A man with MS asking about medicinal cannabis

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A 56-year-old man with multiple sclerosis is experiencing pain, spasticity and poor sleep. Is he a candidate for medicinal cannabis and, if so, is it legal for his son to buy some for him?

Case scenario

Michael, aged 56 years, has chronic relapsing multiple sclerosis (MS) and walks with a frame. He has significant balance problems, reduced strength, particularly of the left leg, and experiences significant muscle cramping in his left calf and hamstring. He has also developed troublesome symptoms related to spasticity affecting the lower limbs and bladder. In addition, he sleeps poorly.

Eight months ago, Michael presented with sciatic pain radiating down the right leg and was diagnosed with facet joint arthritis affecting the right L4/5 nerve outlet. Corticosteroid injections have not improved his pain, and surgery has been deferred. Despite his balance problems, Michael has been taking pregabalin 300 mg twice daily but this also does not satisfactorily control the pain.

Michael wants to know whether he is a candidate for medicinal cannabis (also known as medicinal marijuana), how it may help his cramping and poor sleep and whether he can continue taking pregbalin with cannabis. If cannabis is a suitable treatment for him, can he legally use cannabis that his son purchases for him or would this place his son in legal trouble?

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Commentary

Provision of medicinal cannabis is a topical yet controversial issue currently generating much debate among the general public, healthcare providers and policymakers. Requests similar to Michael's are becoming a relatively frequent scenario encountered by many medical practitioners, whereby patients make desperate enquiries into the use of medicinal cannabis either for symptoms refractory to conventional treatments or for conditions without an effective treatment.

History of cannabis use

For over 4000 years, cannabis has been used medicinally, recreationally and in religious ceremonies in cultures around the world. The earliest evident medicinal use was by the Chinese in around 2700 BC for conditions such as pain, malaria and female reproductive disorders and as an anaesthetic for surgical procedures.[1,2] Reports from the early 19th century have documented the use of cannabis preparations by the Europeans for muscular spasms.[2]

Medicinal cannabis refers to use based on prescription or recommendation by a registered physician for a medical condition in which efficacy has been demonstrated.[1]

Cannabis is the most commonly used illicit drug in the USA and accounts for around 75% of all illegal drug use.[3] This has led to concerns about legalising its use, including that for medicinal purposes.

Constituents and effects

The term marijuana usually refers to crude plant material (e.g. leaves) from *Cannabis sativa* or *C. indica*, while cannabis is a more generic term to encompass the several psychoactive preparations of the *Cannabis* plant.[4] There are over 110 identified cannabinoid compounds found in the plants. Of these, tetrahydrocannabinol (THC) and cannabidiol (CBD) have been most studied for medical purposes. THC is a psychoactive compound well known in the recreational arena for its euphoric effect, while CBD is largely nonpsychoactive.[5]

Cannabinoids exert their effects via cannabinoid receptors (CB1 and CB2). CB1 receptors are concentrated in the central nervous system (CNS), particularly in the brain, spinal cord (especially dorsal root ganglia) and peripheral nerves.[5,6] The CB2 receptors are predominantly found in the immune system's lymphatic tissue and in low concentrations in some brain regions, including the periaqueductal grey matter.[5,6]

THC and CBD have varying affinities for these receptors; this gives them their different effects. When cannabinoid receptors are activated, there are various physiological responses according to the region of the CNS affected. These include:[5]

- a feeling of wellbeing
- psychosis
- reduced spasticity
- reduced nausea
- sleep initiation
- slowing of motor function
- impaired memory and cognition.

Medicinal cannabis

Medicinal cannabinoid preparations are usually administered orally, oromucosally or intranasally. Formulations include various combinations of THC and CBD in different ratios or stand-alone compounds. These can be derived from the natural plant or be synthetically produced.

Nabiximols

A preparation of nabiximols that was first approved in Canada in 2005 [2] has been TGA registered, but not marketed, in Australia since November 2012 as a treatment for moderate to severe spasticity due to MS. This oromucosal spray of nabixomols is extracted from *C. sativa* and contains roughly equal amounts of THC and CBD.

Medicinal uses of cannabis

The greatest evidence for using medicinal cannabis has been in reducing symptoms such as spasticity, chronic neuropathic pain and chemotherapy-induced nausea and vomiting, and in stimulating appetite in patients with cachexia or HIV/AIDs-related anorexia.[1] Preliminary evidence suggests it may be helpful in refractory epilepsy. The most promising and consistent results are from class 1 studies (i.e. randomised controlled trials) in patients with MS. These studies have consistently demonstrated efficacy in the treatment of spasticity and pain.[7]

Use in multiple sclerosis

Early scientific evidence for the effect of cannabis in MS came from rat models showing improvement in spasticity following agonism at the cannabinoid receptors.[5] The American Academy of Neurology has published a recent systematic review that reported strong evidence of cannabinoid use helping to alleviate patients' self-reported symptoms of spasticity, such as reducing frequency of spasms and improving pain scores.[6] However, objective assessments of spasticity, such as the modified Ashwork scale, did not show statistically significant improvements.[6]

Spasticity is a common problem experienced by patients with MS, with a prevalence as high as 84%.[8] Moreover, spasticity is frequently refractory to first-line treatment options such as baclofen and dantrolene – whose use is also limited by their sedative effects. Therefore, in patients with MS, spasticity significantly contributes to reduced quality of life through pain, impaired mobility and function, urinary dysfunction and poor sleep.

As such, it comes as no surprise that up to 20% of patients with MS are reported to use cannabis regularly, with recent Canadian and UK studies finding that about 50% of patients have used it at some point in time.[9,10] Around 90% of patients with MS have reported interest in using cannabis if it was legalised.[9]

Will Michael benefit from medicinal cannabis?

Michael has some symptoms including pain and debility associated with spasticity and cramps, which may qualify him for the use of medicinal cannabis. However, his radicular pain and poor sleep are less likely to respond to cannabinoids. Although cannabinoids have shown some efficacy in pain associated with spasticity in MS, cancer and HIV, evidence in other painful conditions including neuropathic pain is inconclusive.[11]

Sleep quality and spasticity have been shown to improve in patients with MS after cannabis use compared with placebo.[7] However, Michael's poor sleep may be multifactorial in nature and therefore may not appreciably respond to the use of cannabis. Although it may be beneficial for sleep initiation, tolerance may develop over time, potentially leading to cannabis-use disorder. Sleep disturbances are also a primary symptom of cannabis withdrawal and may be a significant risk factor for relapse and abuse.[12]

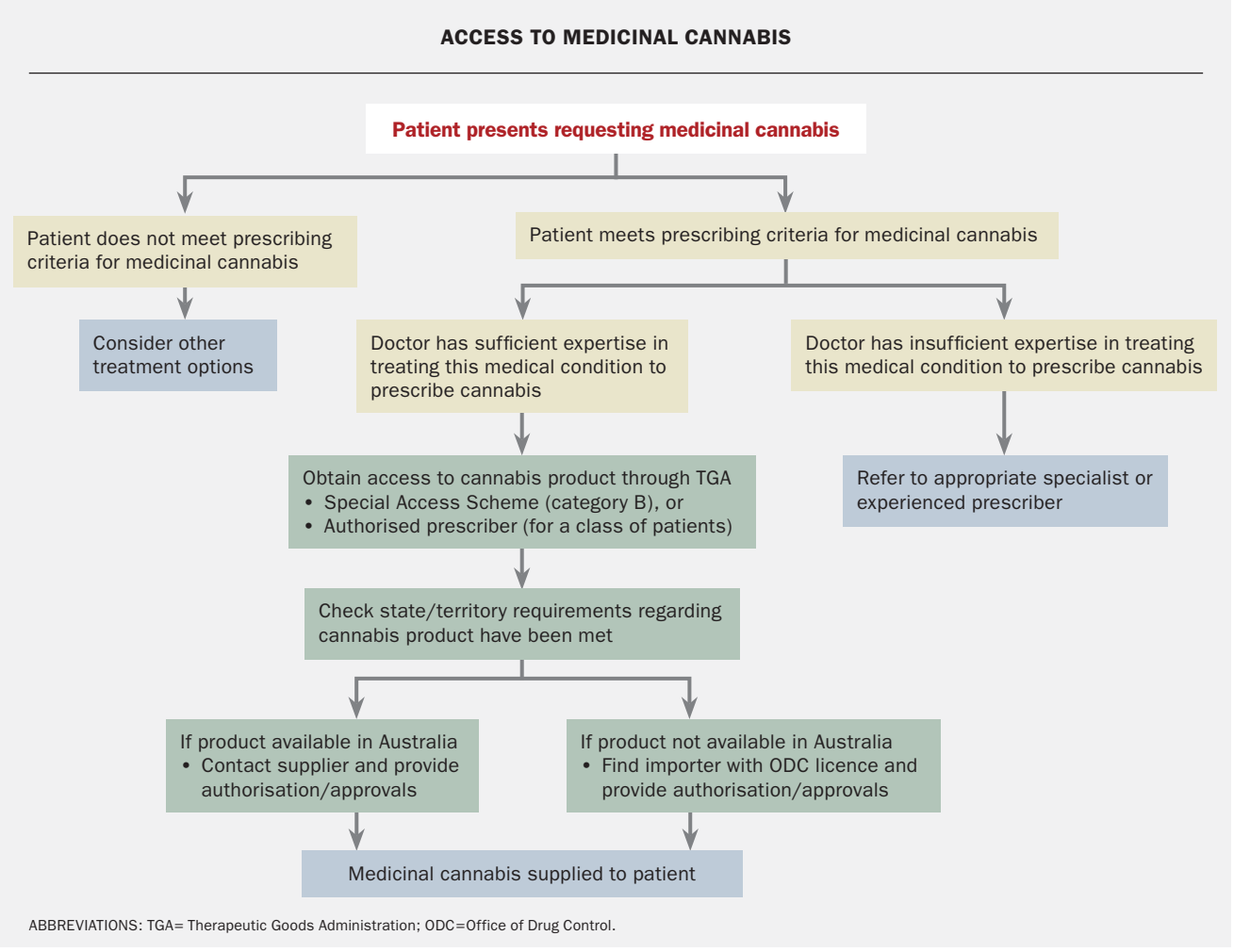
In Michael's case, more conventional treatments will need to have been tried and to have failed before consideration for access to medicinal cannabis. These may include various antispastic medications, such as baclofen and dantrolene, as well botulinum toxin injection, usually in combination with physical therapies, such as muscle stretching and massage. Other neuropathic agents such as tricyclic antidepressants may be useful for his radicular symptoms as well as improving sleep.

It needs to be emphasised to patients such as Michael that although medicinal cannabis may help improve their symptoms, there is currently no evidence that it treats or cures the underlying condition.[3]

Accessing medicinal cannabis

Globally, legislation governing cannabis use is complex and greatly varied for both general and medicinal uses. The use of cannabis-based products is approved in some countries including the UK, Denmark, Czech Republic, Austria, Sweden, Germany and Spain. In the USA, recreational use is legal in 18 states and medicinal use is legal in 23 states.[1]

In November 2016, medicinal cannabis became a controlled drug (Schedule 8) in the Poisons Standard. The states regulate



ABBREVIATIONS: TGA= Therapeutic Goods Administration; ODC=Office of Drug Control.

cannabis cultivation with Victoria having harvested its first cannabis crop for use in patients with epilepsy.

In Australia, the Federal Government facilitates access to medicinal cannabis to appropriate patients for medical conditions where there is documented evidence supporting its use. However, rules relating to its use may differ between states and territories and subsequently may affect access.

The Commonwealth Department of Health regulates medicinal cannabis through the Therapeutic Goods Administration (TGA) and the Office of Drug Control (ODC) – which provides more detailed information online (www.odc.gov.au/australian -advisory-council-medicinal-use-cannabis -aacmc).

Obtaining patient access

Patients wishing to access medicinal cannabis require an Australian registered medical practitioner with appropriate qualifications and/or expertise in treating the specific medical condition to obtain approval under the relevant state or territory laws. The doctor can also apply on the patient's behalf for approval to import and supply such products either through the Special Access Scheme (SAS) or by becoming an Authorised Prescriber. In addition, doctors will then need to obtain import permits from the ODC. The steps required are summarised in the Flowchart.

GPs are not explicitly excluded from applying for authority. However, the applicant is expected to have skills and expertise in managing patients with the disease using the cannabis product, and also to usually have a shared-care treatment arrangement in place with an appropriate specialist. Further information regarding access to medicinal cannabis in Australia is available on the TGA website (tga.gov.au/access-medicinal-cannabis-products and tga.gov.au/ access-medicinal-cannabis-products-steps-using-access-schemes).

Legal considerations

Importantly, cannabis remains a highly regulated drug in Australia. The use and supply for nonmedicinal purposes or access via alternative means is illegal. For this reason, Michael needs to be informed that his son may be contravening the law by purchasing the product.

Legitimate concerns surrounding the use of plant cannabis and other unregulated forms are based on the variations in relative doses of THC, CBD and other components in the plant species and preparations.[3] This results in uncertainties regarding their potential effects or harms in clinical care. Compounding this are concerns pertaining to quality, contamination and lack of close regulation of methods of preparation.

Adverse effects

Patients using medicinal cannabis should be counselled on the potential adverse health effects. Recent reviews have suggested that around 10% of adults who use cannabis develop dependence or addiction and this appears to be higher among younger users.[13]

Acute effects experienced by a non-regular user may encompass impairment of cognitive processes such as attention, concentration, memory, planning and decision-making. Other effects may include lowered impulse control, slower reaction times and impaired motor control.[13]

Among chronic users of cannabis, persistent impairment in cognitive processes has been observed. Withdrawal symptoms may occur on discontinuation of cannabis and may include irritability, anxiety, restlessness and sleep disturbances, occurring within 48 hours and lasting between two to 12 weeks following cessation.[4]

Driving

Patients should be advised against driving or operating machinery while using cannabis due to the CNS effects. Currently under the NSW Road Transport Act, it is illegal to drive under the influence of illicit drugs including cannabis. This is a significant issue in patients who are prescribed medicinal cannabis.

It is contended that roadside drug testing implemented by police can only detect THC in saliva up to a maximum of 12 hours after consumption, but some of the newer devices being used are claimed to detect THC 30 hours after consumption – long after a person stops being affected.

This has created considerable debate about to how long to wait before driving after using cannabis. Attempts to facilitate the use of medical cannabis in Australia will require changes in driving legislation similar to those applying to the consumption of medicinal morphine.

Drug interactions

Evidence regarding drug interactions with cannabis is limited but cannabinoids may interact with a variety of medications, such as opioids, barbiturates, CNS depressants, protease inhibitors, selective serotonin-reuptake inhibitors, sildenafil, tricyclic antidepressants, anticholinergics, sympathomimetics, corticosteroids and antipsychotics. It may also interact with drugs metabolised by various hepatic enzymes including the cytochrome P450 system.[4,13]

Although there is no specific evidence for an interaction with pregabalin, Michael should understand that there may be potential for additive CNS depressant effects.

Conclusion

Unfortunately, there are still major gaps in our knowledge about using cannabis for medicinal purposes. The evidence base for clinical use of herbal cannabis is thin, and a number of fundamental uncertainties remain to be addressed, such as the pharmacological effects of diverse cannabinoid compounds and whether different therapeutic properties are observed with the various strains of cannabis.

The challenge faced by the medical profession is to close this knowledge gap and help our patients make an informed decision, knowing that many patients will manage to obtain access to cannabis in one way or another.

Currently, the process of obtaining cannabis for medicinal purposes is rigorous and requires careful assessment and discussion among patients and healthcare providers regarding potential benefits and risks. Additionally, policymakers need to address related legal matters, such as driving regulations, which represent another barrier in the use of medicinal cannabis. MT

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