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Submission to the Parliamentary Committee for the Public Health (Medicinal Cannabis) Bill 2016

Dear Committee Members,

I am writing as an individual doctor who works within the specialty of palliative medicine. I have developed an interest in the therapeutic benefits of cannabis as a result of experience with terminally ill patients using this drug (without authority) for symptom control.

As a member of the Australian and New Zealand Society of Palliative Medicine (ANZSPM), I assisted in preparing this organisations response to the Inquiry into the Regulator of Medicinal Cannabis Bill 2014. I also represented ANZSPM at this Senate Inquiry.

I have recently completed an expression of interest in securing research funding to study the views of terminally ill patients in relation to accessing cannabis for medical purposes. As part of this funding application, I performed a literature review into the biology and therapeutic benefits of cannabis, and overseas experience in symptom control and issues relating to medicinal cannabis prescribing.

I would like to provide your committee with some of my findings and describe issues that may influence the successful implementation of these legislative changes. My focus is directed at patients in the terminal phase of their illness and the impact it will have on them, as they have been chosen as a particular patient group that would benefit from this legislative change.

BACKGROUND LITERATURE

Research has shown that an endogenous cannabinoid system exists in several mammalian species, including humans. This system consists of several cannabinoid receptors (CB1 and CB2 being the most studied) present at the pre-and post-synaptic membrane of neurons within the central and peripheral nervous system, and on the surface of other cells types within the vascular and immune systems (1,2,3).

Interaction of these receptors with endocannabinoids leads to modification of neurotransmitter release resulting in either up or down regulation of end organ function (1,2,3).

Possible therapeutic benefits from cannabinoid activity include:

- analgesia, through inhibition of pain fibre transmission and inflammation (4,5,6);
- anti-tumour capacity, with inhibition of DNA/RNA/protein synthesis and disruption of cell cycle (7);
- inhibition of blood vessel development to malignant tumours (8);
- anti-nausea capacity, through CB1 receptor activity (9);
- increased appetitive and food-seeking behaviour, through action on the hypothalamus and nucleus accumbens (10);

- anti-epileptic activity via downregulation of genes encoding for neuronal activity and plasticity, synaptic plasticity and nerve growth factors (11);
- decreased spasticity in spinal cord injury, Multiple Sclerosis, dystonias and Tourette's Syndrome (12).

Experience with naturally occurring cannabinoids (phytocannabinoids) indicates that this drug can be used safely. As there are few CB1 and CB2 receptors in the brain stem, thalamus and medulla, cannabis has not been associated with fatal adverse events, such as respiratory depression (unlike opioids) (3). In fact, there is no recorded data of mortality directly related to cannabis itself.

Research also indicates that tolerance or physical addiction to synthetic cannabinoids is low (13). This compares favourably to other medications commonly used in the palliative care setting, such as opioids, where tolerance leads to dose escalation and patients can experience physical withdrawal symptoms if doses are rapidly reduced.

However, though the proposed benefits are promising, there is yet no high level randomized controlled research findings to support many of the therapeutic claims.

A recent systematic review and meta-analysis of past trials on cannabinoids for medical use (n= 79) indicates that current scientific evidence of efficacy is not as robust as commonly claimed (14). According to this study, there is only **moderate-quality evidence** to support the use of cannabinoids in the treatment of chronic neuropathic or cancer pain and spasticity due to Multiple Sclerosis. The use of cannabinoids for other symptoms, such as nausea and vomiting, weight gain and sleep disorders, has only **low-quality evidence** of effectiveness. Also there appears to be only **very poor quality evidence** for improvements in anxiety or depression.

Whilst evidence of benefit is moderate at best, this systematic review did note that there was a heightened risk of short term adverse events, including asthenia, difficulties with balance, disorientation, confusion, dry mouth, nausea and vomiting and somnolence (14).

Despite the lack of robust evidence, many patients claim moderate to marked improvement in problematic symptoms whilst using cannabis. In 2005, Swift, Gates and Dillon, published the results of a survey of Australians using cannabis to treat general medical conditions (n=147). The survey was conducted using either a telephone interview or anonymous questionnaire and found that 86% of responders felt great relief from cannabis use (15). This finding has been supported in overseas studies examining the use of cannabis for medical problems including chronic pain, nausea, poor appetite, stress, insomnia, headaches and depression, with a majority of patients claiming to gain significant improvement with control of these symptoms (16,17).

Research carried out in Israel, where cannabis can be legally prescribed for palliation of symptoms in advanced cancer, indicate that some patients find meaningful reduction in pain and nausea, with improvements in appetite and general well-being (18,19). The researchers found only minimal side effects were experienced by patients agreeing to participate in follow up questionnaires, and these adverse events consisted of increased fatigue and dizziness only. However, these findings were limited to only half of the consented patients being available for follow up. Reasons for incomplete patient data included original prescription never

being presented for dispensing, no repeat script sought after initial use, cessation of cannabis use early due to side effects and progressive functional decline and/or death of the patient. Hence, the experience of cannabis use for at least half of these advanced cancer patients is unknown (18,19).

In Canada, access to “cannabis for therapeutic purposes” (CTP) has been legal since 2001. Authorized patients can either purchase dried cannabis from Health Canada, produce their own cannabis or designate a person to grow cannabis on their behalf. Research on self-identified Canadians using CTP in 2011-2012 (n=628) showed that less than one third accessed cannabis from authorized suppliers. Many of the patients accessing from authorized suppliers also used CTP from unauthorized sources (i.e. friends, black market, unlicensed self-production or grower) to supplement their legal prescription. In fact only seven percent of the sample accessed CTP exclusively from authorized sources. Many barriers preventing access to CTP were identified by respondents, including difficulty in gaining physician support, accessibility to and financial cost of the drug itself, and concern about community attitudes that stigmatized use (20).

POTENTIAL DIFFICULTIES

1/ Lack of Australian Clinical Guidelines and Dosage Schedules

Currently there are no Australian guidelines to influence therapeutic decisions regarding treatment protocols. As the cannabinoids which this Bill is concerned with have not been registered with the Australian Register of Therapeutic Goods (ARTG) and are not widely used overseas, determining how these drugs will be prescribed once legislative change in Queensland is complete is difficult to determine with confidence.

Experience of these cannabinoid agents overseas will have to be used to guide treatment plans, but research on these products has not been directed towards terminally ill patients, who may have multiple comorbidities and organ failure. Australians who have end stage diseases are just as entitled as all other patients to access drugs that have proven therapeutic benefits and safe dosage schedules, not having their health put at risk due to marginally beneficial drugs with unknown therapeutic windows.

Guidelines for use of medicinal cannabinoids will need to be developed quickly to enable Australian doctors, pharmacists and health organisations to feel some confidence in using this new therapeutic agent. However, as federal decisions about which cannabis products will be cultivated and processed for the local market becomes known, then guidelines will need to be amended to facilitate these changes, as it is likely access to Australian product will become the preferred option.

This year, the New South Wales Government is supporting a trial by Associate Professor Meera Agar investigating whether vaporized leaf cannabis or a pharmaceutical cannabis product can be used effectively in a small group of terminally ill patients (n =30). This research focuses on whether cannabis can be delivered successfully in vaporized form, what the tolerated treatment dosages are and potential side effects of this drug in patients with terminal illnesses (21). It has been proposed that initial results of this research project will be available by the end of this year. It is hoped that a further trial with larger patient numbers to determine

treatment effectiveness will begin in late 2017 or early 2018. This will go some way to assist clinicians working in the field of palliative medicine to understand the role these drugs may have in treating difficult to control symptoms.

2/ Medical Profession and Societal Concerns

Cannabis remains a prohibited substance in Queensland, despite these proposed legislative changes. Many within the general population and medical community have strong concerns about the addictive properties of cannabis and may consider the use of this drug for therapeutic purposes with suspicion.

Within our society, it is recognized that both the community and medical fraternity display a fear or aversion to prescribing opioids. This “opiophobia” by both patients and clinicians is a real phenomenon that can preclude effective pain management, particularly on the grounds of fear of addiction (22). Based on the Canadian experience, it is important to determine if a similar phobia may be extended to cannabis here in Australia, due to its previous standing as a banned substance with a perceived high addiction potential leading to further illicit drug use.

It is important to understand if analogous concerns about cannabis might be held by palliative care patients. If it is shown that similar beliefs are held by clinicians and patients, education strategies could be developed to address these concerns, allaying fears and presenting factual information related to therapeutic effects and possible adverse outcomes.

I am not yet aware of the medicolegal opinion of medical defence organisations regarding doctors prescribing cannabis for medical purposes when evidence of efficacy is yet to be robustly proven. Many doctors may feel that they be exposing themselves to legal action if patients suffer adverse outcomes from the use of this drug. Concerns regarding inappropriate diversion already influence opioid prescriptions, and this may also be extended to cannabinoids.

3/ Level of Support by Terminally Ill patients

It is not known if there is widespread support for the use of this drug by Australian patients with end stage diseases. It is also not known how many patients would be personally interested in using cannabis for symptom control if considered appropriate by their treating clinician.

According to statistics collected by the Australian Institute of Health and Welfare, approximately 35% of Australians aged 14 years and over have used cannabis one or more times in their lifetime. Within the last year, approximately 10% of Australians, 14 years or over, have used cannabis (23).

As highlighted earlier, a Roy Morgan telephone survey conducted in October 2015, found that 91% of Australians are supportive of legalization of marijuana for medicinal purposes, and with the strongest support from people aged 50 years and older (24).

As recent media focus on patients with distress secondary to terminal cancer or resistant infantile seizures has probably had some influence on this widespread “in principle” support, it is not known if patients experiencing end of life issues would support the use of these agents.

Patients in the terminal phase of their diseases are very frail and may be susceptible to drug-drug interactions and side effects otherwise tolerated by healthier patients.

Any cannabinoid products, with even moderately low levels of THC, may not be well tolerated by terminally ill patients, leading increased morbidity and suffering. Until completion of high quality randomized control studies of cannabinoids in palliative care patients are completed, it is not known how predictably these patients will benefit (or react) to these products.

It is yet to be seen if there is much support once cannabinoid products (particularly locally sourced cannabis) become available and how these drugs benefit one of the patient groups targeted by this Bill.

4/ Access Issues

For those patients interested in using cannabis to control burdensome symptoms, bureaucratic processes around access and pricing may influence their opinions, interest and behaviour. If the authorization process is considered too burdensome, then patients may decide to either not pursue authorized access further or consider non-authorized supply of cannabis, as is currently happening anecdotally. As the cannabinoid products are not going to be subsidized under the PBS, this may also influence uptake on financial grounds. Many terminally ill patients and their families have invested much of their income and savings into therapies with the hope of prolonging life, with little financial resources left to use as the disease process becomes problematic. Additional costs of medicines can be prohibitive, as cost to benefit ratio becomes more important when discretionary income is minimal.

For doctors, the level of complexity in obtaining approval from both state and federal health organisations prior to commencing treatment may negatively influence doctors. Whilst there is no local cannabinoid products available, the process of sourcing this drug from overseas and negotiating with a pharmacy to dispense this medication, may also been seen as a strong impediment to therapeutic use.

In the palliative care setting, having to wait for up to 90 days for authorization is likely to be considered prohibitive. If this drug is to be used when all other reasonable therapeutic treatments have been exhausted, then having timely access to authorization is necessary when patients are in distress and have limited time to live.

5/ Practical Institutional Issues

Dependent on the level of support, the urgency at which services will need to develop strategies regarding prescribing and dispensing of prescribed cannabis (especially within institutions) to manage the expectations of both patients and their families, needs be identified and strategies created. With no guidelines yet available to direct prescribing, storage and dispensing processes, institutional uptake may be at best unpredictable and probably delayed compared to patient access.

There may be other institutional issues that have not yet been realized with regard the handling of this drug in facilities such as hospitals. I am aware that storage of patients S8 medications (particularly the wide range of various opioid products) in ward safes puts strains on current resources. Having yet another product requiring strict storage and handling obligations may be difficult for some health centres to accommodate. If the cannabinoid product needs aeration, then exposure of staff to components of the drug may occur. If the compound has significant levels of THC, then this may become a health and occupational safety issue.

6/ Post Dispensing Issues

Disposal processes will need to be developed when patients no longer need this agent (due to lack of therapeutic benefit, death, etc,). Currently there are no processes for preventing aberrant use of unused opioids in the community and prescribed cannabinoids may be susceptible to potential misuse. Doctors have no capacity to control the use of drugs once they have been dispensed to patients. Appropriate storage and use of these drugs is at the discretion of the patient and their family. Though patients and families are encouraged to take all unused prescribed medications to their pharmacist for dispensing, it is not known how many actually carry this out. It is not know for sure how many opioids prescribed in good faith to patients are abused by family members, especially once those drugs are no longer required for symptom control.

Doctors may be reluctant to prescribe cannabinoids if there is concern about the medicolegal status with regards diversion of unused drugs within the community. There will be concern that as the prescribing doctor, offences under the Act will be applied to them.

7/ Product Information

Care will need to be taken as to the level of information provided to patients about the use of the cannabinoid product that they have been prescribed. Patients will need to be provided with factual information about the scientific evidence supporting therapeutic use. As these drugs have not undergone the stringent testing procedures that other prescription drugs available within Australia have had, patients need to be aware of this and the implications for them.

8/ Implications regarding driving

As physical tolerance does not appear to be as high as for opioids, patients using cannabinoids will need to be cautioned about the long term risks with regards to driving and using machinery, etc. Road safety and licensing implications will need to be considered. It may be necessary for prescribing doctors to inform licensing bodies of cannabinoid use in their patients.

CONCLUSION

Patients, and their loved ones, who are struggling to deal with a terminal illness are particularly vulnerable to promises of cure or relief of difficult symptoms. They are also physically and psychologically susceptible to the adverse actions of drugs which may further detract from their quality of life. Terminally ill patients deserve to be treated with the most effective therapeutic agents available, with emphasis on improvement in the distress they may be suffering.

Research into cannabinoids is exciting and may promise significant therapeutic applications in the future. However, the evidence of significant efficacy is yet to be realized.

The push for legalization of medicinal cannabis for patient use has been predominantly community led, not by a concerted scientific or medical intent (though improved access to this agent for research purposes is welcomed). The public, especially the more vulnerable members with significant medical problems, need to be protected from possible harm that could be associated with this drug, just like any

other prescribed medication in Australia. This is particularly pertinent as the scientific evidence and knowledge about this therapeutic agent is still in its infancy. I have described issues that may influence the successful implementation of these legislative changes and expressed the concerns have regarding the introduction of this drug into the medical armament.

My concern is for palliative care patients and their doctors in the first instance. As a doctor working in the palliative care setting, I am always interested in new effective ways to control symptoms at end of life, but patient comfort and ease are my primary drivers.

I understand the legislative changes are in response to community support for access to cannabinoids for difficult medical conditions. However, I have concerns that due process in therapeutic drug assessment has not been completed with cannabinoid products, unlike other drugs approved by the Therapeutic Goods Administration.

If cannabinoids are to be made available to patients with significant medical conditions, then it is beholden on the legislature to provide guidelines that the executive can effectively implement and that medical and greater health community can operate under.

Thank you for opportunity to present to the committee. Please do not hesitate to contact me to discuss any of the issues I have raised in further detail.

Yours sincerely,

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REFERENCES

1. Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev. 2003; 83 (3): 1017–66.
2. Malfitano AM, Basu S, Maresz K, Bifulco M, Dittel BN. What we do and do not know about cannabinoid receptor 2 (CB2). Sem Immunol. 2014; 26:369-379.
3. Skaper SD, Di Marzo V. Endocannabinoids in nervous system health and disease: the big picture in a nutshell. Phil Trans R Soc B. 2012; 367: 3193-3200.
4. Akopian A, Ruparel N, Jeske N, Patwardhan A, Hargreaves M. Role of ionotropic cannabinoid receptors in peripheral antinociception and antihyperalgesia. Trends Phamacol Sci. 2009; 30(2): 79-84.
5. Fine PG, Rosenfeld MJ. The Endocannabinoid system, Cannabinoids and Pain. Rambam Maimonides Med J. 2013; 4(4): 1-15.
6. Welch S. Interaction of the cannabinoid and opioid systems in the modulation of nociception. Int Rev Psychiatry. 2009; 21(2):143-151.
7. Anand U, Otto WR, Sanchez-Herrera D, Facer P, Yiangou Y, Korchev Y, Birch R, Benham C, Bountra , Chessell IP, Anand P. Cannabinoid receptor CB2 localisation and agonist mediated inhibition of capsaicin responses in human sensory neurons. Pain. 2008; 138(3):667-680.
8. Cridge BJ, Rosengren RJ. Critical appraisal of the potential use of cannabinoids in cancer management. Cancer Manag Res. 2013; 5; 301-313.
9. Darmani NA. Δ^9 – Tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB_1 receptor antagonist/inverse agonist SR 141716A. Neuropsychopharmacology. 2001; 24(2):198-203.
10. Kirkham TC. Cannabinoids and appetite: Food craving and food pleasure. Int Rev Psychiatry. 2009; 21(2):163-171.
11. FriedmanD, Devinsky O. Cannabinoids in the treatment of epilepsy. NEJM.2015; 373(11): 1048-1058.
12. Koppel BS, Brust JCM, Fife T, Bronstein J, Youssof S, Gronseth G, Gloss D. Systematic review: Efficacy and safety of medical marijuana in selected neurological disorders – Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014; 82: 1556-1563.
13. McLaren J, Swift W, Dillon P, Allsop S. Cannabis potency and contamination: a review of the literature. Addiction. 2008; 103:1100-1109.
14. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use: A systematic review and meta-analysis. JAMA. 2015 Jun 23-30; 313(24): 2456-2473.
15. Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. Harm Reduct J [Internet]. 2005 Oct [cited 2015 Aug 3]; 2:18. Available from: http://www.harmreductionjournal.com/content/2/1/18 DOI:10.1186/1477-7517-2-18.
16. Webb CW, Webb SM. Therapeutic Benefit of Cannabis: A Patient Survey. Hawaii J Med Public Health. 2014; 73(4): 109-111.
17. Borrás R, Modamio P, Lastra CF, Marino EL. Medicinal Use of Cannabis in Spain. Altern Ther Health Med. 2011; 17(5):52-54.
18. Bar-Sela G, Vorobeichik M, Drawsheh S, Omer A, Goldberg V, Muller E. The medical necessity for medicinal cannabis: prospective, observational study evaluating the treatment in cancer patients on supportive or palliative care.

Evid Based Complement Alternat Med. 2013 Jun [cited 2015 Nov 14]. Available from: http://dx.doi.org/10.1155/2013/510392

19. Waissengrin B, Urban D, Leshem Y, Garty M, Wolf I. Patterns of use of medical cannabis among Israeli cancer patients: a single institution experience. J Pain Symptom Manage. 2015 Feb; 49(2): 223-230.
20. Belle-Isle L, Walsh Z, Callaway R, Lucas P, Capler R, Kay R, Holtzman S. Barriers to access for Canadians who use cannabis for therapeutic purposes. Int. J. Drug. Policy. 2014; 25: 691-699.
21. New South Wales Government. Australian-first medical cannabis trial begins in NSW. [Internet]. 2015. [cited 2016 Mar 4] Available from: https://www.nsw.gov.au/media-releases-premier/australian-first-medical-cannabis-trial-begins-nsw.
22. Bennett DS, Carr DB. Opiophobia as a barrier to the treatment of pain. J. Pain. Palliat. Care. Pharmacotherapy. 2002; 16(1): 105-109.
23. Australian Institute of Health and Welfare. Illicit use of drugs (National Drug Strategy Household Survey 2013 key findings). [Internet]. 2016. [Cited 2016 May 3] Available from: http://www.aihw.gov.au/alcohol-and-other-drugs/ndshs/2013/illicit-drug-use/
24. Roy Morgan Research. A massive majority of Australians support the legalisation of medicinal marijuana – Article No. 6517. [Internet]. 2015 Oct 26 [cited 2016 Apr 13] Available from: http://www.roymorgan.com/findings/6517-massive-majority-of-australians-support-legalisation-of-medical-marijuan-20151025317