Safety issues concerning the medical use of cannabis and cannabinoids

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Safety issues are a major barrier to the use of cannabis and cannabinoid medications for clinical purposes. Information on the safety of herbal cannabis may be derived from studies of recreational cannabis use, but cannabis exposure and effects may differ widely between medical and recreational cannabis users. Standardized, quality-controlled cannabinoid products are available in Canada, and safety profiles of approved medications are available through the Canadian formulary. In the present article, the evidence behind major safety issues related to cannabis use is summarized, with the aim of promoting informed dialogue between physicians and patients in whom cannabinoid therapy is being considered. Caution is advised in interpreting these data, because clinical experience with cannabinoid use is in the early stages. There is a need for long-term safety monitoring of patients using cannabinoids for a wide variety of conditions, to further guide therapeutic decisions and public policy.

Key Words: *Adverse events; Cannabis/cannabinoid; Safety; Therapy*

Innocuité du cannabis et des cannabinoïdes utilisés à des fins médicales

Les problèmes d'innocuité représentent un obstacle de taille à l'utilisation du cannabis et des médicaments dérivés des cannabinoïdes à des fins cliniques. Les données d'innocuité relatives à l'utilisation de la plante peuvent en effet provenir d'études sur l'utilisation du cannabis à des fins récréatives. Or, l'exposition au cannabis et ses effets peuvent différer considérablement selon que les utilisateurs le consomment à des fins médicales ou récréatives. Au Canada, on trouve des produits dérivés des cannabinoïdes standardisés et soumis à un contrôle de la qualité et les profils d'innocuité des médicaments approuvés peuvent être consultés par l'entremise du Formulaire canadien. Dans le présent article, l'auteur offre un résumé des principaux enjeux liés à l'innocuité du cannabis dans le but de favoriser un dialogue éclairé entre médecins et patients chez qui on envisage un traitement par cannabinoïdes. La prudence s'impose lorsque l'on interprète les données de la recherche clinique, puisque l'expérience pratique avec les cannabinoïdes en est à ses débuts. Il faudra exercer une surveillance à long terme de l'innocuité des cannabinoïdes chez les patients atteints de divers problèmes de santé pour mieux orienter les décisions thérapeutiques et les politiques en matière de réglementation.

Physicians' concerns about the use of cannabis for medical purposes, particularly in its widely used and unregulated herbal form, are often focused on safety issues. Because herbal cannabis has been used recreationally for many years and has been extensively studied, information on the safety concerns may be obtained by extrapolating results from epidemiological studies. Safety information about medicinal cannabinoid use may also be obtained from preparations of single cannabinoid compounds, which have been approved by regulatory agencies and have been prescribed for more than 20 years. The use of cannabis by patients with diseases such as HIV/AIDS, epilepsy, chronic noncancer pain, glaucoma and multiple sclerosis gives rise to potential safety concerns that are not addressed in observational research on recreational users. Examples of such concerns are potential drug-drug interactions, alterations in the immune functions of immunocompromised patients, and the risk of developing dependency disorders when cannabis is used in a medical context.

The present paper is an overview of safety issues regarding medicinal cannabis use. The aim is to promote a meaningful and informed dialogue between patients and health care providers regarding cannabis use.

METHODS

Search strategy

The published literature on MEDLINE from 1966 to December 2004 was searched using the medical subject headings "marijuana smoking" and "adverse effects", and with the limitations of human studies, studies published in English and studies available with abstracts. Papers on the effects of prenatal cannabis exposure on offspring were not reviewed in detail. Abstracts were reviewed by the lead author (MAW), and relevant papers were obtained and reviewed. The quality of the studies was not formally evaluated. Further safety information was obtained from safety summaries previously prepared by both authors in preparation for clinical trials, and further sources were identified from antecedent references. Where multiple studies were found to report on the same safety concerns, the most recent or representative reports were reviewed.

Data on the adverse events of cannabinoid drugs that are available on the Canadian market were taken from the 2004 *Compendium of Pharmaceuticals and Specialties* (1). Data on investigational cannabinoid drugs in development were not considered.

Major safety issues were categorized and explored in more detail.

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TABLE 1
Incidence of adverse events of regulated cannabinoids: Probable causal relationships with incidences of greater than 1%

Adverse event	Dronabinol (%)	Nabilone (%)
'High'	8–24	38.8
Somnolence	3–10	66
Dizziness	3–10	58.8
Dry mouth		21.6
Euphoria	3–10	4.0
Paranoid reaction	3–10	
Nausea	3–10	
Abdominal pain	3–10	
Thinking abnormalities/confusion	3–10	
Ataxia	>1	12.8
Asthenia	>1	7.6
Amnesia	>1	
Anxiety/nervousness	>1	
Depersonalization	>1	
Vomiting	> 1	
Palpitations	>1	
Tachycardia	>1	
Vasodilation/facial flush	>1	
Blurred vision		12.8
Sensation disturbance		12.4
Anorexia		7.6
Headache		7.2
Orthostatic hypertension		5.2
Hallucinations		2.0

Data from reference 1

RESULTS

One hundred fifty-seven papers were identified from the literature search for adverse effects, of which 79 were felt to be of relevance. The product monographs for nabilone and dronabinol were obtained.

Cannabinoid-based drugs

A summary of the adverse event profiles obtained from the 2004 *Compendium of Pharmaceuticals and Specialties* (1) for dronabinol and nabilone are provided in Table 1. The most commonly reported adverse events are a 'high', drowsiness, dizziness and dry mouth. For further information, refer to the product monographs of these drugs (2,3).

Herbal cannabis

Herbal cannabis is most often smoked. Survey data suggest that patients with chronic pain smoke between one and four puffs from a cannabis joint two to three times a day (4) (although larger doses are also known to be used by some patients). The exposures reported in recreational epidemiological and experimental studies range widely, from single exposures to over 20 years of daily heavy cannabis use.

The major safety concerns may be divided into those about the quality of the product and those about the administration of the drug itself. Drug administration effects are further divided into effects related to the delivery system and effects directly related to the cannabinoid compounds.

Quality concerns

Adverse events due to the use of contaminated cannabis were reported only in cannabis smokers. Contamination with *Aspergillus* has given rise to concerns of lung infections in immunocompromised patients (5-7). Contamination with paraquat (a potent pesticide) has not been associated with adverse effects (8). Contamination with formaldehyde has been reported to impair memory (9) and may be life threatening (10). Cannabis soaked in embalming fluid has been reported to cause phencyclidine-like responses (11).

The sharing of cannabis with contaminated smoking paraphernalia has been associated with small outbreaks of tuberculosis (12) and meningococcal disease (13,14).

Safety concerns related to cannabis smoking: Respiratory function

Cannabis smoking poses a potential health risk. Cannabis smoke has been shown to have qualitatively the same constitution as tobacco smoke but with quantitatively higher concentrations of polyaromatic hydrocarbons, which are known carcinogens (15). Cannabis smoke, like tobacco smoke, contains carbon monoxide, which preferentially binds hemoglobin at the expense of oxygen binding.

A higher prevalence of chronic bronchitis symptoms, such as cough, phlegm and wheeze, has also been noted in cannabis smokers (16-19). All symptoms were most evident in heavy, chronic users, defined as those who had smoked more than three joints per day for 25 years or more. There is a published report (20) of four cases of emphysema in adults with a history of cannabis smoking. However, observational surveys of heavy, chronic cannabis use have failed to find any lung damage in long-term smokers (21). Pneumomediastinum and pneumothorax have been reported following the prolonged Valsalva manoeuvre that may accompany cannabis smoking (possibly through rupturing emphysematous bullae) (22-25).

Several case studies of young patients with carcinoma of the upper respiratory tract have been published (26). There is concern that heavy cannabis smoking is a causative factor of this type of cancer, which is rare in adults under the age of 60 years, even in those who smoke tobacco and drink alcohol (27,28). One case-control study (29) reported an increased risk of upper respiratory tract cancer due to cannabis smoking; however, two recent case-control studies (30,31) have failed to find any increased risk of oral squamous cell cancers due to cannabis smoking. No association between cannabis smoking and tobacco smoking-related cancers was found in a large retrospective cohort study (32).

The effects of exposure to cannabis smoke in low doses in patients using cannabis therapeutically have not been determined. The doses used by patients for symptom relief may be low, and risks increase with heavy, chronic use of cannabis.

Acute effects

Mood effects: Acute reactions, such as nausea, anxiety, paranoia and disorientation often occur in new cannabis users but are uncommon in regular cannabis users (33). Many patients were considered to be asymptomatic after abstinence from cannabis for four months (34). For patients seeking symptom relief, the psychological high associated with cannabis smoke inhalation may be another unwanted effect, but this mood-altering effect may be an important part of the overall therapeutic response. Euphoria, altered time perception and

relaxation are acute reactions that disappear within 3 h to 4 h and are considered part of the high (35).

Acute toxicity: Unlike opioids, cannabis does not cause central respiratory depression (36). Acute hyperthermia has been reported following cannabis use and jogging on a warm day (37). Overdosing is extremely rare and is usually accompanied by the use of other drugs, such as alcohol. A lethal tetrahydrocannabinol (THC) dose has not been reported. From a purely pharmacological perspective, cannabinoids appear to be very safe. For a more detailed review of toxicity, please see the article by Beaulieu (pages 23A-26A). Doctors at the Haight-Ashbury clinic in the San Francisco Bay area who work primarily with drug addicts have stated that it is virtually impossible to die of a cannabis overdose (33).

Anxiety and panic: Acute anxiety and panic are recognized as possible complications of cannabis use, usually in the new user (35,38). Patients usually respond to reassurance. Cannabis use in a relaxed and supportive atmosphere may help reduce anxiety. In addition, patients appreciate being made aware of likely psychoactive effects on first doses, and gradual titration to an effective dose may promote tolerance to adverse psychoactive effects. Some subjects may find the anxiety unpleasant enough to stop using cannabis. Feelings of paranoia have been observed among recreational users with bipolar and panic disorders (39). The illegal status of the drug may be an important confounder in this regard.

Cardiac and other vascular effects: The cardiovascular effects of cannabis were recently reviewed (40). An increased relative risk of nonfatal myocardial infarction in the first hour following cannabis smoking has been described (41). Myocardial infarction following cannabis use and Viagra (Pfizer Canada Inc) consumption has been reported (42). The increase in heart rate following cannabis use may play a role by increasing myocardial oxygen demand, but other factors, such as plaque rupture and arrhythmias, may also have an effect (43-45).

Cannabis smoking-induced tachycardia may be problematic for patients with comorbid ischemic heart disease or arrhythmias. It has been found that inhalation of cannabis smoke reduces the amount of exercise required to cause an attack of angina by 50% (46). Cannabis-induced tachycardia is reduced by clonidine, an alpha-2 agonist, which suggests that THC may play a role in sympathetic nervous system stimulation (47), although a reduction in parasympathetic tone has also been suggested (48).

Cannabis is known to cause postural hypotension immediately after smoking (49). It also causes peripheral vasodilation, resulting in characteristic conjunctival reddening. It is plausible that the increased heart rate and drop in blood pressure may be secondary to a drop in peripheral vascular resistance. In addition, antiretroviral therapy (ie, highly active antiretroviral therapy) has been shown to cause lipid abnormalities in patients with HIV/AIDS. These lipid abnormalities may result in an increased risk for ischemic heart disease, which could be exacerbated by cannabis (50).

Transient ischemic attacks (51) and cerebrovascular stroke, usually following acute cannabis use, have also been reported in several case reports (52-56). Renal infarction following cannabis smoking has also been reported (57).

Cognitive function: Impaired performance has been observed using the circular lights test after subjects smoked two cannabis cigarettes containing 2.8% THC (58). A slight slowing of reaction was found by using digit symbol substitution and automated tracking tests after three doses of 0%, 1.3% and 2.7% THC. Inhalation of cannabis smoke had no effect on performance in the divided attention task (59). Performance measures have shown no dose-related effects on reaction times, but a dose-response effect on accuracy has been observed (60). Acute cannabis exposure has been associated with a hangover or residual effect on psychomotor performance (61,62).

Effects on driving: The literature concerning the risks of cannabis and driving is controversial, and no studies have been published on the effects of medicinal cannabis use on driving. The results are often influenced by the confounding effects of alcohol. Cannabis is known to cause mild euphoria, altered time perception and decreased motor coordination, which affect driving skills. Studies (63) have found that perceptual motor speed and accuracy are impaired after smoking a cannabis joint. However, it has been suggested that, unlike users of alcohol, cannabis users are aware of their level of intoxication and compensate for the effects by becoming very cautious, resulting in a decrease in the speed and the frequency of overtaking, as well as an increase in the following distance (64). It is recognized that cannabis may have significant effects on driving ability, with exaggerated effects in the presence of alcohol (65).

Seizures: Data on the risk of epileptic seizures following cannabis use were nonconclusive (66).

Long-term effects

Dependency: The risk of cannabis dependency is an important consideration when contemplating its medical use. In the present supplement, this is discussed further by Gourlay (pages 38A-43A). Although dependence on cannabis has been described, it is difficult to quantify the extent of this risk. Cannabis has a lower rate of conditional dependence (the risk of developing dependence among those who have used the drug) than alcohol, cocaine, heroin or tobacco, although the rate increases with the amount used (67). Substance abuse rarely begins with therapeutic use alone, as the experience with opioid analgesics has shown (68). Withdrawal symptoms such as cravings, irritability, anxiety, depression, reduced appetite and poor sleep after withdrawal from oral THC and smoked cannabis have been described (69-71), but the symptoms are limited to heavy, chronic users and are relatively short lived (72).

The abuse potential of nabilone (73) and dronabinol (74) have been examined and there is no published evidence that these drugs are prone to abuse or diversion (however, see the article by Gourlay). Long-term monitoring data on addictive behaviours are needed.

Cognitive function: The effects of long-term cannabis use on cognitive function remain controversial (75,76). In chronic users (10 to 15 years), cognitive impairments, such as deficits in memory of word lists, compared with nonusers are observed, but these resolve after 30 days of abstinence and may be related to acute effects (77). A meta-analysis (78) of the residual neurocognitive effects of cannabis use reported decreases in the performance of memory tasks. A recent study (79) suggested that patients with advanced HIV/AIDS may be at risk for aggravated memory impairment due to cannabis use. The long-term effects of cannabis use on neurocognitive function may be due to a direct effect of cannabis use or may be due to confounding effects (80); further research is required to draw conclusions.

Drug interactions: THC and other cannabinoids are metabolized by enzymes that are also responsible for the metabolism of

commonly prescribed medicines. This may potentially result in important drug-drug interactions. At least two cytochrome (CY) P450 enzyme systems, CYP2C and CYP3A, have been shown to be involved in the metabolism of cannabinoids (81). Recently, it was found that although delta-9-THC and antiretroviral drugs are metabolized by CYP3A, administration of THC (smoked or orally) does not significantly reduce plasma concentrations of antiretroviral drugs in patients with HIV/AIDS (82). Potential interactions with tricyclic antidepressants have been reported (83-85), but a conclusive link has not been established.

Immunity: It is apparent that delta-9-THC has immunomodulating effects, but the related health risks are not well defined. The dose required to obtain such effects is greater than that required for psychoactive or therapeutic effects (86). In a randomized, double-blind study of the effects of smoked cannabis (3.95% THC, 1 g three times daily) and oral THC (2.5 mg three times daily) administered over 21 days in patients with HIV/AIDS, neither the smoked nor the oral THC had a significant effect on CD4 cell counts or viral loads compared with placebo (82).

Nausea and vomiting: A recent case series (87) described a cyclical vomiting syndrome associated with chronic, heavy cannabis use ('cannabinoid hyperemesis'), which was linked to an abnormal washing behaviour.

Psychological effects: While cannabis use is associated with depression (88) and anxiety (89), a causative link has not been established. A recent systematic review (90) did not find a strong association between chronic cannabis use in young people and psychosocial harm.

Long-term cognitive effects: The presence of long-term cognitive effects following chronic, heavy use has been shown (75,78), particularly in the domains of memory and learning, and there is debate over whether these effects are reversible (91,92). Under medical use conditions, the relevance of these effects has been questioned (78).

Psychosis and schizophrenia: An association between cannabis use and an increased risk of psychosis and schizophrenia has been reported (93). In a study by Zammit et al (93), cannabis use was found to be a risk factor for developing schizophrenia (in a dose-dependent manner). Cannabis has also been shown to be associated with a schizotypal personality disorder (94), but the direction of this association is unclear. Cannabis has been shown to be a risk factor in the development of psychotic symptoms in young people, particularly among those with a predisposition for psychosis (95). Recent modelling studies (96) have suggested that daily cannabis use is causally associated with the development of psychosis. 'Cannabis psychosis' (97) has been shown to be clinically distinct from acute schizophrenia, with a shorter duration and high rates of remission (98); however, one report (99) has questioned the existence of cannabis psychosis disorder. A recent retrospective study (100) and a review (101) have confirmed the association between cannabis use and precipitation of schizophrenia in predisposed people and in people without a history of schizophrenia.

Effects on pregnancy: The effects of cannabis on the reproductive system in humans are uncertain because the published evidence is limited and inconsistent (35). Results from human epidemiological studies are difficult to interpret because cannabis users are more likely than nonusers to smoke tobacco, drink alcohol and use other illicit drugs during pregnancy. Cannabis use during pregnancy has been correlated with low birth weight (102,103), prematurity (104) and intrauterine growth retardation (105), although contradictory findings have also been reported (106). Frequent maternal cannabis use may be a weak risk factor for sudden infant death syndrome (107).

Risk of death: In one large retrospective cohort study of patients with HIV/AIDS (108), current cannabis use was not associated with an increased risk of non-AIDS death in men (RR=1.72, 95% CI 0.89 to 1.39); however, it was associated with an increased risk of AIDS-related death (RR=1.90, 95% CI 1.33 to 2.73) when compared with nonusers and experimental users of cannabis. For women, current cannabis use was not associated with total mortality (RR=1.09, 95% CI 0.80 to 1.49) (107). It is not clear whether the use of cannabis was causally related to AIDS-related mortality or whether cannabis smoking was used to treat worsening symptoms and was a confounder in this analysis.

Vascular effects: Peripheral arteritis, which is analogous to Buerger's disease in tobacco smokers, has been reported in several case reports (109,110).

DISCUSSION

The use of cannabis in any form poses potential health risks that are well described (although some remain controversial). Cannabis smoking clearly poses unique risks, both from the smoke and from potential contamination. The use of standardized and quality-controlled cannabis preparations with accurate monitoring and follow-up may identify and reduce these risks. The use of pharmaceutical cannabis preparations has risks that are well documented on product labels, but further research is required on the long-term effects of these products. The safety of cannabinoids in children, the elderly and patients with comorbid disorders (eg, diabetes, hypertension, ischemic heart disease, renal and hepatic impairment, and diseases that damage the immune system), as well as the effects of cannabinoid use on concurrent psychiatric illness (eg, depression, anxiety, psychosis and drug abuse) are all subjects for further research.

Some broad clinical recommendations based on existing safety information may be put forward, but these must be continuously revised as new data are published. Patients with a history of a psychotic disorder such as schizophrenia should not use cannabis. The use of cannabis during pregnancy should be avoided. Patients with uncontrolled hypertension and active ischemic heart disease should avoid cannabis. Patients using cannabis therapeutically should not drive or operate heavy machinery while experiencing the psychoactive effects of cannabis (consistent with advice concerning the therapeutic use of other psychoactive agents such as benzodiazepines and opioids). Patients with comorbid depression and other psychiatric disorders should be carefully monitored. Cannabinoids should be administered initially at low doses and titrated slowly to balance the positive and negative acute effects. Patients should be advised of the nature and likelihood of acute effects, and close monitoring is advised during the initial dose titration.

Most of our current knowledge about the risks of herbal cannabis is derived from studies of recreational users, and these risks may or may not be relevant in a medical use paradigm. The doses used may be different, the psychoactive effects at therapeutic doses may have a different impact, and the total lifetime exposure may be different. A considerable cumulative dose response to cannabinoids has been observed in many

areas and, therefore, some risks apply only to those who use cannabis over a long period of time.

CONCLUSIONS

Cannabis is used by many patients with a wide range of chronic disorders. Canadian physicians are being asked to support patient applications for authorizations to cultivate and possess cannabis for medical purposes. Physicians need to be able to provide a concise summary of known or suspected risks to their patients. It is hoped that this review will be a useful tool in this regard.

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