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Marijuana Neurobiology and Treatment

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Abstract

Marijuana is the number one illicit drug of abuse worldwide and a major public health problem, especially in the younger population. The objective of this article is to update and review the state of the science and treatments available for marijuana dependence based on a pre-meeting workshop that was presented at ISAM 2006. At the workshop, several papers were presented addressing the neurobiology and pharmacology of marijuana and treatment approaches, both psychotherapy and medications, for marijuana withdrawal. Medicolegal and ethical issues concerning marijuana medical use were also discussed. Concise summaries of these presentations are incorporated in this article, which is meant to be an updated review of the state of the science. Major advances have been made in understanding the underpinning of marijuana dependence and the role of the CNS cannabinoid system, which is a major area for targeting medications to treat marijuana withdrawal and dependence, as well as other addictions.

Behavioral therapies are efficacious for facilitating abstinence from marijuana. Nefazadone, Marinol, and bupropion are showing early positive signals for efficacy in ameliorating marijuana withdrawal symptoms. Effective psychotherapeutic approaches are available and promising medications studies

need to be confirmed in outpatient trials. The next few years looking promising for translational research efforts to make treatment widely accessible to patients with marijuana dependence.

Keywords

Marijuana; behavioral; pharmacotherapy; neurobiology

INTRODUCTION

Marijuana is the most frequently used illicit drug worldwide, with an estimated annual prevalence of about 163 million or about 3.9% of the global population aged 15 years or above in 2000/2001 (1). In the United States, the 2005 National Survey on Drug Use and Health (NSDUH) reported that 74.2% of the 19.7 million illicit drug users use marijuana (2). The incidence of new marijuana use was 2.1 million people in 2005, a figure similar to the previous 3 years. This equates to approximately 6,000 new initiates per day.

Marijuana use typically starts in adolescence. The mean age of first use in the 2005 NSDUH was 17.4 years. Similar results were found in the National Comorbidity Survey (3). These authors reported that peak initiation occurred at age 18 and that within 10 years 8% of this group will become marijuana dependent. Among new users, 1–2% will develop a clinically significant cannabis dependence syndrome during the first 1–2 years after onset of smoking (4), which translates to about 20,000 to 30,000 recent-onset cannabis users becoming dependent each year in the United States. The fraction of new cannabis users who eventually develop a cannabis dependence syndrome is about one cannabis dependence case for every 9–11 who start smoking cannabis (5,6).

A substantial proportion of teens and adults use marijuana regularly. The rate of current illicit drug use among persons aged 12 or older in 2005 (8.1%) was similar to the rates in 2004 (7.9%), 2003 (8.2%), and 2002 (8.3%). In terms of past month use, marijuana was the most commonly used illicit drug (14.6 million past month users). Among persons aged 12 or older, the rates of past month marijuana use were about the same in 2005 (6.0%) as in 2004 (6.1%), 2003 (6.2%), and 2002 (6.2%). Notably, the rate of current marijuana use among youths aged 12 to 17 declined significantly from 8.2% in 2002 to 6.8% in 2005. Although this dependency risk is lower than that seen with cocaine (16%), the high use rates in the population suggest that treatment needs for marijuana dependence will remain high for the foreseeable future.

According to the Treatment Episode Data Set (TEDS), marijuana is the second most common reason for admission to a drug treatment program (7). Marijuana dependence treatment admissions accounted for 16% of admissions in 2005. Marijuana abuse accounted for 55% of the admissions in the under-19 age group in this data set. The average age for admission for treatment of marijuana dependence to a TEDS reporting facility was 24 years.

Marijuana use can have immediate consequences. According to the DAWN report (8), there were 940,953 emergency department (ED) visits related to drug abuse in the United States. Marijuana was reported in 23% of those visits (73 cases/100,000 population). Although cocaine abuse is reported more frequently in the overall DAWN ED survey, marijuana was the most frequently reported drug in ED visits in youth under the age of 20. Moreover, the number of persons entering treatment programs for a primary problem of marijuana abuse has increased substantially over the past 15 years, such that the percentage of marijuana cases is equal to that of cocaine and heroin dependence (9).

The marijuana plant (*Cannabis sativa*) contains over 400 compounds and a total of 66 cannabinoids. One of the major cannabinoids is tetrahydrocannabinol (THC), which has well-documented behavioral and cardiovascular effects. THC is rapidly absorbed following smoking, with a PK similar to intravenous (i.v.) administration. Its bioavailability is quite variable depending on puff duration, depth of volume inhaled, and duration of breath held. In heavy users the average bioavailability is 23% ($\pm 16\%$) and in light users 10% ($\pm 7\%$) (10). Following oral administration, absorption is slow, erratic, and subject to first pass metabolism, with bioavailability of 6–15%.

After absorption, THC is quickly distributed into tissues and subsequently accumulated in body fat. THC is metabolized rapidly, but the metabolites are slowly eliminated. Approximately 80–90% of the dose is excreted in 5 days, 65–80% in feces and 20–35% in urine. THC is metabolized primarily by CYP3A and CYP2C; over 80 metabolites have been identified. Major metabolites include the non-active THC-9-COOH and the psychoactive 11-OH-THC.

THC is practically not measurable in urine (11). THC-9-COOH is the major metabolite measurable in urine, and the majority of THC-9-COOH is excreted in conjugated form. Urinary THC-9-COOH concentrations are quite variable after a given dose because of variations in urine volume and individual pharmacokinetics. Normalization with urine creatinine levels (THC-9-COOH/creatinine) is used to minimize the variation of urine volume.

Two cannabinoid receptors have been cloned (12). CB1 receptor is located mainly in brain, spinal cord, and peripheral tissue, while CB2 is mainly in immune cells. Cannabinoid effects are CB1 receptor mediated, because the effects of smoked marijuana can be blocked by the CB1-selective cannabinoid receptor antagonist SR-141716 (13,14).

Endocannabinoids are natural chemicals that activate CB1 receptors in the brain (ligands). The most common is anandamide. The system plays a physiological role in many functional states, including reward, cognition, appetite control, and analgesia. Chronic cannabinoid administration leads to dependence; cannabinoids are self-administered by humans and laboratory animals. Cannabinoid agonists and antagonists influence dependence on opioids, alcohol, and nicotine. The CB1 antagonist SR-141716A induced reduction in ethanol preference in the self-administration paradigm in mice (15). Animal studies also showed that the CB1 agonist HU-210 provoked relapse to cocaine after prolonged withdrawal, while the antagonist SR-141716A attenuated cocaine-induced relapse (16).

COGNITIVE EFFECTS

Evaluating the cognitive effects of long-term cannabis use is difficult because of many confounding variables. The judgment as to whether a given effect is a result of cannabis use is complicated by various sources of bias that can occur in naturalistic studies. Experimental data are lacking because one cannot ethically recruit a group of individuals to consume large amounts of cannabis for 20 years, while having a comparison group abstain. The only available data come from naturalistic studies of individuals using cannabis in uncontrolled settings, which are beset by all the usual methodological problems that afflict naturalistic and retrospective studies.

First is the issue of selection bias. Cannabis users who respond to an advertisement for a study may not be representative of the source population from which they are drawn. For example, cannabis users who come into a study may be particularly worried about their cognitive functioning and want to be evaluated, or may have psychiatric symptoms and want to be evaluated by a mental health professional, or may be self-selected in some other way. So for a number of reasons, one might predict that selection factors might bias the results in favor of finding a deficit in cannabis users and rejecting the null hypothesis (type I error).

Second is the issue of information or recall bias. Cannabis users may suspect that they would be rejected from the study, and not get the associated compensation, if they reported significant use of other drugs or psychiatric disorders. This would result in a denial or minimizing of their use of other potentially toxic drugs or the presence of psychiatric disorders, which, in turn, would result in a bias away from the null hypothesis (type I error).

Third, and most serious, is the issue of unmeasured confounding variables, which impacts all naturalistic studies. Even if we could do a perfect study in which we completely eliminated selection bias and completely eliminated information bias, if we found that cannabis users exhibited cognitive deficits, how would we know that these deficits were attributable to cannabis use and not to some other confounding factor such as impaired cognitive functioning prior to cannabis use?

There have been many studies measuring the cognitive effects of long-term cannabis use. This literature lacks consensus, and a 2003 meta-analysis of existing studies that met appropriate methodological criteria failed to find significant cognitive deficits in long-term users (17).

The results from a study by Pope et al. (18), support these findings. They administered neuropsychological tests to 63 current heavy cannabis users who had smoked cannabis at least 5,000 times in their lives and to 72 control subjects who had smoked no more than 50 times in their lives. Although differences between the groups after 7 days of supervised abstinence were reported, no deficits were found after 28 days abstinence, after adjusting for various potentially confounding variables. These findings suggest that cognitive deficits associated with long-term cannabis use are reversible and related to recent cannabis exposure. If further research finds that there are, indeed, irreversible cognitive effects associated with long-term cannabis use, it is likely that the effects will be subtle and not robust.

Regardless of whether cannabis causes permanent or irreversible effects, the study of chronic long-term users by Gruber et al. (19) produced some very disturbing findings. They asked long-term heavy users about various demographic attributes and also about their experiences with cannabis itself. Some striking results appeared when they compared 108 heavy cannabis users to 72 control subjects who had smoked cannabis fewer than 50 times, and a median of only 10 times, in their entire lives. The parental education in both groups was almost the same, with 58% of the heavy cannabis users and 51% of the controls having at least one parent who graduated from college. But the level of college graduation among the subjects themselves was dramatically different, with fewer than half of the heavy cannabis users having obtained a college degree as opposed to almost 80% of the control subjects. Similarly, the family income in both groups was roughly the same, with about 20–25% of the families reporting an income of less than \$30,000 dollars a year. However, the income of the subjects themselves was dramatically different, with more than 50% of the heavy users reporting incomes of less than \$30,000 per year almost twice as frequently as the controls.

One might hypothesize that the effects of cannabis use had nothing to do with these differences in educational attainment and income, that instead the differences arose from a decision by the long-term cannabis users not to pursue cultural norms like going to college or working at a high-level job. If this hypothesis were true, one would expect the long-term cannabis users to deny adverse effects of cannabis use. However, when cannabis users were asked to rate the effects of their own cannabis use as positive, neutral, or negative, they gave overwhelmingly negative ratings of the effects that cannabis had had on their social life (70%), their physical health (81%), their mental health (60%), their cognition (91%), their memory (91%), and their career (79%).

It seems a reasonable hypothesis that the negative effects these long-term heavy cannabis users reported are due to being acutely intoxicated every day. People intoxicated with cannabis

demonstrate impairments in a variety of cognitive, perceptual, and psychomotor tasks. Tasks showing the most impairment involve short-term memory, sustained or divided attention, complex decision-making, and reaction time (20). Ninety-seven percent of the heavy users in the Gruber study reported driving on a regular basis while intoxicated. Studies using driving simulators show marked impairment during acute cannabis intoxication, and accident statistics show that a disproportionate number of accidents occur in individuals intoxicated with cannabis and alcohol (21). Forty-five percent of the heavy users have children. It is reasonable to presume that chronic cognitive impairment will adversely affect one's ability to raise children. Moreover, 44% of the heavy users held jobs that potentially could endanger themselves or others, jobs such as electricians, nurses and pharmacists, chefs, nannies and daycare workers, and truck drivers. Other heavy users held jobs that, poorly performed, could greatly inconvenience others, jobs like postal workers and administrators of various types.

TREATMENT

Until recently, very little research has focused on treatment, because it was thought that marijuana dependence is rarely a primary problem or that no true dependency develops with prolonged use. However in the late 1980s, Roffman and Barnhart (22) found out that of 225 marijuana users surveyed, 74% reported that they were very adversely affected, and more than 68% said they were interested in participating in treatment if it was available. Other studies confirmed these findings (23–25).

Clinical manifestations of chronic use include abuse or dependence, tolerance to the subjective and cardiovascular effects, withdrawal, cardio-respiratory complications, and cognitive changes. Withdrawal symptoms include negative mood, irritability, anxiety, misery, muscle pain, chills, decreased food intake, disrupted sleep, and craving. Resumption of marijuana use alleviates these symptoms. Withdrawal likely contributes to the high rates of relapse observed clinically.

Behavioral Treatment

The treatment outcome literature for adult marijuana dependence indicates that behaviorally based outpatient treatments are effective for reducing marijuana consumption and engendering abstinence. McRae et al. (26) published a good review on behavioral treatment approaches for the management of marijuana dependence. Cognitive-behavioral (CBT; also known as coping skills training) and motivational enhancement (MET) interventions comprise the most common approaches tested with adults. These interventions reflect adaptations of interventions used effectively to treat alcohol dependence (27,28).

CBT for marijuana dependence has typically been delivered in 45- to 60-minute individual or group counseling sessions. The overall focus is the teaching of coping skills relevant to quitting marijuana and coping with other related problems that might interfere with good outcome. Such coping skills include functional analysis of marijuana use and cravings, development of self-management plans to avoid or cope with drug-use triggers, drug refusal skills, problem-solving skills, and lifestyle management. Each session involves analysis and discussion of recent marijuana use or cravings, brief didactic introduction of a coping skill, role-playing, interactive exercises, and practice assignments. The duration of CBT has ranged from 6 to 14 sessions.

MET involves a more nondirective intervention approach than CBT and is delivered in 45- to 90-minute individual sessions. MET is designed to help resolve ambivalence about quitting and strengthen motivation to change. Therapists use a motivational style of interaction to guide the patient toward commitment and action to change. Techniques used include expression of empathy, reflection, summarization, affirmation of self-efficacy, exploration of pros and cons

of drug use, rolling with resistance, and forging a goal plan when ready. Duration of MET has ranged from 1 to 4 sessions.

A series of randomized controlled trials have demonstrated the efficacy of both CBT and MET for adult marijuana dependence (29–31). The most recent and comprehensive of these trials compared a 9-session intervention that combined MET/CBT interventions (see Steinberg et al. (32) for the treatment manual) with a 2-session MET intervention and a delayed treatment control. The MET/CBT and MET interventions produced better marijuana abstinence outcomes than the delayed treatment control. The MET/CBT also showed significantly greater long-term abstinence rates and greater reductions in frequency of marijuana use compared with MET. These findings generalized across three geographically separated sites in the United States and were not moderated by ethnicity, gender, or employment status.

In an effort to further enhance outcomes, treatment approaches have integrated a type of contingency management (CM), i.e., abstinence-based vouchers, with MET/CBT interventions. These CM interventions reflect adaptations of those first developed and demonstrated effective in the treatment of cocaine dependence (33). Briefly, abstinence-based voucher programs provide tangible incentives contingent on marijuana abstinence documented via a systematic urine toxicology, drug-testing program. Vouchers have a monetary value that escalates with each consecutive negative drug test. Such abstinence-based incentive programs enhance the effect of MET/CBT by increasing marijuana abstinence both during treatment and up to one year posttreatment (34–36). Thus, CM in combination with MET/CBT represents the most potent outpatient treatment currently available for marijuana dependence.

Outpatient treatments for cannabis abuse and dependence among adolescents have also received attention in the scientific literature. Multiple clinical trials provide empirical support for brief family-based and group/individual behavioral treatments (37–40). The most comprehensive of these trials compared 5 manualized, outpatient treatment models in a large multisite study. The treatments tested included 5-session MET/CBT, 12-session MET/CBT, MET/CBT plus family support network, community reinforcement approach, and multidimensional family therapy. Across treatments, significant decreases in drug use and in symptoms of dependence were observed. Robust differences in outcomes were not observed between treatments, which unfortunately precludes drawing strong conclusions about their efficacy. Although these results were promising, two thirds of the youth continued to experience significant substance-related symptoms, suggesting that adolescent substance abuse treatments need to be improved and alternative treatment models explored (41).

Similar to treatments for adults, efforts to enhance outcomes by adding a CM intervention for adolescents have emerged. Positive results were observed in an initial pilot trial (42) of a developmentally appropriate MET/CBT plus CM intervention that involved an abstinence-based voucher program and parent-based contingency management (PCM). PCM included a substance use monitoring contract between the parent(s) and adolescent and a manualized parent training program, Adolescent Transitions (43). Preliminary reports from a randomized controlled trial suggest that this combined CM intervention engendered increased rates of marijuana abstinence and effectively maintained abstinence posttreatment (44).

Pharmacotherapy

Clinical studies have shown that marijuana treatment is characterized by low rates of continuous abstinence, comparable to rates for other abused drugs. Given that marijuana dependence is not easily overcome, more treatment options for marijuana dependence are needed. A subset of marijuana smokers report that they are dissatisfied with their use of marijuana yet find it difficult to quit on their own. In fact, marijuana relapse rates are comparable to those of other abused drugs (45), demonstrating that even motivated treatment

seekers often do not achieve abstinence. Understanding the factors contributing to marijuana's high relapse rates may improve treatment options.

There are three potential indications for the treatment of marijuana-dependent patients: management of withdrawal, facilitation of abstinence, and prevention of relapse. THC, the major psychoactive constituent of marijuana, can produce an abstinence syndrome in rhesus monkeys (46,47) and in human subjects (48,49). Haney and others have shown that abstinence following daily marijuana use is often characterized by a time-dependent constellation of clinically significant symptoms that include anxiety, depression, irritability, marijuana craving, decreased quantity and quality of sleep, and decreased food intake compared to baseline conditions. Withdrawal in humans has been reported to occur for the first 14 days after cessation of marijuana use. Symptoms can be alleviated by the resumption of marijuana smoking or by the double-blind administration of oral THC, demonstrating the pharmacological specificity of marijuana withdrawal (50–54). A marijuana abstinence syndrome in treatment-seeking subjects has recently received increased attention (55–57).

Withdrawal may contribute to failing to reach abstinence or having an early relapse. Recent research has focused on the development of a human laboratory studies designed to characterize and test the effects of potential treatment medications on marijuana dependence and relapse (58). An additional objective has been to characterize the interaction between cannabinoids and endogenous opioids, in an attempt to elucidate the neurochemical basis for marijuana's subjective and reinforcing effects.

In the human laboratory model, marijuana smokers who are not seeking treatment for their marijuana use reside in a residential laboratory, where detailed information on mood, physical symptoms, psychomotor task performance, food intake, social behavior, and sleep can be obtained. Participants smoke active and placebo marijuana repeatedly under controlled conditions while maintained on various doses of medication. In this way, the effects of both marijuana and potential treatment medications can be characterized.

Given that withdrawal symptoms likely contribute to maintaining chronic marijuana use, a series of studies were done to test the effects of medications on marijuana withdrawal symptoms. The first medication tested, sustained-release bupropion (0, 300 mg/day), substantially worsened mood ratings (irritability, depression) and ratings of sleep compared to maintenance on placebo (59). Similarly, the mood stabilizer, divalproex (1500 mg/day), significantly worsened mood ratings (irritability, edginess, anxiety), sleep, and cognitive performance in marijuana smokers (60). These data do not support the use of either bupropion or divalproex to treat marijuana withdrawal.

It may be that a medication with stimulant side effects, such as bupropion, is ill suited to treat marijuana withdrawal, which is characterized by irritability, disrupted sleep, and decreased food intake. Thus, nefazodone (0, 450 mg/day), an antidepressant that effectively treats anxiety and has sedative side effects, was assessed. During marijuana withdrawal, nefazodone was found to significantly decrease ratings of anxiety and muscle pain compared to placebo, but other essential features of withdrawal, such as irritability, were unaltered. Thus, maintenance on a moderate dose of nefazodone decreased certain symptoms of marijuana withdrawal but did not improve mood overall (61).

The next approach was to determine whether a cannabinoid agonist, oral THC (dronabinol), would attenuate marijuana withdrawal. Compared to placebo, oral THC administered during abstinence significantly decreased ratings of anxiety, misery, chills, and self-reported sleep disturbance and reversed the anorexia and the weight loss associated with marijuana withdrawal. Oral THC also decreased marijuana craving during abstinence and improved withdrawal-related decrements in psychomotor task performance. Importantly, this attenuation

of withdrawal symptoms occurred even though participants were unable to distinguish oral THC capsules from placebo: oral THC attenuated symptoms of withdrawal at doses that produced no intoxicating effects. Thus, oral THC may be an effective treatment medication in abstinent marijuana smokers. A similar approach is to evaluate extract of *Cannabis* strains that produce exact ratios of THC/cannabidiol. GW Pharmaceuticals has developed a sublingual spray, Sativex, for treatment of multiple sclerosis. This product and other *Cannabis* extracts could be tested in marijuana dependent patients for efficacy to reduce withdrawal and facilitate abstinence.

MODEL OF MARIJUANA RELAPSE

A critical next step was to determine whether medications that decrease marijuana withdrawal would decrease relapse, defined as the resumption of marijuana use after a period of abstinence. Relapse was modeled in non-treatment seekers by structuring the conditions so that a return to marijuana use was costly. During abstinence, individual puffs of marijuana had to be purchased using actual study earnings. A pilot study testing a range of cost conditions found that relapse varied as a function of drug cost. Abstinent marijuana smokers would pay \$10–\$12 for a single marijuana puff but would not relapse if the cost was higher. Thus, non-treatment-seeking heavy marijuana users would limit their marijuana self-administration, compared to when marijuana was available at no cost. This procedure models the attempt of marijuana treatment seekers to remain abstinent.

The objective of the next study was to determine the effect of 2 medications, oral THC and the $\alpha 2$ -receptor agonist, lofexidine, administered alone and together using this model of marijuana relapse. Administration of medications began on the first day of abstinence from active marijuana. Preliminary results show that the combination of lofexidine and oral THC was significantly effective at decreasing marijuana withdrawal symptoms, marijuana craving, and relapse. These data suggest that a combination of 2 medications might be useful in treating marijuana dependence.

CANNABINOID AND OPIOID INTERACTION

In non-human animals, opioid antagonists block the reinforcing and discriminative-stimulus effects of THC, while in human marijuana smokers, naltrexone (50 mg) has been shown to enhance the reinforcing and subjective effects of THC. The objective of this study was to test a lower, more opioid-selective dose of naltrexone (12 mg) in combination with THC. The influence of marijuana use history was also investigated. The results show that in marijuana smokers, low-dose naltrexone blunted the intoxicating effects of a low THC dose (20 mg), while increasing ratings of anxiety at a higher THC dose (40 mg). In non-marijuana smokers, low-dose naltrexone shifted THC's effects in the opposite direction, enhancing the intoxicating effects of a low THC dose (2.5 mg) and decreasing anxiety ratings following a high dose of THC (10 mg). These data demonstrate that the interaction between opioid antagonists and cannabinoid agonists varies as a function of marijuana use history (62).

The CB1-cannabinoid receptor antagonist, rimonabant, blocks acute physiological effects of CB1-cannabinoid agonists in vitro and in animals. This suggested that CB1-receptors mediate cannabis's effects. Two clinical studies document that this is also the case in humans. In the first study, cannabis users received 1, 3, 10, 30, or 90 mg of rimonabant or placebo (63). A 2.64% THC or placebo cigarette was smoked 2 hours later. Heart rate and subjective response (visual analog scales, VAS) were assessed. Cannabis produced tachycardia and psychological responses reflecting intoxication. The 90-mg dose of rimonabant produced significant dose-dependent blockade of VAS for "drug high," "stoned," and "drug strength." There was also a linear trend for rimonabant blockade of cannabis-induced tachycardia. In the second study, effects of single (90 mg) and multiple doses (15 days of 40 mg) of oral rimonabant and placebo

on physiological and behavioral effects were compared. Peak heart rate increases were significantly lower for the 90-mg (64% blockade) and multiple 40-mg (66%) groups. There were 29% and 14% reductions in peak VAS composite scores for the 90- and 40-mg groups, respectively. Rimonabant alone had no significant effect on heart rate or subjective response and did not affect peak THC plasma concentrations or AUC. These findings demonstrate a direct pharmacodynamic blockade of smoked cannabis by rimonabant, with no pharmacokinetic interaction, and confirm the essential role of CB1 receptors in mediating effects of smoked cannabis in humans. At this stage, it is not clear whether an agonist or antagonist approach will prove to be more beneficial in the management of marijuana dependence.

Other approaches involve the evaluation of non-cannabimimetic medications for the management of dependence, withdrawal signs and symptoms, and concurrent depression. Results of initial pilot trials are presented as follows:

Buspirone was administered in an open-label fashion to 11 subjects undergoing treatment for marijuana dependence (64). Participants reported using marijuana on 76.9% of days prior to treatment and 38.9% of days while on buspirone ($p = 0.004$).

Lithium (500 mg, bid) was administered to 20 adolescent marijuana abusers in an inpatient setting for up to 7 days. Decreased anger, improved mood, and decreased anxiety were reported (65). Interestingly, there is evidence that lithium modulated the cannabis withdrawal syndrome via an oxytocin release mechanism (66).

A subgroup analysis of depressed marijuana smokers in a double-blind, placebo-controlled trial of the antidepressant fluoxetine noted that the placebo group had almost 20 times the amount of marijuana use as the fluoxetine group (67).

The data from these pilot studies suggest that more rigorous double-blind, placebo-controlled studies with buspirone, fluoxetine, and lithium should be performed.

Other putative medications to study in humans, based on their preclinical or clinical uses for the management of withdrawal or to prevent relapse, include mirtazapine and an antagonist for corticotropin releasing factor (CRF).

MEDICAL USE OF MARIJUANA

In the past decade, a number of national reports were commissioned from scientific and medical panels to assess the claims of therapeutic benefits from marijuana smoking for an ever-increasing number of medical conditions. Such varied groups included the U.S. Institute of Medicine and the Canadian Senate Committee on Illegal Drugs (68,69). Promising targets for cannabinoid drugs include the alleviation of nausea and vomiting, the relief of progressive anorexia coupled with weight loss among sufferers of HIV/AIDS, the easing of different types of pain, and the control of muscle spasticity. For each target, the effectiveness of cannabinoids is thought to be modest compared to other pharmacological agents available. Oral forms of cannabinoids have existed since the 1970s; namely, dronabinol (synthesized THC) and nabilone (synthetic cannabinoid). Advocates of the liberalization of drug policy express the firm conviction that smoked marijuana provides benefits that are unavailable by other means.

In 1996, California legalized the "compassionate use" of marijuana. In 2001, Canada became the first country to codify the use of herbal marijuana for "medicinal purposes." The medical profession, as prescribers of the product, faced unique and potentially divisive practice challenges, which included:

- the prescription of a largely untested drug as to quality, safety, and efficacy;
- the physician's liability around prescription and supply of the above;
- the potential harm to the patient-physician relationship resulting from polarized positions;
- the advocacy roles of the courts and government in codifying an untested medical prescription;
- the disconnect in public perceptions between smoked marijuana and a public health campaign against smoked tobacco (70).

Canada's national debate and experiences for close to a decade should serve as an example to international practitioners faced with organized consumer advocacy. Currently, less than 2000 patients are federally authorized to possess medical marijuana in a population of 33 million Canadians.

CONCLUSIONS

Our understanding of the pharmacology of THC and the endocannabinoid system has advanced tremendously in the last decade or so. This in turn has led to new insights into the pathophysiology of dependence, possible medical applications of THC and other cannabinoid-like compounds, and how to design better treatments for our dependent patients. These include better understanding of the cognitive effects of long-term use, better characterization of the withdrawal syndrome, more effective behavioral treatment interventions, and the discovery of promising pharmacological treatments. As far as the cognitive effects, there is no clear consensus on whether long-term cannabis use does or does not produce residual cognitive deficits. If there are such effects, they are probably largely reversible and of little clinical relevance. However, it is clear that regular cannabis use, which produces daily acute intoxication with its related cognitive impairments, is associated with impaired functioning, by both objective measures such as education and income and by the subjective reports of the users themselves. In addition, regular cannabis use results in a clear danger to society, increasing the risk of motor vehicle accidents and probably increasing the number of accidents and other types of negative events in the workplace. Further research should examine the impact of chronic, long-term cannabis use on raising children and on real-world job performance.

Behaviorally based outpatient treatments have demonstrated efficacy for cannabis dependence in adults and adolescents. The specific types of treatment (CBT, MET, CM) evaluated in clinical trials are similar to and appear to produce similar effect sizes as those used for other substance dependence problems. The cannabis literature includes 2 notable innovations: the integration of MET/CBT (29), and the use of CM and parent training with adolescents to specifically target drug (cannabis) use.

Despite clear demonstrations of efficacy, these treatments have limitations. Relapse rates remain substantial even with the most potent interventions tested. Moreover, access to and availability of these interventions is limited by a lack of clinicians trained in these approaches, the cost of training and treatment delivery, and a narrow acceptance of the conceptual basis of CM-type interventions. Continued development of cost-effective interventions remains a priority. Suggested areas of focus for development include continued care protocols, exploration of different magnitude and schedules of reinforcement in CM interventions, use of innovative technologies (computer, telephone) to assist in delivery of treatment or continued care, integration of behavioral approaches with effective medications (although there are none yet available), and determination of mechanisms of action that can lead to more focused interventions. The good news is that behavioral-based treatments are the most effective

interventions we have, and innovative applications of the basic principles of behavior analysis and learning that inform these treatments continue to lead to incremental gains in treatment outcome.

Marijuana withdrawal is gaining recognition as a clinically significant component to marijuana dependence. The treatment trials conducted to date have failed to produce long-term marijuana abstinence, and relapse rates observed for marijuana are comparable to those observed for other drugs, indicating that marijuana dependence is not easily overcome. It is clear that more behavioral and pharmacological treatment options for marijuana-dependent individuals are needed. Human laboratory data indicate that oral THC, alone or in combination with lofexidine, shows promise. An additional finding is that the influence of opioid antagonism on cannabinoid effects varies in heavy marijuana smokers and non-marijuana smokers, suggesting that chronic marijuana use increases the opioid contribution to cannabinoid intoxication. Other promising medications in marijuana-dependent or comorbidly affected patients include buspirone, nefazadone, lithium, and fluoxetine. Larger confirmatory studies will need to be conducted for these medications. For nefazadone, liver functions and hepatotoxicity should be closely monitored, especially in a drug-dependent population.

The next few years look very promising for finding effective treatments for different phases of marijuana dependence. Combinations of different behavioral interventions with medications hold great promise for helping patients to remain abstinent and to resume a high degree of functioning.

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