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Use of Dronabinol for Cannabis Dependence: Two Case Reports and Review

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Abstract

Marijuana is the most commonly used illicit drug in the United States and throughout the world. Despite this, the number of laboratory studies that have assessed pharmacologic agents to target cannabis withdrawal symptoms or reduce the reinforcing effects of marijuana has been modest. Unlike alcohol, cocaine, opiates, or nicotine, there has been a minimal number of clinical pharmacologic treatment trials that have targeted marijuana use. Based on recent laboratory studies, dronabinol (delta-9-tetrahydrocannabinol) has been shown to reduce cannabis withdrawal symptoms and the subjective effects of marijuana. Given that agonist agents have been found to be effective for opiate and nicotine dependence, the clinical utility of dronabinol for cannabis dependence is a reasonable approach. Two case reports using dronabinol are presented. The potential benefit, as well as questions that arise from the use of this medication in cannabis-abusing populations, is presented. Also, future areas of research that might be explored are discussed.

Cannabis dependence is a substantial but underappreciated clinical problem. The Office of National Drug Control Policy reports a five fold increase in marijuana mentions in drug related emergency room episodes from 1988 to 2000.¹ Marijuana is the most commonly used illicit drug. Whereas current marijuana use has declined slightly from 17.3% to 16.3% for young adults during the period 2002–2005, the rate of illicit drug use increased among older adults (ages 50–59), from 2.7 to 4.4% during the period 2002 to 2005.² Further, among 12th graders, nearly 42% report lifetime use of marijuana, 18% report use in the past month, and 5% report daily use.³ While this represents a decrease from data collected in 2000, the rates remain concerning.

Despite the magnitude of the problem, there are few empirical studies that have assessed the efficacy of targeted treatment interventions for this subgroup of substance abusers. The most studied approaches in adult cannabis-dependent individuals have consisted of relapse prevention,^{4,5} motivational enhancement techniques,^{5,6} and voucher incentives.⁶ Two large randomized trials in adolescents^{7–10} and adults^{11,12} have compared various single or combined interventions, including motivational enhancement, cognitive behavioral therapy, and family interventions of various lengths. While all interventions were found to be helpful, no specific type of intervention alone or in combination with other treatments was found to be superior. Also, no specific length of treatment was found superior.^{7–10}

To date, little work has been done with pharmacologic strategies for adults with marijuana dependence.^{13,14} This may result from the erroneous perception that regular marijuana use does not lead to physical dependence with an identified withdrawal syndrome. However, both observational studies^{15,16} and laboratory studies have demonstrated that the abrupt cessation

of either oral or smoked marijuana in marijuana-dependent individuals results in a rapid onset of irritability, restlessness, decrease in appetite, sleep disturbances, and, not infrequently, relapse.^{15,17–21}

Specifically, Budney et al. (2003) found that in an outpatient setting, withdrawal symptoms began one day after marijuana cessation and peaked on days 2–6; effects persisted from 4–14 days, depending on the severity of marijuana dependence.²¹

Because of the increased recognition of cannabis withdrawal, there have been several laboratory studies conducted to assess various medications to alleviate withdrawal symptoms.^{20,22,23} To date, an agonist medication, dronabinol, has shown the most promise.^{19,20,24}

Dronabinol is a synthetic form of delta-9-tetrahydrocannabinol, a naturally occurring pharmacologically active component of marijuana. Hart et al.¹⁹ evaluated the utility of dronabinol in reducing self-administration of smoked marijuana by heavy marijuana users under controlled laboratory conditions. Compared to placebo, dronabinol, in doses of 10 and 20 mg four times a day, reduced some of the subjective effects of marijuana (ie, less “good drug effect” and “high”); however, it did not impact on self-administration. Hart and colleagues posit that self-administration may not have been altered because individuals were only maintained on dronabinol for three days, which may not have been an adequate time frame to produce a substantial effect. Also, because these individuals were heavy daily smokers, the behavior of smoking marijuana may have been so well-learned that only an extremely salient alternative reinforcer would have reduced self-administration of smoked marijuana. Further, the administration procedure itself may not have been sensitive enough to demonstrate altered self-administration behavior. Finally, the individuals in this study were not treatment seekers. For individuals who are motivated to stop using, and have a reduction in subjective effects, there may be a greater likelihood of reduced use.

In a subsequent inpatient study with non-treatment seekers, Haney et al.²⁰ compared dronabinol (0 and 10 mg five times a day) to placebo in heavy marijuana users who were experiencing withdrawal symptoms in a laboratory setting. Dronabinol was superior to placebo in reducing withdrawal symptoms and did not produce subjective effects. Similarly, in an outpatient study with non-treatment seekers, dronabinol at low doses (10 mg three times a day) and high doses (30 mg three times a day) suppressed withdrawal symptoms better than placebo during periods of abstinence from marijuana.²⁴ Further, the higher dose produced sufficient suppression of withdrawal such that withdrawal symptom ratings were similar to those when individuals were smoking marijuana as usual. However, neither of these studies targeted cannabis-dependent individuals seeking treatment.

These findings highlight the potential utility in using dronabinol to stabilize a cannabis-dependent patient and then possibly gradually withdraw the patient off dronabinol, the substituted agent. Because of these data, one of the authors (HDK) began to use dronabinol for patients who repeatedly tried to stop using marijuana without success. The two case studies highlight the clinical issues that arise when implementing dronabinol with patients in an outpatient setting.

CASE 1

Mr. A, a 42-year-old white successful businessman, was first seen in 2003. He had been smoking marijuana daily for approximately 20 years with no periods of abstinence longer than a few days, usually resuming his use because of severe irritability and insomnia. He sought treatment because of his inability to stop marijuana use on his own and the increasing problems it was causing at home and work. Other than occasional alcohol use, he denied other drug use. His pattern involved arriving home from work at 5 p.m. and smoking 3–6 joints until 11 p.m. At 5 a.m. he would wake up, read business-related material for a few hours, and then go to

work. Although he denied symptoms consistent with childhood attention-deficit/hyperactivity disorder, he recalled a pattern in adolescence of being a mediocre student despite being very bright. As an adult, he has experienced trouble sitting quietly and reading unless he reads in the early morning after using marijuana the previous evening. He reported no symptoms of mania or major depression.

He never smoked while at work and used more heavily on weekends and vacations. While he felt marijuana helped him cope better with his family, he had come for treatment because his wife was irritated that he “spaced out” in the evening and was disinterested in their children. He recognized that his marijuana use contributed to this behavior. Further, he had become increasingly concerned that law enforcement agencies might find out he had been using and the public disgrace could ruin his career. He had developed an elaborate system to procure marijuana so that he would not be caught buying it. His additional precautions, which he described as due to “paranoia,” included never driving for fear of being stopped or having an accident leading to a blood or urine test (he uses taxis and trains), and never having any marijuana on his person except when he left town.

When Mr. A first entered treatment, he was ambivalent regarding whether he wanted to reduce or to totally stop his use. After three therapy sessions yielded no change in his marijuana use and given the history of irritability and anxiety during previous cessation attempts, a trial of dronabinol (Marinol®) was initiated. The dose was gradually increased to 10 mg three times a day, which for him meant between 5 PM and midnight, and was increased to 40 mg per day after one week. After two weeks, he reported occasional joint use during the week but continued to use marijuana heavily on the weekend, both for the euphoriant effects and to deal with the increased time availability. After four months, his marijuana use had been reduced by 75%, based on how much he had been buying. However, some irritability continued, and divalproex sodium was initiated and titrated to 250 mg am and 500 mg at bedtime. On this regimen, the patient totally ceased marijuana after one month. The dronabinol was tapered by 10 mg/week for three weeks and then 5 mg/week for two weeks. He reported feeling more relaxed and was better able to handle work-related problems.

Currently, the patient has been clean for more than four years and continues on the divalproex at 250 mg at bedtime. His paranoia ceased, he feels healthier and sharper than he has in years, and his marriage has improved. While initially he missed the marijuana effects, especially on weekends, he was determined not to resume use. He now deeply regrets the long-term marijuana use and feels that it interfered with business success, as he often lacked the initiative to follow through with innovative ideas. Thus, even though he was successful financially, he believes he could have been significantly more successful if he had quit earlier.

CASE 2

Mr. B, a 40-year-old white male, was first seen because of concerns about his marijuana use. He had been using marijuana since the age of 16 and was using currently approximately five times a day, starting at 9:30 a.m., when he got to work, and stopping at 3:00 p.m., as he did not want his live-in girlfriend to know about his use. She complained that it decreased his energy and sex drive, and changed the way he related (such as “going on and on about silly things”). She had stopped her own marijuana use about two years earlier and wanted him to stop as well. Both wanted children but she refused to have any until he quit marijuana and, in fact, threatened to leave the relationship unless he stopped.

Although there had been a history of other drug use, the only one of any serious level was alcohol. He described he typically used 3–4 beers in the evening but if he wasn’t careful, he could drink a dozen or more. There is a family history of alcoholism on his father’s side. His longest period off marijuana was six weeks, occurring two years prior to this presentation. He

had a history of attention-deficit/hyperactivity disorder, diagnosed as an adolescent and treated unsuccessfully for two years with methylphenidate. He felt that marijuana helped him with his work in public relations by enhancing his creativity and was afraid that cessation would decrease his ability to come up with novel ideas. Prior quit attempts were complicated, as several other co-workers were also users of marijuana.

Given the history of unsuccessful quit attempts, he was started on dronabinol, 10 mg three times a day. Three weeks later he reported doing well, with a marked decrease in marijuana use except for a period when he ran out of dronabinol and became quite depressed. Two days after re-starting the dronabinol, the depression had passed and he was feeling good again, except for complaints of decreased energy and creativity compared to when he was on marijuana.

Five weeks after beginning dronabinol, he had been off marijuana for two weeks, and was averaging between 40–50 mg of dronabinol per day to “take the edge off his craving.” However, he was drinking excessively, taking in about 50 drinks a week, primarily beer. He missed a number of appointments over a several-week period and when seen again, he said he had been off marijuana for eight weeks and felt good about it. He was using 10 mg four times a day of dronabinol, stated that he had more energy and better relations with his girlfriend, and felt overall sharper with the exception of some short-term memory problems and occasional spaciness. Alcohol use had decreased to 2–3 beers a night. The dronabinol was tapered with a plan to decrease by 5 mg week, down to 20 mg, and then by 5 mg/every 10 days. One month later, his dronabinol was reduced to 10 mg BID and he described doing well except that when he missed a dose he would quickly get depressed. The memory problems had markedly diminished on the lower dronabinol dose.

Over the next few weeks, he developed profound depression even while on the dronabinol and was started on venlafaxine. He did not tolerate the dose escalation to 150 mg a day and had to be cut back to 25 mg a day. At the higher dose, he complained of nausea, vomiting, diarrhea, dizziness, and feeling somewhat high. The patient did not show up for his next few appointments and then did not resume contact for 16 months.

During that time, he had continued on the dronabinol until it ran out, decided he did not need it anymore, and eventually relapsed twice but was able to stop marijuana for periods of time on his own. During the periods of time when he was able to stop marijuana, he had started to drink heavily again. Eventually he began using marijuana again and his girlfriend was very upset with him. They had since married and had a child and she was saying she would leave him unless he stopped using marijuana.

He was started back on the dronabinol and eventually was able to be placed on a dose of 15–20 mg/day in three divided doses. He tried to taper it because his wife complained that if he took it any later than about 3:00 p.m., he seemed stoned in the evening. Putting him on modafinil, 100 mg at the end of the day, solved the energy problem.

Ultimately the dronabinol was cut to 5 mg 2–3 times a day, and on this dose, he said he felt energetic, had a better sex life, and his wife felt he was a better companion. He also continued on 100 mg of modafinil in the evening. His only slip back to marijuana occurred when he ran out of the dronabinol, during a time when he was out of the country and unable to get more of it. He has now been off marijuana for six months, Drinking continues at 2–3 beers a night.

ANALYSIS

The first case illustrates utilizing dronabinol as a useful adjunct in helping marijuana-dependent individuals reduce and stop their use. The second case is more problematic and is a work in progress. The patient resisted an abstinence model, and it is not yet clear whether the dronabinol

can be stopped without the patient either resuming marijuana and/or alcohol use to a problematic extent. Although there is laboratory evidence that oral delta-9-tetrahydrocannabinol is positively reinforcing in marijuana users,^{25,26} a comprehensive literature review and surveys conducted with addiction medicine specialists, oncologists, researchers in cancer and HIV treatment, and law enforcement personnel suggest that there is little evidence of abuse or diversion of dronabinol.²⁷

Given that dronabinol is weakly euphoric, has a gradual onset of action, and a long half-life, it is a reasonable agent for cannabis-dependent individuals. Of note, in the first case the patient had some symptoms associated with adult ADHD and/or a bipolar diathesis but did not fully meet criteria for either disorder. Donovan et al.²⁸ have observed a syndrome of explosive temper and mood lability in marijuana-using adolescents and found that divalproex sodium was superior to placebo in reducing temper outbursts and regulating mood. Recently, Levin et al.¹⁴ found that divalproex sodium did not produce any clear benefit in promoting abstinence compared to placebo. However, the small sample size and compliance issues limit the generalizability of this study.

In the second case, there were symptoms consistent with both ADHD and depression, but the patient did not want medications to treat either disorder. Instead, he preferred to remain on dronabinol and, in fact, resumed marijuana use when the dronabinol was discontinued. What remains an important question is how dronabinol should be utilized. Should it be used temporarily to alleviate withdrawal symptoms, similar to how nicotine gum or patches are used to help alleviate nicotine withdrawal, or should it be used as a maintenance agent to help prevent relapse, similar to methadone or buprenorphine for opiate dependence? Further, are there certain patients that will have greater difficulty in being tapered off dronabinol once it is initiated? It is clear from the two cases that both patients found the induction onto dronabinol helpful. Future investigation might examine the potential benefits of dronabinol as a withdrawal agent or maintenance agent and what the impact of additional psychiatric comorbidity is on the benefit of dronabinol's use in cannabis-dependent populations.

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