Cannabinoids in Pain Management: An Update from the 2009 Canadian Pain Society Meeting, Quebec QC

Commentary by Mark A. Ware, MBBS, MRCP, MSc
Cannabinoids in Pain Management: An Update from the 2009 Canadian Pain Society Meeting, Quebec QC

Commentary by

Mark A. Ware, MBBS, MRCP, MSc
Executive Director, Canadian Consortium for the Investigation of Cannabinoids (CCIC)
Director of Clinical Research, Pain Clinic
McGill University Health Centre (MUHC)
Assistant Professor, Departments of Family Medicine and Anesthesia
McGill University, Montreal QC

Table of Contents

Commentary ................................................................. 3
Responding to the Hurdles:
   Efficacy ................................................................. 5
   Side Effects ............................................................ 7
   Abuse and Addiction .................................................... 10
   Drug-Drug Interactions .................................................. 11
   Long-term Data .......................................................... 13

Cover Photo courtesy of Dr. Ken Mackie, Indiana University
This photo shows the CB-1 cannabinoid receptors (in green) in a cultured hippocampal neuron. This photo originally appeared in the Indiana University magazine Research and Creative Activity – Volume 30, No. 2, Spring 2008. It was contained in the article “Your Brain on Drugs” by Steve Hinnefeld. This magazine can be located at the following url: www.research.iu.edu/magazine

All rights reserved. VIEWPOINTS IN PAIN MANAGEMENT is an independent medical news reporting service providing educational updates reflecting peer opinion from worldwide published medical literature and presentations. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the CCIC. No responsibility is assumed for accuracy of research or typographical errors. Any therapies mentioned in this report should be used in accordance with the recognized prescribing information in Canada. No claims or endorsements are made for any products, uses, or doses presently under investigation. No part of this newsletter may be reproduced in any form or distributed without prior written consent of the CCIC. Information provided herein is not intended to serve as the sole basis for individual care. Our objective is to facilitate physicians’ and allied health care providers’ understanding of current trends in field of pain management.

© 2009 Canadian Consortium for the Investigation of Cannabinoids (CCIC). Published by Baker Edwards Consulting Inc. on behalf of the CCIC.

The purpose of the Canadian Consortium for the Investigation of Cannabinoids (CCIC) is to advance our understanding of the role of cannabinoids in health and disease through research and education.

All correspondence should be directed to: info@ccic.net
Cannabinoids in Pain Management: An Update from the 2009 Canadian Pain Society Meeting, Quebec QC

COMMENTARY

The therapeutic use of cannabis has a long history dating back thousands of years. In the last 10 years, there have been tremendous developments in the clinical application of cannabis and its derivatives (cannabinoids), including work on mechanisms of action, new drug development, examination of safety issues and clinical trials (see Figure 1). Much of this work is being done by Canadian scientists and clinicians in a wide range of therapeutic areas including gastrointestinal function, nausea and vomiting, pain relief and depression.

This overview of findings reported at the 2009 Annual Scientific Meeting of the Canadian Pain Society (CPS) provides an opportunity to examine some of our perceived notions about cannabis and cannabinoids, particularly when used in pain management. The Canadian Consortium for the Investigation of Cannabinoids, a federal non-profit organisation aimed at improving research and education on cannabinoids, has commissioned this report to disseminate these findings to Canadian physicians in a clear and evidence-based manner. The report is structured around several themes which emerged from the conference presentations.

The association between cannabis as a source of medicine and cannabis as a recreational drug gives rise to important safety concerns. It is important, however, to distinguish between these two approaches as not all risks of recreational use may apply to medical users and vice versa. Recreational cannabis users seek altered consciousness, euphoria, and dose themselves accordingly, and tend to use cannabis in a more social context. Medical cannabis users, on the other hand, tend to be more personal in their use, often very shy about it, and they seek symptom

Figure 1. PubMed-indexed publications on cannabis and cannabinoids 1965-2008
relief rather than a ‘high’ in order to function normally. Medical users also tend to be on other medications, which gives rise to possible interactions, both direct (e.g., drug-drug interactions) and indirect (e.g., exacerbation of somnolence). Users of prescribed cannabinoids are often concerned about risks that they have heard of through well-publicised studies on recreational cannabis use, such as psychosis and driving effects, and it is important to be careful in how we extrapolate safety data from one population to another.

Some of the safety issues mentioned above were articulated in a needs assessment study in 2008 in which Canadian physicians identified their concerns about cannabinoids (see Table 1) (Ware and Maida 2009). Issues concerning safety, efficacy and some of the long term effects were addressed at CPS ‘09 in several presentations and these are summarised below, with additional commentary from the principal investigators.

This report does not pretend to give the whole story of medical uses of cannabinoids, but aims to serve as a reminder that there is emerging support from basic science and clinical trials perspectives on the safety and efficacy of cannabinoids. Additional resources and educational opportunities exist, and a dialogue can now begin which is informed by evidence and increasing clinical experience. We invite you to join us in the conversation and help shape the future of therapeutic cannabinoid use, in pain management particularly, but in medical practice in general.

Mark A. Ware, MBBS, MRCP, MSc
Executive Director, Canadian Consortium for the Investigation of Cannabinoids (CCIC)
Director of Clinical Research, Pain Clinic
McGill University Health Centre (MUHC)
Assistant Professor, Departments of Family Medicine and Anesthesia
McGill University, Montreal QC

Table 1. Major barriers to cannabinoid prescribing (number of doctors per province)

<table>
<thead>
<tr>
<th>Reasons</th>
<th>NS</th>
<th>NB</th>
<th>QC</th>
<th>ON</th>
<th>MB</th>
<th>SK</th>
<th>AB</th>
<th>BC</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerns about abuse</td>
<td>4</td>
<td>1</td>
<td>10</td>
<td>35</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>13</td>
<td>73</td>
</tr>
<tr>
<td>Lack of long term data</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>34</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>11</td>
<td>65</td>
</tr>
<tr>
<td>Not sure it will work</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>31</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>Concerns about addiction</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>29</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>11</td>
<td>58</td>
</tr>
<tr>
<td>Stigma of being associated with marijuana</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>33</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>58</td>
</tr>
<tr>
<td>Concerns about side effects</td>
<td>2</td>
<td>0</td>
<td>9</td>
<td>19</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>41</td>
</tr>
<tr>
<td>Concerns about drug-drug interactions</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>11</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>No current indication for pain</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
<td>10</td>
<td>34</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>8</td>
<td>63</td>
</tr>
</tbody>
</table>

Reference: Ware MA, Maida V. What are the needs of physicians considering medical cannabinoids? Pain Res Manag;14(2):165.
Cannabinoids

Efficacy

Cannabinoids have a wide range of potential medical uses in conditions as varied as glaucoma, osteoporosis, anorexia and Alzheimer’s disease (Kogan and Mechoulam 2007). However, their potential as analgesics is the most well developed area and received significant attention at the CPS meeting.

Fibromyalgia

Lena Galimova, assistant professor of physical medicine and rehabilitation at the University of Manitoba in Winnipeg, reported the results of the first randomized, controlled trial published on the use of a cannabinoid in fibromyalgia patients (Skrabek 2008).

“Everybody who deals with fibromyalgia knows that it’s a challenge,” she said. “Many people with fibromyalgia are very sensitive to different pharmacologic agents, which is why it was important to find another effective agent.” Nabilone was investigated after a case series (Ko and Wine 2005) suggested that it was useful as an adjunct pain medication in certain fibromyalgia patients.

Forty fibromyalgia patients were randomized to receive an escalating dose of nabilone, beginning at 0.5 mg hs and increasing weekly up to 1 mg BID, or placebo. After four weeks, there was a four-week wash-out period. Patients were assessed at baseline and after two, four and eight weeks.

“We found a significant improvement in the visual analogue scale [VAS] for pain at week 4,” Dr. Galimova said. “We also found a significant improvement in FIQ [Fibromyalgia Impact Questionnaire] scores, which came back to the previous level after the wash-out period, and an improvement at weeks 2 and 4 in anxiety subscores on the FIQ.” (See page 7 for safety results.)

Figure 2. VAS scores for pain in fibromyalgia patients taking nabilone for four weeks or placebo

A six-month follow-up of those patients who continued to use nabilone after the trial did not produce statistically significant results due to its small sample size. However, Dr. Galimova reported anecdotally that most of those who discontinued nabilone experienced increases in pain and FIQ scores, while those who continued it were more likely to report reductions. There were no reports of the development of tolerance to the analgesic effects of nabilone.

Recent research by William Redmond, a doctoral candidate in physiology at Centre de recherche clinique du centre hospitalier de l’université de Sherbrooke, suggests that the analgesic effects of nabilone in fibromyalgia are at least partly due to its effects on “wind-up” (temporal summation of pain). “Normally when we give noxious stimulations repetitively, the effect of central sensitization will create an increase in...
pain even though we are not increasing the stimulation," he explained. "With fibromyalgia, the windup pain scores are higher and last longer." [Staud et al. 2001] Underlying dysfunctions that may be responsible include a loss of diffuse noxious inhibitory control (DNIC), a descending, opioid-based pain control system that appears to function normally in patients with other kinds of chronic pain but not in fibromyalgia patients.

Redmond studied the effects of nabilone 1 mg on wind-up in healthy volunteers with functional DNIC. He discovered that while nabilone appeared to increase the analgesic effects of DNIC on wind-up, it did so significantly more effectively in women than in men. Given the sex differences in the prevalence of fibromyalgia, further studies on this effect may prove fruitful.

**Cancer pain**

Vincent Maida of the William Osler Health Centre in Toronto presented the results of a recent prospective, observational study in advanced cancer patients, which examined the effect of nabilone on pain scores, other Edmonton Symptom Assessment System (ESAS) parameters, and use of other medication, including opioids (Maida et al. 2008). A hundred and twelve patients, 47 of whom took nabilone, were followed for a mean of 23 days.

“Nabilone usage was associated with improvements in pain scores, nausea, anxiety and global distress and borderline improvement in appetite,” Dr Maida reported. "It was also associated with lower utilization of opioids and reduced overall polypharmacy.”

**Chronic non-cancer pain (CNCP)**

A small pilot study recently looked at nabilone’s effects on sleep in CNCP patients. The poster, presented by Sharon Chung of Toronto Western Hospital, reported on 11 CNCP patients with insomnia who underwent a four-week, double-blinded, randomized, crossover comparison of nabilone and placebo. All patients had significant reductions in pain scores on the McGill Pain Questionnaire and a VAS for pain while taking nabilone; there were no serious adverse events or side effects requiring withdrawal of nabilone and no reports of daytime sleepiness. Five patients experienced consistent sleep improvements and chose to remain on nabilone. A year later, all five reported continued pain relief, good sleep and improved quality of life.

In a retrospective review of nabilone use in 46 CNCP hospital inpatients, 16 patients reported subjective overall improvement and reduced pain intensity with nabilone (0.5 mg hs to 2.0 mg BID). The poster, presented by Judy Boyd of the Chronic Pain Consult Service in Calgary, described a 30% overall reduction in pain intensity in addition to reports of reduced nausea, increased appetite, improved sleep, reduced opioid use and decreased anxiety.

**Neuropathic pain**

Small randomized controlled trials of medical cannabis in neuropathic pain have had positive results [Abrams et al. 2007; Wilsey et al. 2008] and synthetic cannabinoids are also being investigated in neuropathic pain patients. In a poster, Jennifer Bestard of the University of Calgary presented the results of a trial comparing nabilone with gabapentin, both as either monotherapy or adjunct therapy. After
three and six months of treatment, all treatment groups had experienced significant improvements in VAS pain and SF-36 scores, suggesting that nabilone’s efficacy in neuropathic pain is comparable to that of gabapentin, a first-line agent. In addition, patients on nabilone monotherapy reported improved sleep scores.

A larger trial has been examining the efficacy and tolerability of Sativex (delta-9-THC/cannabidiol) in 339 patients with central neuropathic pain due to multiple sclerosis. After a 12-week randomized, double-blind, placebo-controlled, parallel-group trial in which patients self-titrated their medication to a maximum dosage, a subset of patients continued into a 12-week, open-label, follow-on study followed by a 4-week randomized withdrawal period. As reported on a poster presented by Dr. Stuart Ratcliffe, director of pain research at MAC UK Neuroscience in Blackpool, Lancashire, during the withdrawal period significantly more patients experienced treatment failure (defined as a $\geq 20\%$ increase in pain on an 11-point numerical scale) in the group taking placebo than in the Sativex group, demonstrating that Sativex withdrawal leads to worsening outcomes.

References


**SIDE EFFECTS**

Despite decades of use of medicinal cannabinoid compounds, the risks associated with currently available pharmaceutical cannabinoids are frequently assumed to be the same as those seen with the recreational use of herbal cannabis.

“If we go abroad – or even to the United States – we still see people who view cannabis as a dangerous substance,” said Lena Galimova, assistant professor of physical medicine and rehabilitation at the University of Manitoba in Winnipeg. “The regular use of cannabis is known to cause harmful health effects, including dependency with its associated consequences, but all the reports focus on recreational cannabis.”

Fortunately, recent studies have made a distinction, focusing on the safety of medical cannabis or pharmaceutical cannabinoids used for pain management under the care of a physician. As Mark Ware, director of research at the McGill University Health Centre Pain Clinic in Montreal noted, “It’s very important when considering cannabinoids in clinical practice that we separate what we know about adverse events in recreational users from those
in medical users. We cannot assume that because patients are using cannabinoids they’re susceptible to the same risks. It is also important to recognise that the recreational user is seeking a “high”, but the true medical user is seeking symptom relief and improved functionality. The side effects are always balanced against the beneficial effects, and this risk-benefit ratio must be addressed for each individual patient."

**Effects of medical cannabis**

Dr. Galimova reviewed a recent examination of the safety of medical cannabis (Wang et al. 2008), which examined the results of 31 studies, including 23 randomized controlled trials, ranging in duration from 8 hours to 12 months. The incidence of serious adverse events following medical cannabis use was not statistically different from the incidence in the control groups receiving placebo or standard care. The mortality rate also did not significantly differ between the two groups. Although the overall incidence of nonserious adverse events was higher in participants receiving cannabis therapy than in controls (10.37 vs. 6.87 events per person-year), the rate ratios varied widely among the trials reviewed. In total, nonserious adverse events represented 96.6% of all adverse events reported, Dr. Galimova noted.

Longer-term data were gathered in the COMPASS trial, which involved a year of follow-up [see page 13]. Among the 431 pain patients participating, there was no difference in the rate of serious adverse events between those receiving medical cannabis and the control group, reported Tongtong Wang, a doctoral candidate in epidemiology, biostatistics and occupational health at McGill University. There were significantly more nonserious adverse events among the cannabis users than among the controls (4.16 vs. 2.85 events per person-year of use), although these events were more common among ex-users or non-users of marijuana or cannabis, compared with current users. The most commonly reported events in the cannabis group were headache, nasopharyngitis, nausea, somnolence and dizziness; most adverse events were graded as mild (54%) or moderate (45%) in severity.

The acute toxicity of cannabis is extremely low, Dr. Galimova noted, since unlike opioids, cannabis does not cause central respiratory depression. “Studies have shown that it’s virtually impossible to die from the acute administration of THC alone,” she said (Ashton 1999; Beaulieu 2005).

**Effects of pharmaceutical cannabinoids**

Few studies have been done on the safety of the pharmaceutical cannabinoids available in Canada (nabilone and dronabinol). Dr. Galimova’s group was the first worldwide to publish a randomized controlled trial on a cannabinoid in fibromyalgia (Skrabek et al. 2008).

“Because a case series found that nabilone appears helpful as an adjunct pain medication for carefully pre-screened fibromyalgia patients, we decided to get more data,” she said. Her group treated 40 fibromyalgia patients with an escalating dose of nabilone, beginning at 0.5 mg hs and increasing weekly to 1 mg BID. [See page 5 for efficacy results.]

“Our treatment group experienced more side effects per person at weeks 2 and 4,” she reported, with rate ratios of 1.58 (p<0.02) and 1.54 (p<0.05) respectively. The most common
side effects among patients taking nabilone were drowsiness, dry mouth, vertigo and ataxia; no serious adverse effects and no drug interactions were observed.

Similar results were reported by Vincent Maida of the William Osler Health Centre in Toronto, who presented the results of a prospective observational study of nabilone in advanced cancer patients (Maida et al. 2008). Among the 125 patients observed, only eight discontinued nabilone therapy during the first 24 hours due to adverse events, all of which abated within 24 hours of discontinuation. The most common side effects reported were dizziness, confusion, drowsiness and dry mouth.

Appropriate patients for cannabinoid therapy

Gordon D. Ko, medical director of the Physiatry Pain Clinic at Sunnybrook Health Sciences Centre in Toronto, reviewed the “red flags” to look for during the assessment of chronic pain patients (Table 2). He noted that asking patients about their previous experiences with any form of cannabis was useful, since patients who experienced psychotic or paranoid reactions may have similar experiences with pharmaceutical cannabinoids.

**Table 2. “Red flags” when evaluating chronic pain patients**

- Unexplained weight loss
- Fever
- Severe night pain
- Neurological symptoms
- Loss of bowel/bladder control
- Unstable psychiatric history (major depression, borderline personality disorder)
- Stressful disability, litigation claims
- Drug contraindications (specific for cannabis/cannabinoids):
  - previous adverse cannabis/cannabinoid reactions
  - excessive use of benzodiazepines, barbiturates, alcohol

### Side effects of recreational cannabis

Recreational cannabis most commonly causes CNS effects, including dizziness, somnolence, anxiety, euphoria, perceptual alterations, time distortion and impairment of motor skills, reaction time and short-term memory and attention. Cardiovascular effects may include postural hypotension, tachycardia, peripheral vasodilation (causing the characteristic reddened eyes) and an increased risk of non-fatal myocardial infarction in the first hour following cannabis smoking. Chronic heavy cannabis smoking is associated with chronic cough, increased sputum production, wheezing and reduced lung function.

Repeated use induces tolerance within days or weeks to the effects of cannabis on mood, memory, psychomotor performance, sleep, EEG, heart rate, blood pressure and body temperature; the degree of tolerance depends on the dose and frequency of administration.

(For reviews see: Hall and Solowij 1998; Ashton 1999; Kalant 2004; Ware and Tawfik 2005)

### References

ABUSE AND ADDICTION

As our understanding of the development of addiction grows, it is clear that exposure to an addicting substance is not the only factor required for its occurrence. Individual psychosocial and genetic characteristics, as well as environmental factors, play a role in determining which individual will experience dysregulation of endogenous reward centres in response to which substances.

“Like opioids and other pharmaceutical agents, cannabis is known to have addictive potential in recreational users”, said Lena Galimova, assistant professor of physical medicine and rehabilitation at the University of Manitoba in Winnipeg. Current DSM-IV criteria for cannabis dependence (see sidebar) may include withdrawal, although the manual notes that the clinical significance of possible cannabis withdrawal symptoms is uncertain. However, Dr. Galimova pointed out that the addictive potential of cannabis is less than that of alcohol or tobacco: the relative potential for dependence on cannabis, expressed as the risk of developing dependence among those who have ever used the substance, is about 9% – lower than that of alcohol (15%), cocaine (17%), heroin (23%) or tobacco (32%) (Gourlay 2005).

Pharmaceutical and recreational cannabis users also appear to be at different risk levels, a point which is consistent with other drug experiences since a number of studies have found low risks of addiction to potentially addictive pharmaceutical substances when they are used for pain management (Fishbain et al. 2008).

The DSM-IV-TR (2000) does not use the term “addiction” but defines substance dependence as “a maladaptive pattern of substance use leading to clinically significant impairment or distress,” as manifested by at least three of the following occurring during a 12-month period:

- Tolerance (either a need for markedly increased amounts of the substance to achieve intoxication or desired effect, or a markedly diminished effect with continued use of the same amount)
- Withdrawal, as manifested by either the characteristic withdrawal syndrome for the substance* or taking the same (or a closely related) substance to relieve or avoid withdrawal symptoms
- Frequently taking the substance in larger amounts or over a longer period than was intended
- A persistent desire or unsuccessful efforts to cut down or control substance use
- A great deal of time spent in activities necessary to obtain, use or recover from the effects of the substance
- Giving up or reducing important social, occupational, or recreational activities because of substance use
- Continuing the substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

In contrast, the Liaison Committee for Pain and Addiction, created by the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine, defines addiction without the use of the terms dependence, tolerance or withdrawal: “a primary, chronic, neurobiologic disease with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.” (Savage et al. 2003)

* The DSM-IV-TR also notes, “Symptoms of possible cannabis withdrawal have been described in association with the use of very high doses, but their clinical significance is uncertain. For these reasons, the diagnosis of cannabis withdrawal is not included in this manual.”
In the case of cannabinoids, recreational and medical products also differ in their degree of formulation complexity. "Smoked marijuana contains 400 chemical compounds, including 66 cannabinoids," noted Gordon D. Ko, medical director of the Physiatry Pain Clinic at Sunnybrook Health Sciences Centre in Toronto. Any of these compounds may affect the product’s addictive as well as therapeutic potential. Medical marijuana from Health Canada is grown under highly standardized conditions to limit contamination and variability in THC levels, and synthetic cannabinoid products contain well characterized compounds in known quantities.

"During my career in Canada, I haven’t seen a single patient who got addicted to nabilone," observed Dr. Galimova. This may be due to nabilone’s relatively slow onset of action, few metabolites and lack of reinforcing effects, she said. At last year’s CPS meeting, Emmanuelle St. Arnaud-Trempe presented results from a review of a wide range of sources including scientific literature, media, Internet searches and interviews with key stakeholders, suggesting that abuse of nabilone was very rare (St. Arnaud-Trempe and Ware 2008).

Since addiction is always at least a theoretical risk with cannabinoids, prospective users should be screened in the same way potential users of opioids and other agents with addictive potential. Universal precautions in pain medicine (Gourlay et al. 2005) include a complete assessment of patient and family histories of substance abuse, a consideration of patient-centred urine drug testing, a treatment agreement, regular reassessment and comprehensive documentation. Prospective studies addressing the addictive risks of specific cannabinoid agents would also help physicians making pain management decisions.

References

DRUG-DRUG INTERACTIONS

Despite concerns about the interactions between cannabinoids and other drugs, cannabinoid agents available in Canada are associated with fewer potential interactions than many other commonly used pharmaceutical products.

The Canadian product monograph for Sativex (delta-9-THC/cannabidiol) states that its metabolism by the cytochrome P450 enzyme system indicates a possible risk of drug-drug interactions, although clinical trials in which Sativex was taken concomitantly with other drugs metabolized by this system have found no clinically apparent drug-drug interactions at clinical doses. The product monograph for nabilone notes only that its depressant effects
are additive with those of diazepam, sodium secobarbital, alcohol and codeine. Potential drug interactions with dronabinol (synthetic THC) are listed in Table 3.

Recently published clinical trials involving nabilone (Maida et al. 2008; Skrabek et al. 2008) have reported no negative drug-drug interactions, but have observed that nabilone use reduced the need for other analgesic agents, thus potentially reducing polypharmacy and drug interactions among other medications. In a prospective study of nabilone in advanced cancer patients, “the nabilone-treated group used less NSAIDs, less TCAs, less gabapentinoids, less dexamethasone, less metoclopramide and less ondansetron while still achieving improvements in symptom control,” said Vincent Maida of the William Osler Health Centre in Toronto.

Gordon D. Ko, medical director of the Physiatry Pain Clinic at Sunnybrook Health Sciences Centre in Toronto, discussed the results of an Ottawa case series of post-traumatic stress disorder patients, which found that cannabinoids had synergy with opioids, acetaminophen, NSAIDs, bupivacaine and possibly gabapentinoids and probiotics. In fibromyalgia, he said, “we’re definitely minimizing high doses of opioids by using cannabinoids with the opioids.”

References


### Table 3. Drug interaction information on delta-9-tetrahydrocannabinol

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Clinical Effect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline, amoxapine, desipramine, other tricyclic antidepressants</td>
<td>Additive tachycardia, hypertension, drowsiness</td>
</tr>
<tr>
<td>Amphetamines, cocaine, other sympathomimetic agents</td>
<td>Additive hypertension, tachycardia, possible cardiotoxicity</td>
</tr>
<tr>
<td>Antipyrine, barbiturates</td>
<td>Decreased clearance of these agents, presumably via competitive inhibition of metabolism</td>
</tr>
<tr>
<td>Atropine, scopolamine, antihistamines, other anticholinergic agents</td>
<td>Additive or super-additive tachycardia, drowsiness</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>A reversible hypomanic reaction was reported in a 28 year old man who smoked marijuana; confirmed by dechallenge and rechallenge</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>A 21 year old female with depression and bulimia receiving 20 mg/day fluoxetine for 4 weeks became hypomanic after smoking marijuana; symptoms resolved after 4 days</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Increased theophylline metabolism reported with smoking of marijuana; effect similar to that following smoking tobacco</td>
</tr>
</tbody>
</table>
LONG-TERM DATA

Until recently, there were no long-term data and almost no clinical trial data at all on the use of medical cannabis for the management of pain. Two small phase II trials have studied smoked cannabis in neuropathic pain (Abrams et al. 2007; Wilsey et al. 2008) and another is pending publication, but there has never been a long-term safety study of medical cannabis in chronic pain, said Dr. Mark Ware, director of research at the McGill University Health Centre Pain Clinic and assistant professor of anaesthesia and family medicine at McGill University in Montreal.

COMPASS (Cannabis for the Management of Pain: Assessment of Safety Study) has just filled that gap. The one-year, prospective cohort study was designed to collect standardized safety data on the medical use of herbal cannabis for chronic pain, as well as to gather information about dosage patterns, patient satisfaction and predisposing factors for adverse events. The cannabis treatment group included 215 adult Canadians with chronic non-cancer pain for at least six months in whom conventional treatments were medically inappropriate or inadequate. The control group included 216 adult Canadians with chronic non-cancer pain for at least six months who were not currently using cannabis.

Serious and non-serious adverse events

"The incidence of serious adverse events was 23 events per 100 person-years in the cannabis group, which is not different from the 27 events per 100 person-years in the control group," said Tongtong Wang, a doctoral candidate in epidemiology, biostatistics and occupational health at McGill University. "No dose response was observed (Figure 3) and none of the 40 serious adverse events in the cannabis group was considered to be certainly or very likely related to the study cannabis. One event – convulsion – was considered probably related to the study drug."

Figure 3. Incidence rates of serious adverse events by daily cannabis dosage
Non-serious adverse events were reported by 88.8% of cannabis users and 86.1% of controls, but the two groups differed in the incidence rates of these events (4.62 vs. 2.85 events/patient-year). Current cannabis or marijuana users experienced fewer events than naïve or ex-users, but no dose response was seen. The most common non-serious adverse events by category affected the nervous system (20%), gastrointestinal system (13%) and respiratory system (13%); only 40 of the 880 non-serious events reported by the cannabis users were considered certainly or very likely related to the study cannabis.

**Safety parameters**
Blood tests at baseline and after one year of cannabis use (at a mean dosage of 2.49 g/day) showed no differences for any biochemical, liver, renal or endocrine function parameters. However, pulmonary function testing in cannabis users found slight but statistically significant decreases in residual volume, forced expiratory volume (FEV₁) and forced expiratory flow rate (FEF₂₅-₇₅%) after one year. “Discussion with a pulmonary physician suggests that the changes in residual volume and FEV₁ are not clinically meaningful changes,” Dr. Ware said. “However, the change in the FEF₂₅-₇₅% is meaningful, since it’s a 1% drop in the ability of your lungs to move air out.” The majority of the COMPASS cannabis users also used tobacco, making it difficult to separate out the pulmonary effects of cannabis use alone.

Neurocognitive function (measured in tests of recall memory, processing speed and visual analysis) was found to improve on all four tests in both treatment groups over the course of the trial (Figure 4). There was no difference in the extent of improvement.

**Figure 4. Mean raw scores on Verbal Paired Associate I-Recall tests**
Conclusions

“The adverse events in this population using this drug were modest and very compatible with what we see in pharmaceutical grade cannabinoids in clinical trials,” Dr. Ware said. “We need to do more studies to characterize safety issues among new users, we need longer-term studies to look at effects on lung function – adjusting for tobacco – and I think we need to continue to look at cognitive function.”

References


An educational publication of the Canadian Consortium for the Investigation of Cannabinoids (CCIC).

www.ccic.net

The purpose of the Canadian Consortium for the Investigation of Cannabinoids (CCIC) is to advance our understanding of the role of cannabinoids in health and disease through research and education.