Addiction and pain medicine

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The adequate cotreatment of chronic pain and addiction disorders is a complex and challenging problem for health care professionals. There is great potential for cannabinoids in the treatment of pain; however, the increasing prevalence of recreational cannabis use has led to a considerable increase in the number of people seeking treatment for cannabis use disorders. Evidence that cannabis abuse liability is higher than previously thought suggests that individuals with a history of substance abuse may be at an increased risk after taking cannabinoids, even for medicinal purposes. Smoked cannabis is significantly more reinforcing than other cannabinoid administration methods. In addition, it is clear that the smoked route of cannabis delivery is associated with a number of adverse health consequences. Thus, there is a need for pharmaceutical-grade products of known purity and concentration using delivery systems optimized for safety. Another factor that needs to be considered when assessing the practicality of prescribing medicinal cannabinoids is the difficulty in differentiating illicit from prescribed cannabinoids in urine drug testing. Overall, a thorough assessment of the risk/benefit profile of cannabinoids as they relate to a patient's substance abuse history is suggested.

Key Words: Addiction; Cannabis; Risk management; Substance abuse; Urine drug testing

Depending on the prevailing attitudes of the time, certain pharmacotherapies have been perceived as either villains or heroes. At the crux of this debate has been the risk of substance misuse and addiction in the management of chronic pain. As cannabis enters the field of pain medicine, it must also be examined in this light.

THE PAIN AND ADDICTION CONTINUUM

The notion that pain and addiction can coexist is a relatively recent concept. Previously, the literature suggested that the prevalence of addictive disorders in the pain population was so uncommon that it did not merit investigation (1,2). This belief persists today (albeit much less so) despite the fact that the prevalence of addictive disorders within the general population is typically quoted as 10% (3). The reasons for this are complex.

A dichotomous approach to pain and addiction is simple, even if it is potentially incorrect. The only requirement for this approach is to establish a ‘legitimate’ pain diagnosis and, thus, obviate the need to enquire into issues related to substance misuse and addiction. In some circles, asking questions related to drug and alcohol use is seen as tantamount to dismissing the patients’ complaints of pain. In no other area of medicine would such a conclusion be drawn. It is becoming clear that pain and addiction can, and do, coexist (4-7).

La dépendance et les analgésiques

Le cotraitement pertinent de la douleur chronique et des troubles de dépendance est un problème complexe et ambitieux pour les professionnels de la santé. Les cannabinoïdes ont un grand potentiel dans le traitement de la douleur, mais la prévalence croissante d’utilisation récréative du cannabis s’associe à une augmentation considérable du nombre de personnes qui cherchent à se faire traiter pour des troubles liés à l’utilisation du cannabis. Des données montrant que les dommages liés à l’usage de cannabis sont plus élevés qu’on le pensait auparavant laissent supposer que les personnes ayant des antécédents d’abus de drogues seraient plus vulnérables après avoir pris des cannabinoïdes, même pour des besoins médicaux. Le cannabis fumé est un agent considérablement plus renforçant que les cannabinoïdes administrés autrement. En outre, il est clair que la voie d’administration du cannabis fumé entraîne diverses conséquences nocives pour la santé. Ainsi, il est nécessaire de mettre au point des produits de qualité pharmaceutique dont la pureté et la concentration sont connues, au moyen de systèmes de perfusion à l’innocuité optimisée. Un autre facteur dont il faut tenir compte lorsqu’on évalue la possibilité de prescrire des cannabinoïdes médicaux demeure la difficulté de distinguer les cannabinoïdes prescrits des cannabinoïdes illicites dans les tests de dopage. Dans l’ensemble, une analyse approfondie du profil risque-avantage des cannabinoïdes par rapport aux antécédents d’abus de drogues du patient est suggérée.

In understanding the relationship between pain and addiction, part of the problem seems to be nomenclature. Pain specialists and addiction practitioners alike have used common terms that, depending on the individual’s point of view and training, have come to mean entirely different things. To this end, in 1999, the American Pain Society, the American Academy of Pain Medicine and the American Society of Addiction Medicine formed a group called the Liaison Committee for Pain and Addiction. The first task for this group was the creation of a set of definitions for addiction, dependence and tolerance that could be embraced by all three organizations. These definitions were published in 2003 (8).

Addiction

“Addiction is 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.” (8)

Unlike the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (9) definition for addiction,
physical dependency (withdrawal) and tolerance are not considered in making the diagnosis.

The usefulness of the DSM-IV definition is severely reduced when the identified drug of misuse is also a drug which could ultimately be an appropriate part of the patients’ pharmacological management. Although validated tools to assess risk in the context of pain and addiction are being developed (10), at the present time there are no tools that can differentiate between appropriate and problematic use (either misuse or addiction) of a medication where the identified drug of choice may also play a useful role in the management of chronic pain. This is currently the case with opioids used in chronic non-cancer pain management (11) and will undoubtedly present a diagnostic challenge when cannabis becomes more widely used to treat chronic pain.

Physical dependence

“Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.” (8)

The phenomenon of physical dependence is an expected, neuroadaptive change that occurs in response to chronic exposure to certain drugs. It is not, in itself, suggestive of anything beyond this.

Tolerance

“Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.” (8)

In the case of tolerance, it is important to remember that it is neither good nor bad; it simply is. In some cases, such as the cognitive blunting effects of opioids, tolerance occurs relatively quickly and is considered positive. On the other hand, tolerance to the constipating effects of opioids virtually never occurs.

What is particularly important about these definitions is that the boards of representative organizations from both the pain management and addiction medicine communities have endorsed them. While these definitions represent a compromise, they are an important step forward in reducing the risk of the continued use of imprecise terms in both the pain management and addiction medicine literature.

Although the true prevalence of addiction within the chronic pain management population is unknown, the enormous problem that chronic pain represents in the substance abuse treatment population is beginning to be appreciated (12,13). A study by Rosenblum et al (14) found that 37% of patients surveyed within methadone maintenance treatment programs suffered from chronic severe pain. They also concluded that self-medication with psychoactive drugs for pain was especially problematic for substance abusers enrolled in drug-free (abstinence-based) treatment programs.

THE DISEASE OF ADDICTION

Drug abuse and addiction represent challenges to society at several levels. While it is tempting to focus on the impact of addiction on individualistic health, there is also an adverse impact on public health.

In 1998, the Substance Abuse and Mental Health Services Administration estimated that 13.6 million Americans aged 12 years and older had used an illicit drug in the previous month (15). The harm done by this use occurs not only at the level of the brain, but is also seen in increased rates of HIV transmission, hepatitis B and C, and tuberculosis. The societal cost of associated criminality and social dysfunction is difficult to accurately ascertain but has been estimated at US$109 billion annually (16).

There are many different factors that lead to drug use including genetic, physiological and even social factors (17). In addition, there are both risk and protective factors that modify the expression of a substance use disorder. Risk factors include weak family structure, peer group pressures and growing up in high-crime neighbourhoods. On the other hand, strong family bonds and academic achievement may be protective (18).

By stepping beyond the question of why some people choose to use drugs recreationally and by focusing only on those who do, it is realized that in the at-risk individual, the chronic exposure to certain psychotropic substances causes changes in brain structure and function. Addiction is not only a ‘disease of the brain’ (19) but also a disease with both behavioural and social expression. Treatment of addiction requires changes to be made both within the patient and in the surrounding environment.

PREVALENCE OF DRUG USE AND DEPENDENCE

There is considerable variation in the prevalence of drug use depending on the drug being considered and the population under study. Alcohol, tobacco and caffeine are the most commonly used psychotropics (20). Drugs like heroin and cocaine are much less commonly used.

In general, the use of cannabis has remained relatively constant over recent years; however, it is on the rise among young adults in certain ethnic and racial groups (21). In fact, cannabis has been shown to be the most widely used illicit substance in communities around the world (22-24).

In the United States, according to the 2000 United States National Household Survey on Drug Abuse (22), 2.8 million Americans met the criteria in the previous year for either cannabis dependence (1.6 million) or abuse (1.2 million). Furthermore, this survey reported that 25% (713,000) of those with cannabis use disorder actually seek treatment. That is more than those seeking treatment for cocaine, hallucinogens, stimulants, pain relievers, inhalants, tranquilizers, heroin or sedatives (25).

In the United States, it is estimated that of those who have ever used cannabis, 10% will develop dependence (26). Of those who try cannabis more than once, approximately one-third will become regular users even though most will have stopped using it by their late 20s or 30s (27). In fact, the relative potential for dependence on cannabis, expressed in terms of conditional dependence (the risk of developing dependence among those who have ever used that substance) (26), is approximately 9%, which is lower than other substances such as alcohol (15%), cocaine (17%), heroin (23%) or tobacco (32%) (26,28).

In Canada, the number of Canadians aged 15 years and older who admit to using cannabis nearly doubled between 1989 and 2002, with the highest rate among teenagers (29). In fact, 6.5% of Canadians reported using cannabis in 1989, 7.4% in
CANNABIS USE

Cannabis as a drug with abuse liability

For some time, cannabinoids were considered unimportant in brain reward systems, despite the fact that they are clearly euphorogenic in humans and do have abuse liability (32,33). More recent work over the past 15 years has shown cannabinoids to interact with the brain reward systems in a similar fashion to other drugs with addiction liability (34,35).

Drugs with addiction liability often share certain qualities, which can be demonstrated in the animal laboratory setting. One of these is the involvement of the endogenous opioid system even for nonopioid addictive drugs.

In this case, the rewarding effect of cannabinoids can be attenuated by opioid antagonists, which is characteristic of drugs with addiction liability (32). More recently, Justimova et al (36) demonstrated this attenuating effect of the opioid antagonist naltrexone on the reinforcing effects of delta-9-tetrahydrocannabinol (THC) in squirrel monkeys.

Finally, in previously dependent but now abstinent animals, drugs with addiction liability are often able to reinstate drug-seeking and self-administration behaviour in response to a ‘priming’ dose of the drug. Although there is a paucity of data in this area, there is evidence that the intravenous priming of former heroin-dependent rats with cannabinoid agonists can lead to reinstatement of drug-seeking behaviour (32,37).

Recently, it has been demonstrated with cannabis-naïve squirrel monkeys that THC can act as an effective reinforcer of drug-taking behaviour in monkeys with no history of exposure to other drugs. This suggests that self-administration of THC by monkeys may provide a reliable animal model of human cannabis abuse (38).

Thus, it would be reasonable to conclude that cannabinoids share many of the qualities demonstrated in other drugs, which are clearly seen as having a high addiction liability (33). This becomes important when assessing risk in the use of this class of drug for the management of pain, especially in those individuals with a history or an increased risk of a substance use disorder.

Cannabis dependence, tolerance and withdrawal

The existence of a definable withdrawal syndrome with cannabis has long been questioned. Before the publishing of the DSM-IV, cannabis dependence did not exist as a specific diagnostic category (34). More recently, research has begun to characterize this phenomenon more clearly. Tolerance to cannabis can develop after periods of daily use as short as one to three weeks. The resultant withdrawal symptoms that occur on abrupt discontinuation of cannabis typically begin after 24 h, peak at 72 h and are usually over within seven to 10 days (39). The symptoms are nonspecific and include irritability, anxiety, physical tension, and decreases in mood and appetite. In some cases, there is restlessness, tremors, sweating, insomnia and even vivid dreams. The time frame is highly variable and appears to be similar to that seen with other drugs of abuse (40).

Cannabis use disorders

Recent studies in the United States have shown that more people are self-identifying themselves as having cannabis use disorders (as indicated by a tremendous increase in admissions to publicly funded treatment programs). The demand for treatment from health professionals, however, remains low relative to the apparent problem. In 1999, the United States Treatment Episode Data Set (41) recorded more than 220,000 admissions for cannabis use disorder treatment, which represents 14% of all admissions to these facilities – a doubling in rate compared with 1993 (42). By 2000, cannabis admissions accounted for 61% of all adolescent admissions. These trends are also observed in Australia, where they have seen a doubling in the national rates of cannabis treatment-seeking individuals from 2000/2001 to 2001/2002, with an overall rate of 21% and a specific rate of 45% in those younger than 20 years of age (43). There has also been a concomitant increase in cannabis-related emergency room visits in the United States. Adjusting for population changes, this represents a 139% increase in reported visits for the period of 1995 to 2002 (44).

In a recent article (21) examining the prevalence of cannabis use disorders in the United States during 1991/1992 and 2001/2002, the authors indicate that despite an overall stable prevalence of cannabis use, more adults in the United States had a cannabis use disorder in 2001/2002 compared with 1991/1992. While these rates did not increase for young, white men and women, their rates of use remained high (34.4% for 2001/2002). In contrast, the rates of cannabis abuse or dependence increased by 18% from 30.2% in 1991/1992 to 35.6% in 2001/2002 across the general population surveyed (21).

Two important factors were identified that might help to explain the increase in cannabis use disorders. The first is the significant increase in the potency of cannabis from police seizures over the time period of 1992 to 2002 (45). In the absence of any systematic increase in frequency or quantity of cannabis used over the time frame studied, the increasing rates of cannabis use disorders may reflect an increased potency of the cannabis used (21).

Although research clearly indicates that concentrations of seized cannabis have been rising, the actual percentage increase has been difficult to assess (45,46). The cannabinoid concentration of cannabis seized in Canada does appear to have been increasing over the years. Although the concentrations quoted vary widely, depending on the sample and method of analysis, the average cannabinoid concentration of cannabis seized in the 1980s was less than 1%, while the average over the period of 1996 to 2000 was 6.7% (47). The use of selective breeding and hydroponic cultivation has dramatically increased the potency of today's cannabis (48). Information from 'street seizures' in Canada from April 2000 to April 2002 indicates a mean THC content of 10% with a range of 3% to 30% (49). According to the World Health Organization, the average joint contains 0.5 g to 1.0 g of cannabis plant matter (50). This makes the estimation of 'average dose' exceedingly difficult.

The second possible factor to explain increased cannabis use disorders relates to the increase in use observed in the younger age groups. Because an early onset of drug use has been consistently associated with an increased risk of developing a
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commonly seen in drugs of abuse (65). At the present time, Marinol is available in 2.5 mg, 5 mg and 10 mg capsules.

Cesamet
Cesamet is a synthetic cannabinoid that has been developed for use as an antiemetic agent, notably for chemotherapy-induced nausea. It is available as a pulvule (powder-containing capsule) in 0.5 mg and 1 mg strengths. This form of delivery does not appear to lend itself to volatilization or combustion and, thereby, limits misuse via the pulmonary route of administration.

Nabulone has been studied in comparison with the reinforcing properties of oral THC and smoked cannabis in subjects with previous cannabis experience. These data indicate that smoked cannabis was significantly more reinforcing than all other cannabis compounds studied, regardless of drug use history (66).

DRUG MONITORING
Whenever a drug or member of a class of drugs is legitimately present in a test sample, as is the case with any prescribed medication, it becomes very difficult to monitor misuse of that drug or class of drug. An example of this would be the problems associated with monitoring an abstinent heroin user who has been prescribed codeine-containing analgesics for the management of pain. In this case, morphine that results from the metabolism of heroin (diacetyl morphine) will be impossible to distinguish from the morphine that would be expected to be present due to the metabolism of the prescribed codeine (67,68).

From a monitoring perspective, it is relatively difficult to distinguish smoked cannabis from orally administered or smoked Marinol. Both routes of administration produce immunoassay-positive screen results for THC and, because they are identical molecules, they cannot even be distinguished by gas chromatography/mass spectroscopy. Naturally occurring THC-containing products are a mix of cannabinoids. One specific cannabinoid that can be identified by sophisticated testing, delta-9-tetrahydrocannabivarin (THCV), has been proposed as a way to specifically identify the naturally occurring product from the synthetic agent (69,70).

In 2001, ElSohly et al (69) reported results from a cleverly designed study using a small number of cannabis users as test subjects. The study used a three-session, within-subject, crossover design. Each subject randomly received on separate sessions either an oral dose of Marinol (15 mg), a smoked dose of pure THC (16.98 mg dronabinol) in a placebo cannabis cigarette or an equivalent smoked dose of cannabis (2.11% THC and 0.57 mg THCV/800 mg cigarette = 16.98 mg THC and 0.96 mg THCV). They found that use of cannabis with or without Marinol could be distinguished from the use of Marinol alone (69). Previously, they had found that the confirmatory analaytes, THC carboxylic acid and THCV carboxylic acid, found in urine drug specimens supported these findings (70).

Cesamet, however, does not trigger a positive immunoassay screen or a confirmatory gas chromatography/mass spectroscopy test for THC (71). In this context, a positive screen for THC in a patient being prescribed Cesamet is consistent only with the use of a THC-containing product such as cannabis or Marinol.

PRACTICAL CONSIDERATIONS IN DRUG TESTING
Urine drug testing can and should play an important role in chronic pain management. There are, however, some limitations

Method of cannabis use
Cannabis is used in a wide variety of ways. Most commonly, it is smoked either alone as a cannabis cigarette or mixed with tobacco (27). It can also be refined into a smokable resinous mass (hashish) or further refined into a potent oil ('hash oil' or 'honey oil') that is either smoked with tobacco-containing products or vaporized with a constant-temperature device (54). In some cultures, cannabis is taken orally as either an ingredient in foods (55) (eg, 'hash brownies') or as a tea ('ganja tea'). The mode of delivery directly affects the speed of onset and duration of action of the desired (and sometimes undesired) effects of this drug and, therefore, affects the abuse liability.

The speed of drug delivery also affects the reinforcing nature of a drug and, hence, its abuse liability. The inhaled route is a fast and effective method of delivering precise quantities of drug at the instant the individual desires it (56). With inhalation (ie, smoked), the drug is delivered into the cerebral vascular circulation very rapidly. Coupled with the fact that the user can titrate the quantity of drug delivered by the degree of force used during inhalation and the time that the breath is held, the inhaled route is a fast and very reinforcing means of delivering substances to the human brain (57).

Smoking as a delivery system
It is important to separate the drug from the delivery system in the assessment of risk. As presented in other articles in this symposium, there is significant potential for cannabinoids in the treatment of pain. In addition, it is clear that the smoked route of delivery is potentially associated with a number of adverse health consequences (58). Thus, it is a priority to minimize the risks of smoking. Appreciating this point, both natural plant extract (59,60) and synthetic oral cannabinoids have been developed (61).

SYNTHETIC CANNABINOIDS
At the present time, two synthetic cannabinoids are available for medical use in Canada. The first is a true synthetic THC, dronabinol (Marinol, Solvay Pharma Inc, Canada) (62), and the other is a synthetic cannabinoid called nabilone (Cesamet, Valeant Canada limited/Limited) (63).

Marinol
Marinol was first approved for use in the United States in 1985 and it is currently available for two specific indications: the treatment of anorexia associated with weight loss in patients with AIDS, and the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments (62). Marinol is a synthetic THC dissolved in sesame seed oil and, when taken orally, the drug is unpredictably absorbed from the gastrointestinal tract. In contrast to the inhaled route of administration, there is very little opportunity for the patient to titrate the dose to effect. Adverse side effects are common (64).

In the past, it has been reported that the abuse liability of Marinol is low (65); the authors support this by stating that the drug lacks the desirable qualities of rapid onset and titratability

SUBSTANCE USE DISORDER (51-53), the increase in duration of use associated with this younger using population may help to account for the increased prevalence in rates of cannabis abuse and dependence (21).
to its use. Apart from therapeutic drug level monitoring, the application of drug toxicology in clinical medicine has been largely limited to the emergency room setting. Its use is well known within forensic settings, such as the Department of Transportation testing, and in workplace testing. In this context, testing is often adversarial and certainly often not in the patient’s best clinical interests. Drug testing may, however, be patient-centred if used properly (68, 72). Motivating behavioural change, encouraging maintenance of healthy changes already made, advocacy with third parties and early identification of undiagnosed substance use disorders, where they exist, make the rational use of urine drug testing a welcome addition to clinical medicine. No medical test should be used to limit treatment or deny appropriate care. Urine drug testing should be no exception.

Testing techniques can be divided into initial ‘screening’ and the more definitive ‘confirmatory’ tests. Screening tests are commonly immunoassay-based and usually identify classes of drugs rather than specific agents. Screen tests are typically very sensitive because they often react to all members of the test class rather than to simply one specific drug. However, there are exceptions to this, as in the case of methadone. In contrast, confirmatory testing is often less sensitive but able to accurately identify specific drugs. For example, a patient taking codeine would be expected to have an initial positive screen for ‘opiates’, but only on confirmatory testing do the specific agents responsible for this positive screen (codeine and its active metabolite morphine) become identified (67, 68).

It is important to remember that neither screening nor confirmatory testing can detect all substances that may, in fact, be present in a sample. A number of factors, including both concentration effects (dilute urine) and limitations in the testing methodology can account for the failure to detect drugs that may be present in a sample, including prescription drugs that the patient is known to be taking (67, 68).

A detailed description of the patient-centred approach to urine drug testing is beyond the scope of this paper; however, useful recommendations for the use of drug testing in the primary care setting can be found on the Internet at <http://www.alaskaafp.org/udt.pdf> (67), and in a report by Heit and Gourlay (68).

REFERENCES

42. The DASIS report: Marijuana treatment admissions increase:
41. Office of Applied Studies. 1994-1999 Treatment Episode Data Set
40. Hughes JR, Higgins ST, Bickel WK. Nicotine withdrawal versus
39. Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course
37. Fattore L, Spano MS, Cossu G, Deiana S, Fratta W. Cannabinoid
35. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis
34. European Monitoring Centre for Drugs and Drug Addiction. Annual
32. Summary of Findings from the 2000 National Household Survey on
31. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis
30. Tjepkema M. Use of cannabis and other illicit drugs. Health Rep
29. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology
27. McRae AL, Budney AJ, Brady KT. Treatment of marijuana dependence:
26. Room R. Smoking and drinking as complementary behaviours. Addiction