The Sydney Addiction Seminar  Wednesday 17th Oct 2012  “Cannabis use disorders” was lead by Dr Mark Montebello.

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In this wide-ranging seminar, Dr Mark Montebello (MM) took us through the actions of cannabis on the brain, intoxication, dependence, health risks with cannabis use, and the diagnosis and management of cannabis use disorders.

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Epidemiology

Although previous 12-month prevalence of cannabis use has fallen from a high of around 13% in the late 1990s, MM remarked that Australia would still be in sure Olympic medal contention with current annual prevalence of cannabis use >8% (National Drug Strategy Household Survey). Age of onset of cannabis use has been decreasing.

Cannabis use is common, but clearly not everyone using it is psychotic or has other problems from cannabis.

Cannabis contains at least 60 psychoactive cannabinoids, the mix depending on strains, and the ways they are grown. The type of cannabis used varies from country to country. Cannabis sativa is the most common species in Australia, and the most commonly used form are the dried leaves and flowers ("heads"). The heads are preferred as they are the most potent part of the plant. Most people who come into treatment don’t use the leaves, but are “up to the buds”. Australian cannabis users also generally combine it with tobacco, which complicates withdrawal.

Dried cannabis resin known as hashish ("hash"), and its derivative hashish oil, are more commonly used in some other countries.
It was asked why the term marijuana is so commonly used in the USA, even in scientific publications, and whether this refers only to the leaf. MM suggests not to use the term marijuana, which is not used in all parts of USA. ICD and DSM only talk about cannabis.

**Neurochemistry**

Among the psychoactive cannabinoids, the two most important are 9 delta tetrahydrocannabinol (9DTHC) and cannabidiol (CBD). 9DTHC is responsible for most of the effects which users desire, while subjective effects of CBD appear to be calming. CBD may have other benefits, for example it may reduce beta amyloid production in Parkinson's disease and possibly have antipsychotic effects.

The existence of naturally occurring cannabinoid receptors in the brain implies there are endogenous ligands (9DTHC is present only when you use it). The best known endogenous ligand is anandamide (the Sanskrit word for “bliss”), but there are at least 4 others.

Like serotonin receptors 15 years ago, more and more cannabinoid receptor types are being now identified, but the 2 main types are CB1 and CB2, of which the latter are found mainly in immune tissues. MM showed us the wide distribution of CB1 receptors in parts of the brain important in memory (hippocampus, cerebral cortex), motor system (outflow nuclei of the basal ganglia, cerebellum), and in mesolimbic dopaminergic reinforcement pathways.

Is THC content in cannabis increasing in Australia? While there is a “black hole” in the data (police seizures provide limited evidence), in 1972 the usual THC:CBD ratio was 50:50, ie 6%:5%. Now it is around 15%:<0.5%, a ratio of >30:1. This makes sense if breeding/cultivation are taking out the CBD effect, after all THC is the effect that people want.

**Dependence and withdrawal**

While only about one in ten of all cannabis users develop dependence, among the minority (10%) who use daily, 90% meet diagnostic criteria for dependence. Like alcohol, THC is generally associated with a much slower development of dependence than benzodiazepines, opioids, and nicotine. Psychological dependence can develop even without withdrawal.

DSM-IV does not recognise cannabis withdrawal, but it will be coded in DSM-V. Why has it taken so long to recognise withdrawal? THC being highly lipid soluble, it tends to leave brain tissues slowly, which might be one reason for the syndrome being relatively mild. Increasing recognition of cannabis withdrawal might also be related to increasing 9DTHC content, other chemical ingredients, or maybe changing patterns and methods of use (including “bongs” versus joints, use of larger doses and over longer periods).

MM showed us a comprehensive but complex cannabis withdrawal scale of 19 items (Allsop et al 2011) with the ironic comment that “if they can answer the questionnaire, they are probably not dependent”.
DSM-V gets this list down from 19 to 7 criteria. MM finds the criteria for withdrawal are rather non-specific, in fact very similar to symptoms of depression. As to whether there might be a chronic grumbling withdrawal (like for benzodiazepines), THC is still excreted from body for weeks after use, and agitation and anxiety peak at the end of the first week, sleep disturbance at 2 weeks, and cravings persist over 4-6 weeks, so MM wouldn’t discredit that idea.

[There were some brief words about DSM-5, 14 years in the making. The aim is that all diagnoses must have both a biological basis and be evidence based – and there is a sceptical view that this just can’t be done. The important change in addiction is the combination of abuse and dependence in one spectrum “substance use disorder”. Only three criteria are needed for a “substance use disorder”; legal ramifications were dropped and craving was added to the criteria. It was questioned whether this represents a “dumbing down” of diagnosis. Intoxication and withdrawal remain coded in DSM-5]

**Harms associated with cannabis use**

MM referred us to the National Cannabis Prevention Information Centre (NCPIC), a team at NDARC at UNSW, which provides information to professionals, patients, and families (see references).

MM showed us a table of harms associated with cannabis use, on the NCPIC website, adapted from Hall & Solowij, (1998); Room et al., (2008). Briefly:

*Risks of acute intoxication:* include impaired attention, memory, and psychomotor performance; increased risk of motor-vehicle accidents; and cannabis-induced psychosis.

*Among the most probable chronic effects are:* subtle cognitive impairment (of unknown reversibility, unlikely to be grossly debilitating); risk of dependence; and adverse respiratory effects, such as chronic bronchitis

*Possible chronic effects include:* xerostomia (dry mouth) with tooth decay and gum disease; and in children exposed to cannabis in the womb, difficulties with problem-solving and attention, which may continue into adulthood.

There are also probable risks amongst specific populations.

*Adelescent cannabis use* is associated with poorer school performance, lower levels of degree attainment by age 25, higher unemployment, leaving the family home, early sexual activity and teenage pregnancy.

*In women who smoke cannabis during pregnancy:* increased risk of a low birthweight baby.

*Exacerbation of mental health conditions* such as depression, anxiety, and schizophrenia.

Medical problems such as cancer and chronic airways limitation are hard to separate from effects of tobacco smoking where there is dual dependence. It may be expected that with an aging cohort of cannabis smokers problems will become more commonly recognised.

**Cannabis and mental health**
The connection between cannabis and psychosis is complex and hard to explain. MM suggested the simplest way is: if you have a predisposition to schizophrenia, if you have the genes, and especially with use at an early age, cannabis use increases the risk of schizophrenia. According to a meta-analysis of 7 large studies, THC doubles the risk of developing schizophrenia. Despite large increases in cannabis use, schizophrenia hasn’t increased in parallel - though some would dispute this. However incidence of cannabis-related psychosis has increased. One study showed a COMT gene polymorphism indicated 8 times increase in risk of THC-related psychosis, but this has not been replicated.

MM stressed that probably anyone can get an acute psychotic illness if they smoke enough cannabis, but there is little evidence for a chronic toxic psychosis.

However it is not so simple as just that THC makes you psychotic – it may be not just about 9DTHC, but other cannabis constituents which may be pro and anti psychotic. There are also situations where drug use is superimposed on chronic psychosis, such that it may be hard to tell whether a person has stopped cannabis use because they were becoming psychotic, or a chronic psychosis only becomes evident when they stop using.

People tend to overlook the strong association of cannabis with depression and anxiety, the earlier the onset of use the worse, with a 2-3 fold increase in depression and anxiety in teenage starters by their 20s.

It is hard to separate out the contributions of past use versus current use, as many people stop and start, and some are likely to be using other drugs, including binge alcohol, and to have disruptive backgrounds, leaving school early etc. Risk is best described as a cumulative dose effect, with the earlier the use the worse.

Among the anxiety disorders, social anxiety is most strongly, and PTSD, OCD and panic disorder are least likely to be, associated with cannabis use. An audience member remarked that many people describe panic with cannabis use. MM explained this is not the same as panic disorder (chronic recurring panic attacks), rather that cannabis can precipitate a panic attack, especially with first time use.

An amotivational syndrome has been described in chronic users. MM suggested that as acute use decreases motivation, chronic use may amount to a chronic intoxication state. As cannabis stays in the brain for long periods, ones needs to stop use for a while to know. MM described some continuing cannabis users who started in adolescence, who by their 30s seem like teenagers who never grew up. They feel frustrated and left behind, as their mates have moved on, with careers, mortgages, families.

**Screening and interventions**

MM stressed the importance of screening, reminding us that some people don’t even think of cannabis as a drug. There are many settings, from GP to hospital emergency departments, where screening may be appropriate. Warning flags include injury, mental health presentations and respiratory illnesses. There are pitfalls in getting a
good consumption history: MM finds that if some young surfers are smoking as much as they say, it is amazing they are even upright (are they overestimating or do they have high tolerance?). Older users may be using much more than they say. There are various ways to quantitate use, from weight of cannabis used, number of joints or “cones”, or dollars spent.

In screening adolescents, MM recommended the “HEADSS” approach (Home, Education, Activities, Drugs, Sexuality and Suicide/Depression), moving from the least confronting questions (home) to the most confronting (about suicide risk) (see references).

To manage cannabis cessation, one may need to learn more about tobacco smoking. For example, if roll your own cigarettes, the less tightly it is packed the quicker it will burn, and release more psychotogenic and also carcinogenic substances. So rolling your own is not healthier. Generally cannabis joints are not packed so tight => faster burn. A harm reduction message might be: pack it tighter.

There are very few studies of cannabis smoking alone, ie without tobacco, and those have small numbers. In a Toronto study of 25,000 pregnancies, only 150 were pure THC smokers. Likewise also hard to compare results of smoking joints versus bongs: histories are usually mixed.

In terms of therapies, the overwhelming evidence is for psychological interventions, especially cognitive-behavioural therapies (CBT) which “may include motivational interviewing, cognitive restructuring, coping skills training, lifestyle modification and relapse prevention including the management of urges and triggers.”

There is evidence even for one-off sessions in adolescents, but interventions range up to 20 sessions. They are often manualised, 2-6 sessions, the last 2 often not specific. MM finds he can usually only get people to come back for 2-4 sessions, and suspects there is not much increased benefit for 2 versus 6 sessions. Especially in North American studies, contingency management is often thrown in to the mix with CBT: it does seem to improve results. Regarding group vs 1-on-1 CBT, both are effective, but they have never been tested head to head.

If there is cognitive impairment or the person is motivationally impaired it is hard to do the more cognitive parts (like surfing cravings) of the CBT, so MM recommends focussing on the behavioural first, things like eating and sleep. If people sleep well, they are more likely to stick with therapy. Online CBT programmes may be especially helpful for people who can’t leave the house because they are paranoid or anxious.

Current state guidelines (under revision) for management of cannabis withdrawal look rather like the cocktails used for opioids withdrawal a decade ago before buprenorphine became widely used (maybe the partial agonist for cannabis will come along one day…). Although benzodiazepines are often used, there has actually been no study of benzodiazepines for this indication. However there has been a study of long acting zolpidem (Ryan Vandrey has done a number of pharmacotherapy trials). While there is little evidence for cannabis pharmacotherapy, and even less for dual addiction with tobacco, certainly one should treat psychiatric co-morbidities.
MM has been involved in 3 pharmacotherapy studies, over 11 years.

1. *mirtazapine*, a tetracyclic and rather sedative antidepressant, didn’t help other than helping retention via improved sleep.
2. *rimonabant*, a cannabinoid antagonist: a study of only 14 patients, open label, one month, was tolerated. One participant smoked lots of cannabis to overcome the effect of rimonabant. The study was terminated early when post-marketing studies of its use as an appetite suppressant (compare with cannabis users “getting the munchies”) showed it tripled rates of suicide. Dr Simon DeBurgh suggested depression was possibly underdiagnosed in the studies of rimonabant as an appetite suppressant as the investigators were not primarily psychiatrists. MM remarked their own study was, in retrospect, not ideal, as they recruited people with mental health co-morbidities. Also, one might have anticipated with rimonabant in cannabis users the same result as with naltrexone for opioid dependent people – they just don’t like it.
3. *Sativex*, a cannabinoid agonist in a sublingual spray of a 50-50 ratio of THC and cannabidiol (available overseas, mainly in Britain, but not in Australia, as an anti muscle spasticity agent): currently in a double blind trial for cannabis withdrawal management. Retention has been high, however it appears that treatment may need to continue for longer than the protocol 7 days – participants were very heavily dependent, and felt good for only 3 days.

MM mentioned N-acetylcysteine, a glutamate modulating drug which has been shown effective for tobacco cessation in several studies, and recently shown in an 8-week double-blind randomized placebo-controlled trial of cannabis-dependent adolescents to double the odds of having negative urine cannabinoid test results during treatment (Gray et al 2012). N-acetylcysteine is off patent, cheap, and well tolerated.

Agents under development include cannabinoid reuptake inhibitors and partial agonists.

**Stopping cannabis use**

A basic question is whether to cut down versus complete cessation. Some try to stop “cold turkey”, crash and relapse. An alternative is progressively cutting down, some studies with long term follow up showing this lead to subsequent stopping. Start by quantifying use, reducing by 10% per week, “resting” when uncomfortable.

For those wanting to stop tobacco at same time, there is also evidence that cutting down is a viable way to go, though just stopping may be appropriate for the majority. We were reminded of basic rules of nicotine replacement treatment (NRT): use more than one patch, use multiple forms of NRT, continue more than 3 months if needed, no need to reduce the NRT dose before stopping it.

As with tobacco, reducing the number of joints/cones might lead to compensatory changes in “smoking topography”, so that people smoke harder on fewer occasions – there is now evidence for this phenomenon with cannabis too.
NRT should probably be first-line in this context: one study of bupropion for cannabis dependence, unsurprisingly worsened withdrawal symptoms, especially vivid dreams.

Asked if there was evidence for the 5 minute brief intervention as for tobacco, MM confirmed there had been no such study for cannabis, only the adolescent study of one session of 90 mins. He reminded us that, especially with young people, one may get only one bite at the cherry, and there is evidence that brief interventions at a critical time, such as the late teens, may have an effect.

As to whether to treat both at same time ie NRT for tobacco and CBT for cannabis, some practical advice: be flexible, go with what the patients want. Although people with other drug dependence may say “please leave me that last pleasure”, tobacco has perhaps the greatest harm for morbidity.

**Cannabinoid hyperemesis syndrome**

The audience gave a hesitant response to whether they believed in cannabinoid hyperemesis syndrome (CHS). Although there are case series and case reports only, and the syndrome seems rare, there is a classic presentation of severe, intractable (unresponsive to most anti-emetics), often cyclical vomiting associated with what has been called compulsive bathing/showering – at least, people affected by this have discovered for themselves that the symptoms are relieved temporarily by a hot shower or bath. MM described this syndrome often in younger, heavy users, vomiting when they STOP using, however Lucinda Scopelliti has seen it frequently at Liverpool Hospital not associated with withdrawal. As to the possible cause, there are cannabinoid receptors in the gut, and near the central nausea centre. While THC is generally thought to have anti-emetic effects, some constitutients may have pro-emetic effects. Raising body temperature could plausibly mitigate cannabis induced disturbance of thermoregulation. All of this is speculative.

The diagnosis is one of exclusion, one differential diagnosis being cyclical vomiting syndrome which is associated with high rates of psychiatric symptoms – though Dr Danielle Florida's impression has been that there are high rates of comorbid anxiety in people with CHS.

CHS generally improves with longer term abstinence and may reappear on re-challenge with cannabis. Treatment is rehydration where needed and anti-emetics such as ondansetron.

It was suggested that another common cause of morning vomiting in heavy cannabis users is chronic bronchitis with a bolus of phlegm hitting the stomach in the morning.

**Law and harm reduction isssues**

MM mentioned the synthetic cannabinoids such as “Spice”, largely developed by John Huffman, who got grants from NIDA in 1990s to develop synthetic cannabinoids for research purposes. As those results were published, entrepeneuers are going to the scientific journals and making the compounds themselves. “Spice” reportedly showed up in 10% of miners’ urine drug screens in Western Australia recently.
MM discussed the conundrum about regulation: if we try to ban them all, we might be tossing out good and useful agents. Information is freely shared on websites such as http://www.gethigh.com.au/. In NZ, new regulations require that these new cannabinoids are not banned but you need a license, and there is an obligation to carry out Phase 1—3 trials, which makes their use expensive, not illegal. In Australia we are banning as we go.

To the question whether “bush” cannabis is better than hydroponic for harm reduction, latest studies haven’t show any difference.

In the Netherlands, a license is needed to supply cannabis, and the ceiling THC content is 15%, though there is talk about increasing the CBD content, with the idea that people might still get “stoned”, but less agitated.

Regarding claims for smoke–free vapourisers to reduce harms of cannabis smoking (Abrams et al 2007), caution is required: for example “hubbly bubblies” are more harmful than joints, and lead to higher rates of oropharangeal cancer.

It was asked whether rates of incarceration in the USA are related to cannabis. The answer is, it varies: 14 states have legal cannabis and if you can afford a doctor there, you can even get a script. Other states don’t even have drug diversion programmes such as MERIT. Dr David Browne reminded us that 1 in 99 of Americans have been to gaol, and over 2 million are in gaol currently.

References


http://ncpic.org.au/


Summary by Richard Hallinan, based on Dr Montebello’s presentation and also his article “Always Greener - Cannabis Related Disorders: published in Australian Medical Observer