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New Developments in Understanding and Treating Adolescent Marijuana Dependence¹

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Abstract

Background—Marijuana is the most commonly used illicit substance in the United States and worldwide. Marijuana use is a problem of increasing magnitude among adolescents. Use typically begins in adolescence and is associated with a variety of adverse outcomes.

Method—This article will present an overview of trends in marijuana use, and will review the endocannabinoid system and marijuana. It will discuss recent policy developments in US and their implications, especially for adolescents. Existing treatments will be reviewed, including findings from a recent randomized double-blind trial of *N*-acetylcysteine, a compound that reverses the dysregulation of the glutamate system that occurs in substance dependence.

Conclusions—The core treatment approaches include psychosocial interventions, sometimes in combination with each other. While a reduction in days of use is often achieved with most of these approaches, abstinence is a much more elusive goal. The evidence base for effective treatments remains inadequate especially with regard to adolescents, and there is an urgent need for more research in this area. Promising new treatments include *N*-acetylcysteine in conjunction with contingency management.

Keywords

Adolescents; marijuana use disorders; marijuana dependence; cannabis dependence; treatment; *N*-acetylcysteine

INTRODUCTION

Marijuana History

Marijuana is the most commonly used illicit substance in the United States and worldwide. The use of marijuana dates back to at least 2700 B.C. Marijuana is a mixture of dried seeds, stems, leaves, and the flowering tops of the plant *Cannabis sativa*.

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Marijuana Use and Dependence

Marijuana is usually smoked or taken orally. It can be rolled in cigarette paper (a joint) or inserted into a hollowed out cigar (a blunt); or smoked in a pipe (bowl), or in a bong (a pipe with water filtration). Marijuana may also be prepared as a food and eaten, for example baked in the form of brownies. Most people smoke it to get “high.” Acute effects occur almost immediately upon smoking and last 1–3 hours. Some people use marijuana for what they believe to be its therapeutic medicinal purposes for a variety of conditions, and this belief is behind the passage of “medical marijuana” laws in several states. However, there are no FDA approved indications for smoked marijuana, which contains varying levels of dozens of cannabinoid compounds and hundreds of other chemical constituents. A small number of specific cannabinoids have been FDA approved in oral preparations for specific conditions.

While most users have occasional and relatively benign experiences with marijuana, about one in ten users develops dependence. Current societal attitudes toward marijuana are dichotomous; there is a tendency to see it as totally good or totally bad. In contrast, the view of alcohol is more nuanced. It is generally recognized that, while it can be a dangerous and potentially lethal substance for some people, it is also viewed positively by many people and its use by adults generally socially accepted. Ideally, marijuana should be seen in an analogous manner, with an awareness of its dangers and potential for abuse and dependence, together with an understanding that some non-vulnerable adults may occasionally use it without longstanding consequences. To sort out risk versus benefit, it also may be worthwhile to consider the pharmacology and potential therapeutic role of cannabinoids.

Marijuana and Adolescents

There is no question that marijuana use poses particular dangers for adolescents. A higher likelihood of developing marijuana dependence is predicted by earlier age of onset of use and higher frequency of use. The average potency of delta-9-tetrahydrocannabinol (THC) in seized marijuana has increased from 3% in 1992 to 11% in 2010 (White House Office of National Drug Control Policy, 2010). Over this period of time there has been an uptick in the use of marijuana. The increase in potency coincides with an increase in treatment admissions for marijuana use disorders, as is depicted in Figure 1. This is pertinent to think about in counseling parents, who, recalling their own past experiences with marijuana, don’t consider it likely that it could be harmful to their children. They need to be aware that the marijuana of today is very different from the marijuana they recall from their youth.

NEUROBIOLOGY AND PHARMACOLOGY

The Endocannabinoid System

The endocannabinoid system has only recently been identified and studied. It involves receptors that are specific responders to endogenous cannabinoids as well as to those found in marijuana. The endocannabinoid system is located both in the central and peripheral nervous system. It is involved in appetite, pain sensation, mood, memory, immune function, and neurodevelopment. Two cannabinoid receptor subtypes (CB1 and CB2) have been studied and described in details. There are also two well-described endogenous cannabinoids

(anandamide and 2-arachidonoylglycerol), which bind to these receptors. The endogenous cannabinoids are present in the body in much lower concentrations than those that are smoked or ingested in marijuana. Tetrahydrocannabinol (the main psychoactive ingredient in smoked marijuana) binds to both CB1 and CB2 with equal affinity, but it is the binding to CB1 receptors that produces its psychoactive effects. This is an area of active research and there is still much to be learned about endogenous cannabinoids.

Cannabis and Cannabinoids

The terms “cannabis” and “cannabinoids” are not interchangeable. Smoked cannabis (marijuana) contains more than 460 active chemicals and more than 60 unique cannabinoids. Many cannabinoids have dose-dependent effects. Cannabis (including “medical marijuana” in dispensaries) is not standardized in dose, potency, or chemical constituency. Some cannabinoids have been isolated and studied, and some are available upon prescription as oral compounds. Dronabinol (Marinol) is a synthetic oral form of delta-9-tetrahydrocannabinol (THC) that is legally available upon prescription and is stocked in pharmacies. Nabilone (Cesamet) is an oral synthetic cannabinoid similar to THC. Cannabidiol (CBD) is a non-psychoactive cannabinoid being researched for its therapeutic potential. Nabiximols (Sativex) is a 1:1 THC: CBD standard-dose oral spray derived from the cannabis plant.

Cannabinoid Therapeutics

Two key review articles on randomized controlled trials (RCTs) have been published (Ben Amar, 2006; Hazekamp & Grotenhermen, 2010). All together, these authors reviewed over 110 RCTs with a total of around 6100 participants—all adults—across various target conditions. The great majority of the trials involved oral cannabinoid compounds; a few involved smoked marijuana. Their findings were that results were mixed, but areas of therapeutic potential included analgesia in chronic neuropathic pain, appetite stimulation in debilitating diseases (such as cancer and AIDS), and spasticity in multiple sclerosis.

Dronabinol has an FDA indication in adults for loss of appetite in AIDS and chemotherapy-induced nausea and vomiting. Nabilone has an FDA indication in adults for chemotherapy-induced nausea and vomiting refractory to other treatments. Smoked marijuana has no FDA indications.

In considering cannabinoids as therapeutic agents, potential benefits must be weighed against risks. Evidence for efficacy is limited to short-term use in adults with severe conditions. Adverse effects include a risk for abuse and dependence. Specific issues with smoked marijuana include non-standardized dosing and varying ingredients. Finally, smoked delivery is an unsafe way to deliver any compound.

PUBLIC POLICY

How has the evidence for cannabinoid therapeutics and risks been interpreted to influence public policy? First let us consider the differences between federal and state policy in the US.

Federal Marijuana Policy

Marijuana (cannabis), is classified as a Schedule I Controlled Substance by the United States Drug Enforcement Agency (DEA). Substances in this schedule, the DEA has ruled, have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse. Some other examples of substances listed in Schedule I are: heroin, lysergic acid diethylamide (LSD), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine (“Ecstasy”). Multiple standardized randomized controlled trials with standardized agents and doses would be required for approval and these do not exist at the present time, nor is funding likely to be made available for such trials in the near future.

State Marijuana Policy

Despite the DEA’s ruling, twenty states and the District of Columbia have legalized “medical marijuana,” allowing it to be obtained by a physician’s recommendation. State policy is not necessarily science-based and is often fueled by popular perceptions. Definitions of what conditions qualify for the use of medical marijuana vary. California, in 1996 the first to allow persons to legally obtain marijuana for “serious medical conditions,” lists cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, and migraine as conditions for which it may be used, but also states it may be used for “any other illness for which marijuana provides relief,” leaving it to the discretion of the physician to decide. Physicians cannot actually write prescriptions for cannabis, since one cannot prescribe a schedule I drug, but they can give a written recommendation for it, which must include a diagnosis. Patients then can go to a licensed marijuana dispensary to obtain it. There are conditions specified for growing and dispensing marijuana, but no specific requirements for physicians to recommend it other than a California medical license.

There have been concerns about the impact this policy has had, especially on young people. In 2010 *USA Today* reported:

A San Francisco doctor received four years’ probation after she failed to heed a psychiatrist’s request to reconsider her marijuana recommendation to a 19-year-old patient suffering from depression. The patient committed suicide six months later (Leff & Wohlson, Associated Press, 2010).

In the same year, Jaffe and Klein reported the results of a survey of California child and adolescent psychiatrists asking about their experiences with patients since the legalization of medical marijuana. The psychiatrists reported that some of their adolescent patients sought to have them recommend medical marijuana, even threatening to give them poor ratings on on-line physician directory sites if they refused (Jaffe & Klein, 2010).

Perhaps influenced by California’s experience, other states’ laws are stricter, for example, limiting the conditions for which cannabis can be prescribed and requiring patients to register in a statewide registry. However, regulating medical use of cannabis has proven a challenge, and partly in response to the difficulty of doing this, two states (Colorado and Washington) have legalized recreational marijuana use for persons aged 21 and older.

Conflict between Federal and State Laws

Legalization by states has created a dilemma for the federal government, which technically could prosecute the states or people in them for breaking federal law, but has not done so. Recently, the federal government announced that it would not prosecute states for enacting laws allowing marijuana use but would monitor states enforcement of federal laws related to eight priority areas, including use of marijuana by minors, and the involvement of criminal enterprises in trade and distribution (Johnson & Chebium, 2013). This represents a bow to states' rights but at the same time reiterates a policy of focusing on the most dangerous aspects of marijuana consumption and distribution.

ADOLESCENTS AND MARIJUANA

Use and Perceptions of Risk

As practitioners, we are aware of the delicate balance between risk and benefit, even among FDA-approved medications. Many of the medications that we do use have "Black Box" warnings, aimed at engendering caution among prescribers. For a Schedule I substance that has no FDA approved uses, no clear evidence for treating psychiatric disorders, and considerable known risks in the adolescent age group, most psychiatrists and other physicians would easily see the risks as outweighing any potential benefit. However, teens and families may struggle with these nuances, especially in light of the misleading term "medical marijuana," which implies benefit for all and usefulness for a wide range of medical problems, rather than a specific indication for a seriously debilitating condition. It can be useful to discuss with adolescent patients the fact that not everything that occurs in nature is beneficial, for example, poisonous mushrooms are not, and that some medications that are life saving for some can be lethal for others. For example, warfarin, which is used therapeutically as an anticoagulant, is also the active ingredient in rat poison.

Many adolescents assume that "medical" implies "beneficial." Many equate marijuana with "natural", which they may in turn equate with "harmless." Perception is critically important—there is an inverse relationship between use of marijuana and perception of risk, as is shown in Figure 2.

It can be seen from this figure that in the mid-70s when marijuana was perceived as not harmful, use peaked. It subsequently declined in the 1980s when there was an increased awareness of its potential harm. In the years that coincide with medical marijuana movement, the perception of risk has lowered.

Patterns of Use

Marijuana initiation typically occurs during adolescence. Rates of initiation and use are increasing. According to the Monitoring the Future survey, roughly half of high school seniors have tried marijuana, 23% are current users, and 7% use marijuana daily (Johnston, O'Malley, Bachman, & Schulenberg, 2012). Young users are particularly prone to dependence symptoms and inability to cut down their use (Chen & Anthony, 2003). The 7% who are daily users are the ones we should be particularly concerned about. Marijuana dependence is primarily a disorder of young people. Marijuana use disorders (abuse and

dependence) are present in 4% of adolescents and 6% of young adults, compared with less than 1% of adults over age 25 (SAMHSA, 2007).

The Gateway Hypothesis—There is a known association between marijuana use and the subsequent use of other drugs (Patton et al., 2007). But this is not necessarily because using marijuana leads adolescents to desire “harder” drugs. An alternate explanation is that there is a shared vulnerability or liability factor. That is, the same factors that are risk factors for the initiation of marijuana use are risk factors for the use of other drugs. These include the availability of drugs and the presence of substance abusing peers. Marijuana is often the first drug used because it is the most available, and adolescents who are more prone to high-risk decisions will use whatever is available first, and then go on to use other drugs.

ADOLESCENT BRAIN DEVELOPMENT AND MARIJUANA

The advent of structural and functional brain imaging has allowed for visualization of cortical and subcortical structures, elucidating many aspects of adolescent brain development (Casey & Jones, 2010). As a result of these imaging studies, we now know that during adolescence, striatal development of the brain (associated with reactivity to motivational stimuli) occurs in curvilinear fashion, while prefrontal development (associated with cognitive control) occurs in linear fashion. The endocannabinoid system undergoes maturation as well. These findings have important implications. Amid a developmental window in which motivational reactivity outpaces cognitive control, adolescents may be particularly prone to making high-risk choices, valuing immediate reward over long-term considerations. (Casey & Jones, 2010).

During this critical phase of neurodevelopment, adolescents are especially vulnerable to adverse effects of marijuana use (Schneider, Schomig, & Leweke, 2008). In a dose-dependent manner, adolescent marijuana use is associated with adverse academic (Pope, Jr. et al., 2003), cognitive (Jager & Ramsey, 2008)(Meier et al., 2012), behavioral (Rob, Reynolds, & Finlayson, 1990), psychiatric (Fergusson, Horwood, & Swain-Campbell, 2002; Moore et al., 2007; Patton et al., 2002), and substance use (Patton et al., 2007) outcomes.

Many adolescents are unaware of the extent to which their functioning is impaired by marijuana. For example, they often insist that they are better able to concentrate, even in the face of declining grades. Several studies have linked adolescent marijuana use with adverse cognitive outcomes (for review, Randolph et al., 2013). The Dunedin, New Zealand study, which followed a cohort of 1,000 adolescents beginning at age 13 through age 38, with assessments at multiple points in time, found an average decrease of eight points in IQ among those who began using cannabis in adolescence and used heavily (Meier et al., 2012). This finding is controversial, however, and was questioned after a re-analysis of the data, which suggested that the results may have been confounded by socioeconomic status, which not only increased the likelihood of marijuana use, but also the immersion in less cognitively demanding environments, school dropout, and criminal involvement, all of which could potentially contribute to worsening function on neuropsychological tests (Rogeberg, 2013). Nonetheless, it is concerning.

Risk of Psychosis and Other Psychiatric Disorders

Marijuana use in adolescence is associated with increased incidence and worsened course of psychotic, mood, and anxiety disorders (Hayatbakhsh et al., 2007; Moore et al., 2007). Cases of marijuana induced acute psychoses are not infrequent in inpatient settings. Here again, however, the fact that there is an association does not necessarily imply causation. Our current understanding is that for adolescents who are at risk for psychotic disorders, for example those who have a strong family history of these disorders, marijuana acts as an environmental insult, which may bring about psychotic symptoms.

There is a hypothesis that the endocannabinoid system may actually be protective against psychosis and that exogenous cannabinoids might disrupt that protective system. According to this hypothesis, there are individuals who may have been protected against psychosis until they used marijuana, and marijuana counteracts the protection.

TREATMENT

In general, the long-term abstinence rates are frustratingly poor for treatments targeting adolescent substance use in general and marijuana use in particular. There is a lack of strong support for superiority of any one substance abuse treatment compared to the others. A recent meta-analysis of 46 psychosocial treatment approaches revealed that, although all were modestly efficacious, no particular intervention was clearly superior to others (Waldron & Turner, 2008).

Treatment of marijuana use disorders is particularly challenging. The research literature documents that long-term outcomes are remarkably poor with evidence-based adolescent marijuana cessation treatments (Compton & Pringle, 2004; Dennis et al., 2004; Waldron & Turner, 2008). While reduction in use is commonly achieved, long-term abstinence is much more difficult.

The Cannabis Youth Treatment (CYT) Study

The largest study to date is the Cannabis Youth Treatment (CYT) study (Dennis et al., 2004), which involved 600 adolescents between 12 and 18 (most were 15–16). This multi-site study was designed to compare four promising manualized treatment interventions in terms of efficacy and cost-effectiveness (one of the treatments involved two different numbers of sessions for the same intervention). The treatments varied in terms of the amount of time and staff they involved. The study involved two community-based treatment programs and two major medical centers. Criteria for participants were that they had used marijuana in the past 90 days, and met one or more criteria of dependence or abuse. Participants were randomized to one of two or three conditions depending on the site.

Outcome was measured by (a) the days of abstinence over the follow-up period and (b) the percent of adolescents in recovery (no use or abuse/dependence problems while living in the community) at the end of the follow-up period.

The interventions included

1. 5 sessions of a combination of motivational enhancement therapy (MET), and cognitive behavioral therapy (CBT), or MET/CBT.
2. 12 sessions of MET/CBT
3. Adolescent Community Reinforcement Approach (ACRA; Godley, et al., 2001)
4. Family Support Network (FSN; Bunch, Hamilton, Tims, Angelovich, &, McDougall, 1998). This approach enriched the MET/CBT12 with parent education, home visits, referred to self-help support groups and case management.
5. Multidimensional Family Therapy (MDFT; Liddle, 2002)

Various structured assessment tools, including self- and collateral reports, and urine drug testing were used to measure outcome up to 12 months post-discharge.

There was a similarly modest effect across interventions. Days abstinent per 90-day quarter increased from 52 to 65. Of particular note was that the briefest and least resource intensive intervention (5 session MET/CBT) was about as effective as the more intensive treatments, and that family therapy did not seem to add significant benefit. The researchers speculated that there might have been non-specific factors involved in the improvement across conditions.

Reduction in days of use as a primary outcome is potentially problematic. The pre- and post-treatment results separated statistically because of the large number of participants in the sample, but the clinical significance is unclear. Comparing rates of abstinence, rather than reduction in use, may be a more clinically useful outcome when evaluating the efficacy of treatments.

Contingency Management

There is emerging evidence that contingency management may enhance treatment outcomes (Kamon, Budney, & Stanger, 2005; Stanger, Budney, Kamon, & Thostensen, 2009). This is a very straightforward approach; contingency management involves giving a reward for desired behavior, and has an established role in the treatment of adult substance abuse disorders, although it has not been as well studied in adolescents. A reward in contingency management is very different from a bribe, in which the reward is given in advance of the behavior in hopes that the behavior will follow. For example, if the desired behavior is having a “clean” urine, then a patient is rewarded for having a urine that tests negative for substances. In a contingency management program, adolescents may be given help to work on skills to help them abstain. If they objectively demonstrate success with the new skills, they receive a reward. Different schedules can be used. In escalating reinforcement, for example, the value of the reward progressively increases as the desired behavior continues. A five dollar gift card might be the reward for the first week of desired behavior, and if the behavior continues into the following week the reward might be a seven dollar gift card, and so on, which reinforces continued abstinence. There are variations, for example, escalating reinforcement with resets. If a patient has a “dirty” urine (one that tests positive for substances) they go back to zero and have to start over. Given what we know about adolescents’ increased sensitivity to rewards, the use of contingency management for

adolescent substance abuse is a rational approach, especially for those with low motivation, as it gives them an opportunity to experience abstinence as rewarding.

What should we do clinically?

Amid a limited evidence base, and study results that suggest only modest efficacy across treatments, clinicians may be free to choose evidence-based interventions that they are most familiar with and are best able to implement. They can incorporate a variety of treatment elements to help optimize outcomes. Treatment should be individualized, taking into consideration what the adolescent and family are able to do and trying to optimize outcomes by choosing among interventions. Despite the best efforts of the therapist, an outcome of abstinence may not be achieved. Cognitive-behavioral approaches, family therapy and contingency management interventions all have some demonstrated efficacy in the adolescent population and are all reasonable approaches. Aspects of each of these and the following interventions can be incorporated into clinical practice.

Multisystemic therapy—Multisystemic therapy (MST; (Henggeler, Schoenwald, Borduin, Rowland, & Cunningham, 2009) is an example of a treatment approach that combines multiple interventions. Originally developed to treat delinquent adolescents, who are often in very chaotic family situations, MST is designed to help the family in whatever ways are possible. A central theme incorporated in MST is the use of functional behavioral analysis, which begins with identification of a problem behavior. The behavior is then diagrammed by drawing a circle with the behavior written in it, and with arrows signifying antecedents and consequences of the behavior going to and from it. The next step is to identify which of the antecedents and consequences are constants and which are variables, i.e., things that can be changed. The focus is then on modifying the variables to decrease the likelihood of the problem behavior. Presenting this deliberately simplified schema can clarify a complex situation for a family in crisis, and increase the family's "buy in" to the treatment.

Motivational enhancement therapy—Motivational enhancement techniques are also absolutely essential. It is a rare adolescent who will say to a therapist, "I need to see you because of my marijuana use." At best, adolescents who come treatment are ambivalent about stopping their marijuana use. Generally they are coming to treatment because of some outside pressure. According to their perspective, it is the legal system, the school system, or their parents are the ones who have a problem with their marijuana use, not they themselves. Telling an adolescent that he or she must stop using before treatment can begin will not work. Instead, it is helpful to explore the reasons for their marijuana use. Asking about what it is that marijuana does for them, inquiring, "What are some of the positives and what are some of the negatives?" can be helpful. I begin by saying "I understand that marijuana does something for you." I explain that there usually are some reasons for using it—maybe it's just to get high. For some adolescents marijuana is closely tied to their identity. When I suggested to one patient that he could continue doing everything he was already doing except for smoking marijuana, he replied, "I can't do that. That's what I do—I'm the guy who deals for our school. I'm a cool guy because I deal marijuana and I know marijuana."

Marijuana use was a bigger problem for him than for someone else whose use was solely recreationally using on occasions.

Strategies for Engaging Adolescents in Treatment

One aspect of marijuana use that an adolescent will usually agree is a problem, even on the first visit, is parents' reactions to marijuana use. Accordingly, an adolescent will usually agree to a treatment goal of "getting my parents off my back" and the therapist's suggestion that "maybe there are some things that you can change to get them off your back." This may allow the adolescent and parents work toward shared, rather than competing, goals.

Skill building—It is important to talk about refusal skills, as the adolescent is still going to live in a setting where (s)he will be presented with opportunities to use marijuana. Similarly, helping him to navigate these situations, deal with withdrawal symptoms and with cravings is also important.

Family therapy—Work with families is absolutely key, and often includes such interventions as increasing parental monitoring and supervision. In addition, there are some very natural contingency management interventions that can be incorporated into the treatment, for example, the adolescent could have access to the family car or to his/her telephone for having a negative urine test.

IS THERE A ROLE FOR PHARMACOTHERAPY?

Psychosocial treatment approaches, such as those described above, are the core interventions for substance use disorders in both adults and adolescents. Until fairly recently the idea that there might be a role for pharmacotherapy was not seriously considered. However, advances in the understanding of brain functioning and the role of neurotransmitters in addictions has led to a considerable amount of research on pharmacological agents, with a sizeable number now approved for substance use disorders. Most of this research has involved adults (albeit many studies have included older adolescents and young adults), and whether it is applicable to adolescents generally still needs to be determined. Potential behavioral targets of pharmacotherapies for substance use disorders include reducing withdrawal and reducing craving/drug seeking. Additional strategies include causing negative effects with drug use (aversion), reducing positive effects with drug use (decreased reward), and reducing symptoms that may lead to drug use (e.g., anxiety, insomnia). Potential neurotransmitter targets of pharmacotherapies for substance use disorders include dopamine, norepinephrine, serotonin, glutamate, GABA, nicotine, cannabinoid receptors, and others.

For example, agents used in smoking cessation include bupropion SR, a norepinephrine and dopamine reuptake inhibitor and nicotinic antagonist, which decreases withdrawal and craving. Varenicline is a nicotinic receptor partial agonist, which reduces cravings and reduces the pleasurable effects of smoking. Nicotine replacement therapy involves delivery of nicotine (via transdermal patch, gum, lozenge, inhaler, or nasal spray) to replace nicotine delivered by smoking cigarettes. These medications are all approved by the FDA for "smoking cessation assistance."

For alcohol dependence, benzodiazepines, including chlorazepate, oxazepam, diazepam, and chlordiazepoxide are agonists that work by enhancing GABA-A effects and counteract withdrawal effects. They have FDA indications for treating alcohol withdrawal syndrome and are used for acute detoxification. Disulfiram, which blocks the metabolism of alcohol via blockade of acetaldehyde dehydrogenase, creates a buildup of acetaldehyde, and causes an unpleasant reaction when drinking, and is thus a form of aversive treatment. Naltrexone, an opioid receptor antagonist, reduces acute and long-term craving. Acamprosate is an NMDA antagonist and GABA-A agonist, with downstream glutamatergic effects, and is approved for treatment of alcoholism and maintenance of abstinence.

Opioid dependence pharmacotherapies include methadone, a long-acting opioid agonist used for drug detoxification and maintenance therapy of opioid abuse. Buprenorphine/naloxone (Suboxone) is a combination of an opioid agonist (buprenorphine) and antagonist (naloxone) which is used for opioid dependence. Naltrexone is an opioid antagonist and blocks the euphoric effects of opioids. It has FDA approval for treatment of relapse following detoxification, and prophylaxis.

In contrast to the advances in pharmacotherapy for other substance abuse disorders, little progress has been made in medication development specifically for marijuana dependence. Most studies thus far have had negative, discouraging, or mixed results. Studies of bupropion (Carpenter, McDowell, Brooks, Cheng, & Levin, 2009), divalproex (Levin et al., 2004), mirtazapine (Haney et al., 2010), nefazodone (Carpenter et al., 2009), and dronabinol (oral THC) (Levin et al., 2011) have been generally disappointing. There is some question in the latter study about whether the dosing of dronabinol was adequate at 20 mg twice a day, as it reduced withdrawal symptoms but did not yield a reduction in marijuana use when compared to placebo treatment. There have been some encouraging recent preliminary studies. These include pilot RCTs of buspirone (McRae-Clark et al., 2009) and gabapentin (Mason et al., 2012), and a human laboratory study of oral THC + lofexidine, an alpha (2)-adrenergic receptor agonist (Haney et al., 2008). A caveat is that none of these studies focused on young marijuana users, and none has yielded a significant primary intent-to-treat effect on marijuana use. My colleagues and I have been studying *N*-acetylcysteine (NAC), which acts on the glutamate system, and we believe that this drug holds promise for the treatment of marijuana dependence in adolescents. I will discuss this work in the following section.

The argument for *N*-acetylcysteine (NAC)

The rationale for studying NAC in marijuana use disorders begins with the understanding of the role of glutamine dysregulation in the nucleus accumbens. Glutamate plays an important role in addictive processes across multiple substances of abuse, including marijuana (Gass & Olive, 2008). Glutamate dysregulation in the core of the nucleus accumbens underlies drug seeking (Lalumiere & Kalivas, 2008; McFarland, Lapish, & Kalivas, 2003). *N*-acetylcysteine (NAC) administration activates the cystine/glutamate antiporter, leading to reduction in reinstatement of drug seeking in animal models (Baker et al., 2003; Madayag et al., 2007; Moran, McFarland, Melendez, Kalivas, & Seamans, 2005). In laboratory research, NAC has been found to prevent relapse in rats who were made cocaine dependent, deprived

of cocaine, and re-exposed (Baker et al., 2003). Chronic cocaine administration produces neuro-adaptational changes which are normalized by NAC.

Since drug administration down-regulates the cystine/glutamate antiporter (Kau et al., 2008), up-regulation of the exchanger via NAC administration directly normalizes a drug-induced pathology (Kalivas, 2009). NAC is also believed to have downstream effects on the dopamine system. Glutamate is thought to play an important role in a variety of neuropsychiatric conditions, including schizophrenia and Parkinson's disease, both of which involve dopamine. NAC may act via modulation of NMDA glutamate receptors or by increasing glutathione. It has been studied in humans in autism, schizophrenia, depression and bipolar disorder. Glutamate is now thought to additionally regulate dopaminergic activity in the ventral tegmental reward area.

Unlike many other potential candidate medications for cannabis dependence treatment (see Hart, 2005, for review), NAC has a long-established safety record in adults and children, with FDA approval since 1963 for a variety of conditions.

NAC is well tolerated, inexpensive, and readily available over-the-counter at nutritional supplement stores. It is rapidly absorbed after an oral dose. These factors offer significant appeal in light of escalating FDA, healthcare provider, patient, and family concerns about potential adverse effects of psychoactive medications in children and adolescents.

Our open-label pilot study in young marijuana users supported feasibility and tolerability for further study (Gray, Watson, Carpenter, & Larowe, 2010). Subsequently we undertook a randomized double-blind study of 116 treatment-seeking marijuana-dependent youth (Gray et al., 2012). The participants ranged in age from 15–21 with mean age of 18.9 and an average duration of marijuana use of 4.2 years. Over 80% were white. All participants received a contingency management (CM) intervention reinforcing study retention and abstinence (Carroll et al., 2006) and weekly brief (10 min) physician-delivered cessation counseling over a period of eight weeks. Half were randomized to receive *N*-Acetylcysteine (NAC) 1200 mg twice daily, while the control group received a matched placebo twice daily. The primary outcome measure was the proportion of negative urine cannabinoid tests submitted during active treatment, compared between the two treatment groups. Participants were followed throughout the 8-week active treatment and seen at a post-treatment follow-up visit at week 12.

Adherence was measured by self-report medication diaries and blister pack pill counts; 95% of dispensed NAC doses and 93% of dispensed placebo doses were taken. One participant in the NAC group discontinued medication due to severe heartburn, but no other participants discontinued treatment due to adverse effects, although AEs of vivid dreams were deemed at least possibly treatment-related and occurred in 3 participants in the NAC group. Treatment response was calculated on an intent-to-treat basis that included all randomized participants, with participants assumed to be non-abstinent at any missed visit. Main outcome analysis was repeated measures intent-to-treat (ITT) analysis of weekly urine cannabinoid testing (Generalized Estimating Equations), by treatment group (NAC+CM versus placebo + CM). NAC participants had more than twice the odds of submitting a drug free urine specimen

during treatment, compared to placebo participants (odds ratio = 2.4; $p = 0.029$). The results were similar with a modified ITT analysis, which included all participants receiving at least one dose of study medication (OR=2.1, $p=0.047$) and per-protocol analysis, which included all participants submitting urine sample on a given week (OR=2.4, $p=0.036$).

End-of-treatment abstinence, defined as self-reported abstinence confirmed by negative urine testing throughout the last 2 weeks of treatment, numerically differed between the groups (OR=2.3; $p=0.054$), though the study was not adequately powered to evaluate this outcome statistically. Significant positive findings remained even when excluding participants with negative baseline urine cannabinoid tests.

We concluded that NAC, compared to placebo, significantly improved treatment outcome among this group of cannabis dependent adolescents who were participating in a psychosocial cannabis cessation program of contingency management and brief weekly counseling (Gray et al., 2012). This study needs to be replicated and raised other questions that should be addressed with future studies: for example, it is not known if marijuana-dependent adults respond to NAC, and we are beginning a similar study of treatment-seeking adults (CTN 0053: *ACCENT (Achieving Cannabis Cessation—Evaluating N-Acetylcysteine Treatment)*). It is possible that NAC requires a contingency management or other psychosocial treatment platform to be effective. This study used a fixed dose for all participants in the drug treatment arm, but there might be a greater benefit in dose adjustment. Finally, NAC might be effective in other substance use disorders in adolescents or adults.

CONCLUSION

Marijuana use commonly begins during adolescence, when the brain is still undergoing development, and is in a state of heightened vulnerability to the neurodevelopmental effects of marijuana and other drugs of abuse. This makes the need for effective treatments all the more urgent. The evidence base for treatment of marijuana dependence is inadequate, especially in adolescents, where relatively little research has been done. Results of clinical trials of psychosocial treatment approaches have been disappointing. Testing new treatment modalities is critical. There are a number of plausible research approaches. One avenue of research is testing modifications to existing treatment modalities. Another is testing combinations of existing treatments in the hope that combining therapies might increase their efficacy. Finally, researchers are beginning to consider that there might be a role for medication, an idea that would have been dismissed until recently. Psychosocial interventions are the core treatment approach and are likely to remain so. While there is not, and likely never will be, a “magic pill” for any addiction, medications are used successfully in adult substance dependence treatment to augment psychosocial interventions and enhance outcomes. Encouraging findings with NAC suggest that this is potentially fruitful area for further investigation and treatment development for adolescent substance use disorders.

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Biography

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Figure 1.
Marijuana users, treatment admissions, and average potency, 1986 – 2010

Figure 2.