Submission to the Victorian Law Reform Commission

MEDICINAL CANNABIS REFERENCE

Number	24
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To VLRC
Re Medicinal Cannabis Issues Paper March 2015

Firstly may I congratulate all concerned on the quality and range of material covered in the March Issues Paper.

I do not intend to comment here on many details, but on the critical issues, which will have to be resolved to achieve a workable outcome.

There are, in my view, three outstanding areas where careful planning must be undertaken.

- **One is that, as documented below, the 'skunk' cannabis with very high THC content which has flooded the market over more than a decade is not appropriate for use as medicinal cannabis. It will be necessary to oversee development of a relatively low cost product with equivalent levels of both THC and CBD, and ideally, also a high CBD content product with negligible THC to be available as an alternative. Expert international advice may be needed, or access to specialized strains now in use in some locations overseas.**
- **The second issue is complying with International and Commonwealth legislation. Gaining joint action with other States (initially NSW) may well be necessary for this. I believe it will end being designated as a regulated 'herbal' product rather than registered under the Therapeutic Goods Act. Regulation would be a requirement of the Commonwealth to meet constrains of the Narcotic Substances Act etc. Development of purified, TGA registered products entails long delays and high prices. Recipients are likely to fall back on use of illegal marijuana, at a fraction of that cost, despite its hazards.**
- **Use of a herbal product without the usual rigorous trials with testing of outcomes, dose and side effects would be unlikely to be acceptable to medical practitioners for**

'prescription'. However, a patient becoming an authorized recipient might require a statement from an appropriate medical practitioner as to clinical status if distribution is regulated by the State for sufferers of particular medical causes.

The legal issues to be resolved with the Commonwealth are formidable. Having NSW on the same path, and a public expression of support from the Prime Minister in 2014, will both help. The discussion of Regulatory issues in Section 4 is valuable.

There was reluctance of the TGA and Health officers to be involved, which I heard before the Senate Committee on Legal and Constitutional Issues in Canberra on 2 April. A number of practical issues were raised before the Senate Committee, including oversight of manufacturing, testing of quality, management of emerging evidence of side-effects as normally handled by TGA. There were references to Commonwealth and State roles in opium processing and manufacturing. The 2014 Bill before the Senate is seen as having many problems quite apart from the issue of a separate and costly regulatory structure in parallel with the TGA.

My view is that a relatively simple arrangement, explicitly built around State legislation, with national consultation, through a Standing Committee of AHMAC, is preferable. This could provide communication and co-ordination between the Commonwealth and States in regulating the production and use of cannabis products for medicinal purposes. Such an approach would require full consultation seeking common ground on important matters, with expert and professional advice as necessary. Consensus could be sought on many issues to facilitate Commonwealth support. Appropriate agreement on sharing of information and products between States would be desirable.

Commonwealth resolution of the legal obstacles could be made contingent on such common agreement between States; this would be a powerful incentive to gain consensus. AHMAC's Standing Committee could provide a channel for ongoing consultation between the Commonwealth and the States. Legal, medical and scientific advice could readily be provided to this Committee. States already have legal responsibility for regulation of opium poppy production and manufacturing; this framework could be applied to cannabis.

The proposed structure would not require major legislation or budgetary provision if the two largest 'players' have planning and development programs underway.

There is widespread reluctance within the medical profession to prescribing medicinal cannabis. An important issue frequently raised is literature pointing to a link of cannabis with the onset of psychosis, particularly schizophrenia. The link is far from simple. Opponents putting this view ignore much important recent research, raising the possibility of producing a form of cannabis not carrying this risk. The other substantive objection is the lack of rigorous clinical trial evidence, largely due to the current illegal status of cannabis and its variable herbal nature. Doctors handle single pharmaceutical agents subject to normal randomized, double blind testing with careful categorization of outcomes, dose response relationships, evidence of side effects and interactions with other pharmaceuticals. These issues raise questions of medical-legal risk associated with medical prescribing of medicinal cannabis.

There is now growing evidence that one component of cannabis – cannabidiol or CBD - counteracts the negative effects of the potent and psychotogenic THC on the brain.□ A very important paper is from the London Maudsley Institute, of which the leading British research psychiatrist Sir Robin Murray is an author.[2] It provides direct evidence that the problem is with the type of marijuana used.
In study of a large group of persons with first-onset psychosis, the strong association with use of cannabis is confined to 'skunk' cannabis - approximately 2/3rds of cases of psychosis - whereas even heavy use of 'hash' cannabis (more commonly used in South London than 'skunk') showed no association with psychosis. The difference is attributable to CBD and presumably other elements derived from the stems and leaves of the plant such as 'terpenes' present in 'hash' cannabis.

CBD is not 'stimulatory' in the psychoactive sense and suppresses the effects of THC on the CB1 and CB2 cannabinoid receptors. The study in [(1)] demonstrated there was no overlap between the areas of brain stimulated by THC and CBD and there are now studies of possible benefit from CBD treatment in early psychosis.[3,4] CBD is probably the principal agent suppressing seizures in Dravet Syndrome and related conditions. Formal trails are in progress internationally.[5]

The Maudsley research group has also played a key role in identifying the genetic factors which lead to some individuals being susceptible the psychotogenic effects of THC, the most important of which is a variant of the AKT1 gene, one of the genes known to be associated with schizophrenia.[6] They see these genetic elements as an important subset of the causes of schizophrenia.[7]

Those proposing purified CBD as the answer to medicinal cannabis need to be aware of cost. The British company producing Savitex, which contains both TCA and CBD (G W Pharmaceuticals) is conducting Phase 3 trials in juvenile epilepsy of a 'nabiximol' of CBD (Epidiolex containing no THC). England and Scotland rejected funding for Savitex, for use in muscle spasm and pain in MS. Epidiolex being developed for the much smaller market of juvenile epilepsy is unlikely to be less costly. In several countries Savitex is available as a medicinal cannabis, but people can fall back on using cheap and readily available illicit marijuana as an alternative. Nonetheless, the company has successfully listed on NASDEQ.

The preparations approved by the Dutch Office for Medicinal Cannabis, through Bedrocan BV, are less refined products than the British nabiximols. It offers five with regulated content of THC and CBD - one with CBD content slightly above THC (Betroil) and one (Betrolite) with high CBD and little or no THC; others are high in THC content. Bedrocan BV supplied Italy with its standard product for their medicinal cannabis program in 2014, but charged 37.5 Euros for 5g when a daily dose was up to 1.5g. Italy has now decided to produce its own to bring down the cost. It is interesting that Bedrocan BV became an approved supplier for medicinal cannabis in Canadian in January 2015, setting up a subsidiary in Canada. It is offering its five products, at a price of $C 7.5 for 1g of each product. It has also had a highly successful NASDEQ listing. It owns stains of cannabis plants, one producing CBD but no THC. This makes manufacturing simple to achieve the desired ratios of active ingredients.[8]

Israel has a patented strain of cannabis producing CBD but not THC and seeks international collaborations. Other strains, such as that of 'Charlotte's Web' cultivated for high CBD to treat Dravet Syndrome in the US, are also to be found on the Web. Some US States have approved only use of

CBD rich 'medicinal cannabis' and processes are being developed to simplify removal to THC from existing cannabis preparations, without diminishing CBD content.

The findings of the studies cited in the footnotes open the way to development of relatively simple and cheaply produced medicinal cannabis products in Australia to form the basis of clinical use in affording relief to patients in need, such as those suffering painful cancer and the traumatic processes of intensive chemotherapy and to support the conduct of further trials in other conditions.

Other comments on the Issues Paper are as follow:

1. **P 9, 2.17 – I do not believe the statement in the last sentence is supported by reliable science and its presence is confusing. Early studies were likely to be confused by minor impurities in TCA and CBC. The study referred to in [(1)] is not compatible with this statement in 2.17.**
2. **P 11 ref 32 is a matter of opinion not supported by the many recently committed trials in clinical situations. There are many reports of its use.**
3. **The section on Nabiximols, p 16, 17 discusses GW Pharmaceuticals products at length but no mention is made of the competing Dutch Bedrocan products. Whilst these are less refined, they are direct competitors with regulated concentrations of TCA and CBD. They are mentioned on pp110, 111 and 126.**
4. **The section on potential side-effects pp42-48 needs to be reconsidered as most data relates to whole and uncontrolled cannabis use. The lack of evidence in many clinical situations reflects the influence of its illicit status, whereas other recent findings in US States with long-standing medicinal cannabis laws[9], indicate widespread use in those States with very significant reduction in overdose deaths from opioids, suggesting opioid users are turning to cannabis through choice.**
5. **Developmental research on potential cannabis products will be needed. Reliable cannabis products from a stable strain, with identified content of THC and CBD, should be produced, and another rich in CBD and related compounds such as 'terpines' found in 'hash oil' products. The latter will take longer to achieve.**
6. **There is an important task in liaising with the medical professional education once safeguards to be applied**

with the products to be used are defined. There needs to be recognition that further valuable products and reliable evidence of benefits from use in particular situations will evolve over at least the coming 5-10 years.

7. Fears over medico-legal hazards in prescribing a herbal remedy can be overcome if effective regulation of the products is established, and the role of the medical practitioner is that of certifying, with the patient's agreement, the nature of the patient's clinical condition, in relation to those uses approved by legislation. The legislation could require this as a condition to register as a medicinal cannabis user. The relationship between doctor and patient would not be disturbed with the doctor free to give advice at any stage.
8. There is a strong need for clinical trials in various targeted clinical conditions, but in reality these will mostly need to be 'open label' trials rather that randomized double blind trials as recipients are committed to receiving the medication. Formal randomized trials, where conducted, would need to be fully funded over extended periods whereas 'open label' trails would still produce valuable clinical information, of particular relevance to new domains of use.
9. Trials in new fields should require sponsorship by a senior specialist or organization in that field, taking account of number of subjects, cost, the likely benefit or any risk entailed, and processes for regular reporting unless being conducted as a strict conventional double blind trial in comparison with current therapy

Further comments on specific Questions from pp 170, 171 are attached and expand on the above.

[1] Bhattacharyya S, Morrison P.D, Fusar-Poli P et al 2010 Opposite effects of Δ -9-tetrahydrocannbinol and cannabidiol on human brain function and psychopathology. 2010 Neuropsychopharmacology 35:764-774 An international paper which includes Murray RM as a co-author.

[2] Di Forti M, Marconi A, Carra E, et al Proportion of patients in South London with first-episode psychosis attributable to use of high potency cannabis: a case-controlled study. 2015 Lancet Psychiatry 2:233-8

[3] Morgan CJ and Curran HV Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis 2008 Br. J Psychiatry192: 306-7

[4] Englund A, Morrison PD, Nottage et al Cannabidiol inhibits THC elicited paranoid symptoms and hippocampal-dependent memory impairment. 2013 J. Psychopharmacol 27:19-27

[5] http://www.dravetfoundation.org/research/participate-in-research (accessed 13.5.15)

[6] Di Forti M Iyegbe C, Sallis H et al Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. 2012 Biol Psychiatry 72: 811-6

[7] Howes OD and Murray RM Schizophrenia: an integrated sociodevelopmental-cognitive model. 2014 Lancet 383:1677-87.

[8] Information on both GW Pharmaceuticals PLC including its range of clinical trials and Bedrocan NV and its Canadian derivative, together with data on their products, are accessible on their websites (accessed on 4. 4.15)

[9] Bachhuber MA, Sloner B, Chinazo O et al. Medical cannabis laws and opioid analgesic overdose deaths in the United States 1999-2010. 2014. JAMA Intern Med 174: 1668-73.

VLRC Medicinal Cannabis Inquiry

Answers to specific numbered Questions in March Issues Paper (Question not repeated):

1. (a) and (b).

2. Cancer patients with pain unresponsive to treatment to a level coping with a patient's needs, and patients undergoing intensive chemotherapy with severe nausea not readily controlled by other medication. Adults with painful muscle spasms associated with multiple sclerosis. Children with intense epilepsy not readily controlled by normal anti-epileptic therapy. Consideration should be given to including 'patients living with HIV', some of whom have real disabilities.

3. (a) Should be covered by parental consent following medical advice.
(b) Next of kin should be able to authorize.

4. (a) A list of medical conditions as long as there is a capacity to explore further conditions on the basis of trials (including open label trials).
(d) The term 'failed' needs qualification. Results, such as heavy use of morphine may be partially effective, but still not provide sufficient support to the patient who finds morphine addiction distressing. The 'euphoria' component of sensations which can be associated with THC use is a valid benefit to a distressed patient in a long painful process leading to death.

5. Yes as discussed in my comments.

6. I strongly support the strategy suggested in Section 4.

7. I suggest persons approved as recipients under the legislation, following a report on their condition from an appropriately qualified medical practitioner, should be registered as a user and warned not to drive a car whilst under the influence of cannabis. A panel of patient advisors should be recruited who are knowledgeable about alternative products and methods of administration. The Cancer Council of Victoria might assist with this process for cancer sufferers.

8. The Legislation should provide adequate protection, by agreement with VicPol.

9. The pattern of supervision of opium crops should be followed. There are several producers currently approved in Victoria and might well diversify to grow particular cannabis crops, once approved strains have been selected and are available.

10. Processing and wholesale distribution will need to be through an authorized producer appointed by Government, subject to observing the *Australian Code of Good Manufacturing Practice for Medicinal Products.* Retailing should be by approved pharmacists.

11. By agreement with the Commonwealth, common principles should apply to State based authorized processes. Such continuing consultation to ensure agreement between States should be through a new Standing Committee of AHMAC, with representation of each State considering supply. Agreement to should be sought to share access to medicinal cannabis products between States.

12. Medical practitioners should authorize the clinical status as warranting access to medicinal cannabis in accordance with the legislation, but not to formally prescribe the herbal remedy which will not have been entered into the Register of Medical Products by TGA.

13. Certainly recognized specialists in the field of disease from which the patient is suffering. Palliative care is now increasingly being offered at the primary care level, seeking to have more patents die at home. Under these circumstances where a patient desires access to medicinal cannabis, I believe a GP should be able to authorize registration and access. New uses and proposers of trials should necessarily involve specialist practitioners in the field concerned with a central panel advising the 'Secretary of Health' prior to final approval.

14. Monitoring and data collection on outcomes and side effects is highly desirable, but should not be so complex as to impair establishment of a successful program. A nominating medical practitioner might be requested to report on the patient after each 6 months. Adding a GP jointly with the primary nominator (usually a specialist) might be a good alternative approach.

15. Important not to be unduly intrusive or regulatory. GPs to manage.

16. As discussed on my general comments, I believe there will be a need for two:
(1) a general purpose product with comparable content of THC and CBD (the latter with other 'hash components'). This will entail removal of excess THC in the 'manufacturing' stage, unless we have accessed a strain providing the necessary balance.
(2) A CBD rich preparation with little or no THC, for use by any people who are troubled by the psychotropic effects of THC in the above preparation, and for use in neurological conditions.

17. Should be supplied as desiccated, fragmented leaf, or 'hash oil', with external designation of %content of THC and CBD, in a quantity appropriate for up to 2 weeks supply at a dose, based initially on Dutch experience of 0.5-1.4g daily. Recommend use as 'tea' or through cooking with known number of drops of oil per morsel, matching the above. Use of vaporizers is supported, at the patient's cost. Smoking is discouraged but it will be impossible to prevent.