means that with the approval of the regulator, MDMA is available for prescription in New Zealand by doctors[18]. In Australia, MDMA is federally classified as a S9 substance[3]. This means that MDMA can be legally made available for use in research and doctors can only access this medicine for patients with an appropriate approval under the TGA's Special Access Scheme-B (SAS-B) or its Authorised Prescriber Scheme[19]. Even though MDMA is federally scheduled as a prohibited substance, several patients with otherwise treatment-resistant conditions, have been approved to receive MDMA therapeutically under SAS-B[20]. The complication in Australia comes at the State level. Victoria provides for access through a permit system whilst NSW prohibits the medical use of MDMA (even with TGA approval) through provisions that were designed to prohibit the recreational use of this substance.

3.2. Ketamine

The next medicine to evaluate is ketamine. The RANZCP note in its *Psychedelic Therapy* CM, that ketamine has its own RANZCP clinical memorandum[2]. Ketamine is described in multiple scientific literature as a psychedelic[21-24]. Between the years 1985 and 1995, ketamine was studied successfully in over 1,000 participants for its use in psychedelic-assisted psychotherapy[21]. Ketamine has recently gained application once again for use in psychedelic-assisted psychotherapy[22]. The TGA has approved the psychedelic ketamine (ingredient ID: 70736) and its enantiomer esketamine (ingredient ID: 114417) for use in medicine in Australia[25]. There are currently 13 approved medicines listed on the Australian Register of Therapeutic Goods (ARTG) containing ketamine[26].

3.3. 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[27-30]. The *Amanita spp.* are federally not scheduled in Australia[3] nor New Zealand[17]. However, *Amanita spp.* are prohibited for use in food in both countries[31]. The primary psychedelic compounds in the mushroom are ibotenic acid and muscimol[31]. Ibotenic acid is a prodrug for muscimol. Ibotenic acid is not scheduled in Australia[3] nor New Zealand[17]. In Australia, ibotenic acid (ingredient ID: 105657) has been approved for use in medicine by the TGA[25]. Muscimol is classified as a S9 substance in Australia[3], but unscheduled in New Zealand[17].

3.4. Harmala (Ayahuasca) alkaloids

Harmala alkaloids have become renowned for their application in the South American Ayahuasca tea[32]. 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 containing 0.1% or less of harmala alkaloids or in divided preparations containing 2mg or less of harmala alkaloids per recommended daily dose[3]. A protocol for the therapeutic use of harmala alkaloids is prescribed by the TGA. Further to this, the psychedelic plant *Peganum harmala* (ingredient ID: 83330) has been approved by the TGA for use in medicine[25]. *Peganum harmala* is used as a substitute for *Banisteriopsis caapi* in the Ayahuasca tea[33]. *Peganum harmala* has a rich history of entheogenic and spiritual use[34, 35].

3.5. DMT

In regards to DMT, DMT is federally a S9 substance in Australia[3] and a class A controlled drug in New Zealand[17]. However, the TGA have approved a handful of DMT-containing plants for use in medicine.

The ARTG lists one medicine containing *Acacia longifolia* (ARTG ID: 176056)[26]. The medicine is listed for wellbeing and contains equivalent of 500mg of *Acacia longifolia* per mL. According to Lim 2014, there would be 1-1.5mg of DMT per mL[36].

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

Plant	ID[25]	Psychedelic	Amount
Acacia longifolia	86827	DMT	0.2-0.3%[36]
Phalaris arundinacea	87004	DMT NMT 5-MeO-DMT 5-MeO-NMT β-Carbolines	0.2-0.7%[37, 38]
Mucuna pruriens	83253	DMT Bufotenine	Unspecified[39]

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

3.6. Ibogaine

In Australia, the powerful psychedelic ibogaine and its metabolite noribogaine are schedule 4 (S4; prescription only) medicines in Australia[3] and in New Zealand are classified for prescription without restrictions or controls[40]. The rescheduling of ibogaine in Australia (from S9 to S4) and New Zealand occurred in 2010[41]. 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:

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. Opinion that although ibogaine's appeal as a recreational drug was low, there were dangers in *ad hoc* use as a self medication for drug addiction following potential media interest.

4. Reason for rescheduling MDMA and psilocybin

The RANZCP's position on the use of psychedelics in therapy is in direct contradiction with the reasons the NDPSC, TGA, and MCC had for scheduling ibogaine. If the above committee points are taken into consideration for the current psychedelics in MMA's submissions (for MDMA and psilocybin) the proposed rescheduling is likely to be approved.

5. Psychedelic patterns of use in medically-controlled environments

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. MDMA and psilocybin have gained much attention as potential 'cures' for these disorders on mainstream Australian media (ABC[42], 7NEWS[43], The Sydney Morning Herald[44], and 60 minutes[45, 46]), particularly in the last two years. The FDA have granted both MDMA and psilocybin-assisted therapies 'breakthrough therapy' status in the US[47, 48], the FDA have opened an 'expanded access scheme' for treating PTSD with MDMA[49], the Israeli Ministry of Health has embraced the treatment of PTSD with MDMA under 'compassionate use'[50], and compassionate MDMA therapy has been conducted in Switzerland[51]. The state of Oregon in the US has legalised psilocybin therapy[52] whilst Canada has approved for patients to use psilocybin-assisted psychotherapy for depression and end-of-life anxiety[53, 54].

The Honourable Canadian Health Minister has granted patients suffering with anxiety associated with terminal illness lawful access to psilocybin therapeutically under section 56(1) of the *Controlled Drugs and Substances Act*[55]. Psychedelic-assisted psychotherapy clinics have opened up in Toronto[56], New York City, Los Angeles, Chicago, with a psilocybin microdose dispensary for therapeutic use opened in Canada[57]. 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.

According to the NDPSC, TGA, and MCC, given the increasing public awareness of uses around the world of the psychedelic substance ibogaine, there is increased risk of self-medication if there is not an accessible route through the medical system[41].

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[2],

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

The above statement is misleading because, whilst there is 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 jurisdictions. In the case of ibogaine, it is available in Australia and New Zealand through prescription, also through clinics in Canada[58-60], Mexico[61, 62], Gabon[63], South Africa[64], Costa Rica[65] and the Bahamas[66]. Ayahuasca is also being medically administered as part of therapy for the rehabilitation of violent and sexual offenders in Brazilian jails[67, 68].

6. Safety profile of medicinal MDMA and psilocybin

6.1. Medicinal MDMA

Dangers of self-medication is a critical part of the discourse on uncontrolled unsupervised use verses controlled and medically-supervised treatments. With MDMA use, morbidity and mortality has only occurred in uncontrolled non-clinical settings[51]. All serious adverse effects in a clinical setting have been rare and non-life threatening[69].

The risks of self-medication (because of barriers for use in the medical system) was one of the key arguments behind the rescheduling of ibogaine in Australia and New Zealand. RANZCP state in its CM in relation to MDMA that[2],

> *"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."*

The above statement is in reference to what appears to be a very dated MAPS MDMA poster[70]. The CM states in its referencing that the poster was published in 2019 (reference [17])[2]. 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'*[70]. On page 54 of a 2013 Investigator's Brochure publication, MAPS state, *'as of November 2012, 811 participants have received MDMA in trials'*[71]. This coincides with the poster publication of the number of MDMA trial participants. Although the poster does not show on its face when it was published, the American Counselling Association (ACA) make reference to an archived version of the poster in 2018[72]. It is logical to assume the release date of the poster is older than the archived version of the poster that the ACA cite.

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 poster does not cite the original source. The RANZCP clearly did not fact check the poster against the original scientific data and is incorrectly representing that this data is recent. Relevant scientific publication should be cited when discussing the regulation and medical impact of drugs and medicines. The RANZCP is of the opinion 760 individuals have participated in MDMA studies. However MAPS, which is sponsoring the current Phase 3 trials has reported much larger numbers.

MAPS report since 2001, 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 adverse event reported in the last 20 years of trials, the significance falls from 0.13% to less than 0.03%.

Table 2. MAPS reported trial participants who have received MDMA.

Year	# of participants	Source
Pre-1987	> 500,000	Investigator's Brochure 2020, p. 56[73]
2000-2012	811	Investigator's Brochure 2013, p. 54[71]
as of 2015	1,180	Investigator's Brochure 2016, p. 92[74]
as of 2016	1,280	Investigator's Brochure 2017, p. 133[75]
as of 2018	> 1,500	Investigator's Brochure 2018, p. 127[76]
as of 2019	(MAPS) 1,837	Investigator's Brochure 2019, p. 63[69]
as of 2020	(non-MAPS) 1,431	Investigator's Brochure 2020, p. 14[73]
in 2020	79	Safety Update Report 2020, p. 29[77]

Several sources have published that thousands of participants undertook MDMA-assisted psychotherapy until prohibition in 1987[69, 71, 73-76, 78], with MAPS publishing there were an estimated 500,000 participants in these early psychotherapy sessions[73]. 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[78]. It would appear that the RANZCP are 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[2],

"Since 2006, there have been several pilot trials and randomised controlled trials using psychedelics in various non-psychotic psychiatric disorders."

Since 2009, 34 completed trials for MDMA alone have been published on www.clinicaltrials.gov, with over 50 completed psychedelic-medicine trials in total. MAPS report there are 76 recent MDMA trials completed[73]. The trials are reported in Table 3. As there are so many 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).

The RANZCP position of 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.

As previously discussed, MDMA trials have over 3,000 recent participants and approximately 500,000 pre-prohibition participants, with over 40 years worth of data. MDMA was first synthesised in 1912 by Merck[79] 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[80]. In assessing the safety of MDMA, important distinctions need to be made between medicinal MDMA and the street-drug ecstasy[20]:

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, 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 10-20mg/kg[81]. The largest dose used in clinical studies is 1-2mg/kg[82]. 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[83].

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[84]. However, only 14 deaths between 2000 and 2018 occurred solely due to MDMA toxicity (ie. multiple drugs weren't detected).

In its CM under the heading *Risks and side effects* the RANZCP make the following observation[2],

"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 have omitted the following information:

i. Morbidity and mortality of MDMA use has only occurred in uncontrolled non-clinical settings[51];
ii. All serious adverse effects of MDMA in a clinical setting have been rare and non-life threatening[69];
iii. Early psychotherapeutic use of MDMA was without complication[78];
iv. MDMA administered therapeutically in a controlled environment does not produce dependence[85];
v. Therapeutic treatment with MDMA has not been shown to increase illicit drug use[51].

6.2. Psilocybin

Psilocybin is of concurrent importance with MDMA in the ethos of psychedelic-medicines as a way of changing the current mental health treatment paradigm in Australia. The RANZCP have published in the *Australian and New Zealand Journal of Psychiatry*, that many Australians with key mental illnesses are not getting well[86]. Moreover, some mental health medicines (such as antidepressants) can have serious and debilitating side-effects[87].

The RANZCP state in its CM, that it is not satisfied with the safety profile of psychedelics in psychiatric use. But psychedelics range over 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[2],

*"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 the medical controlled use.

When the references used by RANZCP in the CM for HPPD and psychosis (in the CM [18, 19]) are evaluated, the authors in both articles do not state that psilocybin or MDMA are associated with HPPD or psychosis[88, 89]. In [18], the authors stipulate that cannabis, cannabis co-administered with MDMA, LSD, cannabis co-administered with LSD, phencyclidine (PCP), and risperidone are associated with HPPD[88]. In [19], the authors conclude that the most common cause of drug-induced psychosis is from alcohol[89]. From the meta-analysis' study inclusions, 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 95.5% 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 everyone 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[90]. 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 involved 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[91].

Nevertheless, if used within a controlled setting, psilocybin has been shown to have little to no adverse reactions[92, 93]. Early therapeutic use of the pharmaceutical psilocybin (Indocybin® developed by Sandoz) was without complication[79]. In more recent trials, there have been no significant adverse events with psilocybin administration in a controlled setting[94].

The toxicity of psilocybin and psilocybin-containing mushrooms is very low[95]. The lethal dose of psilocybin is extrapolated to 6g in humans. This is 300 times the typical therapeutic dose of 20mg. 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 ingestion of psilocybin-containing mushrooms is extremely rare[96, 97]. 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[98]. For comparison, the ABS reported 276 deaths from antidepressants and 663 deaths from anti-anxiety medication during 2016 just within Australia[99]. The lethal toxicity of fresh psilocybin-containing mushrooms in humans is 17kg[98]. It would be highly unusual and very challenging to consume 17kg of mushrooms in one sitting.

6.3. 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 NDPSC, TGA, and MCC, this media interest will be intrinsically linked to an increased risk of self-medication[41]. 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 hazard's of self-medication from occurring.

7. How MDMA and psilocybin work in the brain

An interesting statement from the RANZCP appears in the CM[2],

"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[100-105]. 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[103].

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[106-111].

What is unknown is the way and why the 'mystical experience' associated with positive therapeutic outcomes is created in the brain[112, 113]. A topic bordering on the nature of human consciousness, which we are barely at the beginning of understanding.

8. The need for further research

The RANZCP note in its CM that[2],

"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 treatment-resistant-depression and treatment-resistant PTSD of between 60-80%, for both psilocybin and MDMA when used as an adjunct to therapy[77, 114]. As previously mentioned, both therapies have been awarded 'breakthrough therapy' status by the FDA[47, 48] with the first MDMA Phase 3 trials successfully complete[77]. Given the high incidence of depression and PTSD in Australia[115] and associated high levels of suicide[99, 116], 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 unknown therapeutic mechanism of action, such as paracetamol[117], lithium[118], general anaesthetic[119, 120], and modafinil[121]. For example, the exact way in which lithium helps stabilise mood is unknown[122-125], however its use is not questioned. Further, toxicity is a known long-term consequence of lithium, yet it continues to be prescribed[118].

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. The RANZCP further says that[2],

"The treatments can be expensive and the short timeframes of application (1-2 sessions) suggested by early research puts 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.

9. 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[2]. They further state, that there is only some evidence that psychedelics may have therapeutic potential.

Thousands of patients had received MDMA in psychotherapy from the 1960s until prohibition in 1986[78]. The first clinical study for MDMA in psychotherapy occurred in 1984[126]. The FDA began approving clinical trials for treating PTSD with MDMA in 2000[127]. With the first post-prohibition clinical trial complete in 2001 and the first MDMA phase 3 trial successfully completed in 2020[77]. We have 20 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[52] and is being administered medically to patients in Canada[53-55]. 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

Table 3. Completed psychedelic studies since 2009.

#	Year complete	Psychedelic substance	Condition or illness	Reference
1	2020	MDMA	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		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	Psilocybin	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		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	Ayahuasca	Treatment-Resistant Depression	https://doi.org/10.1017/S0033291718001356
44	2019		Major Depression Disorder (MDD)	https://doi.org/10.3389/fpsyg.2019.0123
45	2017		MDD	https://clinicaltrials.gov/ct2/show/NCT02914769
46	2020	LSD	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		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

tobacco and alcohol cause significantly more harm to the user and society than either MDMA or psilocybin[128, 129].

Regulating MDMA and psilocybin under strict medical guidelines and supervision will further mitigate associated risks with self-medication.

10. Questions to RANZCP

Given the high remission rates being achieved in overseas trials, the safety data outlined above, the inadequacy of current treatments for many Australians, and the risks associated with self-medication:

1. What is the precise research that the RANZCP believes needs to be undertaken 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? Further, how can this time lag be justified?

11. Conclusion

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

Conflicts of interests

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.

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Abbreviations

2-CB	2,5-Dimethoxy-4-bromophenylamine
5-HT$_{2A}$	Serotonin subtype-2A receptor
5-MeO-DMT	5-Methoxy-N,N-dimethyltryptamine
5-MeO-NMT	5-Methoxy-N-methyltryptamine
5-OH-DMT	5-Hydroxy-N,N-dimethyltryptamine
ABS	Australian Bureau of Statistics
ACA	American Counseling Association
ARTG	Australian Register of Therapeutic Goods
CM	Clinical memorandum
CNS	Central nervous system
D_2	Dopamine type-2 receptor
DOM	2,5-Dimethoxy-4-methylamphetamine
FDA	Food and Drugs Administration
GAD	General Anxiety Disorder
HPPD	Hallucination Persistent Perception Disorder
LSD	Lysergic acid diethylamide
MAPS	Multidisciplinary Association of Psychedelic Studies
MCC	Medicines Classifications Committee
MDA	3,4-Methylenedioxyamphetamine
MDD	Major Depressive Disorder
MDMA	3,4-Methylenedioxymethampehetamine
MMA	Mind Medicine Australia
NMT	N-Methyltryptamine
NDPSC	National Drugs and Poisons Schedule Committee
PCP	Phencyclidine
PTSD	Post-Traumatic Stress Disorder
RANZCP	Royal Australian College of Psychiatrists
S4	Schedule 4
S8	Schedule 8
S9	Schedule 9
S10	Schedule 10
SAS-B	Special Access Scheme-B
SAD	Social Anxiety Disorder
TGA	Therapeutic Goods Administration

References

1. MMA. TGA Rescheduling Submissions, 2020. MMA. https://mindmedicineaustralia.org.au/tga/ (accessed Jan 2021).
2. RANZCP. Clinical Memorandum Therapeutic use of psychedelic substances, May 2020, 2020. RANZCP. https://www.ranzcp.org/files/resources/college_statements/clinical_memoranda/cm-therapeutic-use-of-psychedelics.aspx (accessed Dec 2020).
3. *Poisons Standard February 2021* (Cwlth).
4. Nutt D. Psychedelic drugs-a new era inpsychiatry? *Dialogues Clin Neurosci* 2019; 21: 139-147.
5. Steele TD, McCann UD & Ricaurte GA. 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy"): pharmacology and toxicology in animals and humans. *Addiction* 1994; 89: 539-51.
6. Amoroso T. The Psychopharmacology of +/-3,4 Methylenedioxymethamphetamine and its Role in the Treatment of Posttraumatic Stress Disorder. *J Psychoactive Drugs* 2015; 47: 337-44.

7. Moreno JL, Holloway T, Albizu L, et al. Metabotropic glutamate mGlu2 receptor is necessary for the pharmacological and behavioral effects induced by hallucinogenic 5-HT2A receptor agonists. *Neurosci Lett* 2011; 493: 76-9.
8. Jalal B. The neuropharmacology of sleep paralysis hallucinations: serotonin 2A activation and a novel therapeutic drug. *Psychopharmacology (Berl)* 2018; 235: 3083-3091.
9. Seeman P, Guan HC & Hirbec H. Dopamine D2High receptors stimulated by phencyclidines, lysergic acid diethylamide, salvinorin A, and modafinil. *Synapse* 2009; 63: 698-704.
10. Giacomelli S, Palmery M, Romanelli L, et al. 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* 1998; 63: 215-22.
11. Schmidt CJ. Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *J Pharmacol Exp Ther* 1987; 240: 1-7.
12. Trachsel D. Fluorine in psychedelic phenethylamines. *Drug Test Anal* 2012; 4: 577-90.
13. Baggott MJ, Garrison KJ, Coyle JR, et al. Effects of the Psychedelic Amphetamine MDA (3,4-Methylenedioxyamphetamine) in Healthy Volunteers. *J Psychoactive Drugs* 2019; 51: 108-117.
14. Eckler JR, Chang-Fong J, Rabin RA, et al. Behavioral characterization of 2-O-desmethyl and 5-O-desmethyl metabolites of the phenylethylamine hallucinogen DOM. *Pharmacol Biochem Behav* 2003; 75: 845-52.
15. Papaseit E, Farre M, Perez-Mana C, et al. Acute Pharmacological Effects of 2C-B in Humans: An Observational Study. *Front Pharmacol* 2018; 9: 206.
16. *Misuse of Drugs (Changes to Controlled Drugs) Order 2005*.
17. *Misuse of Drugs Act 1975*.
18. Controlled Drugs, 2019. Ministry of Health. https://www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/controlled-drugs (accessed Dec 2020).
19. *Therapeutic Goods Act 1989* (Cwlth).
20. MMA. Application to Reschedule N,α-DIMETHYL-3,4(METHYLENEDIOXY)PHENYLETHYLAME (MDMA) from Schedule 9 to Schedule 8 of the Poisons Standard, 2020. MMA. https://mindmedicineaustralia.org/wp-content/uploads/2020/08/Mind-Medicine-Australia-MDMA-Rescheduling-S9-to-S8-15-July-2020-FINAL.pdf (accessed Dec 2020).
21. Krupitsky EM & Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs* 1997; 29: 165-83.
22. Kolp E, Friedman HL, Krupitsky E, et al. Ketamine Psychedelic Psychotherapy: Focus on its Pharmacology, Phenomenology, and Clinical Applications. *Int J Transpers* 2014; 33.
23. Bowdle TA, Radant AD, Cowley DS, et al. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. *Anesthesiology* 1998; 88: 82-8.
24. Lim DK. Ketamine associated psychedelic effects and dependence. *Singapore Med J* 2003; 44: 31-4.
25. *Therapeutic Goods (Permissible Ingredients) Determination (No. 4) 2020* (Cwlth).
26. ARTG Search, 2020. TGA. http://tga-search.clients.funnelback.com/s/search.html?collection=tga-artg&profile=record&meta_i=176056 (accessed Dec 2020).
27. Feeney K. Revisiting Wasson's Soma: exploring the effects of preparation on the chemistry of Amanita muscaria. *J Psychoactive Drugs* 2010; 42: 499-506.
28. Ott J. Entheogens II: on entheology and entheobotany. *J Psychoactive Drugs* 1996; 28: 205-9.
29. Falandysz J, Hanć A, Barałkiewicz D, et al. Metallic and metalloid elements in various developmental stages of *Amanita muscaria* (L.) Lam. *Fungal Biology* 2020; 124: 174-182.
30. Trutmann P. The Forgotten Mushrooms of Ancient Peru. In: Fungi and Mountains Publication Series. Lima, Peru: Global Mountain Action, 2012: 1-33.
31. *Australia New Zealand Food Standards Code - Schedule 23 - Prohibited plants and fungi* (Cwlth).
32. Callaway JC, Raymon LP, Hearn WL, et al. Quantitation of N,N-dimethyltryptamine and harmala alkaloids in human plasma after oral dosing with ayahuasca. *J Anal Toxicol* 1996; 20: 492-7.
33. Kaasik H, Souza RCZ, Zandonadi FS, et al. Chemical Composition of Traditional and Analog Ayahuasca. *J Psychoactive Drugs* 2020: 1-11.
34. Moloudizargari M, Mikaili P, Aghajanshakeri S, et al. Pharmacological and therapeutic effects of Peganum harmala and its main alkaloids. *Pharmacogn Rev* 2013; 7: 199-212.
35. Mina CN, Farzaei MH & Gholamreza A. Medicinal properties of Peganum harmala L. in traditional

Iranian medicine and modern phytotherapy: a review. *J Tradit Chin Med* 2015; 35: 104-9.

36. Lim T. Acacia longifolia. In: Edible Medicinal And Non-Medicinal Plants: Volume 7, Flowers: Springer Science, 2014: 738-742.
37. Østrem L. Studies on genetic variation in reed canarygrass, *Phalaris arundinacea* L. I. Alkaloid type and concentration. *Hereditas* 1987; 707: 235-248.
38. 38.Woods D & Clark K. Genetic Control And Seasonal Variation Of Some Alkaloids In Reed Canarygrass'. *Can J Plant Sci* 1971; 51: 323-329.
39. 39.Kavitha C & Thangamani C. Amazing bean "Mucuna pruriens": A comprehensive review. *J Med Plants Res* 2014; 8: 138-143.
40. Medsafe. Classification Database, 2020. New Zealand Medicines and Medical Devices Safety Authority. https://www.medsafe.govt.nz/profs/class/classintro.asp (accessed Dec 2020).
41. NDPSC. Record of Reasons 58th Meeting 16-17 February 2010, 2010. TGA. https://www.tga.gov.au/sites/default/files/ndpsc-record-58.pdf (accessed Dec 2020).
42. Malcom L & Bedi G. MDMA–its potential therapeutic use podcast extra, 2018. ABC. https://www.abc.net.au/radionational/programs/allinthemind/mdma-and-its-potential-therapeutic-use—a-podcast-extra/10200140 (accessed Dec 2020).
43. Daoud E. Mind Medicine Australia urges psychedelic drugs for mental health treatment during COVID-19, 2020. 7NEWS. https://7news.com.au/lifestyle/health-wellbeing/mind-medicine-australia-urges-psychedelic-drugs-for-mental-health-treatment-during-covid-19-c-977749 (accessed Dec 2020).
44. McCauley D. Regulator weighs push to legalise MDMA for mental health treatment, 2020. The Sydney Morning Herald. <https://www.smh.com.au/politics/federal/regulator-weighs-push-to-legalise-mdma-for-mental-health-treatment-20200901-p55rch.html (accessed Dec 2020).
45. Taylor S. Using MDMA to cure PTSD: How a revolutionary ecstasy trial saved the life of a former police officer traumatised by the Port Arthur massacre, 2020. 60 minutes. https://9now.nine.com.au/60-minutes/nick-watchorn-says-mdma-saved-his-life-after-post-traumatic-stress/de8472fb-7f95-45c5-9669-d9786eec5133 (accessed Dec 2020).
46. Abo S. Revolutionary drug trial could see ecstasy used as prescription medicine for those living with PTSD and mental illness, 2020. https://9now.nine.com.au/60-minutes/revolutionary-mdma-trial-changing-lives-of-those-with-mental-illness-60-minutes/6e9f2a9d-e88c-49b5-9654-a2636fec7db9 (accessed Dec 2020).
47. Feduccia AA, Jerome L, Yazar-Klosinski B, et al. Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline. *Front Psychiatry* 2019; 10: 650.
48. Nichols DE. Psilocybin: from ancient magic to modern medicine. *J Antibiot (Tokyo)* 2020; 73: 679-686.
49. Brewerton TD, Lafrance A & Mithoefer MC. The potential use of N-methyl-3,4-methylenedioxyamphetamine (MDMA) assisted psychotherapy in the treatment of eating disorders comorbid with PTSD. *Med Hypotheses* 2020: 110367.
50. MAPS. Israel Approves Compassionate Use of MDMA-Assisted Psychotherapy for PTSD, 2019. MAPS. https://maps.org/research/mdma/ptsd/phase3/timeline/7631-israel-approves-compassionate-use-of-mdma-assisted-psychotherapy-for-ptsd (accessed Dec 2020).
51. Sessa B, Higbed L & Nutt D. A Review of 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy. *Front Psychiatry* 2019; 10: 138.
52. Oregon Measure 109, Psilocybin Mushroom Services Program Initiative (2020), 2020. BallotPedia. https://ballotpedia.org/Oregon_Measure_109,_Psilocybin_Mushroom_Services_Program_Initiative_(2020) (accessed Dec 2020).
53. Carpenter D. Four Terminally Ill Canadians Gain Legal Right To Use Magic Mushrooms For End-Of-Life Distress, 2020. Forbes. 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 (accessed Dec 2020).
54. Semley J. Canada Is Allowing People With Depression to Do Psychedelic Mushrooms, 2020. Vice.

https://www.vice.com/en/article/4adw4w/canada-is-allowing-people-with-depression-to-do-psychedelic-mushrooms (accessed Dec 2020).
55. Wood E, Christie D, Maté G, et al. Email correspondence to the Honourable Canadian Health Minister, 2019. Numinus Wellness Clinical Advisory Board. https://numinus.ca/dist/assets/docs/Health-Canada-Briefing-Note.pdf (accessed Dec 2020).
56. Psychedelic therapies that bring you to life, 2020. Field Trip Health Inc. https://www.fieldtriphealth.com (accessed Dec 2020).
57. Access to microdoses of psilocybe mushrooms for therapeutic purposes, 2020. Medicinal Mushroom Dispensary. https://mushroomdispensary.com (accessed Dec 2020).
58. IbogaSoul. IbogaSoul is proud to operate in the exquisite beauty of West Vancouver, British Columbia, Canada, 2020. Ibogasoul Shamanic Healing LTD. http://ibogasoul.com/contact/ (accessed).
59. Specializing in opiate addiction detox, 2020. Inner Realms Center. https://www.innerrealmscenter.com> (accessed Dec 2020).
60. Sacred Soul Therapy • Squamish, Vancouver, BC, Canada, 2021. Sacred Soul Therapy. http://sacredsoultherapy.ca (accessed Jan 2021).
61. Ibogaine Treatment Center Mexico, 2020. IbogaQuest. https://ibogaquest.com (accessed Jan 2021).
62. We are the World's Foremost Experts in Medically-based Ibogaine Treatment, 2020. Clear Sky Recovery. https://clearskyibogaine.com (accessed Jan 2021).
63. Iboga Retreat Gabon, West Africa, 2019. Bwiti Healing. http://bwitihealing.com/africa-retreat/ (accessed Jan 2021).
64. Underwood MS. At Magalies Wellness Centre, we facilitate journeys of transformation, 2020. Magalies Wellness Centre. https://www.magalieswellnesscentre.com (accessed Jan 2020).
65. Boutique Hotel & Retreat Center, 2020. Costa Rica Yoga Spa. https://www.costaricayogaspa.com (accessed Dec 2020).
66. The Avante Ibogaine Treatment Centre, 2020. The Avante Institute. https://avanteibogaine.com (accessed Dec 2020).
67. Rocha JM & Rossi GN. Meet the Person Serving Ayahuasca to Inmates in Brazil: An Interview with Edilsom Fernandes, 2019. Khapi. https://kahpi.net/ayahuasca-prisoners-brazil-edilsom-fernades/ (accessed Dec 2020).
68. Romero R. In Brazil, Some Inmates Get Therapy With Hallucinogenic Tea, 2015. The New York Times. https://www.nytimes.com/2015/03/29/world/americas/a-hallucinogenic-tea-time-for-some-brazilian-prisoners.html (accessed).
69. MAPS. Investigator's Brochure, 2019. https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/mdma/MDMA-Investigator-Brochure-IB-11thEdition-MAPS-2019-07-10.pdf (accessed).
70. MAPS. Treating PTSD with MDMA- Assisted Psychotherapy, n.d. MAPS. https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/PTSDandMDMA.png (accessed Dec 2020).
71. MAPS. Investigator's Brochure, 2013. https://maps.org/research-archive/mdma/MDMA_FINAL%20_IB-edition-7_1Aug13.pdf (accessed).
72. ACA. Psychedelic Assisted Treatments - Testing the Waters, 2018. ACA. https://fusion.counseling.org/news/aca-blogs/aca-member-blogs/aca-member-blogs/2018/06/22/psychedelic-assisted-treatments---testing-the-waters (accessed Dec 2020).
73. MAPS. Investigator's Broochure, 2020. https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/MDMA+IB+12th+Edition+Final+17AUG2020.pdf (accessed).
74. MAPS. Investigator's Brochure, 2016. https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/MDMA_IB_FINAL_30Mar2016_Linked.pdf (accessed).
75. MAPS. Investigator's Brochure, 2017. https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/MDMA_IB_9thEd_FINAL_21MAY2017+linked+TOC+gray+table+shading.pdf (accessed).
76. MAPS. Investigator's Brochure, 2018. https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/MAPS_2018_MDMA_Investigators_Brochure_Edition10_10JUL2018.pdf (accessed).
77. MAPS. Development Safety Update Report 3,4-methylenedioxymethamphetamine (MDMA), 2020.

https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/mdma/Development-Safety-Update-Report-on-MDMA-DSUR-11DEC2020.pdf (accessed).

78. Passie T. The early use of MDMA ('Ecstasy') in psychotherapy (1977–1985). *Drug Science, Law and Policy* 2018; 4: 1-19.
79. Passie T, Seifert J, Schneider U, et al. The pharmacology of psilocybin. *Addict Biol* 2002; 7: 357-64.
80. Armenian P, Mamantov TM, Tsutaoka BT, et al. Multiple MDMA (Ecstasy) overdoses at a rave event: a case series. *J Intensive Care Med* 2013; 28: 252-8.
81. Jerome L, Schuster S & Yazar-Klosinski BB. Can MDMA play a role in the treatment of substance abuse? *Curr Drug Abuse Rev* 2013; 6: 54-62.
82. MAPS. Protocol MAPP1 IND #063384, 2018. https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/mdma/mapp1/FINAL+MAPP1+Public+Protocol+A4V1_+22MAY2020.pdf (accessed).
83. Wong SK. Analysis of Drug Overdose in Teenagers. *Hong Kong Journal of Emergency Medicine* 2002; 9: 144-149.
84. Roxburgh A & Lappin J. MDMA-related deaths in Australia 2000 to 2018. *Int J Drug Policy* 2020; 76: 102630.
85. Kalant H. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *CMAJ* 2001; 165: 917-28.
86. Jorm AF. Why hasn't the mental health of Australians improved? The need for a national prevention strategy. *Aust N Z J Psychiatry* 2014; 48: 795-801.
87. Cartwright C, Gibson K, Read J, et al. Long-term antidepressant use: patient perspectives of benefits and adverse effects. *Patient Prefer Adherence* 2016; 19: 1401-1407.
88. Martinotti G, Santacroce R, Pettorruso M, et al. Hallucinogen Persisting Perception Disorder: Etiology, Clinical Features, and Therapeutic Perspectives. *Brain Sci* 2018; 8.
89. Murrie B, Lappin J, Large M, et al. Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. *Schizophr Bull* 2020; 46: 505-516.
90. Johansen PO & Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study. *J Psychopharmacol* 2015; 29: 270-9.
91. Carbonaro TM, Bradstreet MP, Barrett FS, et al. Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *J Psychopharmacol* 2016; 30: 1268-1278.
92. Strassman RJ. Adverse reactions to psychedelic drugs. A review of the literature. *J Nerv Ment Dis* 1984; 172: 577-95.
93. Carhart-Harris RL, Bolstridge M, Day CMJ, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl)* 2018; 235: 399-408.
94. Dos Santos RG, Bouso JC, Alcazar-Corcoles MA, et al. 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* 2018; 11: 889-902.
95. Gable RS. Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction* 2004; 99: 686-96.
96. McCawley EL, Brummett RE & Dana GW. Convulsions from psilocybe mushroom poisoning. *Proc West Pharmacol Soc* 1962; 5: 27-33.
97. Gonmori K & Yoshioka N. A fatal case of mushroom poisoning by hallucinogenic species. *Jpn J Legal Med* 2002; 56: P-15.
98. van Amsterdam J, Opperhuizen A & van den Brink W. Harm potential of magic mushroom use: a review. *Regul Toxicol Pharmacol* 2011; 59: 423-9.
99. ABS. 3303.0 – Causes of Death, Australia, 2016, 2018. Australian Government. https://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3303.0Main+Features62016?OpenDocument (accessed).
100. Nichols DE, Johnson MW & Nichols CD. Psychedelics as Medicines: An Emerging New Paradigm. *Clin Pharmacol Ther* 2017; 101: 209-219.
101. Moya EA & Powell FL. Serotonin and Adenosine G-protein Coupled Receptor Signaling for Ventilatory Acclimatization to Sustained Hypoxia. *Front Physiol* 2018; 9: 860.
102. Maple AM, Zhao X, Elizalde DI, et al. Htr2a Expression Responds Rapidly to Environmental Stimuli in an Egr3-Dependent Manner. *ACS Chem Neurosci* 2015; 6: 1137-42.

103. Carhart-Harris RL, Roseman L, Bolstridge M, et al. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Sci Rep* 2017; 7: 13187.
104. Ray TS. Psychedelics and the human receptorome. *PLoS One* 2010; 5: e9019.
105. Yu B, Becnel J, Zerfaoui M, et al. Serotonin 5-hydroxytryptamine(2A) receptor activation suppresses tumor necrosis factor-alpha-induced inflammation with extraordinary potency. *J Pharmacol Exp Ther* 2008; 327: 316-23.
106. Bremner JD, Vermetten E, Schmahl C, et al. 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* 2005; 35: 791-806.
107. Carhart-Harris RL, Wall MB, Erritzoe D, et al. The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *Int J Neuropsychopharmacol* 2014; 17: 527-40.
108. Feduccia AA & Mithoefer MC. MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms? *Prog Neuropsychopharmacol Biol Psychiatry* 2018; 84: 221-228.
109. Thal SB & Lommen MJJ. Current Perspective on MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder. *J Contemp Psychother* 2018; 48: 99-108.
110. Doss MK, Weafer J, Gallo DA, et al. MDMA Impairs Both the Encoding and Retrieval of Emotional Recollections. *Neuropsychopharmacology* 2018; 43: 791-800.
111. Amoroso T & Workman M. Treating posttraumatic stress disorder with MDMA-assisted psychotherapy: A preliminary meta-analysis and comparison to prolonged exposure therapy. *J Psychopharmacol* 2016; 30: 595-600.
112. Griffiths R, Richards W, Johnson M, et al. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol* 2008; 22: 621-32.
113. Griffiths RR, Johnson MW, Richards WA, et al. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology (Berl)* 2011; 218: 649-65.
114. Agin-Liebes GI, Malone T, Yalch MM, et al. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *J Psychopharmacol* 2020; 34: 155-166.
115. Mills KL, McFarlane AC, Slade T, et al. Assessing the prevalence of trauma exposure in epidemiological surveys. *Aust N Z J Psychiatry* 2011; 45: 407-15.
116. Qi X, Hu W, Page A, et al. Spatial clusters of suicide in Australia. *BMC Psychiatry* 2012; 12.
117. Toussaint K, Yang XC, Zielinski MA, et al. What do we (not) know about how paracetamol (acetaminophen) works? *J Clin Pharm Ther* 2010; 35: 617-38.
118. Hedya SA, Avula A & Swoboda HD. Lithium Toxicity. In: StatPearls. Treasure Island (FL)2020.
119. Pavel MA, Petersen EN, Wang H, et al. Studies on the mechanism of general anesthesia. *Proc Natl Acad Sci U S A* 2020; 117: 13757-13766.
120. Mashour GA, Forman SA & Campagna JA. Mechanisms of general anesthesia: from molecules to mind. *Best Pract Res Clin Anaesthesiol* 2005; 19: 349-64.
121. Gerrard P & Malcolm R. Mechanisms of modafinil: A review of current research. *Neuropsychiatr Dis Treat* 2007; 3: 349-64.
122. Oruch R, Elderbi MA, Khattab HA, et al. Lithium: a review of pharmacology, clinical uses, and toxicity. *Eur J Pharmacol* 2014; 740: 464-73.
123. Risby ED, Hsiao JK, Manji HK, et al. The mechanisms of action of lithium. II. Effects on adenylate cyclase activity and beta-adrenergic receptor binding in normal subjects. *Arch Gen Psychiatry* 1991; 48: 513-24.
124. Treiser SL, Cascio CS, O'Donohue TL, et al. Lithium increases serotonin release and decreases serotonin receptors in the hippocampus. *Science* 1981; 213: 1529-31.
125. Jakobsson E, Arguello-Miranda O, Chiu SW, et al. Towards a Unified Understanding of Lithium Action in Basic Biology and its Significance for Applied Biology. *J Membr Biol* 2017; 250: 587-604.
126. Downing J. The psychological and physiological effects of MDMA on normal volunteers. *J Psychoactive Drugs* 1986; 18: 335-40.
127. Doblin R. A clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): partnering with the FDA. *J Psychoactive Drugs* 2002; 34: 185-94.
128. Bonomo Y, Norman A, Biondo S, et al. The Australian drug harms ranking study. *J Psychopharmacol* 2019; 33: 759-768.

129. Nutt DJ, King LA, Phillips LD, et al. Drug harms in the UK: a multicriteria decision analysis. *Lancet* 2010; 376: 1558-65.