ACNEM
TRANSFORMING GLOBAL HEALTH

APPLICATION TO RESCHEDULE MDMA FROM SCHEDULE 9 TO SCHEDULE 8 OF THE POISONS STANDARD

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This application is made in support of Mr Peter Hunt, the Chairman of Mind Medicine Australia and his application for MDMA to be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard.

1) Proposed rescheduling of the poisons standard

Overview

Description

MDMA is a ring-substituted phenethylamine. MDMA is described as an 'entactogen' for its ability to produce anxiolytic and prosocial effects. MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA (Shulgin, 1986). The MDMA which has been used in all clinical trials to date is racemic, containing roughly equal amounts of each enantiomer (MAPS, 2019). There is currently limited evidence of differential effects of either enantiomer in humans. The racemic anhydrous hydrochloride salt of MDMA is readily water soluble with a pKa of 9.9. MDMA is stable at room temperature

Toxicity

For a comprehensive review of toxicity data please also see the Multidisciplinary Association for Psychedelic Studies (MAPS) Investigators Brochure section 4.4 Toxicity in Animals and Epidemiological settings (MAPS, 2019).

In assessing this application an important distinction needs to be made between medicinal MDMA and the street-drug Ecstasy for the following reasons:

• Ecstasy may only contain a minimal amount of MDMA, if any at all.

• Ecstasy may contain other ingredients unknown, thus being dangerous.

• Dosage of Ecstasy cannot be regulated.

• Ecstasy use is uncontrolled.

• Ecstasy users do not undergo any testing to ensure that they are fit to consume.

Medicinal MDMA, administered in a medically - controlled clinical setting, is pharmaceutical grade, dosage is known, patients are properly screened, the use of the medicine is regulated and the medicine is administered only by trained health professionals. Understanding the distinction between the two types of drugs is fundamental. This application reports the benefits, toxicity and harm associated with medicinal MDMA. Recreational ecstasy is discussed but differentiated by name in the case of recreational nonclinical use

Effects in Humans

Under the influence of MDMA, patients can more readily experience and process their emergent psychological material in a state of psychological ease and safety (Amoroso, 2015). In a controlled setting, MDMA supports patients in reprocessing traumatic and painful memories, making MDMA efficacious for treating PTSD and addictions associated with trauma (Feduccia & Mithoefer, 2018). MDMA in this context facilitates:

• Feelings of closeness and affiliation

• Increased awareness of emotions

• Greater compassion and understanding of interpersonal relationships

• A sense of well-being

• Sensory intensification

• Changes to the encoding of emotional memory

• Reduction of fear response

Possible adverse effects

<u>Medical Condition Contraindications</u>

1) Cardiovascular and Cerebrovascular Risks

   Current clinical trials exclude individuals with uncontrolled blood pressure (MAPS, 2018). In a therapeutic setting cardiovascular health will be assessed prior to use and a physician is to be on premises at all times.

2) Thermoregulatory Risks

Although body temperatures remain stable in clinical settings, in uncontrolled settings there is a greater risk of hyperthermia (Drafter, 1995). A physician is recommended to assess patients for thermoregulatory risk.

3) Osmoregulatory Risks

MDMA administered in controlled settings is not expected to pose osmoregulatory risks as patients are relaxed and are provided with electrolyte water. However, in uncontrolled settings, particularly in hot environments accompanied by physical exertion, MDMA may produce electrolyte imbalances which can be dangerous in vulnerable individuals (Baggott et al, 2016). It is recommended to assess patients for osmoregulatory risk and to have electrolyte supplements available on premises.

Pharmaceutical Contraindications

1) Monoamine oxidase inhibitors (MAOIs).

   Their combination with MDMA predisposes individuals to serotonin syndrome and has been the cause of some fatalities (Pilgrim, 2012).

2) Caution must be used if MDMA is co-administered with drugs that are also metabolised by CYP2D6 due to the possibility of increased concentrations of MDMA caused by enzyme saturation.

3) Tramadol which acts as a serotonin norepinephrine reuptake inhibitor and is metabolised by CYP2D6 enzymes is known to increase the risk of serotonin syndrome (Hassamal et al, 2018).

4) In clinical trials all psychiatric medications are stopped to ensure MDMA's effectiveness. A two-week washout period is followed prior to treatment. This is because many psychiatric medications may reduce MDMA's efficacy (MAPS, 2019)

Increased Health Risks with High Doses

Adverse effects increase with higher non-therapeutic doses (Vollenweider, 1999). It is therefore recommended that prescription of MDMA follow the dosing protocol.

Increased risk in uncontrolled non-clinical settings

Morbidity and mortality have only occurred in uncontrolled, non-clinical settings (Sessa, 2019). This application is for the prescription of MDMA for in clinic settings only.

Acute spontaneous reactions in clinical trials

MDMA can elicit a range of acute spontaneous reactions rated mild to moderate, the majority of which resolve with 24 hours and the remainder within a week. The most common are nausea, jaw clenching, muscle aches, numbness, dizziness, headache, sweating, and

decreased appetite (Thal & Lommen, 2018). These reactions are not considered to be significant hazards.

Range of use: What are the benefits?

1) Positive psychological effects
2) Reduction of fear response and memory reconsolidation
3) Promising results from phase 2 clinical trials and from phase 3 interim analysis
4) Low risk of dependence
5) Historic therapeutic use without issue

Why is rescheduling so important?

The rescheduling will enable psychiatrists and specialist addiction physicians to more easily access these medicines to augment therapy for patients suffering from key mental illnesses such as depression, PTSD and the depression and anxiety often associated with a terminal illness diagnosis.

It will also relieve a significant part of the regulatory burden associated with undertaking trials with these medicines in Australia. Rescheduling is critical for a number of major reasons:

a) To expand the medical treatment paradigm in Australia

Trials to date have shown these medicines when used with proper protocols in a medically controlled environment:

- can provide high remission rates for key classes of mental illness when compared to current treatments (such as antidepressants and conventional therapy)
- require only 2 -3 dosed sessions with the medicines (in contrast to a permanent or long-term use of pharmaceutical substances such as antidepressants)
- have minimal side effects (again in contrast to pharmaceuticals such as antidepressants).

b) To educate Australians

Rescheduling will educate all key stakeholders in our medical system (eg. medical practitioners, other health workers, politicians, regulators, people suffering from mental illness and other members of the general public) that these substances can be used positively and safely in a medically controlled environment to broaden the treatment paradigm for mental illnesses in Australia and substantially reduce the incidence of mental illness in our community.

c) To remove stigma

To help the general community understand that the prohibition of psychedelics was not based on any scientific or medical rationale and the failure of our system to recognise these substances can be used effectively as medicines in a medically controlled environment is detrimental to the health and welfare of a huge number of Australians.

What Does Rescheduling Mean?

MDMA and psilocybin are currently Schedule 9 substances under the Commonwealth Standard for the Uniform Scheduling of Medicines and Poisons (often referred to as the Poisons Standard). This standard is designed to create a national system in Australia by classifying medicines and poisons into schedules for inclusion into relevant State and Territory legislation. At the moment MDMA and psilocybin are classified in the Poisons Standard as Schedule 9 substances.

Schedule 9 substances are described as; "Prohibited substances - substances that may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except where required for medical or scientific research, or for analytical teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities". This designation doesn't acknowledge these substances can be used as medicines and as a consequence, makes it much harder and more expensive for our medical practitioners and researchers to access these substances.

ACNEM is seeking to have these medicines rescheduled to Schedule 8 of the Poisons Standard. Schedule 8 substances are described as; "Controlled Drug - Substances which should be available for use but require restriction on manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence". The proposed rescheduling will make it easier for clinical trials to take place in Australia and for patients to access these medicines through their psychiatrists and specialist addiction physicians in a medically controlled environment under proper supervision. Moving the medicines to Schedule 8 will acknowledge that these substances can be used as medicines. Many of the medicines prescribed by medical specialists are Schedule 8 medicines.

2) Why MDMA should be in Schedule 8

This application has supplied evidence that MDMA shows strong therapeutic benefit for individuals suffering from PTSD whose condition has not improved after standard forms of treatment.

Given the therapeutic benefits and high remission rates shown in clinical trials, alongside the FDA's designation of Breakthrough Therapy status and use in several international "Expanded Access Schemes", including Australia's own SAS-B scheme, it is apparent that MDMA used in a medically controlled environment does not fit within the requirements of a Schedule 9 Substance and more closely reflects the requirements of Schedule 8.

The current Schedule 9 classification of MDMA places hurdles on research (cost, stigma and ease of access) and on its use in a medically controlled environment as part of evidence-based treatment. Reclassifying MDMA as a Schedule 8 substance will reduce cost and improve ease

of access for researchers and specialist medical practitioners for treatment of individuals seeking relief for treatment resistant conditions via the Special Access Scheme.

MDMA treatment is only to be used in clinical settings according to the guidelines of a Schedule 8 controlled substance in the Poisons Standards Act 2020 and in accordance with strict safety protocols for supplying MDMA-assisted therapy through health care providers in a medically controlled environment.

As the evidence shows, MDMA in a controlled clinical setting has shown limited abuse, misuse, or overdose potential internationally. With the breakthrough therapeutic potential discussed we submit MDMA should be rescheduled to Schedule 8.

ACNEM would also like to declare its support of the Mind Medicine Australia Limited application to the Therapeutic Goods Administration to amend Poisons Standard by rescheduling psilocybin from Schedule 9 (prohibited substance) to Schedule 8 (Controlled Drug).

3) Conclusion

Australia is in the midst of a mental health crisis, which has only been exacerbated by the current pandemic. The key diseases, depression, anxiety, PTSD, and addiction can be crippling for the individual, and also for communities. Unfortunately, the existing medications for these conditions are not effective in a substantial amount of people, and often have unacceptable side effects such as emotional numbing and increased suicidality. ACNEM believes there is an urgent need to explore other treatment modalities, including pharmacotherapies, which are showing to be effective in supporting mental health.

There is the demonstrated efficacy of MDMA for PTSD and potentially for substance dependence in cases where the dependence originates in trauma. MDMA also demonstrates low toxicity and low abuse potential when administered in a medically controlled setting. It is therefore detrimental for Australians suffering from treatment-resistant PTSD and addictions associated with trauma not to have medically supervised access to this breakthrough medicine. Increasing access would not only represent a large saving to the Australian economy by reducing service use and increasing productivity once people suffering from such mental illnesses achieve remission but would importantly improve the quality of life of Australians suffering from these debilitating illnesses. We acknowledge and support the premise that the use of MDMA should only be authorised by psychiatrists and specialist addiction physicians and only be used under strict medical supervision in a medically controlled environment. We believe that it is reasonable to reschedule MDMA from being a Schedule 9 drug to being a Schedule 8 drug when used according to the conditions described above

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