The myths of medical marijuana

by Dr John Whitehall



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NSW Premier Mike Baird, supported by Prime Minister Tony Abbott, has announced plans to begin clinical trials of medical marijuana. The move follows a vigorous media campaign, backed by Greens, Coalition and Labor MPs.

Professor Whitehall raises key questions Australian governments need to consider before the trials begin.

Refractory epilepsy used to be considered a curse, and remains one of life's great afflictions. So it is not surprising that parents of an afflicted child will consider all possibilities for cure. But what should be made of recent publicity that "medical marijuana" has stopped convulsions and reduced associated brain dysfunction in two children in such miraculous manner that its advantages deserve to be available not only for epilepsy but for all kinds of other diseases?

Such publicity recently emerged in the US. Charlotte Figi (aged 7) suffers from Dravet Syndrome, a rare genetic disorder associated with severe developmental delay and sudden convulsions or "fits". These seizures in Dravet Syndrome resist medication and may occur throughout the day and night.

Charlotte was afflicted until reportedly transformed by a tincture of marijuana or cannabis provided by private growers in Colorado. She has become a kind of mascot for the medical use of the herb in the US. The strain of marijuana she takes is known as *Charlotte's Web*, and Congress in Pennsylvania has just introduced a bill to legalise its distribution in that state. The bill is known as "Charlotte's Web Medical Hemp Act" and, if passed, Pennsylvania will join the 23 other US states that have legalised marijuana for medical purposes.

The story of Australia's Tara O'Connell (aged 8), has also emerged. Media reports have told how Tara had been stricken with convulsions and neurological damage since she was a baby. Then a tincture of marijuana supplied free of charge from Nimbin in northern NSW stopped the fits, virtually from the first dose.

But can marijuana prevent fits? Despite the rare but exciting anecdotes, no one knows. No reliable trials have been published anywhere in the world, according to the reputable Cochrane system of review. The drug has been available for medical purposes, including epilepsy, in California for almost 20 years. It is now available in 22 US states. But there is nothing to report!

Despite repeated claims of "potential" for the drug, there is silence, though all humanity is crying out for better anti-epileptic drugs. This silence could mean there is no convincing effect, or that the doctors who prescribe it have no idea of what is happening to their so-called patients. If it were a miracle drug, it could be expected that the purveyors of marijuana would trumpet statistical success.

What is 'medical marijuana'?

Medical marijuana is said to be an extraction from *Cannabis sativa* and *Cannabis indica* plants containing over 60 chemicals in the cannabinoid family, the most abundant ones being tetrahydrocannabinol (THC) and cannabidiol (CBD).

THC is known for its psychoactive effects. It stimulates receptors on brain cells that constitute a complex neuronal circuit that involves at least the mid-brain, temporal lobe and frontal cortex. Stimulation of the circuitry by THC produces the euphoria and associated cognitive effects that constitute the "high" – the reason it is consumed in "recreational" use.

CBD does not stimulate those receptors but acts on other, as yet undefined receptors in brain, blood and lymph tissue. One of the actions of CBD appears to be a kind of check and balance on the stimulatory effect of THC. These natural receptors were not discovered until the 1980s. It took several more years to elucidate the existence of natural cannabinoids, which are produced in the brain in tiny amounts to act upon the various receptors which are now known to exist throughout and beyond the brain.

Much of the details of the natural system remain unknown, but tiny and controlled amounts of cannabinoids contribute to brain cell proliferation, migration and maturation, including the establishment of the myriads of connections between the cells. As well as being involved in brain development, natural cannabinoids also appear to modulate the functioning of the established brain. As various cannabinoid receptors have been found in blood, immune and gut cells, their function is diverse. The receptors are found throughout the placenta, with implications for the unborn baby.

Medical marijuana is an unquantified mixture of cannabinoids and other components derived from cannabis (marijuana) plants. It is usually inhaled or swallowed in order to stimulate the natural receptors in the hope of masking pain, spasms, nausea and, in Tara's case, the uncontrolled electrical events of epilepsy. With epilepsy, the modulating CBD appears more relevant than the psychoactive THC, but THC appears more relevant for pain and spasms. Plants can be grown to maximise one component while reducing the other.

What does marijuana do to the brain?

Reports of marijuana's harmful effects on the brain continue to accumulate. US experience reveals that, although the drug was released for the stated purpose of relieving pain in the terminally ill, its use has spread far more widely.

The brain is thought to consist of over a trillion cells. It beggars imagination that each of the neurons may have up to 10,000 connections with close and distant neighbours and is maintained by even more numerous supporting cells that provide nutrition, remove waste, ensure consistency of surrounding fluid, lay down insulation to speed the passage of information, and fight infection. Of course, this magnificent mass is not constructed overnight. Much growth occurs before birth, but much continues throughout adolescence with delicate fine tuning and pruning of cells and circuits. If the system is guided in any way by tiny amounts of natural cannabinoid secreted and removed in accordance with local needs, it is not hard to imagine that relative and recurrent deluges of exogenous cannabinoids may mess it up.

The literature on brain damage from

cannabis is extensive and grows yearly. Former Professor of Anaesthesiology and now Adjunct Professor of Law at Georgetown University, Peter Cohen, who is prominent in the National Institute on Drug Abuse, says the consensus of "workers in the field" is that chronic use may be associated with lasting cognitive dysfunction and "that this significant pathology is related to structural changes in the brain".

There are, indeed, growing numbers of reports from around the world regarding structural changes in the brain in cannabis users, revealed by modern imaging techniques. These include a Swiss study published in 2014, finding that "regular cannabis use is associated with gray matter volume reduction" in areas of the brain "associated functionally with motivational, emotional and affective processing".

It is true that some studies have not demonstrated change in human brains. What absence indicates is that research on the effects of marijuana is difficult because of the variation in composition of the extract, the amount, frequency, and length of use, and objectivity of reporting. This indicates the difficulties of evaluating herbal cannabis if the populist push for its research is successful. On the other hand, how many shrunken brains does it take to suggest there may be serious complications?

The American Academy of Pediatrics summarised the clinical effects of cannabis on the brain over a decade ago. They include "negative effects on short-term memory, concentration, attention span, motivation and problem solving, which clearly interfere with learning". Recent studies confirm "neuropsychological decline from childhood to midlife" which correlates positively with reducing age of onset and increasing dose. Greater understanding of the molecular biology reveals how drugs of abuse, including cannabis, can hijack synaptic plasticity mechanisms in key brain circuits to cause dependence which, in the case of cannabis, is reported to occur in nine per cent of users.

Marijuana and psychosis

Many reports also confirm a "component causal association" of cannabis use and psychosis, from depression to schizophrenia. One study published in *The Lancet* in 2007 noted that "the risk of psychosis increased by roughly 40% in people who have used cannabis, and that there is a dose-response effect, leading to an increased risk of 50–200% in the most frequent users". The authors could not definitely rule out psychotic disease preceding cannabis or predisposing to its use, but an accompanying editorial praised the paper for being more reliable than any preceding work. The paper concluded that 14 per cent of psychotic outcomes in the UK would be avoided if cannabis was not used. This would amount to 800 yearly cases.

What about the effect of maternal cannabis on the brain of the unborn?

Guidelines from Australia's National Drug Strategy, and a "state-of-the-art" review of international research by paediatricians from several Australian hospitals conclude that deleterious effects on "visual memory, analysis and integration appear to persist beyond late childhood into adolescence", and that adolescent depression and behaviour problems are more common.



Is this where Australia is heading?

It could be argued that side effects of cannabis might be acceptable in the desperate situation of a child with uncontrollable seizures. Seizures themselves are known to damage the brain, and standard drugs have their own side effects. The value of cannabis, therefore, depends on its effectiveness and that, to repeat, is unknown in epilepsy. Anecdotes should not be the basis for medical policy, and each anecdote should be closely examined.

For example, the website of the supplier for Tara O'Connell has published letters allegedly from her physician. These suggest the child may not have ever been treated with the anti-epileptic drug stiripentol, which is used internationally for Dravet Syndrome. The disease can be unpredictable, with idiosyncratic variations in natural history and response to individual therapies. Had stiripentol been used, we might now be singing its praises.

There may also be alternatives within cannabis which are not being acknowledged in the push to release the raw plant. International research is proceeding on these alternatives, described below. Results showing the effect on epilepsy of one of marijuana's purified, quantified components are likely to be available soon. Why the rush for the raw plant?

How should trials be conducted?

Research on the medical value of a substance begins with pre-clinical consideration of biological plausibility, purification of product, standardisation of dose, understanding of absorption, bodily distribution, breakdown and excretion, and evaluation in animal studies.

It then moves through ascending phases of complexity, beginning in a small cohort of healthy human volunteers to whom the drug is administered in increasing doses, then to a larger but restricted cohort of people affected by a diagnosed disease, and then, if results permit, to a broad cohort of a thousand or more patients in which the drug is usually compared with a placebo in a blinded, randomised, cross-over pattern.

If the drug is known to lead to tolerance and dependency and to have side effects that accrue over time, the balance of benefit and side effect may be very difficult to assess, and the study will be prolonged. Ultimately, the proposed therapy must be compared with known alternatives.

This rigorous vetting process has evolved in order to prevent such tragedies as the effects of thalidomide on the unborn. It seemed a good idea at the time to give the drug to pregnant women because it reduced morning sickness. But no evaluations of unexpected complications had been performed, and babies were born without limbs. The vetting process is mandated in Australia by the Therapeutic Goods Act and protects against unwanted results from "good ideas". It also protects against vested ideological and financial interests.

Many of the side effects of cannabis are already known, as is its popular ability to produce an altered mental state. But its anti-epileptic effect is unknown and ought to be submitted to standard rigorous assessment. Particular difficulties for scientific analysis of the raw herb and epilepsy would involve its varying composition, the variety of molecular bases and the genetic predisposition of epilepsy, the unknown pharmacology in children (how much is absorbed, where does it accumulate, how fast is it destroyed and where?), the difficulty in measuring effect (convulsions range from "grand" to so "petit" they may not be obvious, and how do you count them at night?), the difficulty in measuring neurological and psychological effect (it can take hours to assess these, especially in a child with disabilities; how often should they be performed and by whom?), and the difficulty in assessing side effects (one anti-epileptic drug which appeared effective was discontinued when long-term follow-up revealed an unwanted effect on blood).

Other difficulties result from the rarity of some epileptic diseases, which will make statistical assessment very difficult, as will their often contrary response to medication. Worse, sudden unexpected death is much more common than realised, with a reported six per cent of sufferers of Dravet Syndrome dying each year in ways not explained by convulsions themselves. Perhaps the molecular problem that predisposes to epilepsy exists in cardiac muscle as well as the brain.

Another problem for rushed research on cannabis might be the opinion of "ethics committees" which must approve research in hospitals and universities. It would be interesting to see response to an application for a trial on children of a substance you could not chemically define, for effect that might not be obvious, with known ability to shrink a brain or precipitate madness, and create dependence in nine per cent, complicated by the expectation of sudden death, underpinned by contradictory effects on animals, and all because it seemed a wonderful idea to the media, and had the support of a few politicians!

What has been happening in the United States?

We need to examine the US experience closely, because it contains profound warnings. The push for medical marijuana began with compassionate attempts to relieve pain in dying patients, but has deteriorated into mayhem in which a time-honoured system of medical care appears to be suffocating in chits for cannabis.

California legalised marijuana for the medical purposes of relieving pain, anorexia, vomiting, nausea and epilepsy in 1996. Since then, 22 other states have followed suit with many different laws and practices that function despite federal prohibition. The meanings of the words *doctor, patient care, prescription, dispensary and carer* in the US system of medical marijuana do not carry the Australian meanings or, for that matter, the original meanings in the US, whose system has been transformed.

Essentially, the role of the doctor is merely to listen to the client's claim to have one or more of the several symptoms for which marijuana can be supplied. Without any legal or ethical obligation to question, examine, investigate or contact other physicians for past history, the doctor is merely obliged to check the patient's identification before signing a prescription for marijuana.

The "prescription" does not carry our Australian meaning. It is merely a chit the "patient" can produce to an inquisitive policeman to show that marijuana is possessed for medical reasons. In some states, the doctor must forward a minimum of information about the patient and his chit to central authorities. For his services, the doctor will receive at least $100. Though the chit will last for one year, there is no requirement to see the doctor again. At present, it can be renewed indefinitely by merely paying a $20 annual fee to the state.

The "patient" then heads for a "dispensary", which is nothing like one of our pharmacies. Dispensaries are basically shops of varying attractiveness, that cluster in suitable parts of the city to sell the marijuana herb and all its paraphernalia. The shop assistant (not the doctor) suggests the type and dose of marijuana suitable for the complaint, and is permitted by law to sell certain maximum quantities per visit. In Colorado it is two ounces, or six plants, three of which must not be mature. Under "special circumstances" the limit may be increased but, in any case, there is no limit to the number of regular purchases.

The shopkeeper procures processed marijuana and plants from private growers who have been known to set up mobile "clinics" in caravans next to the "dispensary" on advertised days to ensure fresh and abundant supply. "Care givers" may be nominated to grow the herb on behalf of the patient and a "carer" may grow for more than one patient. Some have been found "caring" for as many as six patients. It is not surprising that produce has been diverted into the black market.

Parents can apply on behalf of minors less than 18 years old. The only stipulation is that two doctors must sign the chit. As of June 2014, 357 minors were registered in Colorado. According to registration data, 50 Colorado physicians were responsible for 85 per cent of the chits. A small group of 15 doctors was responsible for 49 per cent, with one single doctor registering six per cent of all patients. After its effective legalisation in October 2009, 163,856 people were registered for medical marijuana by 2011: over two per cent of the state's population.



Medical marijuana lollies: temptation for toddlers

Many of the doctors were "principally or exclusively" involved in this branch of medicine. The conflict of interest was obvious, especially as some doctors "practised" in a marijuana dispensary. The odour of corruption prompted the Colorado senate to legislate in 2010 against marijuana physicians from holding "an economic interest" in supply, and from practising within dispensaries. The Senate Bill 109 also sought to ensure a "bona fide" doctor-patient relationship, which would involve "full assessment of the patient's medical history and current condition", and availability for follow-up.

But there is doubt that the system has changed. There is no obligation on the doctor to be educated about marijuana, to record failure of other treatments, to identify who might be harmed by the drug (such as pregnant women or the mentally ill) or who might be addicted to other drugs.

Colorado is not unique. In Arizona, where doctors of osteopathy, homeopathy and naturopathy as well as medical physicians can issue marijuana certificates, only 24 doctors signed 73 per cent of the 28,977 registrations in an early year after legalisation. They comprised 17 naturopaths, one osteopath and only six of the state's 22,111 medical doctors. One survey of 520 physicians in Colorado revealed that 46 per cent did not support medical marijuana, and only 19 per cent believed doctors should prescribe it. Most agreed marijuana poses serious mental (64 per cent) and physical (61 per cent) risks. A minority believed it conferred physical (27 per cent) and mental (15 per cent) benefits. The media was a major source of education about marijuana for the physicians, with doctors complaining of a lack of formal education.

Who are the patients?

The picture painted by the media of medical marijuana use is for someone dying in unrelieved pain, for example from cancer and AIDS-related conditions. These diseases are now are in the minority of registrations. Data from nine California Assessment Clinics reveals 73 per cent of registrants to be males aged between 18 and 44 – hardly the usual cohort of current chronic disease sufferers, although it would have characterised patients in the early AIDS epidemic.

In Colorado there is a similar cohort in which 68 per cent are males with a mean age of 42 years. Female users in that state are of similar age to males. Thus in Colorado, some 50,000 women of child-bearing age are being assisted to consume marijuana regularly – with all the implications for their children.

The listed complaints of the Californian cohort reveal pain from back and neck injuries to be the most common (82.6 per cent), followed by sleep disorders (70.7 per cent), the need for relaxation (55.1 per cent), muscle spasms (41.1 per cent), headaches (40.7 per cent), anxiety (37.8 per cent), nausea and vomiting (27.7 per cent), depression (26.1 per cent), the need for better concentration (22.5 per cent), anger control (22.4 per cent), more energy (15.9 per cent), diarrhoea (5 per cent), seizures (3.2 per cent) and itching (2.8 per cent). Three-fifths of patients had been using marijuana for recreational purposes before applying for medical consideration. Two thirds continued to use it daily.

The authors of the Californian survey state: "Cynics have argued that some medical marijuana patients are gaming the system to get marijuana for non-medical use" – but say their research does not "give any clear cut … estimate of the scale of such diversion".

What has been the effect on society?

Is anyone surprised that there has been an overall 30 per cent increase in recorded consumption of marijuana across America since legalisation, and that consumption has been increasing in legalised states? It appears, overall, that greater access to marijuana is leading to use at increasingly younger ages, with greater potential for damage to the developing brain.

The potency of marijuana has also increased in association with legalisation for medical marijuana. The reasons are not clear, but agricultural improvements, guaranteed marketing to dispensaries and beyond, and less dilution by street pedlars are considered to be important, and to have contributed to a reduction in unit cost of marijuana by up to 50 per cent. The greater potency is, of course, relevant to brain damage.

Greater potency and availability in Colorado are believed responsible for a new phenomenon: marijuana intoxication in children. Once such ingestions were very rare, but 14 cases have been identified in one children's hospital since legalisation.

Many of the children were toddlers, and the effects ranged from somnolence to respiratory failure, for which there was no antidote. The underlying cause is argued to be the explosion of medical marijuana dispensaries and an increase in medical marijuana cards, promoted by widespread medical marijuana advertising. The authors of a Colorado study report that in 2010, "Denver issued more than 300 licences [for marijuana dispensaries], roughly twice the number of the city's public schools". They conclude that "proponents of marijuana suggest it is safer than alcohol" but in their study period, only two children under 12 were evaluated for alcohol ingestion and "marijuana was associated with greater need for hospitalisation, including intensive care". The specific reason for marijuana ingestion by toddlers is that the medical marijuana industry "provides attractive and palatable marijuana-infused solid and liquid products, including cookies, candies, brownies and beverages".

Is medical marijuana effective?

In 1999 the US Institute of Medicine declared that there was some potential for positive effect of marijuana in relieving pain, nausea, vomiting and spasm – advocating that federal restriction on marijuana's availability for research be lifted. Since then, research has not offered much guidance. "None" to "limited" to "modest" to "significant" effects on symptoms by herbal marijuana have been found, but no reassuring long-term assessments on tolerance, dependence, or neurological and psychiatric manifestations.

In the meantime, research on purified components of cannabis has led to the development of pharmaceutical derivatives such as *Sativex*, which will be released in Australia for spasticity associated with multiple sclerosis.

What motivates the campaign?

Many advocates for medical marijuana are motivated by a desire to relieve suffering – but could there be other motivations? Freelance journalist Owen Dyer, writing in the British Medical Journal about the "formidable lobby" for legalisation, concludes: "…the real driving force and the money behind state campaigns often comes from the local marijuana enthusiasts and would-be entrepreneurs who hope to run growing operations and dispensaries after passage" of legislation.

According to Dyer, this program is assisted by "patients and their families [who] offer compelling testimony, and national pressure groups [that] offer advice and legal help". He might have added sensationalist media and populist politicians, but the effect is the same: desensitisation of the public to the damaging effects of marijuana and the promotion of the concept that it is good for you, just like a medicine but better, because it is one of "nature's herbs".

It is surely by design that a major marijuana proponent in the US and Australia, the National Organisation for the Reform of Marijuana Laws, goes under the banner "NORML". The real campaign is for the normalisation of marijuana consumption. In adolescence, normalisation is associated with greater consumption. In the current campaign for marijuana for childhood epilepsy, concern for children's health is selective: while condemning epilepsy, it overlooks schizophrenia.



Medical marijuana is big money in the US

Could the ethical, scientific basis of medicine and the traditional doctor-patient relationship be overturned by media and politics in Australia, as in the US? Our cultures are very similar. In June 2014, the NSW Parliamentary Resource Service published an "Issues Backgrounder", a year after the NSW Legislative Council General Purpose Standing Committee No 4 had investigated the use of cannabis for medical purposes.

The Legislative Council committee had concluded in 2013 that "cannabis products" are emerging as a "promising area of medicine" and that a "compassionate approach is appropriate".

The committee therefore recommended "a complete defence from arrest and prosecution for the use and possession of cannabis [within limits], to cover the authorised medical use" for terminal illness and HIV/AIDS. The defence would extend from patient to "carer". A register would be kept of people with authorised use.

The committee considered the tricky business of how the marijuana herb might made available, given international and Commonwealth bans on production and transportation, complicated by the fact that "cannabis as a crude plant product is very unlikely" to be approved by the Therapeutic Goods Administration (TGA).

The committee admitted that "there are very few data from controlled clinical trials on the efficacy of cannabis for treating the recommended conditions". It agreed that "there are serious concerns about the safety of smoked cannabis, especially in the treatment of chronic conditions" and that "quality is also problematic, because crude forms of cannabis contain variable amounts of THC and other cannabinoids".

The committee decided that dronabinol – a purified, quantified and evaluated derivative of cannabis that has been developed overseas – was too expensive for general use. It then considered the "Special Access Scheme", which allows patients with certain conditions to be given drugs without TGA approval.

The committee listed "supply options": licensing cultivation of marijuana for medical purposes; decriminalising privately cultivated amounts; allowing cannabis dispensaries - "compassion clubs" - to provide the drug free of charge.

Does this sound familiar? The US began with a Compassionate Use Act which allowed an illegal drug to bypass normal assessment, and to be cultivated, trafficked and distributed without sanction.

In almost 50 years of studying and practising medicine, I have seen almost more than I can bear of brain-damaged and dying human beings. I believe relief of pain is one of the greatest benefits a doctor can share, and scientific evaluation one of the greatest gifts we all enjoy.

I think, therefore, we should wait a little longer for scientific revelation of the effects of the components of the natural marijuana herb. If those effects are positive, we should use them. In the meantime, we should not unleash a destructive force, despite the persuasion of anecdote.

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