SUBJECT MATTER EXPERT REPORT: CHRONIC/GENERALIZED ANXIETY DISORDER

PETITION OVERVIEW

MATERIALS SUBMITTED	DESCRIPTION
4731-32-05 (E)(3) *[The board shall consult with one or more experts who specialize in the disease or condition:]*	**Solomon Zaraa, DO** **szaraa@compassionatecleveland.com** **Compassionate Cleveland** **23250 Chagrin Blvd; Suite 310** **Beachwood, OH, 44122** **(216) 586-2606**
4731-32-05 (C)(1)	Original petition *"0108 - Rosenberger – Generalized Anxiety Disorder (trade secret).pdf"* submitted on 12/31/2018 by Thomas Rosenberger Rosenberger@nciaohio.org Original petition *"110 – McIntyre – Chronic Anxiety Disorder.pdf"* submitted on 12/31/2018 by Dawn McIntyre dawnm@sistersoflotus.com
4731-32-05 (C)(2)	**"Chronic/Generalized Anxiety Disorder"**
4731-32-05 (C)(3) *[Information from experts who specialize in the study of the disease or condition:]*	Refer to: **Expert Summary** (below) **Expert Conclusion** (below) **Expert Report** (below)
4731-32-05 (C)(4) *[Relevant medical or scientific evidence pertaining to the disease or condition:]*	Refer to: **Expert Report** (below) **References** (below)
4731-32-05 (C)(5) *[Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition:]*	Refer to: **Expert Report** (below) *Also refer to original petitions:* *"0108 - Rosenberger – Generalized Anxiety Disorder (trade secret).pdf"* *"110 – McIntyre – Chronic Anxiety Disorder.pdf"*
4731-32-05 (C)(6) *[Evidence supporting the use of medical marijuana to treat or alleviate the disease or*	Refer to: **References** (below)

condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation:]

4731-32-05 (C)(7)	Refer to:
[Letters of support provided by physicians with knowledge of the disease or condition. This may include a letter provided by the physician treating the petitioner, if applicable]	*"0108 - Rosenberger – Generalized Anxiety Disorder (trade secret).pdf"* *"110 – McIntyre – Chronic Anxiety Disorder.pdf"*

APPLICABLE STATUTES & RULES

PURSUANT TO OAC 4731-32-05, THE SUBJECT MATTER EXPERT SHALL REVIEW THE ABOVE-REFERENCED MATERIALS AND ISSUE A WRITTEN OPINION REGARDING THE CURRENT TREATMENT MODALITIES FOR THE PROPOSED DISEASE OR CONDITION AND WHETHER A MEDICAL MARIJUANA RECOMMENDATION COULD BE BENEFICIAL TO THE PROPOSED DISEASE OR CONDITION.

SUMMARY OF PROPOSED DISEASE OR CONDITION

[THE SUBJECT MATTER EXPERT WILL PROVIDE A BRIEF SUMMARY OF THE PROPOSED DISEASE OR CONDITION AND ITS CURRENT TREATMENT MODALITIES]

Anxiety disorders are one of the most prevalent mental health conditions with a point prevalence of up to 13% of the population and a lifetime prevalence of up to 28%. Anxiety disorders are implicated in negative work productivity and economic loss, health issues, and substance use. Current treatment standards for anxiety disorders include counseling/therapy or medications, followed by a combination of both if response is inadequate. However, nearly half of people who undergo all conventional treatments do not experience adequate therapeutic response. Furthermore, conventional prescription treatments are associated with risk of suicide, fatal overdose, or fatal withdrawal.

CONCLUSIONS REGARDING MEDICAL MARIJUANA

The following is my expert opinion to a reasonable degree of medical certainty regarding the applicability of recommending medical marijuana for the proposed disease or condition:

It is my expert opinion to a reasonable degree of medical certainty that Medical Marijuana, as defined by the Ohio Medical Marijuana Control Program, *has evidence* for safety, tolerability, and efficacy in the treatment of Chronic/Generalized Anxiety Disorder.

Therefore, *I recommend* that Chronic/Generalized Anxiety Disorder be considered as a qualifying condition for treatment with medical marijuana in the state of Ohio.

There is robust preclinical data and some clinical data regarding the effectiveness of cannabis or cannabinoids for the treatment of anxiety. Large-scale patient surveys identify improvement in core anxiety symptoms and reduction in potentially risky prescription medications. Most clinical data reports efficacy of moderate-dose CBD or THC/CBD combinations in treating anxiety. Research suggests that THC may have benefit at lower doses but not higher doses. There is conclusive clinical evidence from multiple randomized placebo-controlled trials regarding the safety and tolerability of high dose cannabidiol in children and adults with severe neurologic or psychiatric disorders.

If applicable, here are the strains and/or dosages that may be appropriate when using medical marijuana for the proposed disease or condition:

- Oral:
    - Based on a randomized placebo controlled trial, use of oral THC is well tolerated in adults at 7.5mg or below per dose. However, benefits of THC were not present at 12.5mg per dose.
    - 1:1 ratios of THC:CBD appear to be most effective with good tolerability.
        - Treatment with CBD alone requires high dosing (up to 10mg/kg in adults) that may cause potential risk of elevated liver enzymes.
        - Synergistic effect of CBD and THC improves efficacy.
        - CBD's antagonism of CB1 sensitivity reduces side effects with higher doses of THC.
- Inhaled:
    - Large patient surveys report effective management of anxiety symptoms with inhaled cannabis. Dose ranges are well within the Ohio Medical Marijuana Control Program's daily limits. (Lucas 2019).
    - 1:1 ratios of THC:CBD appear to be most effective with good tolerability.
- Other:
    - Preclinical data suggests strains containing *linalool* may be of best benefit for anxiety.

EXPERT REPORT

4731-32-05 (C)(5) [Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition]

Impact and Scope

Anxiety disorders are one of the most prevalent mental health conditions with a prevalence of up to 13.3% of people in the U.S. and have a lifetime prevalence of 28% of individuals[1]. Anxiety disorders are reported to negatively impact work productivity, health, and substance use risk[2]. There are many factors that contribute to the development of anxiety disorders: environmental stressors, medical illness, and neurologic functioning. Current treatment recommendations include starting with either counseling/therapy or medications and proceeding to a combination of both counseling/therapy and medications if initial response was inadequate[3].

Efficacy of Conventional Therapies

Conventional medical therapies for anxiety disorders include Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Norepinephrine Reuptake Inhibitors (SNRIs), and Benzodiazepines, just to name a few[4]. Clinical studies report that 40-50% of people with anxiety do *not* respond to conventional medical therapies[7].

Risks of Conventional Therapies

Despite their widespread use, benzodiazepines are no longer considered first-line treatment due to risk of abuse, dependence, potential for fatal withdrawal, potential for fatal overdose, severe fall risk in elderly, and impaired cognition and coordination[5]. Unfortunately, SSRIs and SNRIs are also associated with an elevated risk of suicide[6].

4731-32-05 (C)(6) [Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation]

Preclinical studies using animal models of anxiety or healthy human volunteers report an anxiolytic response with certain cannabinoids[8]. (REF). Brain imaging in multiple preclinical studies consistently demonstrate that cannabidiol (CBD) is effective in reducing anxiety-related behaviors across multiple anxiety disorders with improved function in areas of the brain related to anxiety: the limbic and paralimbic system[9, 10]. Neuroimaging studies also report that CBD attenuates human brain activity by mediating serotonin receptor transmission, reducing sensitivity of CB1 receptors, and changes in regional blood flow[11, 12, 13, 14].

Efficacy, Safety, & Tolerability

Clinical data reports that unlike d9-tetrahydrocannabinol (THC), cannabidiol (CBD) does not produce psychotropic or euphoric effects. Furthermore, even high-dose CBD demonstrated low abuse potential in highly sensitive populations of polydrug abusers. The effect of high-dose CBD does not approach the clinical effects of Xanax (alprazolam) or Marinol (dronabinol)[15]. Additionally, CBD appears to be effective in reducing THC-related anxiety side effects[16, 17]. Like other cannabinoids, CBD appears to have a biphasic response; CBD at a low-to-moderate doses appear to improve anxiety, but at higher doses may have limited benefit[8,10].

The therapeutic effects of cannabis for anxiety disorders are not only limited to CBD, as preclinical and clinical data suggests that other cannabinoid and non-cannabinoid compounds found in cannabis may offer therapeutic benefit[18, 19, 20, 21, 22]. When exposed to environmental stressors, study participants who do not use cannabis reported a subjective increase in stress reactivity and had increased blood serum concentrations of the stress hormone cortisol, however cannabis users reported decreased reactivity to environmental stressors and had no increase in blood concentrations of cortisol[23]. Clinical data from a study of 42 healthy volunteers suggests that THC improved anxiety symptoms at low doses[24]. Data from a large survey of nearly 2,830 cannabis patients reported significant reductions in anxiety and associated symptoms of irritability, insomnia, mood swings, decreased stress, muscle pain, and fatigue[25]. Another large survey measuring 11,953 sessions of cannabis use reports that 58% of users experienced a reduction of anxiety and stress with 2 puffs of cannabis[26]. A review of cannabis for medical use identified 8 cross-sectional studies reporting reduction of anxiety symptoms[27]. Finally, national survey results report that patient utilization of medical cannabis has resulted in a 30% reduction in benzodiazepine prescriptions[28] with direct substitution of benzodiazepines for cannabis in 13% of cases[29].

In clinical studies, two double-blind placebo-controlled trials of CBD in children report that CBD was overall well tolerated with most adverse events being mild to moderate in severity. However, high dose CBD increases the risk of elevated liver transaminases when combined with the anti-epileptic drug valproate[30, 31]. Fortunately, there was no drug-induced liver injury identified and liver enzymes normalized once the CBD dose or valproate dose was reduced or stopped[32, 33]. Another double-blind placebo-controlled trial reports that, unlike prescription SSRIs and SNRIs, there is no identified suicide risk with CBD even in patients with severe psychiatric illness and rates of adverse events were similar to placebo[34]. Currently, an active randomized, double-blind, placebo-controlled study is exploring the potential benefit of CBD for treatment of anxiety symptoms in adults who had previously had limited benefit to therapy alone[35].

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Notes on Anxiety, Depression, and Insomnia

Introduction

"Scientific investigation of the therapeutic application of terpenoids in psychiatry has been hampered by methodological concerns, subjective variability of results, and a general dearth of appropriate randomized controlled studies of high quality" (Russo 2001, Bowles, 2003, Lis-Balchin 2010). Data from the Releaf® application show that among cannabis patients, use in depression, anxiety, and insomnia was 25.21%, 31.89%, and 8.29% respectively. In a self- reporting style, patients reported overall success rate of 67.54%, 67.18%, and 62.29% respectively.

Even though depression, anxiety, and insomnia are among some of the most commonly reported uses for cannabis, very few states actually include these in their list of qualifying conditions. Currently, New Jersey, California, Oklahoma, and Puerto Rico and Pennsylvania include anxiety, but not a single state lists insomnia and depression. Missouri includes a condition on their list for debilitating psychiatric disorder. States where the physician is allowed to decide the medical necessity like Virginia, California, and Oklahoma, or states like Maryland that include a legal provision like "and other condition which is severe, other treatments have failed, or symptoms may be reasonably expected to be relieved by medical use of cannabis" (Maryland Medical Cannabis Law subtitle 33, 13-3301) have reported significant use.

Part of the problem with cannabis and psychiatric disorders lies within the very nature of the ambiguous nature of the

diagnosis, and lack of objective tests (i.e. blood work, etc.). Secondly, as with other traditional psychiatric treatments, different levels of THC and/or CBD can have widely differing clinical effects. In some cases, high levels of THC can actually induce or worsen anxiety, whereas CBD can act like an antidepressant/anxiolytic compound.

It is the opinion of this reviewer that there is great deal of interconnection between these three disorders. For example, a person with poor sleep habits may become anxious about their insomnia, or conversely the anxious patient cannot quiet their thoughts to allow for proper sleep. All of these conditions can potentially bring on depression when there is a feeling of hopelessness to find relief.

Accordingly, it is the recommendation of this reviewer, that these three petitions be either accepted or rejected together, and in reviewing the supporting evidence presented in the petitions, it is recommended that the state of Ohio accept these.

Realizing that including insomnia and depression as listed conditions would be a first in the US, and anxiety is rare, we propose a novel approach to conditionally accept these new conditions. Specifically, it is proposed that these conditions be accepted with a commitment to assess use and outcomes for the 12 months following state acceptance. Then, the state can review real patient use data, and decide if these conditions should continue to be listed. This could be accomplished in a number of ways using self -reporting applications or registries for reporting safety and effectiveness.

Review and Comment of Each Petition

<u>Insomnia</u>

Insomnia is often a comorbidity of other conditions like anxiety, depression, chronic pain, cancer chemotherapy treatment, etc. Traditional pharmaceutical sleep aids are either not approved for chronic use and are associated with extreme side effects. Very little data exist to assess the long term effects of these insomnia treatments. One of the most prescribed compounds for insomnia is trazadone (Desyrel®) which is only FDA approved for depression. Barry Krakow et.al. (2009) describe treatment resistance and tolerances with traditional sleep aids that can result in escalating doses and higher incidence of undesired side effects. Benca (2005) presented epidemiologic studies that suggest the needs of patients with insomnia remain unmet.

In support of insomnia as a new listed condition in Ohio, 2 key studies are presented in this petition. In 2007, Russo and Guy (GW Pharma) reviewed sleep improvement in 2000 patients representing 1000 patient years using Sativex® (1:1 ratio THC:CBD). Results reported a marked improvement in sleep parameters, while not observing tolerance or dose escalation. As a matter of fact, sleepiness is listed as a common side effect of Sativex® use.

The second study of significance was a prospective evaluation of 409 patients in New Mexico (Vigil et.al. 2018). In this study, patients reported significant improvement in sleep patterns with variation in results depending on the chemovars and cannabinoid and terpenoid profiles. Russo in 2011, reported on

the roles of certain terpenes like myrcene and nerolidol as sedatives and their role in sleep.

Based on these studies, all of the evidence presented in this petition, and the safety profile of cannabis, approval of insomnia as a new Ohio condition is recommended.

Depression

Depression is a very serious disease with potentially life and death consequences. There is a strong link between persistent insomnia and suicidal ideation, and treating insomnia is one of the highest priorities in treating depression (Takahashi, 2001). Affect disorders are a set of psychiatric disorders that include depression, bipolar, and anxiety disorders like PTSD, social anxiety, generalized panic, and OCD. Bostwick et.al. (2000) reported a life time prevalence of suicide in patients hospitalized for suicidality at 8.6%.

Symptoms of depression include: prolonged sadness, irritability, lethargy, lack of interest in normal activity, changes in eating and sleeping difficulty concentrating, feelings of guilt, non-physical aches and pains, suicidal thoughts, unusual chronic mood swings, and low self- esteem.

Traditional medication assisted treatments include antidepressants, mood stabilizers, and anti-psychotic drugs. These medications are often linked with suicidal ideations especially in certain age groups. Many of these SSRIs and SNRIs include black box warnings on their label for increased risk of suicide. In addition to suicide, antidepressants are associated with many other serious side effects and can also lose effectiveness over time resulting in dose escalation. Many are

also associated with discontinuation (withdrawal) symptoms. Within the population of treatment resistant patients, approximately 30% of these patients do not respond to any treatment options (Al Harbi, 2012).

Support for cannabis therapy for treating depression is observational and anecdotal at this point. While there is much published about the potential therapeutic benefits, no adequate and well controlled studies have been conducted to support the use of cannabis in depression. However, two important points must be made. First, in the long list of depression symptoms, included are symptoms which cannabis is known to ameliorate (eg. changes in eating and sleeping). Secondly, if the requirements for state accepted medical conditions rely only on "the gold standard for clinical trials", most if not all of the listed conditions would not meet this hurdle.

With this in mind, the petition did thoroughly review all the available evidence including a 2015 Arizona patient review that showed 28.9% of surveyed patients used cannabis for depression. A similar study in California reported that 26.1 % of surveyed patients also used cannabis for depression. Since depression is often associated with other comorbidities, evidence of effectiveness has been reported. For example, in 2005 Woolridge et.al. with cannabis use in HIV positive patients, 86% of the patients reported improvement with depression symptoms. A 2016 article by Huang discussed pain and it's intersection with depression and found that when pain is successfully treated, depression symptoms will improve as well.

Based on the evidence presented in this petition, the following conclusions can be made. There is a need for treatment modalities for two key groups of depression patients. Firstly, those patients who have tried and failed with traditional treatments (treatment resistant patients) should have access to a safe, and potentially therapeutic alternative (cannabis) under the careful diagnosis and recommendation of a mental health professional. Secondly, for those patients suffering from depression with suicidal ideation, cannabis therapy is less likely to induce this serious side effect and should be available as an option.

Other options to consider while evaluating cannabis and depression may include co-administering cannabis with other traditional medications in order to enhance effectiveness or manage side effects.

Caution should be exercised in patients for whom cannabis has been a substance of abuse or has exacerbated depressive symptoms.

In summary and in consideration of the interconnectedness of depression, anxiety, and insomnia, it is recommended that this petition be approved with the condition that patient diagnosis, treatment, and outcomes be closely monitored.

Chronic and Generalized Anxiety Disorder (GAD)

GAD could be compared to major depression as a debilitating and difficult to treat condition. Bystritsky et. al. in 2013 reported that about 13% of the US population suffers from anxiety disorders. Included in the list of anxiety disorders are panic, panic with agoraphobia, social phobia, specific phobias,

PTSD, acute stress disorder, and OCD (DSM IV). Anxiety also can and does occur in context with other medical illness when patients have anxious feelings, abnormally process medical information, and lack coping strategies.

Wittchen (2002) defined GAD as a persistent and severe mental disorder of the anxiety spectrum (six months or more of excessive worrying, tension, and hypervigilance) with a high level of comorbidity with depression, panic disorder, social anxiety, and PTSD.

Symptoms of anxiety disorders include constant worry, obsessive thought, restlessness, trouble concentrating, trembling, irritability, sleep disorder, sweating, nausea, and rapid heart rate.

Neurotransmitters most commonly involved in anxiety disorders are dopamine, glutamate, norepinephrine, serotonin, and GABA. Traditional therapies target these neurotransmitter levels, but this is complicated because anxiety is not a deficiency of a transmitter, but rather complex interrelationships of transmitters, multiple feedback mechanisms, and complex receptor structures.

Thus, medication effectiveness can be unpredictable. Affecting levels of dopamine with treatments is widely used. Anti-psychotic agents can also be anxiolytic and pro-dopaminergic drugs like buproprion can improve or exacerbate symptoms. Glutamate is the primary excitatory neurotransmitter in normal and pathological anxiety states. Many of the physiological symptoms of anxiety are mediated by norepinephrine and antagonists like propranolol are used to reduce symptoms of rapid heart rate and hand tremor.

Between 50-60% of anxiety patients will respond clinically to treatment, but only 1/3-1/2 attain full remission (Rickels, 2006). Many of the treatments are approved for only short term use and treatment resistance is being seen with more and more of these drugs. SSRIs are most often used for depression but also for anxiety even though the mechanism of action in anxiety is not well understood. SNRIs are only used if the SSRI fails and patient response can vary widely. Barbiturates and benzodiazepines can decrease anxiety, but are associated with serious side effects so are no longer a treatment of choice. Anti-seizure drugs have been used off label to treat anxiety but high doses have a similar side effect profile as the benzodiazepines. Hydroxyzine has been used in OCD and may be used in conjunction with SSRIs or SNRIs and tri-cyclic antidepressants are rarely used due to a high side effect profile. In summary, as with depression, polypharmacy is always a problem with anxiety disorders (especially panic disorder) and monitoring drug-drug interactions is very critical.

In support for cannabis therapy in the treatment of anxiety disorders, two key studies are described in the petition for chronic anxiety disorder. Crippa et.al. (J Psychopharm 2011) studied CBD (400mg orally) in generalized social anxiety and a significant decrease in symptoms over the placebo group was observed. Bergamaschi et.al. (J Neuropsychopharm 2011) saw significant reduction in social anxiety symptoms with CBD (600mg orally) in a double blind placebo controlled trial.

Schier (2011) reviewed 17 animal studies and 6 human trials which evaluated CBD as an anxiolytic and found it to be effective and well tolerated at lower doses.

It is important to note two things. Cannabis (THC and CBD and the minor cannabinoids) generally exhibits a strong biphasic effect, meaning low doses may be anxiolytic and high doses could actually exacerbate symptoms. As reported, most of the studies have evaluated CBD and not THC. CBD is most likely a serotonin receptor (5-HT1a) agonist (Crippa et.al. 2011). THC without CBD may actually cause symptoms of paranoia and agitation, so as a treatment for anxiety the THC should be balanced with CBD in at least a 1:1 ratio.

In a final agency decision in March 2018, the New Jersey DOH concluded that after a rigorous review found that anxiety was "debilitating" and "medical marijuana is more likely than not to be a potential benefit to treat or alleviate the debilitating effect of this condition". Furthermore, in the 2017 National Academy of Science report, cannabis was considered an effective treatment for anxiety based on the assessment of the public speaking test.

Considering the evidence and the supporting data presented in these two petitions, it is recommended that these petitions be approved with the condition that patient diagnosis, treatment, and outcomes be closely monitored.

Mark J. Woyshville M.D.
Diplomate, American Board of Psychiatry and Neurology
Diplomate, American Board of Sleep Medicine
Diplomate, American Board of Preventative Medicine, Addiction Medicine

May 5, 2019

State Medical Board of Ohio
30 East Broad Street 3rd Floor
Columbus, Ohio 43215-6127

RE: Executive Summary: Review of Petitions to allow Additional Conditions under the State of Ohio Medical Marijuana Control Program

Greetings:

Please accept this narrative as the Executive Summary of the four petitions on which I have been asked to render an expert opinion. In particular, condition petitions were received and thoroughly reviewed for (Generalized) Anxiety, (Major) Depression, Insomnia, and Opioid Use Disorder. It is my opinion that all four conditions should be allowed.

The strength of the evidence in support of these petitions, in conventional scientific terms, is greatest for anxiety, then insomnia; then depression and, finally, opioid use disorder. This is because of circumstances unique to cannabis, such as its being a Schedule I substance under the DEA classification scheme. This has served to put native plant material largely beyond the reach of scientists who would be inclined to investigate cannabis using modern methods. However, to the conventional scientific strength-of-evidence paradigms must be added the voices of physicians who have amassed anecdotal evidence that is convincing in its own right, and admittedly has influenced my opinion to allow these conditions, especially for opioid use disorders.
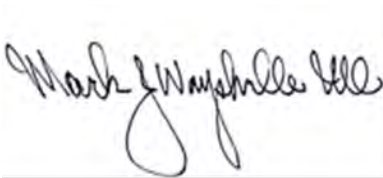
It seems amazing that the sole psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol, or THC. This compound has been well-characterized and is even available as a pharmaceutical, dronabinol (Marionol), albeit subject to restrictions. THC has revealed that the the human nervous system and other tissues have receptors for which THC is a partial agonist, broadly referred to as CB-1 and CB-2, both members of the G-protein-coupled super-family. These receptors bind endogenous cannabinoids, both of which are derived from arachidonic acid: the ethanol amide arachidonylethylamide, or anandamide, and the monoacyl glycerol 2-arachidonylglycerol. These are unique amongst neurotransmission schemes by being *retrograde*, signaling *backwards* from the post-synaptic neuron, where the endocannabinoid is synthesized as-needed, to the receptors binding them at the pre-synaptic neuron, where their effects are largely inhibitory. There, the endocannabinoid is quickly hydrolyzed to inactivity, terminating the signal. The endcannabinoid neurotransmission is *ad-hoc*, *retrograde*, and *fast*.

However neat the above characterization of endocannabinoid action may be, it must be distinguished from the therapeutic action of plant material, which contains a plethora of phytocannabinoids such as cannabidiol, or CBD, as well as other active compounds, broadly referred to as *terpenoids* and *flavonoids*. Even THC has effects *not* mediated by the CB-1 and CB-2 receptors, as biological action due to THC is seen in CB-1 and CB-2 knockout mice. The implications of all this will become clearer in the context of the individual petitions.

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The use of marijuana for medicinal purposes is unlike the development of any modern chemotherapeutic agent for any disease. The underlying neurobiology is unlike that of any previously-elicited neuromodulatory signaling scheme. The social dimensions of the entire process knows no peer in the evolution of any other plant-based medicinal. It is both exciting and daunting to consider the implications of allowing the four conditions subject to this petition review. However, although the net effect of my analysis is to conclude the condition petitions should be granted, it is not without due consideration given to the negative aspects of the risk/benefit calculus applied in each instance. The individual petition reviews will delineate these negative aspects of each new indication, and the reasoning eventuating in the recommendation to allow.

It is recommended that the petition opinions be read in order, as the technical aspects build one upon the other. The order is anxiety, insomnia, depression, and opioid use disorders.

Professionally Submitted,

Mark J. Woyshville MD

SUBJECT MATTER EXPERT REPORT: GENERALIZED ANXIETY DISORDER

PETITION OVERVIEW

MATERIALS SUBMITTED	DESCRIPTION
4731-32-05 (C)(1)	1. Thomas Rosenberger 2. Dawn McIntyre
4731-32-05 (C)(2)	Generalized Anxiety Disorder/Chronic Anxiety Disorder
4731-32-05 (C)(3)	1. Overview 2. Generalized Anxiety Disorder: Prevalance, Burden, and Cost to Society 3. Final Agency Decision: Petitions to Establish Additional Debilitating Medical Conditions Under the New Jersey Medicinal Marijuana Program – New Jersey Department of Health 4. Current Diagnosis and Treatment of Anxiety Disorders
4731-32-05 (C)(4)	1. Overview 2. Generalized Anxiety Disorder: When Worry Gets Out of Control – National Institute of Mental Health
4731-32-05 (C)(5)	1. Overview 2. Generalised Anxiety Disorder in Adults: Management in Primary, Secondary and Community Care 3. Achieving Remission in Generalized Anxiety Disorder
4731-32-05 (C)(6)	1. Key Findings 2. Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug 3. The Endocannabinoid System and the Brain 4. Anxiogenic-like effects of chronic cannabidiol administration in rats 5. Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow 6. Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders 7. Cannabidiol as a Potential Treatment for Anxiety Disorders 8. Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report 9. Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics 10. Therapeutic Benefits of Cannabis: A Patient Survey 11. Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization 12. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects

13. Patient-Reported Symptom Relief Following Medical Cannabis Consumption
14. Confidential: Data provided by Releaf
15. Medical Marijuana for Psychiatric Disorders
16. Can CBD oil help anxiety?
17. Scientific guidelines for using cannabis to treat stress, anxiety, and depression
18. Neural basis of†anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report
19. Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

4731-32-05 (C)(7)	
	1. Martha Hackett, MD
	2. Peter Howison, MD
	3. Sharrie Ann Ray, MD
	4. Cynthia L. Dietrich, DO
	5. Solomon Zaraa, DO
	6. Nora McNamara, MD
	7. Noah Miller, MD
	8. Paul Y. Song, MD
	9. Anand Dugar, MD
	10. Oscar B. Cataldi, Jr., MD
	11. Timothy Thress, MD
	12. Karin Cseak, DO

APPLICABLE STATUTES & RULES

PURSUANT TO OAC 4731-32-05, THE SUBJECT MATTER EXPERT SHALL REVIEW THE ABOVE-REFERENCED MATERIALS AND ISSUE A WRITTEN OPINION REGARDING THE CURRENT TREATMENT MODALITIES FOR THE PROPOSED DISEASE OR CONDITION AND WHETHER A MEDICAL MARIJUANA RECOMMENDATION COULD BE BENEFICIAL TO THE PROPOSED DISEASE OR CONDITION.

SUMMARY OF PROPOSED DISEASE OR CONDITION

Generalized Anxiety Disorder (GAD) is a pervasive condition amongst those suffering with mental illness. It is associated with substantial distress and impairment and indeed, at its worst, is debilitating. In fact, the morbidity attending anxiety disorders equals that of Major Depressive Disorder.

While many therapeutic modalities exist for managing GAD, it tends to chronicity even with treatment. As time goes by, the condition becomes increasingly resistant to non-medication therapies and pharmacotherapy short of benzodiazepines. I make this statement from my perspective on the disorder as a psychiatrist practicing for 30 years. As most initial treatment is provided by non-psychiatric and even non-physician practitioners, the psychiatrist of today finds his practice filling up with those patients who have been otherwise treated, with less than optimal outcomes. For these reasons many, if not most, of these patients end up on benzodiazepines which, while effective, come with severe liabilities. In particular, ongoing use can eventuate in tolerance, requiring ever-increasing doses to keep symptoms at bay. Precipitous withdrawal can be life-threatening. There can be significant cognitive impairments, especially as the patient ages. The drugs are euphorigenic, and subject to diversion. And this last concern is the greatest. While no one has ever died due to respiratory depression overdosing on benzodiazepines alone, benzodiazepine street use in combination with opioids is an especially potent cocktail for respiratory depression, and subsequent death. For these reasons, alternative treatments are desperately needed.

There is good evidence that medical marijuana is an effective alternative treatment for anxiety conditions, but there is an underlying seeming paradox. THC, the psychoactive constituent of cannabis plant material, can itself be anxiogenic. So how can plant material help? It is due to the presence of the phytocannabinoid *cannabidiol*, or CBD. CBD mitigates the anxiogenic effect of THC. Indeed, although not mediated by either CB-1 or CB-2 receptor binding, CBD alone is anxiolytic, probably through a gaba-ergic and/or serotonergic interaction. There is also evidence for an *entourage effect*, involving especially the terpenoid constituents of the plant material. This means that the net effect of the action of the various constituents of native plant material manifests a synergistic salutary effect which is greater than the mere sum of the effects of the constituents taken individually. The chief bearer of this effect in anxiety is CBD; but the terpenoids also play a role. Terpenes are pungent compounds built up by serial application of the isoprene rule. They are perforce hydrocarbons; but chemically related compounds bearing oxygen and nitrogen have some of the same properties, and are therefore in aggregate referred to as *terpenoids*.

Negatives related to the use of cannabis to manage anxiety disorders are primarily intoxication syndromes, and these are due to THC. Also, the endocannabinoid system readily develops tolerance to agonist biding at CB-1 and CB-2 sites. The response to both of these liabilities is to start low (the equivalent of 1mg THC and 1mg CBD as a sublingual tincture) and go slow. The dose is built up by taking the medication at intervals throughout the day, and increasing the dose day to day, until the lowest effective dose is found. This will in most (nearly all) cases lead to a regimen which while effective for the illness under treatment, is well below intoxicating doses.

Finally, I wish to make mention of the biphasic response of illness symptoms to varying doses of cannabis material, manifest clinically as the observation that euphoria and relaxation or dysphoria and anxiety may obtain in normal users of the same plant material.   This "upside down U" dose-response relationship is seen across illness indications with cannabis medicine, and serves as part of the motivation for using high doses in some patients, or the strategy of stopping cannabis medicine for a time in an attempt to recapture sensitivity to the therapeutic effects.

CONCLUSIONS REGARDING MEDICAL MARIJUANA

The following is my expert opinion to a reasonable degree of medical certainty regarding the applicability of recommending medical marijuana for the proposed disease or condition:

If applicable, here are the strains and/or dosages that may be appropriate when using medical marijuana for the proposed disease or condition:

As detailed above, I opine at the level of reasonable medical certainty that the benefits of cannabis medication far outweigh the risks for the management of Generalized Anxiety Disorder, and recommend that it be added as an allowed condition for treatment.

SUBJECT MATTER EXPERT REPORT: INSOMNIA

PETITION OVERVIEW

MATERIALS SUBMITTED	DESCRIPTION
4731-32-05 (C)(1)	Thomas Rosenberger
4731-32-05 (C)(2)	Insomnia
4731-32-05 (C)(3)	Clinical Pharmacology in Sleep Medicine
4731-32-05 (C)(4)	1. Overview 2. Insomnia, American Academy of Sleep Medicine
4731-32-05 (C)(5)	1. Overview 2. Patients with Treatment-Resistant Insomnia Taking Nightly Prescription Medicines for Sleep: A Retrospective Assessment of Diagnostic and Treatment Variables 3. Diagnosis and Treatment of Chronic Insomnia: A Review
4731-32-05 (C)(6)	1. Key Findings 2. Effectiveness of Raw, Natural Medical Cannabis Flower for Treating Insomnia under Naturalistic Conditions 3. Patient-Reported Symptom Relief Following Medical Cannabis Consumption 4. Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials of Sativex, a Cannabis-Based Medicine 5. Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats 6. Endocannabinoid Signaling Regulates Sleep Stability 7. Therapeutic Benefits of Cannabis: A Patient Survey 8. Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics 9. Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report 10. Data provided by Releaf
4731-32-05 (C)(7)	Letters provided by: 1. Martha Hackett, MD 2. Peter Howison, MD 3. Sharrie Ann Ray, MD 4. Cynthia L. Dietrich, DO 5. Solomon Zaraa, DO 6. Nora McNamara, MD 7. Noah Miller, MD 8. Paul Y. Song, MD 9. Anand Dugar, MD 10. Oscar B. Cataldi, Jr., MD 11. Timothy Thress, MD

APPLICABLE STATUTES & RULES

PURSUANT TO OAC 4731-32-05, THE SUBJECT MATTER EXPERT SHALL REVIEW THE ABOVE-REFERENCED MATERIALS AND ISSUE A WRITTEN OPINION REGARDING THE CURRENT TREATMENT MODALITIES FOR THE PROPOSED DISEASE OR CONDITION AND WHETHER A MEDICAL MARIJUANA RECOMMENDATION COULD BE BENEFICIAL TO THE PROPOSED DISEASE OR CONDITION.

SUMMARY OF PROPOSED DISEASE OR CONDITION

Insomnia is a common condition, both as a primary illness in its own right, and as a morbid factor amongst others in various disease states. The public health burden of insomnia is substantial, most significantly due to inattentiveness at work, home, or while commuting. The patients themselves are frequently unaware of this impairment, and soon become inured to the decrement in productivity and physical and mental health. However, society pays for the lost productivity, the increase in workplace accidents, and, most importantly, the morbidity and mortality attending "drowsy driving," with a mortality rate approaching that of drunk driving. It is clear that treatment of insomnia is necessary and indeed, is a multi-billion-dollar indication for the pharmaceutical industry.

Many cases of insomnia are psychophysiologic, responding well to conservative measures such as sleep hygiene and cognitive-behavioral therapy. These patients are not the subject of this opinion. Other patients may have sleep disorders with insomnia as a primary manifestation; these patients benefit most from appropriate treatment of the underlying sleep disorder, for example, disorders of circadian rhythmicity. However, this leaves a large number of patients with insomnia requiring independent management. Current treatment is largely with benzodiazepines, or non-benzodiazepine benzodiazepine-receptor agonists – they both have the same liabilities (see the Generalized Anxiety Disorder opinion). The need for alternative therapeutic modalities without these liabilities is manifest.

Cannabis medication has been recognized since antiquity for its dormitive powers. In modern times, much of the evidence in support of its efficacy in insomnia has been the observation of the improvement in sleep parameters in studies of other conditions, specifically the use of cannabis medication to manage chronic pain. Indeed, the pharmaceutical preparation Sativex, derived from plant material, caries a 1:1 THC:CBD ratio, appears to be ideally suited to manage insomnia. CBD-dominant cannabis medicines tend to be activating, and THC-dominant strains confer a liability for residual daytime sedation. In fact, a common paradigm for the use of cannabis medication is to use as CBD-dominant strain in the morning, and a THC-dominant strain in the evening. Of interest, however, is the biphasic effects of cannabis medication in which the exact opposite effects obtain amongst patients who are otherwise indistinguishable. Therefore, individualization of therapy is always necessary. Finally, consider the *entourage effect*, conferred by the presence of terpenoids which are sedating in their own right (see the Generalized Anxiety Petition).

In humans, it is noteworthy that subjective measures of sleep improve with cannabis medicine in excess of what would be expected from objective data obtained in the sleep lab. This effect is most strikingly seen amongst insomniacs comorbid for chronic pain. Of interest, there was no evidence for tolerance or tachyphylaxis using cannabis medicine to manage insomnia in this population.

Negative aspects of the use of cannabis medication are few and largely avoidable though judicious dosing that avoids daytime sedation or psychomotor slowing.

CONCLUSIONS REGARDING MEDICAL MARIJUANA

The following is my expert opinion to a reasonable degree of medical certainty regarding the applicability of recommending medical marijuana for the proposed disease or condition:

If applicable, here are the strains and/or dosages that may be appropriate when using medical marijuana for the proposed disease or condition:

As reasoned above, I opine at the level of reasonable medical certainty that the condition petition for Insomnia be allowed.

SUBJECT MATTER EXPERT REPORT: DEPRESSION

PETITION OVERVIEW

MATERIALS SUBMITTED	DESCRIPTION
4731-32-05 (C)(1)	Thomas Rosenberger
4731-32-05 (C)(2)	Depression
4731-32-05 (C)(3)	1. Overview 2. Depression and Suicide Affective Disorders and Suicide Risk: A Reexamination
4731-32-05 (C)(4)	1. Overview 2. Depression, National Alliance on Mental Health 3. Depression and Suicide 4. Affective Disorders and Suicide Risk: A Reexamination
4731-32-05 (C)(5)	1. Overview 2. Treatment-resistant depression: therapeutic trends, challenges, and future directions 3. Side Effects of Current Antidepressants
4731-32-05 (C)(6)	1. Key Findings 2. Patient-Reported Symptom Relief Following Medical Cannabis Consumption 3. Cannabis Use in HIV for Pain and Other Medical Symptoms 4. Who Are Medical Marijuana Patients? Population Characteristics from Nine California Assessment Clinics 5. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects 6. Cannabinoids Elicit Antidepressant-Like Behavior and Activate Serotonergic Neurons through the Medial Prefrontal Cortex 7. Endocannabinoid system: Role in depression, reward and pain control (Review) 8. The endocannabinoid system and emotional processing: A pharmacological fMRI study with Δ9-tetrahydrocannabinol 9. A possible role for the endocannabinoid system in the neurobiology of depression 10. Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization 11. Therapeutical use of the cannabinoids in psychiatry 12. Do Patients Use Marijuana As An Antidepressant? 13. Confidential: Data provided by Releaf
4731-32-05 (C)(7)	1. Martha Hackett, MD 2. Peter Howison, MD 3. Sharrie Ann Ray, MD 4. Cynthia L. Dietrich, DO 5. Solomon Zaraa, DO

6. Nora McNamara, MD
7. Paul Y. Song, MD
8. Anand Dugar, MD
9. Oscar B. Cataldi, Jr., MD
10. Timothy Thress, MD

APPLICABLE STATUTES & RULES

PURSUANT TO OAC 4731-32-05, THE SUBJECT MATTER EXPERT SHALL REVIEW THE ABOVE-REFERENCED MATERIALS AND ISSUE A WRITTEN OPINION REGARDING THE CURRENT TREATMENT MODALITIES FOR THE PROPOSED DISEASE OR CONDITION AND WHETHER A MEDICAL MARIJUANA RECOMMENDATION COULD BE BENEFICIAL TO THE PROPOSED DISEASE OR CONDITION.

SUMMARY OF PROPOSED DISEASE OR CONDITION

Depression is not rare. In fact, one in ten men and one in four women will develop Major Depressive Disorder at some point in their lifetime; and far more will experience the debilitating effects of depression in various other contexts. The fact that depression is associated with severe morbidity and even mortality is well-known. Therefore, effective treatments are critical. However, 50%–66% of patients with depression do not recover fully on an antidepressant medication. Further, failure to respond to a given antidepressant medication predicts failure to respond to any subsequent medication. Finally, as depression goes on, especially in the context of failed treatment trials, the illness develops treatment refractoriness, motivating the search for therapies directed towards these resistant cases. Modalities such as transcranial magnetic stimulation and esketamine are two examples of recent technologies with promise. However, as of now, these modalities are reserved for patients who are already resistant. What is needed is a therapeutic modality that can reduce depressive distress, impairment, morbidity, and mortality that can be deployed at any point in the clinical evolution of the illness, and medical cannabis is certainly a candidate for such a treatment.

Unlike the previous two condition petitions, the data for a salutary effect of cannabis medicine on depressive morbidity and mortality *per se* is a bit thin. However, much of the benefit of cannabis medicine can be applied to symptom dimensions within major depressive disorder – such as insomnia (independently associated with depressive relapse in people who are otherwise responders) and anxiety. Indeed, Major Depression with Anxious Features is a particularly dysphoria-producing form of the disease that is hard to treat, but the kind most likely to respond to cannabis medicine, based on its clearly salutary effects seen in Generalized Anxiety Disorder.

Pre-clinical data point to the CB-1 receptor as an important target for drug development in the brain, based largely on its neuroanatomical distribution, and clinical data using THC demonstrates a reduction in negative bias in emotional processing. However, agonist development must minimize the unwanted psychotropic effects of potential therapeutic agents, including but not limited to a reduced ability to recognize stimuli with negative emotional content. Interestingly, though, we tolerate this very same effect when seen with antidepressant therapy, especially with selective serotonin reuptake inhibitors. Finally, a paper authored in part by renowned affective disorders researcher Harrison Pope summarized five cases in which "the evidence seems particularly clear that marijuana exerted an antidepressant effect," (Depression 4:77-80 (1996). This seems promising, and it is likely that clinical data evolving in the context of more liberal access to cannabis medicine might well build on these early but robust findings.

Considering the safety of cannabis medication relative to standard treatments for depression, one need look no further that the fact that we tolerate an increase in suicidality in such patients as a risk to be borne for the potential

benefit of antidepressant activity. But so far, there is no evidence that any such compromise must be made with cannabis medication.

CONCLUSIONS REGARDING MEDICAL MARIJUANA

The following is my expert opinion to a reasonable degree of medical certainty regarding the applicability of recommending medical marijuana for the proposed disease or condition:

If applicable, here are the strains and/or dosages that may be appropriate when using medical marijuana for the proposed disease or condition:

As reasoned above, I opine at the level of reasonable medical certainty that Depression be added to the allowed conditions for treatment with cannabis medicine.

SUBJECT MATTER EXPERT REPORT: OPIOID USE DISORDER

PETITION OVERVIEW

MATERIALS SUBMITTED	DESCRIPTION
4731-32-05 (C)(1)	1. Thomas Rosenberger 2. F. Stuart Leeds MD MS 3. Robert Ryan
4731-32-05 (C)(2)	Opioid Use Disorder/Opiate Addiction
4731-32-05 (C)(3)	1. Overview 2. Opioid Summaries by State - Ohio, National Institute on Drug Abuse 3. OUD Petition - Information from Experts: Frederic Stuart Leeds, MD, MS (Lead Author) 4. Information from experts who specialize in the study of the disease or condition. Ohio Patient Network
4731-32-05 (C)(4)	1. Overview 2. What Is Opioid Use Disorder? Implications for Its Treatment and Management, Ron Jackson, M.S.W., L.I.C.S.W. 3. OUD Petition: Relevant Scientific or Medical Evidence (Leeds) 4. Relevant Medical or Scientific Evidence… Ohio Patient Network
4731-32-05 (C)(5)	1. Overview 2. High Mortality among Patients with Opioid Use Disorder in a Large Healthcare System 3. Medications to Treat Opioid Use Disorder, NIDA 4. OUD – Consideration of Insufficient Therapies (Leeds)
4731-32-05 (C)(6)	1. Key Findings 2. The Analgesic Potential of Cannabinoids 3. Cannabinoid and opioid interactions: implications for opiate and withdrawal 4. Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization 5. Emerging Evidence for Cannabis' Role in Opioid Use Disorder 6. Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage 7. The effects of dronabinol during detoxification and the initiation of treatment with extended release Intermittent Marijuana Use Is Associated with Improved -Retention in Naltrexone Treatment for Opiate-Dependence 8. Cannabinoid–Opioid Interaction in Chronic Pain

9.   Cannabidiol, a Nonpsychotropic Component of Cannabis, Inhibits Cue-Induced Heroin Seeking and Normalizes Discrete Mesolimbic Neuronal Disturbances
10. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross- Sectional Survey of Patients With Chronic Pain
11. OUD – Evidence Supporting Use Of MMJ – Leeds
12. Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies and other types of medical or scientific documentation – Ohio Patient Network
13. How to Use Cannabis to Reduce and Replace Opioid Medications by Dr. Dustin Sulak, Co-founder, Healer

4731-32-05 (C)(7)	
	1. Martha Hackett, MD
	2. Peter Howison, MD
	3. Sharrie Ann Ray, MD
	4. Cynthia L. Dietrich, DO
	5. Solomon Zaraa, DO
	6. Nora McNamara, MD
	7. Noah Miller, MD
	8. Paul Y. Song, MD
	9. Anand Dugar, MD
	10. Oscar B. Cataldi, Jr., MD
	11. Timothy Thress, MD
	12. Paul J. Hershberger, Ph.D., ABPP
	13. Margaret M. Dunn, M.D., M.B.A., FACS
	14. S. Bruce Binder, M.D., Ph.D.
	15. Peter L. Reynolds, M.D., FAAFP
	16. Joy Forcier, LISW
	17. F. Stuart (Skip) Leeds, M.D., M.S.
	18. Dr. Russo
	19. Dr. Blatman
	20. Dr. Sawyer
	21. Dr. Kollman
	22. Dr. Austin
	23. Dr. Simmons
	24. Dr. Mooney

APPLICABLE STATUTES & RULES

PURSUANT TO OAC 4731-32-05, THE SUBJECT MATTER EXPERT SHALL REVIEW THE ABOVE-REFERENCED MATERIALS AND ISSUE A WRITTEN OPINION REGARDING THE CURRENT TREATMENT MODALITIES FOR THE PROPOSED DISEASE OR CONDITION AND WHETHER A MEDICAL MARIJUANA RECOMMENDATION COULD BE BENEFICIAL TO THE PROPOSED DISEASE OR CONDITION.

SUMMARY OF PROPOSED DISEASE OR CONDITION

The opioid overdose death crisis in which we are now immersed needs no further introduction from me. However, the bulk of the material submitted for my review is focused on the urgency of the crisis, with less evidence beyond clinical experience to make the case for cannabis medicine qualifying as an ameliorative factor.

For example, it is stated that "In order to protect patients suffering from opioid use disorder, their families, friends, and neighbors, it is imperative that we give physicians every tool possible to address this disorder." But will cannabis medicine help, and what is the evidence that it can?

It is clear that while cannabis medicine works synergistically with opioid medications in chronic pain patients, as evidenced by substantial lowering of the opioid burden, it is less clear that this finding translates into a benefit for the patient with an opioid use disorder, which by far most chronic pain patients are *not*.

Some evidence exists both for and against the use of cannabis medicine in opiate use disorders. For examples against, cannabis use was associated with more rapid relapse to heroin use within a cohort enrolled in a methadone maintenance treatment program, and cannabis use was associated with drug-dealing and needle-sharing. Further, following inpatient treatment for substance abuse, post-discharge cannabis use was associated with faster relapse to alcohol and cocaine use. Finally, among individuals receiving chronic opioid therapy for pain, the presence of cannabis use was a positive predictor of opioid abuse. On the plus side, intermittent cannabis use is associated with improved retention in naltrexone treatment amongst opioid dependent patients, although cannabis abstinence and regular cannabis use was associated with higher drop-out rates. Subjective reports of symptom relief in opioid-dependent patients using cannabis medicine was 75%; dronabinol reduced opiate withdrawal symptoms during the acute inpatient phase (the first few days) of opiate detoxification; and, *most compellingly*, states which have enacted medical marijuana laws have seen a decrease in overall opioid death rates, although a causal connection has not been established.

In summary, the direct evidence for the clinical utility of cannabis medicine for the management of opioid use disorder is very thin, and most of it reflects poorly on the outcomes when cannabis is used by opioid use disorder patients. HOWEVER, this data was not garnered in the context of a controlled and structured interaction with a physician with a Certificate to Recommend, and it seems likely that, given that opioid use disorder patients respond positively to structure and supervision, providing cannabis medicine in this context could benefit at least some patients with opioid use disorders.

CONCLUSIONS REGARDING MEDICAL MARIJUANA

The following is my expert opinion to a reasonable degree of medical certainty regarding the applicability of recommending medical marijuana for the proposed disease or condition:

If applicable, here are the strains and/or dosages that may be appropriate when using medical marijuana for the proposed disease or condition:

*As reasoned above, I opine at the level of reasonable medical certainty that a potential benefit exists for the provision of cannabis medicine to patients struggling with Opioid Use Disorder, in the context of a **bona fide** relationship with a physician with a Certificate to Recommend, and should therefore be allowed.*

Review of proposal to approve the use medical marijuana to treat the symptoms of autism.
Submitted by Dr. Gary L. Wenk

Professor, Psychology & Neuroscience
Director, Neuroscience Programs
The Ohio State University
Member of the Harvard Autism Consortium, 1996 - 2005

Status of current therapies for treating autism:

Physicians currently use a combination of behavioral therapies coupled with a variety of drugs that have been approved by the FDA, such as anti-psychotics, as well as many that have not been approved and are recommended off-label. The brains' of ASD patients show an extensive array of serious anatomical malformations. This likely explains why there is no medication or other therapy that can cure ASD or reduce the impact of most of its symptoms. Some medications can reduce irritability and repetitive behaviors, but most have no impact on language, cognition, behavior, communication, symptom severity or socialization. In addition, the medications produce significant side-effects that can limit their effectiveness, including weight gain, sedation, and extrapyramidal effects.

Review of evidence provided in the proposal:

- ASD patients show alterations in numerous biomarkers of endocannabinoid function, such as the eCB receptor gene.
- The eCB neurotransmitter system in ASD patients was sensitive to modest stimulation by acetaminophen. Acetaminophen is enzymatically converted into a metabolite that enhances eCB neurotransmission.
- THC treatment reduced the amount of self-injurious behaviors in a small population of ASD subjects.
- CBD-rich cannabis reduced the symptom severity in a small group of children with ASD. The CBD-rich cannabis in this study was roughly 2:1 CBD:THC; this relative ratio will produce significantly elevated levels of THC in the blood.
- Small studies of a few ASD patients reported a positive response to oral cannabis.
- Transgenic mouse models that reproduce some phenotypic components of autism, such as enhanced basal spontaneous locomotor behavior, showed a positive response following treatment with THC.

Relevant evidence not provided in the proposal:
The proposal failed to include some recently published studies.

1) Deficient adolescent social behavior following early-life inflammation is ameliorated by augmentation of anandamide signaling. By: Doenni, V. M.; Gray, J. M.; Song, C. M.; et al. BRAIN BEHAVIOR AND IMMUNITY Volume: 58 Pages: 237-247, 2016.

   Decreased adolescent social behavior (play and social non-play) in males and females is accompanied by decreased CB1 binding, increased anandamide levels and increased FAAH activity. FAAH metabolizes the eCB anandamide and shows a mutation in ASD patients. The

authors concluded that inhibition of FAAH could be a novel target for disorders involving social deficits such as social anxiety disorders or autism.

2) Endocannabinod Signal Dysregulation in Autism Spectrum Disorders: A Correlation Link between Inflammatory State and Neuro-Immune Alterations. By: Brigida, Anna Lisa; Schultz, Stephen; Cascone, Mariana; et al. INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES   Volume: 18 Number: 1425, 2017

   A cellular model of autism showed that the mRNA and protein for the CB2 receptor and endocannabinoid enzymes were significantly dysregulated. The authors conclude that the eCB system could represent a novel target option for autism pharmacotherapy.

3) Medication Treatment for Autism | NICHD - Eunice Kennedy Shriver National Institute of Child Health and Human Development. https://www.nichd.nih.gov/health/topics/autism/conditioninfo/treatments/medication-treatment

   The eCB system is altered at the genetic level in ASD leading to abnormalities in anandamide activity. Anandamide is the endogenous eCB neurotransmitter. Plasma anandamide concentrations are lower in children with autism spectrum disorder.

4) Lower circulating endocannabinoid levels in children with autism spectrum disorder. By: Aran, Adi; Eylon, Maya; Harel, Moria; et al. MOLECULAR AUTISM   Volume: 10 Article Number: 2, 2019.

   The eCB system is a major regulator of synaptic plasticity and neuromodulation. Alterations of the ECS have been demonstrated in several animal models of ASD. This study found significantly lower levels of the main endocannabinoid metabolites in the serum of 93 ASD patients.

5) Perry, E., Lee, M., Martin-Ruiz, C., Court, J., Volsen, S., Merrit, J., Folly, E., Iversen, P., Bauman, M., Perry, R., & **Wenk, G.L** Abnormalities in the Cerebral Cortex and Basal Forebrain. AMERICAN JOURNAL OF PSYCHIATRY, Volume 158, Pages 1058-1066, 2001.

   Marchalant, Y., Baranger, K., **Wenk, G.L.,** Khrestchatisky, M. & Rivera, S. Can the benefits of cannabinoid receptor stimulation on neuroinflammation, neurogenesis and memory, JOURNAL OF NEUROINFLAMMATION, Volume 9, Pages 10-13, 2012.

   Wenk, G.L. The role of inflammation in the BDNF and dopamine dysfunction in autism, In: M.L. Bauman & T.L. Kemper, (Eds.) THE NEUROBIOLOGY OF AUTISM, 2nd Ed., The Johns Hopkins University Press, Baltimore, MD, pp. 362-370, 2004.

   These three publications from my laboratory demonstrate that 1) the brains of children with ASD have extensive neuroinflammation that impacts brain chemistry and function, and 2) that stimulation of eCB receptors by THC-like chemicals significantly reduces the

level of neuroinflammation. <u>Taken together, these findings provide a potential mechanism to explain how medical marijuana may benefit patients with ASD</u>.

Conclusions drawn from available human and animal publications regarding the efficacy of medical marijuana for the treatment of autism:

- ASD patients are born with significant genetic alterations in many different genes that control the production of enzymes, neurotransmitters and receptors for multiple neurotransmitter systems.

- The eCB system is in the brains' of these patients is significantly altered. The levels of eCB are consistently reduced. This evidence partially guided the decision by many different laboratories to administer eCB receptor agonists in order to compensate for the reduced eCB function.

<u>Final Recommendations</u>:

Currently available evidence supports the use of medical marijuana for the treatment of symptoms associated with ASD.

The evidence indicates that THC provides the principle benefits when patients are treated with medical cannabis.

Currently available evidence does not support the use of CBD.

SUBJECT MATTER EXPERT REPORT: AUTISM SPECTRUM DISORDER

PETITION OVERVIEW	
MATERIALS SUBMITTED	**DESCRIPTION**
4731-32-05 (E)(3) *[The board shall consult with one or more experts who specialize in the disease or condition:]*	**Solomon Zaraa, DO** **szaraa@compassionatecleveland.com** **Compassionate Cleveland** **23250 Chagrin Blvd; Suite 310** **Beachwood, OH, 44122** **(216) 586-2606**
4731-32-05 (C)(1)	Original petition "*"0109 - Rosenberger - Autism Spectrum Disorder.pdf"* " Submitted on 12/31/2018 by Thomas Rosenberger Rosenberger@nciaohio.org Original petition *"0111 - Carwile - Autism Spectrum Disorder.pdf"* Submitted on 12/28/2018 by Tiffany Carwile autismallianceofohio@gmail.com
4731-32-05 (C)(2)	**Autism Spectrum Disorder**
4731-32-05 (C)(3) *[Information from experts who specialize in the study of the disease or condition:]*	Refer to: **Expert Summary** (below) **Expert Conclusion** (below) **Expert Report** (below)
4731-32-05 (C)(4) *[Relevant medical or scientific evidence pertaining to the disease or condition:]*	Refer to: **Expert Report** (below) **References** (below)
4731-32-05 (C)(5) *[Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition:]*	Refer to: **Expert Report** (below) Also refer to original petitions: *"0109 - Rosenberger - Autism Spectrum Disorder.pdf"* *"0111 - Carwile - Autism Spectrum Disorder.pdf"*
4731-32-05 (C)(6) *[Evidence supporting the use of medical marijuana to treat or alleviate the disease or*	Refer to: **References** (below)

condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation:]

4731-32-05 (C)(7) *[Letters of support provided by physicians with knowledge of the disease or condition. This may include a letter provided by the physician treating the petitioner, if applicable]*	Refer to: *"0109 - Rosenberger - Autism Spectrum Disorder.pdf"* *"0111 - Carwile - Autism Spectrum Disorder.pdf"*

APPLICABLE STATUTES & RULES

PURSUANT TO OAC 4731-32-05, THE SUBJECT MATTER EXPERT SHALL REVIEW THE ABOVE-REFERENCED MATERIALS AND ISSUE A WRITTEN OPINION REGARDING THE CURRENT TREATMENT MODALITIES FOR THE PROPOSED DISEASE OR CONDITION AND WHETHER A MEDICAL MARIJUANA RECOMMENDATION COULD BE BENEFICIAL TO THE PROPOSED DISEASE OR CONDITION.

SUMMARY OF PROPOSED DISEASE OR CONDITION

[THE SUBJECT MATTER EXPERT WILL PROVIDE A BRIEF SUMMARY OF THE PROPOSED DISEASE OR CONDITION AND ITS CURRENT TREATMENT MODALITIES]

Autism Spectrum Disorder (ASD) is a condition that affects 1 of 59 children in the United States. Individuals with ASD are at an increased risk of severe behavioral episodes and require a significantly higher amount of outpatient, emergency, and hospital services despite FDA-approved antipsychotic medications for the treatment of these high-risk behavioral symptoms. These conventional treatments are associated with significant side effects and are not effective for the core symptoms of ASD. To date, there are no known treatments for the core symptoms of ASD. Severe behavioral symptoms of ASD have been reported in all ages at a prevalence of approximately 25% of diagnosed individuals.

Studies have identified unique differences in brain functioning in people with ASD versus people without ASD. Emerging evidence suggests that cannabis-derived compounds normalize certain brain functions in people with ASD. Population-based studies have reported that various types of cannabis products demonstrate improvement of symptoms of ASD; industry-sponsored randomized-controlled trials of cannabinoids have reported safety and tolerability even in young children with some risk of elevated liver enzymes under specific conditions.

Please refer to the report below for details.

CONCLUSIONS REGARDING MEDICAL MARIJUANA

The following is my expert opinion to a reasonable degree of medical certainty regarding the applicability of recommending medical marijuana for the proposed disease or condition:

It is my expert opinion to a reasonable degree of medical certainty that Medical Marijuana, as

defined by the Ohio Medical Marijuana Control Program, *has significant evidence* for safety, tolerability, and efficacy in the treatment of Autism Spectrum Disorder (ASD).

Therefore, *I recommend that Autism Spectrum Disorder be considered* as a qualifying condition for treatment with Medical Marijuana in the state of Ohio.

If applicable, here are the strains and/or dosages that may be appropriate when using medical marijuana for the proposed disease or condition:

- Current research data suggests that an oral tincture of 10:1 or 20:1 CBD:THC would be appropriate for Autism Spectrum Disorder. Tinctures in studies using a 20:1 ratio contained a concentration of 160mg CBD / 8mg THC per mL.
    - Ratios of 10:1 or 20:1 CBD:THC exhibit the best response with the least risk of tolerability or adverse events.
    - Initial dosing would therefore be 1mg/kg/day CBD: 0.05mg/kg/day THC divided between 3 doses in a single day.
        - Maximum dosing in the studies were 10mg/kg/day CBD & 0.5mg/kg/day THC divided between three doses in a single day.
    - For example, initial dosing in a 25kg child would be approximately 8mg CBD/ 0.4mg THC given three times a day.
        - Maximum dosing in this example would be 80mg CBD / 4 mg THC given three times a day.
    - At maximum dosing, patients on valproate will require regular hepatic monitoring
        - It may be more appropriate to reduce the maximum dosing of CBD to no greater than 5mg/kg/day CBD / 0.25mg/kg/day THC to avoid elevated hepatic enzymes.
- Studies utilizing a THC-only therapy identified capsules of 2.5mg twice a day up to 5mg four times a day as effective for treatment in ASD in adolescents (a range of 5mg to 20mg THC equivalents in 24 hours).
- The single case report of THC used in a 6 year old used a dose of 1.2mg of THC given three times a day. This dose would be approximately 0.2mg/kg/day of THC.

EXPERT REPORT

4731-32-05 (C)(5)   [Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition]

Impact and Scope

Autism Spectrum Disorder (ASD) is a condition that affects 1 of 59 children in the United States[1], including an estimated 43,000 children in Ohio[2]. There is no treatment for the core features or causes of Autism Spectrum Disorder (ASD). Autism Spectrum Disorders is a diagnosis that describes a specific set of functional issues due to a wide variety of known and unknown causes. Autism Spectrum disorder is a condition defined by the persistent deficits in social-emotional functioning, nonverbal communication, developing and maintaining relationships, stereotyped or repetitive movements, ritualized patterns of verbal and nonverbal behaviors, restricted interests, and inappropriate reactivity to sensory input or environmental factors[3].

Some people living with Autism Spectrum Disorder experience severe behavioral symptoms including irritability, agitation, self-injurious behaviors (SIB), or aggression episodes. Based on survey data from the Autism and Developmental Disabilities Monitoring (ADDM) Network, 28% of children with ASD exhibit SIB; 25% of adults with ASD continue to experience SIB[4, 5]. Although SIB is not included in the diagnostic criteria for ASD, ASD is one of the highest risk factors for self-injurious behaviors[4].

Currently, risperidone and aripiprazole are the only drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe behavioral symptoms associated with Autism Spectrum Disorders (ASD) [6,7,8]. Risperidone is FDA approved for irritability in ASD in children age 5-17, while aripiprazole is approved for the same indication for ages 6-17[6,7]. No other drugs are approved for the treatment of ASD despite widespread off-label prescribing practices[9].

Even with widespread use of FDA-approved and off-label prescriptions for ASD-related severe behavioral symptoms, people with ASD are twice as likely to be hospitalized for self-injurious behaviors, have a 2 day longer average length-of-stay, and have hospital costs that are 36.8% higher than those without ASD[10]. In one study from University Hospitals of Cleveland, youth with ASD were 30x more likely to utilize the emergency department. Furthermore, 13% of youth with ASD versus 2% of youth without ASD were seeking help for psychiatric or behavioral issues[12]. In another study, 22% of individuals with ASD have utilized the emergency room in the previous 12 months[13].

In the community setting, people with ASD experience more lifetime impairment in global functioning compared to those without ASD and require more educational, medical, and mental health services. Despite representing a fraction of the total population, people with ASD require a disproportionately high amount of health services to maintain their health and safety[13]. A retrospective data analysis of Medicaid expenditure data reveals that compared to

adults without ASD, adults with ASD utilize outpatient office visits 32x more, take double the prescription medications, and have emergency department costs that are 6x higher than adults without ASD. An ASD diagnosis appears to be the primary risk in increased healthcare utilization; the difference between expenditures of adults with ASD compared to those without ASD were minimally impacted by other comorbid illnesses[14].

Risks of Conventional Therapies

Risperidone and aripiprazole both atypical antipsychotic medications and are associated with risks for several adverse events including long-term neuromuscular side effects such as Extra-Pyramidal Side-effects (EPS) and Tardive Dyskinesia (TD) in individuals with ASD[15, 16,17]. 1 of 6 children with ASD are treated with atypical antipsychotics and, over time, proportions increase to nearly 1 of 4[18]. Atypical antipsychotics are implicated in directly causing or worsening diabetes, hyperlipidemia, and increasing the risk of sudden cardiac death[19, 20, 21]. Risperidone causes significant elevation in prolactin levels in children with ASD that can lead to disordered growth, sexual dysfunction, gynecomastia risk, and osteoporosis; hormone disruptions from risperidone have been documented even in preschool-aged children with ASD[22, 23, 24, 25, 26, 27].

4731-32-05 (C)(6) [Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation]

Humans create their own endocannabinoids, including anandamide, to maintain normal physiologic functioning[27]. There is evidence correlating dysfunctional human Endocannabinoid System (ECS) and Autism Spectrum Disorders. Children with ASD have been noted to have lower concentrations of anandamide[29] and ECS functioning appears to influence the core symptoms of ASD, including social behavior[30]. One brain imaging study identifies key differences in excitatory and inhibitory brain pathways and responses in those with ASD[31].

Efficacy, Safety, & Tolerability

Cannabis-based phytocannabinoids bind to human endocannabinoid receptors[32]. The most studied phytocannabinoids for ASD include Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Some studies have utilized laboratory-synthesized THC in the form of dronabinol (Marinol), which is a federally legal Schedule III drug.

One open label trial of dronabinol reports 70% of youth with ASD and treatment-resistant self-injurious behaviors experienced benefit[33]. Another small study involving youth and adults with ASD administered a mixture of CBD and THC demonstrated improvements in the core symptoms of ASD[34]. A larger retrospective study involving 60 children with ASD reported a 29% reduction in disruptive behaviors after administration of CBD and THC[35]. A large prospective study of 188 people with ASD reports that an oral dose of a cannabis-based CBD and THC extract was well-tolerated and was associated with a moderate to robust improvement in functioning in 83% of study subjects[36]. Interestingly, one neuroimaging study in subjects with ASD reports unique effects of CBD that "shifts" certain brain regions from an excitatory to inhibitory state; these effects were not noted in subjects without ASD[37]. Thus,

there is hope that the emerging pre-clinical research may help identify future treatments for core symptoms of ASD.

Two randomized placebo-controlled trials of CBD have noted that the treatment was generally well tolerated with most side effects consisting of mild to moderate somnolence, decreased appetite, or diarrhea. There was an estimated 9-19% occurrence of elevated liver enzymes with the highest doses of CBD[38, 39] in children were also taking valproate, however there was no drug-induced liver injury identified. Liver enzymes normalized once the CBD dose or valproate dose was reduced or stopped[40, 41].

Dosing

A comprehensive review of research literature identifies specific dosing ranges that may be useful for the treatment of Self-Injurious Behaviors (SIB) in Autism Spectrum Disorders (ASD)[43]. One case study reports improvement in symptoms of ASD in a 6-year-old when given a total of 3.63 mg/day dronabinol, a lab-created delta-9-tetrahydrocannabinol[42]. One study reports 70% of adolescents had reductions in SIB when they were treated with dronabinol 2.5mg twice a day up to 5mg four times a day (a range of 5mg to 20mg THC equivalents in 24 hours)[33]. A prospective study of 188 ASD patients reports that 83% of patients experienced moderate to significant improvement in agitation symptoms and 89% of patients demonstrated an improvement in "rage attacks" when given a cannabis oil containing a 20:1 ratio of CBD:THC[36]. A double-blind randomized placebo-controlled trial for the treatment of behavioral issues in 150 children with ASD with a 20:1 ratio of CBD:THC has completed data collection in October 2018 but has not yet published results. The study's protocol initiates dosing at 1mg/kg/day of CBD divided between three daily doses up to a maximum of 10mg/kg/day of CBD divided between three daily doses[44].

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SUBJECT MATTER EXPERT REPORT: DEPRESSION

PETITION OVERVIEW

MATERIALS SUBMITTED	DESCRIPTION
4731-32-05 (E)(3) *[The board shall consult with one or more experts who specialize in the disease or condition:]*	**Solomon Zaraa, DO** **szaraa@compassionatecleveland.com** **Compassionate Cleveland** **23250 Chagrin Blvd; Suite 310** **Beachwood, OH, 44122** **(216) 586-2606**
4731-32-05 (C)(1)	Original petition *"0105 - Rosenberger – Depression (trade secret).pdf"* submitted on 12/31/2018 by Thomas Rosenberger Rosenberger@nciaohio.org
4731-32-05 (C)(2)	**"Depression"**
4731-32-05 (C)(3) *[Information from experts who specialize in the study of the disease or condition:]*	Refer to: **Expert Summary** (below) **Expert Conclusion** (below) **Expert Report** (below)
4731-32-05 (C)(4) *[Relevant medical or scientific evidence pertaining to the disease or condition:]*	Refer to: **Expert Report** (below) **References** (below)
4731-32-05 (C)(5) *[Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition:]*	Refer to: **Expert Report** (below) Also to original petition submitted 12/31/2018: *"0105 - Rosenberger – Depression (trade secret).pdf"*
4731-32-05 (C)(6) *[Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation:]*	Refer to: **References** (below)
4731-32-05 (C)(7) *[Letters of support provided by physicians with knowledge of the disease or condition. This may include a letter provided by the*	Refer to: *"0105 - Rosenberger – Depression (trade secret).pdf"*

physician treating the petitioner, if applicable]

APPLICABLE STATUTES & RULES

PURSUANT TO OAC 4731-32-05, THE SUBJECT MATTER EXPERT SHALL REVIEW THE ABOVE-REFERENCED MATERIALS AND ISSUE A WRITTEN OPINION REGARDING THE CURRENT TREATMENT MODALITIES FOR THE PROPOSED DISEASE OR CONDITION AND WHETHER A MEDICAL MARIJUANA RECOMMENDATION COULD BE BENEFICIAL TO THE PROPOSED DISEASE OR CONDITION.

SUMMARY OF PROPOSED DISEASE OR CONDITION

[THE SUBJECT MATTER EXPERT WILL PROVIDE A BRIEF SUMMARY OF THE PROPOSED DISEASE OR CONDITION AND ITS CURRENT TREATMENT MODALITIES]

Major depressive disorder (MDD) is a condition present in 7.1% of all adults and is defined by 8 symptoms that can impact functioning and safety. Current initial treatments for MDD include either medication management or talk therapy/counseling. If those treatments fail, patients are treated with a combination of both medication and therapy. However, 10-30% of people experiencing major depression have treatment-refractory symptoms. Treatments for severe treatment-refractory MDD include esketamine or electroconvulsive therapy (ECT), however 30-50% of patients utilizing these modalities do not experience benefit.

CONCLUSIONS REGARDING MEDICAL MARIJUANA

The following is my expert opinion to a reasonable degree of medical certainty regarding the applicability of recommending medical marijuana for the proposed disease or condition:

It is my expert opinion to a reasonable degree of medical certainty that Medical Marijuana, as defined by the Ohio Medical Marijuana Control Program, does _not_ have sufficient evidence for efficacy in the treatment of Depression.

At this time, I _cannot recommend_ that *Depression* should be a qualifying condition for treatment with medical marijuana in the state of Ohio.

If applicable, here are the strains and/or dosages that may be appropriate when using medical marijuana for the proposed disease or condition:

N/A

EXPERT REPORT

4731-32-05 (C)(5) [Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition]

Major Depressive Disorder (MDD) is comprised of 8 symptoms including depressed mood, diminished interest or pleasure, weight or appetite change, sleep disturbances, feelings of restlessness or sluggishness, fatigue or energy loss, feelings of guilt or worthlessness, decreased concentration, and suicidal thoughts and behaviors[1].

According 2017 National Survey on Drug Use and Heath data provided by the National Institute of Mental Health (NIMH), an estimated 7.1% of all adults experience Major Depressive Episode symptoms[2, 3]. Current treatment strategies for depression include either medication or talk therapy, with a combination of both modalities if depression symptoms are severe or if patients do not respond to a single modality. Patients who do not respond to several medication and therapy treatment attempts are experiencing treatment-resistant depression. Electro-convulsive therapy[4] (ECT) or esketamine[31, 32] are FDA-approved for treatment-resistant depression.

Efficacy of Conventional Therapies

Approximately 10-30% of people with depression do not respond to any conventional medical therapies[5, 6, 31, 32]. Therefore, we can estimate that approximately 820,000 Ohioans are currently experiencing depression with 82,000-240,000 Ohioans suffering from treatment-resistant symptoms[7]. Suicide is the second leading cause of death in Americans ages 10-34 and the fourth leading cause of death in those ages 35-54[8]. In 2017, an estimated 1,706 Ohioans died from suicide[35].

Risks of Conventional Therapies

Antidepressants are considered generally safe. However, according to the FDA, antidepressants are required to include a black box warning for increased suicide risk in children, adolescents, and young adults. According to the pooled event data from 24 short-term studies, antidepressants double the risk of suicidal thinking and behavior in children, adolescents, and young adults with major depressive disorder (MDD)[33, 34]. Risks of Electroconvulsive therapy include short-term memory loss and learning difficulty.

4731-32-05 (C)(6) [Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation]

Preclinical data identifies cannabinoid activity in parts of the brain associated with depression; cannabinoid administration results in improvement in mood functioning in human and animal models[9, 10, 11, 12, 13.]

Efficacy, Safety, & Tolerability

Several large surveys have identified improvement in depressed mood[17, 18, 19.] A 2017 systematic review identifies 7 clinical studies that report mood improvement during therapeutic cannabis use. These results are consistent across different patients groups including those with pain, HIV, multiple sclerosis, and wide ranges of other diagnoses[14, 20]. There is a randomized placebo-controlled trial of patients with chronic neuropathic pain who demonstrated statistically significant improvements in depression when treated with high dose THC[15]. A review of the highest quality studies of cannabis reports benefits for depression symptoms in patients with other severe medical conditions; many of these conditions are already qualifying diagnoses for the Ohio Medical Marijuana Control Program[16]. However, most of the studies referenced in the review do not use validated scales for depression nor screeners for suicide[25, 26, 27]. One study from the review utilized a validated scale for mental health screening but benefits were not statistically significant[28]. A randomized placebo-controlled study reported that children ages 12-17 with depression and cannabis use disorder identified no worsening of depression or suicide symptoms when treated with an antidepressant, despite ongoing cannabis use[29]. Adolescents and young adults with active cannabis use disorders did not demonstrate worsening depression symptoms after a year of treatment with a combination of Prozac (fluoxetine) and Cognitive Behavioral Therapy[30]. However, in both of latter studies, no benefit was noted from use of cannabis. At this time, there does not appear to be any high quality studies demonstrating efficacy of cannabis for the treatment of Major Depressive Disorder.

Most cannabis research focuses on recreational or non-medical use. Recreational or non-medical use of cannabis is correlated with increased risk of depression[14] with heavy users demonstrating even higher risk for depressive disorders[21]. One retrospective study of nearly 14,000 twins found that depression and suicide risk was identified in cannabis users at nearly double the rate as their non-using twin[22]. In adolescents, there is a similarly reported correlation between risk for suicide attempts and cannabis[23]. However, a nation-wide analysis of 465,000 hospitalizations of recreational cannabis users reports that 3.6% of psychiatric hospital admissions were due to suicide[24]; these results appear to suggest similar prevalence of severe suicide symptoms compared to non-cannabis users[3].

Discussion

One plausible explanation for the seemingly contradictory information is people with a primary depressive disorder may use cannabis for improvement in mood with varying levels of benefit, however the data suggest that cannabis does not appear to be effective at reducing hospitalization secondary to severe symptoms of depression such as suicidality. This would potentially occur if cannabis were simply correlated with depression risk factors rather than a causal relationship and would be consistent with the results from short-term randomized placebo-controlled trials as well as long-term follow-up studies of patients utilizing typical depression treatments while using cannabis[29, 30]. Nevertheless, there is no data regarding

cannabis's utility in achieving major goals of depression treatment: the reduction of suicide attempts and suicidal thoughts.

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Review of proposal to approve the use medical marijuana to treat the symptoms of insomnia.
Submitted by Dr. Gary L. Wenk

Professor, Psychology & Neuroscience
Director, Neuroscience Programs
The Ohio State University

Definition of the Disease State

insomnia is difficulty falling asleep or staying asleep. People with insomnia can feel dissatisfied with their sleep and usually experience fatigue, low energy, difficulty concentrating, mood disturbances, and decreased performance in work or at school. Insomnia may be characterized based on its duration. Acute insomnia is brief and often happens because of life circumstances. It tends to resolve without any treatment. Chronic insomnia is disrupted sleep that occurs at least three nights per week and lasts at least three months. Chronic insomnia can be due to changes in the sleep environment, unhealthy sleep habits, shift work, other clinical disorders, and certain medications. Chronic insomnia can be comorbid, meaning it is linked to another medical or psychiatric issue. Insomnia has high prevalence rates and is associated with significant personal and socioeconomic burden.

Status of current therapies for treating insomnia:

- Current treatment options do not help all patients, do not produce normal sleep patterns (reduced NREM) and do not produce restful sleep.
- Current treatments show tolerance with repeated use that requires higher dosing or drug holidays.
- Current treatments have significant withdrawal symptoms, including insomnia.
- Current treatments are often addicting.

Review of evidence provided in the proposal:

1) The major finding of this work is that direct activation of CB1 receptors increased the total time spent in NREM sleep. Thus, CB1 activation induces abnormal sleep patterns with an overall reduction in REM sleep.
2) The conclusion from this single case study is that CBD oil can reduce insomnia due to anxiety secondary to PTSD. In my opinion, the results from a study of the response of one person are completely unreliable.
3) The principle data in support of medical marijuana is presented in a publication by Vigil et al (2018) in the journal <u>Medicines</u> that is published by MDPI. MDPI is regarded as a predatory publisher that publishes everything that is submitted, for a fee, without regard to quality. Due to the limitations associated with conducting a clinical trial with a scheduled compound the authors used self-collected data and user experiences recorded with the ReleafAppTM. Unfortunately, this subjective approach offers highly variable data that may not be statistically valid, reliable or consistent across subjects. In addition, the study had many significant fatal

design flaws. There was no control group and the authors did not control for the use of other medications or existing psychological or medical problems that might contribute to the outcome. I have additional concerns about the potential confound of user-selection bias and exclusion of users that failed to complete sessions or even use the Releaf App™ due to a lack of symptom relief or negative side effects. The authors have no way of knowing which subjects dropped out of the study and why this decision was made. Three of the authors work for the company that sells the testing device raising a significant concern about conflict of interest.

4) The 2007 publication by Russo et al., conducted by GW Pharmaceuticals, the manufacturer of the THC and CBD products, examined the effects THC and/or CBD on sleep in the context of medical treatment for neuropathic pain and symptoms of multiple sclerosis. They report marked improvement in subjective sleep parameters provided by the patients with a wide variety of pain conditions including multiple sclerosis, peripheral neuropathic pain, intractable cancer pain and rheumatoid arthritis. Chronic pain, neurological illness, and sleep disorders are clearly comorbid conditions with insomnia. The reliability of the principle independent variable in this study, i.e. subjective feedback, is poor in my opinion.

5) Murillo-Rodrıguez et al (2006) found that CBD administered to rats during the lights-on period increased wakefulness and decreased REM (dream) sleep. CBD administered to young adults increased wakefulness during sleeping time. These results strongly argue against the use of CBD for the treatment of insomnia.

6) The publication by Pava et al., (2016) in the journal Plos One support the hypothesis that endocannabinoid signaling through CB1 suppresses REM. The data do not support a role for eCB signaling in sleep homeostasis. Sleep homeostasis is an internal neural system that operates as a kind of timer or counter, generating a pressure to sleep and regulating sleep intensity. The regular suppression of REM sleep may result in significant cognitive deficits during the daytime.

7) The study by Webb and Webb (2014), published in an incredibly obscure journal with virtually no impact factor (meaning that no one reads this journal, so why publish here unless the data are unreliable), reported that cannabis (with no distinction between THC and CBD) appears to alleviate pain, reduce the associated anxiety and reduce the symptoms of insomnia. The authors did not dissociate the effects of marijuana on pain and anxiety from its potential benefits for insomnia without these comorbid symptoms.

8) Reinarman et al (2011) relied upon self-reports from people who chose to contact one of the reporting clinics; thus, the study was flawed by a significant self-selection bias. Most of the patients were white males.

9) Shannon & Opila-Lehman (2016) published a study in another incredibly obscure journal with virtually no impact factor (again, I have significant concerns about the reliability of their data) about a single patient who suffered trauma and suffered with primary anxiety with associated insomnia. I find these single case studies inadequate and untrustworthy. CBD oil resulted in a maintained decrease in anxiety and a steady improvement in the quality and quantity of the patient's sleep.

Relevant evidence not provided in the proposal:

1) Sleep continuity, architecture and quality among treatment-seeking cannabis users: an in-home, unattended polysomnographic study. By: Pacek, Lauren R.; Herrmann, Evan S.; Smith, Michael

T.; et al. EXPERIMENTAL AND CLINICAL PSYCHOPHARMACOLOGY Volume: 25 Pages: 295-302, 2017

Conclusion: **The large majority of participants exhibited disordered, i.e. abnormal, sleep patterns in response to marijuana use.**

2) Marijuana use patterns and sleep among community-based young adults. By: Conroy, Deirdre A.; Kurth, Megan E.; Strong, David R.; et al. JOURNAL OF ADDICTIVE DISEASES Volume: 35 Pages: 135-143, 2016.

Conclusion: **When the results were adjusted for presence of depression and anxiety, there was no difference between insomnia severity scores for marijuana users and controls. Daily marijuana users reported significantly more sleep disturbances than did non-daily users.**

3) Cannabis withdrawal and sleep: A systematic review of (36) human studies. By: Gates, Peter; Albertella, Lucy; Copeland, Jan. SUBSTANCE ABUSE   Volume: 37   Pages: 255-269, 2016

Conclusions: **Sleep problems, mostly frequent night-time awakenings, during withdrawal from cannabis use common.**

4) Dose-dependent cannabis use, depressive symptoms, and FAAH genotype predict sleep quality in emerging adults: a pilot study. By: Maple, Kristin E.; McDaniel, Kymberly A.; Shollenbarger, Skyler G.; et al. AMERICAN JOURNAL OF DRUG AND ALCOHOL ABUSE   Volume: 42   Pages: 431-440, 2016

Conclusions: **Cannabis use was dose-dependently associated with poorer sleep quality. Depressed patients who used cannabis had significantly more sleep impairments.**

5) Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. By: Hsiao, Yi-Tse; Yi, Pei-Lu; Li, Chia-Ling; et al. NEUROPHARMACOLOGY Volume: 62 Pages: 373-384, 2012

Conclusions: **Cannabidiol (CBD), a constituent of marijuana, disrupted sleep patterns by reducing both NREM (slow wave) sleep and REM (dream) sleep in normal healthy rats.**

6) Sleep disturbance in heavy marijuana users. By: Bolla, Karen I.; Lesage, Suzanne R.; Gamaldo, Charlene E.; et al. SLEEP   Volume: 31 Pages: 901-908, 2008

Conclusions: **Discontinuation of heavy marijuana use was associated with poor sleep quality**.

7) Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. J PAIN SYMPTOM MANAGE. Volume 39, pages 167-79, 2010.

Conclusion: **No effect on sleep quality and "insomnia" severity**

8) The effects of cannabinoid administration on sleep: a systematic review of human studies. Peter J. Gates, Lucy Albertella, Jan Copeland, SLEEP MEDICINE REVIEWS Volume 18, pages 477-487, 2014

Cannabis is not beneficial for insomnia except among medicinal cannabis users who are identified by the presence of pre-existing sleep interrupting symptoms such as pain. As such, cannabis may be thought to improve sleep via the mediating improvement of pain symptoms.

9) Cannabis use and the development of tolerance: a systematic review of human evidence. By: Colizzi, Marco; Bhattacharyya, Sagnik, NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS Volume: 93 Pages: 1-25, 2018

Conclusions**: Repeated cannabinoid administration consistently produces tolerance. Cognitive function shows the highest degree of tolerance, with some evidence of full tolerance. The acute intoxicating, psychotomimetic, and cardiac effects also show significant tolerance with regular exposure.**

Conclusions drawn from available human and animal publications regarding the efficacy of medical marijuana for the treatment of insomnia:

•   Medical marijuana is as safe as the standard OTC and prescription medications currently available. However, medical marijuana shares many of the same problems associated with standard OTC and prescription medications currently available.

•   The endogenous cannabinoid neurotransmitter system is not directly involved in the onset or maintenance of normal sleep cycles. Therefore, marijuana cannot, and does not, produce normal sleep patterns. Marijuana increases stage 4 (NREM slow wave sleep) and decreases REM (dream) sleep. REM sleep loss is associated with increased inflammatory responses, increased risk for obesity, and significant memory problems.

•   Marijuana reduces the symptoms of insomnia primarily via its ability to reduce anxiety and somatic pain, the two most common causes of insomnia.

•   Regular repeated use of marijuana produces tolerance that requires higher dosing and drug holidays.

•   Withdrawal from marijuana use, such as during drug holidays to reduce tolerance, is associated with poor sleep quality and insomnia.

Final Recommendations:

Currently available evidence shows that medical marijuana is not superior to currently available medications.

Overall, the use of marijuana for the treatment of insomnia is associated with side-effects that are similar to those associated with standard insomnia therapies.

If approved, medical marijuana could be recommended for the treatment of insomnia that is due to pain or anxiety.

Most importantly, the use of medical marijuana for insomnia should be limited to only occasional use in order to avoid the development of tolerance, rebound insomnia and the negative consequences of long-term REM sleep suppression upon daytime cognitive functioning.

CBD is not an effective treatment for insomnia.

The Opioid Crisis
Opioid Use Disorder (OUD) and Cannabis As Part of a Treatment Option

By: David Bearman, M.D.

Introduction

The question is whether or not to add the treatment of opioid use disorder (OUD) to the list of medical conditions for when medical cannabis can be recommended by the physicians of Ohio. The answer is a resounding yes.

History

Cannabis has been a medicine and been used as an analgesic for over 4,000 years. It appears in every major materia medica ever written. Numerous animal studies verify cannabis's analgesic properties and human use with such products as Nabixamols (tincture of cannabis) and many similar cannabis products available in dispensaries have demonstrated good results in treating pain. There are over twenty countries where based on double blind studies Nabixamol's (tincture of cannabis) is legal to use in treating neuropathic pain. As long ago as 2010 a phase III Nabixamols study preformed in upstate New York revealed the benefit of using Nabixamols in treating intractable pain.

Given the staggering U.S. statistics regarding opioid use disorder (OUD) and the related social disruption and mortality, there exists a clean need for us to do more to address this vexing problem. This proposal to employ cannabis to help mitigate the impact of OUD offers an opportunity for Ohio to contribute to the possible effective treatment solutions for OUD.

Cannabis has been used for years by patients both as an illicit and as a licit substance to routinely, safely and successfully reduce, if not eliminate, opioid use. Furthermore, those clinicians who work directly with patients and utilize cannabis as a therapeutic agent have seen first-hand that cannabis is an excellent choice to address OUD. This decreased use of opioids by adding cannabis to the treatment regimen is documented in multiple articles published in numerous peer reviewed professional journals.

The safety of cannabis has been affirmed throughout history. This includes not only by thousands of years of experience, but also by the 1937 testimony of the AMA's Chief Legal Counsel William C. Woodward, M.D. who testified that "The AMA knows of no known dangers of the use of cannabis. It is affirmed by"The DEA's Chief ALJ in his 1988 Finding of Fact (after a two year rescheduling hearing) where he found that cannabis was "one of the safest therapeutic agents known to man," The Nixon Marijuana Commission recommended legalizing cannabis for recreational purposes. This was in part because the Commission found that Cannabis was not addictive.

In 1999 the Institute of Medicine reported that cannabis had analgesia value and that its side effects were in the range at most prescribed medications then on the market. This is

consistent with the side effect of Marinol (synthetic THC) being a Schedule III drug. Actually in my experience the side effects of cannabis are less than with Marinol.

Some medical conditions have contributed to the opioid problem. They include not only dealing with pain, but also PTSD – untreated or under-treated, ADD – untreated, unidentified, Autism Spectrum Disorder – untreated or under-treated.

A.   Risk Factors for Substance Abuse
The factors for substance misuse and abuse are many and complex.

The Dysfunctional Family
 They include such family factors as growing up in a dysfunctional family, chaotic home environment, parental dysfunction, ineffective parenting, little attachment and nurturing by parents, history of substance abuse in the family, history of mental illness in the family, being ignored or devalued by parents, being in an abusive environment, such as physical abuse, sexual abuse, and/or emotional abuse.

Here is a fairly typical quote from a child abuse survivor: "Abuse hurts us a lot. Many of us who suffer from child abuse develop depression, isolationism and suicidal thoughts and low self-esteem as a result." This survivor went on to say that once in a while he/she suffers from bouts of depression and suicidal thoughts.

Resent Factors
Then there are the personal factors. Low academic aspirations, poor social coping skills, low self-esteem, poor decision making skills, feeling unloved, ignored. Then we have feelings of hopelessness and helplessness that can be compounded by low imploded opportunities.

While cannabis is a very useful component in our OUD treatment program it is not the whole story. This is because the causes for opiate abuse include but are not limited to low self-esteem, lack of coping skills, lack of job skills, lack of parenting skills, having a poor job and/or job prospects, hopelessness, growing up in a dysfunctional family, and from having ADD or PTSD. A problem using cannabis that appropriately address, these issues give increased hope for progress to be made the success or failure.

If Not Now, When? If Not Us, Who?
We know that our criminal justice approach to regulating recreational drugs such as alcohol, cannabis, heroin, or other substances, has been tried for decades, and found wanting. A Rasmussen poll a few years ago revealed that just 3% of Americans think that the U.S. is "winning" the war on drugs, while 84% did not. The evidence of that is confounded by the fact that in 2016 there were 50,000 opiate overdose deaths.

 Nevertheless these failed policies have resulted in the bulk of public funding being invested in law enforcement while paying little attention to treatment. Here is an opportunity for Ohio to rectify that. A strong case can be made that prohibition policies

for alcohol, cannabis and opioids have made matters worse with both intended and unintended negative consequences. These policies have demonstrated that jail is not the most effective place for intervention or treatment of substance abuse. We need a new paradigm.

It has been clear for decades that the U.S. needs a new more pragmatic drug policy paradigm. Some changes have been occurring in public perception, for instance, a headline in the December 7, 2012 *U.S.A. Today* blared, "Public to Feds: Back Off State Pot Laws." As far back as July 27, 2014 the need for a new paradigm became so apparent that the *New York Times* ran an editorial calling for federal legalization of marijuana.

We need to reframe our approach to opioid abuse with a new paradigm. This ought to be one that recognizes harm reduction principles. The use of cannabis should be one part of the "New Paradigm". Many cannabinoid medicine specialists have already recognized cannabis as an exit drug. It has a record of being efficacious with a wide variety of substances including not only opiates but also alcohol and cocaine.

The use of cannabis either alone or as part of a multi modularly approach, is already being contemplated (and in some locals implemented) as part of the start of a more comprehensive holistic approach to the issue of combating substance abuse. Future comprehensive approaches might include providing adequate funding for early intervention and treatment. Clearly we should have a robust approach to address what former President Barack Obama dubbed "the battle against drug cartels that are robbing so many of a future".

We know from studies by Bradford and Bradford (cited by Dr. Leeds) that adding cannabis availability in a state leads to hundreds of millions of dollars in Medicaid and Medicare savings The Bradford's found that legal medical cannabis in a state was associated with a reduction in the number of prescriptions paid for by Medicare and Medicaid. A close look at the data, reveals that opioid analgesics are among the drug classes that are most affected by this prescription decline.

Dr. Liccardo Pacula said, "Clearly I think clinical trials, as this, would be the gold standard, where you can have randomization of chronic pain patients who take a version of a cannabis product and see what happens to their use and/or need for other opioids versus patients who are given a placebo product that looks like a cannabis product".

Drug abuse treatment and prevention professionals see early intervention measures as a better, more effective way of addressing substance abuse problems than the present heavy emphasis on criminal justice strategies that address substance abuse latter in its natural history. Cannabis can be useful early on as an analgesic and also for intervention subsequently if a person develops OUD to reduce craving and opiate use and abuse.

The issue is being reframed from sin, the devil and crime to what's best for the economy, best for the taxpayer, best for the at-risk population, best for the American family and best for health, medicine and research and best for America.

This change in cultural attitude is being fueled by the recognition that the current failed U.S. drug policies just don't work. Not only that, but as we learn more about cannabis, cannabinoids, and the endocannabinoid system (ECS) cannabis is emerging as a valuable tool to combating substance abuse in general and opiate abuse in particular in a comprehensive treatment approach,

The drug war has not only been an abject failure, but at the same time the "War on Drugs" has created extensive collateral damage. This damage includes, but is not limited to providing funding for gangs and terrorists, the death of tens of thousands of innocents in Central America, the fraying of the Constitution, waste and misuse of our tax dollars and destroying the integrity of many American families. It is well past time to move on.

The Specific Opiate Use Disorder Condition
There is no agreement that the condition of opioid use disorder exists. It not only exists but it needs to be intelligently addressed. As many experts, including the Director of NIDA, Dr. Nora Volkow, have noted, cannabis should play a central role in treating pain. According to Dr. Mark Wire at the 2016 American Society of Addiction Medicine her first bullet point was that cannabis should be the first choice for analgesic.

The use of cannabis in combating opioid use disorder can be maximized by including it in a comprehensive multi-modality approach and having a program that also addresses the underlying causes of opiate use disorder – poor parenting, PTSD, pain, hopelessness and helplessness. While cannabis is but one component of any successful approach to opiate use disorder, it is the tent post that provides a space for a comprehensive approach to be successful.

The material attached to Dr. Leeds proposal provides a good overview of the extensive literature on the problem of OUD. As noted above there is no question that this is not only a real condition but it is one that is quite prevalent in areas of declining employment such as locations where the coal industry, the auto industry, the steel industry, the fishing industry and the forestry industry once flourished.. This is why this problem is prominent in Ohio, Michigan, Pennsylvania, Kentucky, West Virginia, Tennessee, Vermont, New Hampshire and Maine.

What About Other Treatment Modalities
This is not really an either/or issue. A wide variety of approaches to the issue of opiate some of had considered seeing others not so much with rescheduling and lack of sufficient abuse have been tried. The other treatment modulate include heroin maintenance clinics in the early 1920s, the prison farms in Lexington, Kentucky and Fort Worth in the 30s and 40s, Methadone Treatment states we will benefit from one more tool in our tool kit. Maintenance beginning in 1963, Buprenorphine (Suboxone) started about 30 years ago. There have been multimodality residential programs such as

Delancey Street in San Francisco and numerous for-profit programs in places like Malibu and Palm Springs. Since 1970s, these programs have met with mixed success and governmental acceptance. They are however lengthy and costly and relapse dates occur.

Education
We need to recognize that at least some folks are educatable. No doubt the most effective drug law ever passed was the Pure Food and Drug Act of 1906. It required that all major ingredients of patent medicine be placed on the bottle. In less than two years the sale of patent medicines, many of which contained opium, fell by 50%. Education can be a useful component of a multi modality approach.

Heroin Maintenance
Many of the heroin maintenance clinics were quite successful, however the one in New York was notably poorly run and unsuccessful. In 1924 federal law shuttered these facilities. Opiate maintenance has been used for many years with some success in Switzerland and other countries in the world. In the U.S. it has run into heavy political Opposition.

Lexington and Fort Worth Hospital's
The drug treatment facilities in Lexington and Fort Worth were visionary for their time and well-intended. Unfortunately as report by Edward Brecker, in Licit and Illicit Drugs, they had a proven failure rate of 92%, when failure was measured by relapse, which was probably not the best measure to use.

Methadone Maintenance
Methadone Maintenance started out with an impressive success rate measured by participates remaining in the program (85%) and then either returning to work or going to or staying in school. As time has gone on the programs have decreased being primary government run and have become very commercialized. While they continue to be helpful, the program has drawbacks, including not dropping from the program those who violate program standards and are continued opiate abusers. This program also offers an opportunity to interact with others who continue to be drug abusers despite being enrolled in the program.

Buprenorphine and Naltrexone
Buprenotphine, has been useful for some opiate abusers. It does not require daily attendance to get the medication and has less stigma attached to it than methadone

Naltexone has had some reported success, but it is not widely available.

Room For More Options
With the high recidivism rate seen in many treatment modalities and the current magnitude of the problem of opiate abuse disorders, it is clear that the field would benefit form new treatment options. So that said, there is a role for programs using cannabis as a harm reduction substitute.

The research and epidemiology studies that have been done regarding cannabis use as an analgesic are numerous. Epidemiological reports such as the 2014 JAMA article demonstrates a dramatic decrease in opiate OD deaths in medicinal cannabis states, compared to states where cannabis remains illegal, provides dramatic evidence that adding the availability of cannabis to the treatment options for OUD it is a worthwhile experiment.

Letters of Support
  These letters of support speak for themselves. Given the context of our historical experience there is every reason to consider these letters credible and recognize the support in the medical community for the use of cannabis as an analgesic as well as a harm reduction substitute.

It is important to note that the reason for the effectiveness of cannabis is because of the endocannabinoid system. There is a cannabinoid medicated pain center in the brain. This is the largest neurotransmitter system in the human brain. It modulates the speed of neurotransmission and is central to homeostasis. So phytocannabinoids not only slow the speed of pain stimuli but they stimulate the endocannabinoid mediated pain center. In addition to addressing pain the cannabinoids are useful in treating anxiety and depression, two triggers of substance abuse. Further cannabis is useful as a sleep aid. This too can be of assistance in treating OUD. The proposition laid out in the request that "cannabis is opioid sparing, can mitigate symptoms and reduces relapse" is well documented by research.

Efficacy of Existing Therapies /Relapse
Opioid withdrawal, this is usually effective for those pain patients who do not progress to the OUD. It can be aided by appropriate medical treatment with a variety of medications including muscle relaxants and tapering the opiate dose preferably by the original prescribing physician.

Relapse can occur with buponorphine, methadone as maintenance and Naltrexone. Relapse is a hallmark of substance abuse; substance abuse is a chronic relapsing condition. Dole and Nyswanger recognized this feature and that is why they saw Methadone as a lifetime treatment, much like insulin for diabetes.

 Cannabis has been shown to be an aid in combating relapse and craving.. Cannabis can be used on a regular basis without adverse consequences to the patient. According to DEA ALJ Francis Young in his 1988 Finding of Fact, after a two year rescheduling hearing for cannabis, where he recommended down-scheduling to schedule II he found that cannabis was "one of the safest therapeutic agents known to man."

CONCLUSION
Pain is a challenging condition to treat. There is today a concerted effort to address pain with traditional prescription medication, as well as other modalities such as electro-stimulation, chiropractic, massage, acupuncture, magnets, improved mattresses, better shock-absorbing shoes,. The use of harm reduction substitutes such as cannabis is but

one of those options.. The case of cannabis for   the purpose of being a harm reduction substance is strong. This is because of the role of the ECS.

Dr. Russo, a neurologist who practiced in Missoula, Montana for over 20 years, is past president for the ICRS and has written extensively on cannabis and cannabinoids. Dr. Russo's. Power Point presentation is thorough and compelling. His slide show vividly demonstrates that cannabis has been effectively used as an analgesic for over 4,000 years. It is a very quick useful overview of the utility of cannabis for treating pain and as a harm reduction substitute.

The state of Ohio would be well served to approve Fr. Leeds proposal and add Opiate Use Disorder (OUD) to the list of conditions for which cannabis may be used to treat.

 Sincerely
David Bearman, M.D.

April 26	Review of _____	1.0 hr.
April 27	Additional review	1.0 hr.
April 28	Draft report	1.5 hr.
April 29	Draft report	1.0 hr.
April 30	Draft report	2.0 hr.
May 1	Draft report	1.0 hr.
May 2	Draft report	1.0 hr.
May 4	Draft report	1.5 hr.
May 5	Draft report	1.5 hr.
May 6	Edit report	<u>2.5 hr.</u>

14.0 hr. @ $200 = $2800

• An Abridged History of opiates in the United States

We have had opiate in the history of the U.S. for over one hundred and seventy-five years. In 1828 Charles Russell and Company started transporting opium from India to China in conjunction with the British East India Company, a lynch pin in British opioid trade, Eliahu Yale had made _____ worked for the British Company. Yale used some of his wealth from the opium trade to start the University that bears his name.

There have been intermittent attempts to deal with the opiate medically. Some have such as suboxone, methadone, have shown benefit others have not been so successful like the opium treatment facilities in Lexington and Ft. Worth. But these were part of our criminal justice approach. To date, history has shown us that approaching substance abuse from a criminal justice perspective has not been that effective. Further focusing on the drugs rather than the motivation of the person using the drug is another ingredient in this recipe for failure.

At least since 1873 when smoking opium but not the opium used for patent medicine (e.g., Lydia Pinkham's Vegetable Compound for the treatment of women's unmentionable ills) was made illegal in San Francisco. As the past one hundred and thirty-five years have proven this has not been particularly effective.

It is generally conceded by drug policy historians that the most effective federal law ever passed on regulating psychoactive drugs was the Pure Food and Drug Act of 1906. This law prohibited nothing. It _____ that patent medicine ingredients be placed on the table. Within less than five years after passage the sale of patent medicine had dramatically decreased. Many of these nostrums contained alcohol, opium and cocaine. It prohibited nothing. It relied on the concept that if people better understood what was in the nostrums they could cease using it if they knew it was dangerous.

Multi Modality Approach

We propose a multi-disciplinary, holistic approach to treatment of this generation's opioid substance abuser. It may have the possible fringe benefit of decreasing the intergenerational aspect of their condition. This is a proposal to study whether a robust multi modality interdisciplinary approach to addressing the opioid crisis will provide evidence that works can be effective. The program will make an effort to address some of the underlying causes of the opiate epidemic.

Our proposed opioid intervention treatment program is aware of and will address some of the causes that have led to this epidemic. To reiterate some causes for opiate abuse include but are not limited to low self-esteem, lack of coping skills, lack of job skills, lack of parenting skills, having a poor job and/or job prospects, hopelessness, growing up in a dysfunctional family, and from having ADD or PTSD. Unless these issues are appropriately addressed, there is little hope for progress to be made. Our program will

make every effort to address the undeniable causes as opposed to only treating the symptoms. We proposed a study that will collect data to measure its success or failure.

This Treatment Program is Based on Common Sense

Strangely enough everyone viscerally knows the answer to preventing substance abuse: knowledge (self, science and spirituality), common sense, good parenting, good jobs, love, and genuine family values. Unfortunately the solution is not very exotic so it is all too common to give little more than lip service in support of measures that support effective prevention and intervention efforts. We propose exposing patients to treatment modalities that give them the skills to better cope with their substance abuse issues.

Here is what Milton Friedman, Nobel Prize-winning, conservative economist (1912-2006) had to say in his assessment of prohibition policy. "There is no light at the end of the tunnel. How many of our citizens do we want to turn into criminals before we yell, 'Enough!'?"

The demonizing, racist, punitive, criminal-justice system approach has been a failure. It is not only a costly failure; it encourages the dark side of the American psyche. America would be better off by far if government policies were based on the most positive aspects of American values and heritage – those of enlightenment, knowledge, family, community, understanding and forgiveness.

This proposal has a full spectrum approach that is based on harm reduction principles. It includes skill building, decision making, counseling, medical and psychological

treatment, building self-esteem, and use of cannabis as an exit drug. We propose using on physical medicine, psychology, career counseling, resume writing, spirituality, physical therapy and cannabis.

The care of human life and happiness, and not their destruction, is the first and only object of good government.

—Thomas Jefferson

U.S. President, 1801-09 and writer of the Declaration of Independence

DAVE: THIS PAGE WAS WAY TOO HARD TO DECIPHER.

YOU WILL NEED TO REDO (NEATLY, PLEASE) SO I CAN UNDERSTAND.

Here are some of what we de_____

Planning Committee:

Steve Hosea, MD

If Not Now, When? If Not Us, Who?

We know that our prohibition heavy approach to regulating recreational drugs alcohol, cannabis, heroin, or other substances, has been tried in spades, and found wanting. A Rasmussen poll a few years ago revealed that just 3% of Americans think that the U.S. is "winning" the war on drugs, while 84% did not. Evidence of that is that in 2016 there were 50,000 opiate overdose deaths. Nevertheless these failed policies have resulted in the bulk of public funding to go to law enforcement while paying little attention to

funding effective treatment, prevention and early intervention programs. A strong case can be made that prohibition policies made matters worse with both intended and unintended negative consequences and that jail is not the most effective place for really useful intervention or treatment of substance abuse.

It has been clear for decades that the U.S. needs a new more pragmatic drug policy paradigm and some changes have been occurring. For instance, a 2012 *U.S.A. Today* headline from December 7 blared, "Public to Feds: Back Off State Pot Laws." On July 27, 2014 the need for a new paradigm became so apparent that the *New York Times* ran an editorial calling for federal legalization of marijuana.

We need to not only reframe our approach to opioid abuse with a new paradigm that recognizes harm reduction principles and utilizes cannabis as the exit drug it is. We need a better approach to dealing with substances of potential abuse. This new paradigm includes adequate funding for providing early intervention and treatment to address what former President Barack Obama dubbed "the battle against drug cartels that are robbing so many of a future." The issue is being reframed from sin, the devil and crime to what's best for the economy, best for the taxpayer, best for the at-risk population, best for the American family and best for health, medicine and research and best for America.

We know from studies by Bradford and Bradford that adding cannabis availability provides hundreds of millions of dollars in Medicaid and Medicare savings.

The authors found that medical cannabis laws may be associated with a reduction in the number of prescriptions filled by Medicare and Medicaid. If you look more closely at the data, you see that t here are suggestions that opioid analgesics are among the drug classes that are most affected by this decline.

Dr. Liccardo Pacula said, "Clearly I think clinical trials, as this would be the gold standard, where you can have randomization of chronic pain patients who take a version of a cannabis product and see what happens to their use and/or need for other opioids versus patients who are given a placebo product that looks like a cannabis product."

Opinion shapers are moving toward a more enthusiastic embrace of a strategy that places an increasing emphasis on early intervention and treatment. Studies have shown the effectiveness of multi-modality interdisciplinary approaches. Drug abuse treatment and prevention professionals see early intervention measures as a better, more effective way of addressing substance abuse problems than the present heavy emphasis on criminal justice strategies.

This change in cultural attitude is being fueled by the recognition that the current failed U.S. drug policies just don't work. Not only that, but as we learn more about cannabis, cannabinoids, and the ECS cannabis is emerging as a valuable tool to combating substance opiate abuse in a comprehensive approach treatment.

The drug war has not only been an abject failure, but at the same time the "War on Drugs" has created extensive collateral damage. This damage includes, but is not limited to providing funding for gangs and terrorists, the death of tens of thousands of innocents in Central America, the fraying of the Constitution, waste and misuse of our tax dollars and destroying the integrity of many American families. It is well past time to move on. We are proposing a multi-disciplinary approach that recognizes a harm reduction approach for substance abuse, including the use of cannabis.

• An Abridged History of opiates in the United States

We have had opiate in the history of the U.S. for over one hundred and seventy-five years. In 1828 Charles Russell and Company started transporting opium from India to China in conjunction with the British East India Company, a lynch pin in British opioid trade, Eliahu Yale had made _____ worked for the British Company. Yale used some of his wealth from the opium trade to start the University that bears his name.

There have been intermittent attempts to deal with the opiate medically. Some have such as suboxone, methadone, have shown benefit others have not been so successful like the opium treatment facilities in Lexington and Ft. Worth. But these were part of our criminal justice approach. To date, history has shown us that approaching substance abuse from a criminal justice perspective has not been that effective. Further focusing on the drugs rather than the motivation of the person using the drug is another ingredient in this recipe for failure.

At least since 1873 when smoking opium but not the opium used for patent medicine (e.g., Lydia Pinkham's Vegetable Compound for the treatment of women's unmentionable ills) was made illegal in San Francisco. As the past one hundred and thirty-five years have proven this has not been particularly effective.

It is generally conceded by drug policy historians that the most effective federal law ever passed on regulating psychoactive drugs was the Pure Food and Drug Act of 1906. This law prohibited nothing. It _____ that patent medicine ingredients be placed on the table. Within less than five years after passage the sale of patent medicine had dramatically decreased. Many of these nostrums contained alcohol, opium and cocaine. It prohibited nothing. It relied on the concept that if people better understood what was in the nostrums they could cease using it if they knew it was dangerous.

Multi Modality Approach

We propose a multi-disciplinary, holistic approach to treatment of this generation's opioid substance abuser. It may have the possible fringe benefit of decreasing the intergenerational aspect of their condition. This is a proposal to study whether a robust multi modality interdisciplinary approach to addressing the opioid crisis will provide evidence that works can be effective. The program will make an effort to address some of the underlying causes of the opiate epidemic.

Risk Factors for Substance Abuse

These factors for substance misuse and abuse are many and complex. They include such family factors as growing up in a dysfunctional family, chaotic home environment, parental dysfunction, ineffective parenting, little attachment and nurturing by parents, history of substance abuse in the family, history of mental illness in the family, being ignored or devalued by parents, being in an abusive environment, such as physical abuse, sexual abuse, and/or emotional abuse.

Here is a fairly typical quote from a child abuse survivor: "Abuse hurts us a lot. Many of us who suffer from child abuse develop depression, isolationism and suicidal thoughts and low self-esteem as a result." This survivor went on to say that once in a while he/she suffers from bouts of depression and suicidal thoughts.

Some medical conditions have contributed to the opioid problem. They include not only dealing with pain, but also PTSD – untreated or under-treated, ADD – untreated, unidentified, Autism Spectrum Disorder – untreated or under-treated.

Then there are the personal factors. Low academic aspirations, poor social coping skills, low self-esteem, poor decision making skills, feeling unloved, ignored. It has become conventional to treat some problems associated with drug abuse problems, as medical issues and others as criminal justice. We believe that this is the way to go.

Our proposed opioid intervention treatment program is aware of and will address some of the causes that have led to this epidemic. To reiterate some causes for opiate abuse

include but are not limited to low self-esteem, lack of coping skills, lack of job skills, lack of parenting skills, having a poor job and/or job prospects, hopelessness, growing up in a dysfunctional family, and from having ADD or PTSD. Unless these issues are appropriately addressed, there is little hope for progress to be made. Our program will make every effort to address the undeniable causes as opposed to only treating the symptoms. We proposed a study that will collect data to measure its success or failure.

This Treatment Program is Based on Common Sense

Strangely enough everyone viscerally knows the answer to preventing substance abuse: knowledge (self, science and spirituality), common sense, good parenting, good jobs, love, and genuine family values. Unfortunately the solution is not very exotic so it is all too common to give little more than lip service in support of measures that support effective prevention and intervention efforts. We propose exposing patients to treatment modalities that give them the skills to better cope with their substance abuse issues.

Here is what Milton Friedman, Nobel Prize-winning, conservative economist (1912-2006) had to say in his assessment of prohibition policy. "There is no light at the end of the tunnel. How many of our citizens do we want to turn into criminals before we yell, 'Enough!'?"

The demonizing, racist, punitive, criminal-justice system approach has been a failure. It is not only a costly failure; it encourages the dark side of the American psyche. America would be better off by far if government policies were based on the most positive aspects

of American values and heritage – those of enlightenment, knowledge, family, community, understanding and forgiveness.

This proposal has a full spectrum approach that is based on harm reduction principles. It includes skill building, decision making, counseling, medical and psychological treatment, building self-esteem, and use of cannabis as an exit drug. We propose using on physical medicine, psychology, career counseling, resume writing, spirituality, physical therapy and cannabis.

The care of human life and happiness, and not their destruction, is the first and only object of good government.

—Thomas Jefferson

U.S. President, 1801-09 and writer of the Declaration of Independence

DAVE: THIS PAGE WAS WAY TOO HARD TO DECIPHER.

YOU WILL NEED TO REDO (NEATLY, PLEASE) SO I CAN UNDERSTAND.

Here are some of what we de_____

Planning Committee:

Steve Hosea, MD

SUBJECT MATTER EXPERT REPORT: MEDICAL CANNABIS TO TREAT OPIOID ADDICTION

PETITION OVERVIEW

MATERIALS SUBMITTED	DESCRIPTION
4731-32-05 (C)(1)	Ted Parran MD FACP FASAM
4731-32-05 (C)(2)	11.20 Opioid Substance Use Disorder Moderate or Severe
4731-32-05 (C)(3)	The question is, could or should medical cannabis be recommended for the treatment of opioid addiction (F11.20 and F11.23).
	In order to make a recommendation for a medication or in the case of medical cannabis a medicinal, in the treatment of any diagnosis it is important to establish three things. First it is essential to establish the **safety** of the medicinal *in the proposed patient population*. The importance of starting with safety concerns first, is due to the preeminent ethical importance of the principle of "first do no harm" in the practice of medicine. Second it is necessary to establish the effectiveness or efficacy of the medicinal in the management of the proposed diagnosis. Third, it is important to weigh that efficacy, or lack of established efficacy, in light of the efficacy of currently available treatments. I have great concern and alarm about the prospect of the State Medical Board of Ohio adding Opioid SUD M-S to the list of diagnosis for which medical cannabis can be recommended, and this concern arises from all three of these important areas of consideration.
	Dangers of medical cannabis in opioid SUD M-S
	I will first start with the dangers of THC administration to patients with opioid addiction. This is because, as mentioned above the basic principle of the practice of medicine starts with the ethical obligation to do no harm. If the use of THC caries substantial risk of doing harm in individuals with Opioid SUD M-S, then the recommendation to provide THC to individuals with Opioid SUD M-S flies in the face of the basic ethical tenant of the practice of medicine, namely do no harm. In fact THC, a ubiquitous substance in virtually all formulations of medical cannabis, is a substantial dopamine surge agent which produces euphoria in the human brain.(1) People with addictive disease cannot reliably self-control their use of ANY dopamine surge agents, whether they are opioids, cannabinoids, alcohol, sedatives, or stimulants. When they use these substances, they either develop out-of-control addictive behavior around them, or the use triggers relapse back to prior addictive substances, or both.(2, 3) In facy, *marijuana is the most common illicit drug causing dependence in the United States*, according to a 2011 survey from the Substance Abuse and Mental Health Services Administration.

Therefore, people with addictive brains cannot safely take substances containing THC. All patients with Opioid SUD M-S have addictive brains, by definition, so they cannot safely receive substances containing THC. In summary the first risk of giving THC containing compounds like medical marijuana, to people with opioid addiction is that it will activate addictive behavior around the THC itself. This would endanger the health and safety of the patient, and thus be inconsistent with the usual course of medical practice.

Secondly, THC use continues to kindle cravings in the addictive brain for other substances of abuse and addiction. Even as weak a euphoriant as nicotine in cigarette smoking increases relapse to alcohol, opioid and other drug addiction. (4,5,6) If the weakest euphoriant (nicotine) increases relapses, then the ongoing use of a much more potent euphoriant (THC) clearly increases the risk of relapse. That is why individuals with addiction who are pursuing sobriety cannot safely take compounds that contain THC, or any other substance that triggers acute surges of dopamine from the mid-brain to the fore brain. (16) If they don't develop compulsive addictive behavior related to the THC itself, its use will continue to kindle cravings for their prior substances of addiction. Therefore the use of THC containing compounds in a patient with a history of opioid addiction will continue to increase the patient's risk of relapse back to opioid addiction. That is why methadone maintenance programs for over four decades – dealing solely with patients who have Opioid SUD M-S – do not condone the use of marijuana. It is why recovering professionals programs consider the use of THC containing compounds to be inconsistent with sobriety and consistent with relapse. Opioid relapse indicates out of control behavior, and a danger to the health and safety and liberty and life of a patient. The use of THC containing compounds does increase the risk of ongoing opioid use *in patients with* Opioid SUD M-S. There is some research that cannabinoid antagonists can aid in drug treatment – the opposite of giving medical cannabis to treat OUD. (17, 18)

Third, the combination of THC with opioids can increase sedation via a drug – drug interaction. It cannot increase respiratory depression or the depression of other vital signs, but it can increase sedation. It also can increase discoordination and poor psychomotor coordination. Therefore combining THC with opioid use, even in the name of treating the opioid use disorder, can increase the risk pharmacologically of over sedation and psychomotor retardation, and therefore can increase the risk of all of the social family and medical risks associated with that drug - drug interaction. These are the three major reasons from an increased risk standpoint that medical marijuana should not be recommended or permitted as a so-called treatment for opioid addiction. A recent large controlled study from the Lancet indicates that MJ use is even problematic in chronic pain management, not to mention opioid addiction. (14)

From an ethical standpoint, there are only two controlled drugs which have been well studied, endorsed by NIDA and SAMHSA for safe use in the treatment of addictive disease. These are methadone and buprenorphine. They have both been subjected to careful prospective placebo-controlled randomized trials to demonstrate first their safety and secondly their efficacy as an adjunct in the treatment of addiction. Medical marijuana has

NEVER been endorsed by NIDA or SAMHSA or ASAM or AAAP for the treatment of any addictive disorder, has never been identified to be safe in addictive disorders by these federal agencies and addiction treatment organizations. Medical cannabis has certainly never been identified as being efficacious by either of these data-driven research-based federal agencies.

In Robert Ryan's PDF, section 2 (6 pages long) describes the problems with current treatment of OUD M-S. This is well known information. What is NOT emphasized is that the currently available treatment for OUD M-S is exceedingly effective if patients adhere to the treatment. Robert Ryan's Section 3 (7 pages) implies that MAT is not as effective as it clearly is, reports that 12-step treatment is not effective and implies that coercive treatment is largely ineffective (i.e. Drug Courts … but also Medical Board supervised treatment is coercive treatment). This is in total contradiction to both research and to the experience of the State Medical Board of Ohio in its experience with recovering physicians over decades.

Conclusions

In conclusion, the opioid epidemic is a statewide and national catastrophe. Any safe and efficacious intervention that shows promise should be closely considered. Medical marijuana has no evidence to indicate that it is safe to be used as a treatment for opioid addiction or as an adjunct in the treatment of opioid addiction. There is much evidence that ongoing use of *any dopamine surge agent (including THC)*, other than buprenorphine or methadone, by the opioid addicted brain, increases instability in that individual and decreases safety in that individual, and decreases the chance of sobriety in that individual. There is no prospective randomized controlled data to support the hypothesis that medical marijuana use results in a substantial decrease in opioid use by people with addiction.

Given that there are substantial risks to patient safety in introducing a completely unproven controlled drug intervention (medical cannabis) into the disease of opioid addiction, and the fact that ongoing use of any euphoria producing drug (like medical cannabis) can increase instability in the addictive brain, and given the fact that there are several excellent evidence-based efficacious interventions for opioid addiction already available to Ohioans who are suffering from this devastating disease of OUD M-S, there is no reason to consider opioid addiction as a legitimate reason to recommend medical marijuana in the state of Ohio.

4731-32-05 (C)(4)	[Relevant medical or scientific evidence pertaining to the disease or condition] #8 is a good review of effective opioid treatment. #12 is a NEJM review of the treatment of opioid use disorders. #13 is a review of the role of dopamine in drug abuse and addiction. #2 is a chapter on prescription drug abuse (and all constituents of medical cannabis that have been licensed by the FDA have been controlled drugs). #13 is a National Academies of Medicine review of effective OUD medical treatment.
4731-32-05 (C)(5)	[Consideration of whether conventional medical therapies are insufficient to treat or alleviate the disease or condition] **Efficacy of currently existing treatment of OUD M-S**

If there were no good treatments available for opioid addiction, then the argument could be made that it would be reasonable to try to use medical marijuana on a research basis. This is not the case. There are high quality very efficacious treatments available for opioid addiction. (#8) These include medication-assisted treatment (MAT) with naltrexone, buprenorphine, and methadone. Even harm reduction treatment with naltrexone, buprenorphine, and methadone have demonstrated efficacy in decreasing mortality and morbidity. There are even good abstinence-based treatments for opioid addiction including counseling, 12-step meetings, social supports and recovery coaches. All of these approaches are supported by evidence and are demonstrated to have substantial efficacy in the treatment of opioid addiction. Therefore, the argument that there are not currently high-quality, efficacious, safe, data-driven treatments for opioid addiction is totally false.

There are many years of experience with the use of THC by patients with opioid addiction. These decades of experience in methadone programs demonstrate that patients who continue to use THC are less stable from a sobriety standpoint then methadone patients who cease using THC. In fact methadone patients in reputable certified methadone programs in the State of Ohio are considered not sober and ineligible for methadone take-home doses if they continue to use THC. The fact that methadone programs often permit patients to continue to use THC while on methadone *does not mean that they are considered stable, does not mean that the THC in anyway is considered a treatment for the opioid addiction, but only means that the methadone program has chosen not to dismiss the patient from harm reduction methadone treatment in the face of continued non-adherence with the treatment plan and continued THC use*.

4731-32-05 (C)(6)	[Evidence supporting the use of medical marijuana to treat or alleviate the disease or condition, including journal articles, peer-reviewed studies, and other types of medical or scientific documentation]

Evidence for the efficacy of medical cannabis in OUD M-S

The second major category of reasons to not recommend THC in the treatment of opioid addiction involves a total lack of evidence to indicate efficacy.

Given that there are clear-cut risks outlined above, in order to appropriately recommend medical marijuana in the treatment of opioid addiction would require clear-cut strong evidence of efficacy. There is none. There are no prospective trials of medical marijuana in the treatment of opioid addiction in the medical literature – not a single one. There is *one epidemiologic report* from JAMA that indicates that there is an *association* between States with Medical MJ and lower death rates due to opioid overdose. (7) All physicians understand that epidemiologic research is not compelling regarding efficacy, it is only suggestive regarding and association. In addition, given the above reports of actual research indicating increased risk (4,5,6), one epidemiologic report is not convincing in the least. This complete lack of well designed research to support the use of medical marijuana in the treatment of opioid addiction leads to the

inescapable conclusion that there is no established efficacy of medical marijuana in the treatment of opioid addiction.

I have carefully reviewed the power-point presentation provided by Dr Russo. There is no evidence presented in this entire 60 slide PPT of a controlled prospective nature to indicate efficacy of medical cannabis in OUD M-S. In fact the PPT constantly shifts back and forth between historical accounts of the use of cannabis – some thousands of years old, to poorly done research suggesting use of medical cannabis (actually CBD NOT THC) in chronic pain management (NOT in opioid use disorder), to claims that *since the opioid epidemic is so severe medical cannabis should be tried*. The pictures are great, and as a history major in undergraduate school the historical vignettes are interesting, but this is NOT medical evidence for the efficacy of cannabis in OUD M-S treatment.

I have carefully reviewed the PDF from Robert Ryan. Section 1 merely describes opioid addiction. Section 2 describes the difficulties in treating opioid use disorder, and has been discussed above. My review of literature regarding efficacy of medical cannabis in the treatment of OUD M-S, indicates that there are some animal model studies of totally purified CBD (without any THC or CBN constituent) in addictive behavior, and some early clinical trials of this compound in humans, but no substantial controlled trials in humans. (9)

January 2017 exhaustive review of recreational and medicinal cannabis by the National Academy of Medicine does not endorse medical cannabis for OUD treatment, and in fact by my review appears to not even mention it. (10)

March 2019 National Academy of Medicine thorough review of the efficacy of medications in the treatment of OUD M-S does not mention medical cannabis at all, although it strongly endorses all of the MAT medications mentioned above. (11)

Robert Ryan's PDF Section 4 cites evidence to support medical MJ in OUD M-S. The very first page continues to conflate the use of medical cannabis in "conditions where opioids can be prescribed" with the proposition that it helps treat OUD M-S. Decreased prescribing of opioids in medical MJ States has *nothing* to do with recommending the addictive substance THC as a treatment for opioid addiction!

4731-32-05 (C)(7)	[Letters of support provided by physicians with knowledge of the disease or condition, which may include a letter provided by the physician treating the petitioner, if applicable]

APPLICABLE STATUTES & RULES

PURSUANT TO OAC 4731-32-05, THE SUBJECT MATTER EXPERT SHALL REVIEW THE ABOVE-REFERENCED MATERIALS AND ISSUE A WRITTEN OPINION REGARDING THE CURRENT TREATMENT MODALITIES FOR THE PROPOSED DISEASE OR CONDITION AND WHETHER A MEDICAL MARIJUANA RECOMMENDATION COULD BE BENEFICIAL TO THE PROPOSED DISEASE OR CONDITION.

SUMMARY OF PROPOSED DISEASE OR CONDITION

[THE SUBJECT MATTER EXPERT WILL PROVIDE A BRIEF SUMMARY OF THE PROPOSED DISEASE OR CONDITION AND ITS CURRENT TREATMENT MODALITIES]

CONCLUSIONS REGARDING MEDICAL MARIJUANA

The following is my expert opinion to a reasonable degree of medical certainty regarding the applicability of recommending medical marijuana for the proposed disease or condition:

In summary, to within a reasonable degree of medical certainty: 1) there is no clinically robust data to support the efficacy of medical cannabis in the treatment of opioid use disorder, 2) there are no endorsements of for the use of medical cannabis in the treatment of OUD by any federal institutes (NIH, NIDA, NIAAA, SAMHSA, CSAT, CSAP, CDC, ONDCP) or addiction treatment oriented societies (ASAM, AAAP, AMERSA), 3) there are existing treatments for opioid use disorder that are safe and efficacious supported by well-designed prospective clinical trials, and 4) there are substantial risks involved in the recommending of an addictive substance like cannabis for the treatment of addictive disease like opioid use disorder. For these reasons, Ohio should certainly not consider identifying opioid use disorder as one of the conditions for which medical cannabis could or should be recommended.

If applicable, here are the strains and/or dosages that may be appropriate when using medical marijuana for the proposed disease or condition:

NONE

Dan L. Longo, M.D., *Editor*

Neurobiologic Advances from the Brain Disease Model of Addiction

Nora D. Volkow, M.D., George F. Koob, Ph.D., and A. Thomas McLellan, Ph.D.

THIS ARTICLE REVIEWS SCIENTIFIC ADVANCES IN THE PREVENTION AND treatment of substance-use disorder and related developments in public policy. In the past two decades, research has increasingly supported the view that addiction is a disease of the brain. Although the brain disease model of addiction has yielded effective preventive measures, treatment interventions, and public health policies to address substance-use disorders, the underlying concept of substance abuse as a brain disease continues to be questioned, perhaps because the aberrant, impulsive, and compulsive behaviors that are characteristic of addiction have not been clearly tied to neurobiology. Here we review recent advances in the neurobiology of addiction to clarify the link between addiction and brain function and to broaden the understanding of addiction as a brain disease. We review findings on the desensitization of reward circuits, which dampens the ability to feel pleasure and the motivation to pursue everyday activities; the increasing strength of conditioned responses and stress reactivity, which results in increased cravings for alcohol and other drugs and negative emotions when these cravings are not sated; and the weakening of the brain regions involved in executive functions such as decision making, inhibitory control, and self-regulation that leads to repeated relapse. We also review the ways in which social environments, developmental stages, and genetics are intimately linked to and influence vulnerability and recovery. We conclude that neuroscience continues to support the brain disease model of addiction. Neuroscience research in this area not only offers new opportunities for the prevention and treatment of substance addictions and related behavioral addictions (e.g., to food, sex, and gambling) but may also improve our understanding of the fundamental biologic processes involved in voluntary behavioral control.

In the United States, 8 to 10% of people 12 years of age or older, or 20 to 22 million people, are addicted to alcohol or other drugs.[1] The abuse of tobacco, alcohol, and illicit drugs in the United States exacts more than $700 billion annually in costs related to crime, lost work productivity, and health care.[2-4] After centuries of efforts to reduce addiction and its related costs by punishing addictive behaviors failed to produce adequate results, recent basic and clinical research has provided clear evidence that addiction might be better considered and treated as an acquired disease of the brain (see Box 1 for definitions of substance-use disorder and addiction). Research guided by the brain disease model of addiction has led to the development of more effective methods of prevention and treatment and to more informed public health policies. Notable examples include the Mental Health Parity and Addiction Equity Act of 2008, which requires medical insurance plans to provide the same coverage for substance-use disorders and other mental illnesses that is provided for other illnesses,[5] and the proposed bipartisan Senate legislation that

From the National Institute on Drug Abuse (N.D.V.) and the National Institute of Alcohol Abuse and Alcoholism (G.F.K.) — both in Bethesda, MD; and the Treatment Research Institute, Philadelphia (A.T.M.). Address reprint requests to Dr. Volkow at the National Institute on Drug Abuse, 6001 Executive Bld., Rm. 5274, Bethesda, MD 20892, or at nvolkow@nida.nih.gov.

363

would reduce prison sentences for some nonviolent drug offenders,[6] which is a substantial shift in policy fueled in part by the growing realization among law-enforcement leaders that "reducing incarceration will improve public safety because people who need treatment for drug and alcohol problems or mental health issues will be more likely to improve and reintegrate into society if they receive consistent care."[7]

Nonetheless, despite the scientific evidence and the resulting advances in treatment and changes in policy, the concept of addiction as a disease of the brain is still being questioned. The concept of addiction as a disease of the brain challenges deeply ingrained values about self-determination and personal responsibility that frame drug use as a voluntary, hedonistic act. In this view, addiction results from the repetition of voluntary behaviors. How, then, can it be the result of a disease process? The concept of addiction as a brain disease has even more disconcerting implications for public attitudes and policies toward the addict. This concept of addiction appears to some to excuse personal irresponsibility and criminal acts instead of punishing harmful and often illegal behaviors. Additional criticisms of the concept of addiction as a brain disease include the failure of this model to identify genetic aberrations or brain abnormalities that consistently apply to persons with addiction and the failure to explain the many instances in which recovery occurs without treatment. (Arguments against the disease model of addiction and counterarguments in favor of it[8] are presented in Box S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Advances in neurobiology have begun to clarify the mechanisms underlying the profound disruptions in decision-making ability and emotional balance displayed by persons with drug addiction. These advances also provide insight into the ways in which fundamental biologic processes, when disrupted, can alter voluntary behavioral control, not just in drug addiction but also in other, related disorders of self-regulation, such as obesity and pathologic gambling and video-gaming — the so-called behavioral addictions. Although these disorders also manifest as compulsive behaviors, with impaired self-regulation, the concept of behavioral addiction is still controversial, particularly as it relates to obesity. (Behavioral addictions are described in Box S2 in the Supplementary Appendix.[9]) This research has also begun to show how and why early, voluntary drug use can interact with environmental and genetic factors to result in addiction in some persons but not in others.

STAGES OF ADDICTION

For heuristic purposes, we have divided addiction into three recurring stages: binge and intoxication, withdrawal and negative affect, and preoccupation and anticipation (or craving).[10] Each stage is associated with the activation of specific neurobiologic circuits and the consequential clinical and behavioral characteristics (Fig. 1).

BINGE AND INTOXICATION

All known addictive drugs activate reward regions in the brain by causing sharp increases in the release of dopamine.[11-13] At the receptor level, these increases elicit a reward signal that triggers associative learning or conditioning. In this type of Pavlovian learning, repeated experiences of reward become associated with the environmental stimuli that precede them. With repeated exposure to the same reward, dopamine cells stop firing in response to the reward itself and instead fire in an anticipatory response to the conditioned stimuli (referred to as "cues") that in a sense predict the delivery of the reward.[14] This process involves the same molecular mechanisms that strengthen synaptic connections during learning and memory formation (Box 2).
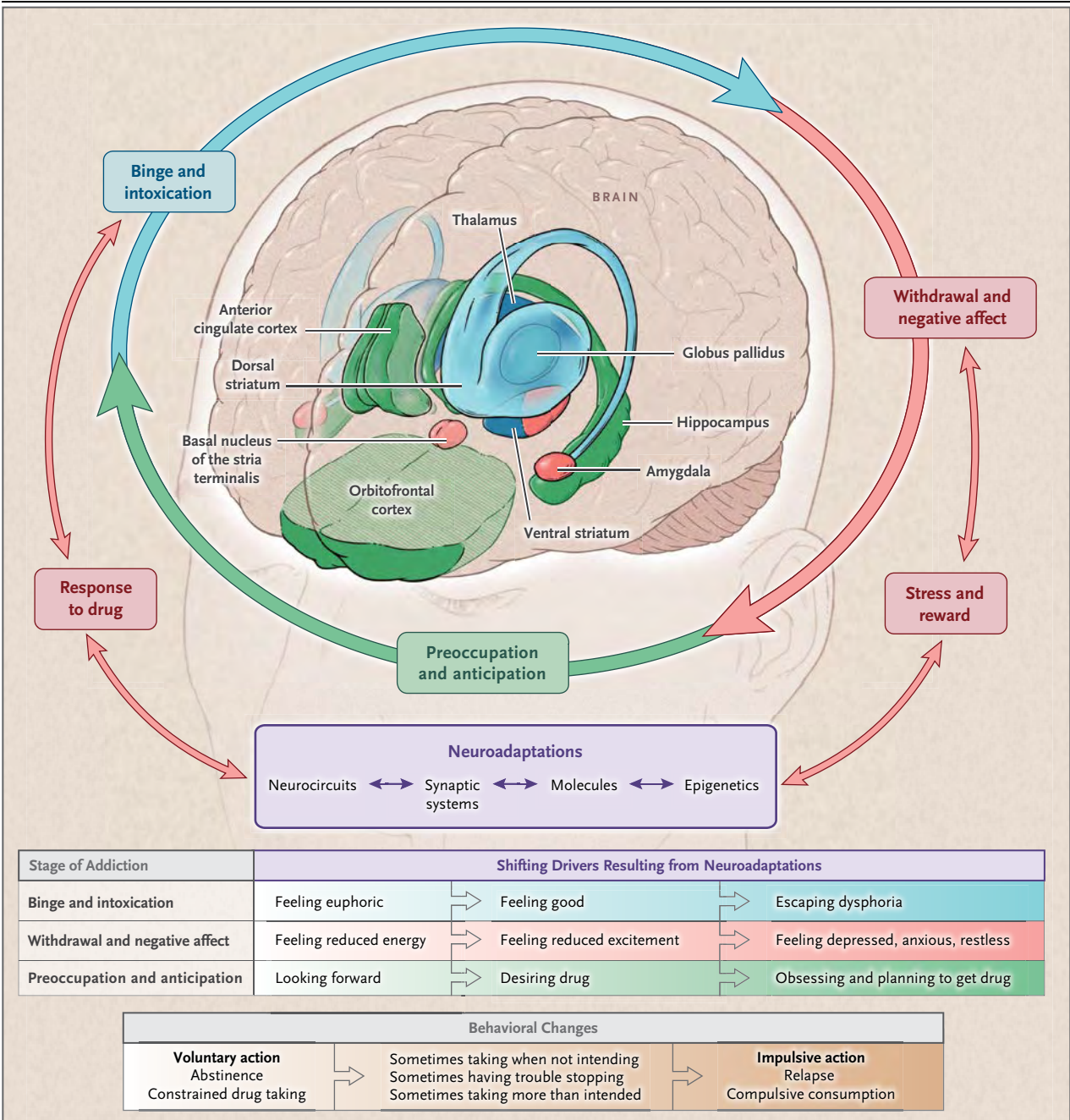
Figure 1. Stages of the Addiction Cycle.

During intoxication, drug-induced activation of the brain's reward regions (in blue) is enhanced by conditioned cues in areas of increased sensitization (in green). During withdrawal, the activation of brain regions involved in emotions (in pink) results in negative mood and enhanced sensitivity to stress. During preoccupation, the decreased function of the prefrontal cortex leads to an inability to balance the strong desire for the drug with the will to abstain, which triggers relapse and reinitiates the cycle of addiction. The compromised neurocircuitry reflects the disruption of the dopamine and glutamate systems and the stress-control systems of the brain, which are affected by corticotropin-releasing factor and dynorphin. The behaviors during the three stages of addiction change as a person transitions from drug experimentation to addiction as a function of the progressive neuroadaptations that occur in the brain.

Box 2. Drug-Induced Neuroplasticity.

The drug-induced release of dopamine triggers neuroplasticity (systematic changes in the synaptic signaling, or communication, between neurons in various reward regions of the brain).[15,16] These neuroplastic changes are fundamental to learning and memory. Experience-dependent learning (such as that which occurs in repeated episodes of drug use) may invoke both long-term potentiation, in which the transmission of signals between neurons increases, and long-term depression, in which signal transmission decreases.

Synaptic strength is controlled by the insertion or removal of receptors that are stimulated by the excitatory neurotransmitter glutamate (which acts largely through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] and N-methyl-D-aspartate [NMDA] receptors) and by changes in the composition of the subunits of these receptors. Specifically, the insertion of a subunit of the AMPA receptor that is highly permeable to calcium, glutamate receptor 2 (GluR2), enhances the efficiency of transmission and has been shown to contribute to long-term potentiation in animal studies of addiction.[17] Changes in long-term potentiation and long-term depression are in turn associated with larger or smaller synapses, respectively, and with differences in the shapes of the dendritic spines in the receptive site of the receiving neuron.[18]

The up-regulation of AMPA receptors that are highly permeable to calcium increases the responsiveness of the nucleus accumbens to glutamate, which is released by cortical and limbic terminals when exposed to drugs or drug cues.[17] Neuroplastic changes triggered by drugs have been uncovered not only in the nucleus accumbens (a crucial brain-reward region) but also in the dorsal striatum (a region implicated in the encoding of habits and routines), the amygdala (a region involved in emotions, stress, and desires), the hippocampus (a region involved in memory), and the prefrontal cortex (a region involved in self-regulation and the attribution of salience [the assignment of relative value]). All these regions of the brain participate in the various stages of addiction, including conditioning and craving (see Fig. 1). These regions also regulate the firing of dopamine cells and the release of dopamine.[19]

In this way, environmental stimuli that are repeatedly paired with drug use — including environments in which a drug has been taken, persons with whom it has been taken, and the mental state of a person before it was taken — may all come to elicit conditioned, fast surges of dopamine release that trigger craving for the drug[20] (see Box 2 for the mechanisms involved), motivate drug-seeking behaviors, and lead to heavy "binge" use of the drug.[21-23] These conditioned responses become deeply ingrained and can trigger strong cravings for a drug long after use has stopped (e.g., owing to incarceration or treatment) and even in the face of sanctions against its use.

As is true with other types of motivational learning, the greater the motivational attribute associated with a reward (e.g., a drug), the greater the effort a person is willing to exert and the greater the negative consequences he or she will be willing to endure in order to obtain it.[24,25] However, whereas dopamine cells stop firing after repeated consumption of a "natural reward" (e.g., food or sex) satiating the drive to further pursue it, addictive drugs circumvent

natural satiation and continue to directly increase dopamine levels,[11,26] a factor that helps to explain why compulsive behaviors are more likely to emerge when people use drugs than when they pursue a natural reward (Box 2).

WITHDRAWAL AND NEGATIVE AFFECT

An important result of the conditioned physiologic processes involved in drug addiction is that ordinary, healthful rewards lose their former motivational power. In a person with addiction, the reward and motivational systems become reoriented through conditioning to focus on the more potent release of dopamine produced by the drug and its cues. The landscape of the person with addiction becomes restricted to one of cues and triggers for drug use. However, this is only one of the ways in which addiction changes motivation and behavior.

For many years it was believed that over time persons with addiction would become more sensitive to the rewarding effects of drugs and that this increased sensitivity would be reflected in higher levels of dopamine in the circuits of their brains that process reward (including the nucleus accumbens and the dorsal striatum) than the levels in persons who never had a drug addiction. Although this theory seemed to make sense, research has shown that it is incorrect. In fact, clinical and preclinical studies have shown that drug consumption triggers much smaller increases in dopamine levels in the presence of addiction (in both animals and humans) than in its absence (i.e., in persons who have never used drugs).[22,23,27,28] This attenuated release of dopamine renders the brain's reward system much less sensitive to stimulation by both drug-related and non–drug-related rewards.[29-31] As a result, persons with addiction no longer experience the same degree of euphoria from a drug as they did when they first started using it. It is for this same reason that persons with addiction often become less motivated by everyday stimuli (e.g., relationships and activities) that they had previously found to be motivating and rewarding. Again, it is important to note that these changes become deeply ingrained and cannot be immediately reversed through the simple termination of drug use (e.g., detoxification).

In addition to resetting the brain's reward system, repeated exposure to the dopamine-enhanc-

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ing effects of most drugs leads to adaptations in the circuitry of the extended amygdala in the basal forebrain; these adaptations result in increases in a person's reactivity to stress and lead to the emergence of negative emotions.[32,33] This "antireward" system is fueled by the neurotransmitters involved in the stress response, such as corticotropin-releasing factor and dynorphin, which ordinarily help to maintain homeostasis. However, in the addicted brain, the antireward system becomes overactive, giving rise to the highly dysphoric phase of drug addiction that ensues when the direct effects of the drug wear off or the drug is withdrawn[34] and to the decreased reactivity of dopamine cells in the brain's reward circuitry.[35] Thus, in addition to the direct and conditioned pull toward the "rewards" of drug use, there is a correspondingly intense motivational push to escape the discomfort associated with the aftereffects of use. As a result of these changes, the person with addiction transitions from taking drugs simply to feel pleasure, or to "get high," to taking them to obtain transient relief from dysphoria (Fig. 1).

Persons with addiction frequently cannot understand why they continue to take the drug when it no longer seems pleasurable. Many state that they continue to take the drug to escape the distress they feel when they are not intoxicated. Unfortunately, although the short-acting effects of increased dopamine levels triggered by drug administration temporarily relieve this distress, the result of repeated bingeing is to deepen the dysphoria during withdrawal, thus producing a vicious cycle.

PREOCCUPATION AND ANTICIPATION

The changes that occur in the reward and emotional circuits of the brain are accompanied by changes in the function of the prefrontal cortical regions, which are involved in executive processes. Specifically, the down-regulation of dopamine signaling that dulls the reward circuits' sensitivity to pleasure also occurs in prefrontal brain regions and their associated circuits, seriously impairing executive processes, among which are the capacities for self-regulation, decision making, flexibility in the selection and initiation of action, attribution of salience (the assignment of relative value), and the monitoring of error.[36] The modulation of the reward

and emotional circuits of prefrontal regions is further disrupted by neuroplastic changes in glutamatergic signaling.[37] In persons with addiction, the impaired signaling of dopamine and glutamate in the prefrontal regions of the brain weakens their ability to resist strong urges or to follow through on decisions to stop taking the drug. These effects explain why persons with addiction can be sincere in their desire and intention to stop using a drug and yet simultaneously impulsive and unable to follow through on their resolve. Thus, altered signaling in prefrontal regulatory circuits, paired with changes in the circuitry involved in reward and emotional response, creates an imbalance that is crucial to both the gradual development of compulsive behavior in the addicted disease state and the associated inability to voluntarily reduce drug-taking behavior, despite the potentially catastrophic consequences.

BIOLOGIC AND SOCIAL FACTORS INVOLVED IN ADDICTION

Only a minority of people who use drugs ultimately become addicted — just as not everyone is equally at risk for the development of other chronic diseases. Susceptibility differs because people differ in their vulnerability to various genetic, environmental, and developmental factors. Many genetic, environmental, and social factors contribute to the determination of a person's unique susceptibility to using drugs initially, sustaining drug use, and undergoing the progressive changes in the brain that characterize addiction.[38,39] Factors that increase vulnerability to addiction include family history (presumably through heritability and child-rearing practices), early exposure to drug use (adolescence is among the periods of greatest vulnerability to addiction), exposure to high-risk environments (typically, socially stressful environments with poor familial and social supports and restricted behavioral alternatives and environments in which there is easy access to drugs and permissive normative attitudes toward drug taking), and certain mental illnesses (e.g., mood disorders, attention deficit–hyperactivity disorder, psychoses, and anxiety disorders).[40,41]

It is estimated that the most severe phenotypic characteristics of addiction will develop in

approximately 10% of persons exposed to addictive drugs.[42] Thus, although long-term exposure to drugs is a necessary condition for the development of addiction, it is by no means sufficient. Yet for those in whom there is progress to addiction, the neurobiologic changes are distinct and profound.

IMPLICATIONS OF THE BRAIN DISEASE MODEL OF ADDICTION FOR PREVENTION AND TREATMENT

As is the case in other medical conditions in which voluntary, unhealthful behaviors contribute to disease progression (e.g., heart disease, diabetes, chronic pain, and lung cancer), evidence-based interventions aimed at prevention, along with appropriate public health policies, are the most effective ways of changing outcomes. A more comprehensive understanding of the brain disease model of addiction may help to moderate some of the moral judgment attached to addictive behaviors and foster more scientific and public health–oriented approaches to prevention and treatment.

BEHAVIORAL AND MEDICAL INTERVENTIONS

The findings from neurobiologic research show that addiction is a disease that emerges gradually and that has its onset predominantly during a particular risk period: adolescence. Adolescence is a time when the still-developing brain is particularly sensitive to the effects of drugs, a factor that contributes to adolescents' greater vulnerability to drug experimentation and addiction. Adolescence is also a period of enhanced neuroplasticity during which the underdeveloped neural networks necessary for adult-level judgment (the prefrontal cortical regions) cannot yet properly regulate emotion. Studies have also shown that children and adolescents with evidence of structural or functional changes in frontal cortical regions or with traits of novelty seeking or impulsivity are at greater risk for substance-use disorders.[43-45] Awareness of individual and social risk factors and the identification of early signs of substance-use problems make it possible to tailor prevention strategies to the patient. According to research related to the brain disease model of addiction, preventive in-

terventions should be designed to enhance social skills and improve self-regulation. Also important are early screening and intervention for the prodromal presentation of mental illness and the provision of social opportunities for personal educational and emotional development.[46-49]

When prevention has failed and there is need for treatment, research based on the brain disease model of addiction has shown that medical treatment can help to restore healthy function in the affected brain circuitry and lead to improvements in behavior. The health care system already has at its disposal several evidence-based treatment interventions that could improve clinical outcomes in patients with substance-use disorders if properly and comprehensively implemented. During treatment, medication can assist in preventing relapse while the brain is healing and normal emotional and decision-making capacities are being restored. For patients with opioid-use disorder, maintenance therapy with agonists or partial agonists such as methadone or buprenorphine can be essential in helping to control symptoms of withdrawal and cravings.[50] Opioid antagonists such as extended-release naltrexone may be used to prevent opioid intoxication.[51] Naltrexone and acamprosate have been efficacious in the treatment of alcohol-use disorders, and other medications can help in the recovery from nicotine addiction.[27]

The brain disease model of addiction has also fostered the development of behavioral interventions to help restore balance in brain circuitry that has been affected by drugs.[52] For example, strategies to enhance the salience of natural, healthy rewards such as social contact or exercise could enable those rewards to compete with the direct and acquired motivating properties of drugs. Strategies to mitigate a person's stress reactivity and negative emotional states could help to manage the strong urges they engender, and strategies to improve executive function and self-regulation could help recovering patients plan ahead in order to avoid situations in which they are particularly vulnerable to taking drugs. Finally, strategies to help patients recovering from addiction to change their circle of friends and to avoid drug-associated environmental cues can reduce the likelihood that conditioned craving will lead to relapse.

PUBLIC HEALTH POLICY

A compelling argument for the translational value of the brain disease model of addiction is the knowledge that the prefrontal and other cortical networks that are so critical for judgment and self-regulation do not fully mature until people reach 21 to 25 years of age.[53] As a result, the adolescent brain is much less able to cognitively modulate strong desires and emotions. This observation is particularly relevant to the establishment of 21 years of age as the legal drinking age in the United States, a ruling that is often questioned even though a dramatic reduction in highway deaths followed its institution.[54] One could legitimately argue that the study of the neurobiology of addiction provides a compelling argument for leaving the drinking age at 21 years and for increasing the legal smoking age to 21 years, by which time the brain networks that underlie the capacity for self-regulation are more fully formed.

The brain disease model of addiction has also informed policies that take advantage of the infrastructure of primary health care to address substance-use disorders and to provide a model for paying for it through the Mental Health Parity and Addiction Equity Act (MHPAEA) and the Affordable Care Act. Although it is still too early to evaluate the effects of these policies on the nation, an initial examination of the MHPAEA in three states showed increased enrollment and care delivery among patients with substance-use disorders and an overall reduction in spending on emergency department visits and hospital stays.[55]

The social and financial effects of these laws are also illustrated in the recent legal action taken by the State of New York against Value Options and two other managed-care organizations for alleged discrimination against patients who were wrongly denied benefits related to addiction and mental health after patients with diabetes were used as the comparators. The action was taken on the basis of the amount and extent of preauthorization required for the treatment of patients with substance-use disorder versus those with diabetes, the arbitrary and capricious manner in which the insurers stopped treatment, and the lack of treatment alternatives offered or even suggested to patients.[56] The settlement has not been contested, and the organizations stopped their discriminatory preauthorization procedures. A similar suit has been filed in California.

Similarly, there are early indications that the integration of primary care and specialty behavioral health care can substantially improve the management of substance-use disorders and the treatment of many addiction-related medical conditions, including the human immunodeficiency virus, hepatitis C virus, cancer, cirrhosis, and trauma.[57,58]

Despite such reports of benefits to the public from practices and policies generated by research based on the brain disease model of addiction, mobilizing support for further research will require the public to become better educated about the genetic, age-related, and environmental susceptibilities to addiction as they relate to structural and functional changes in the brain. If early voluntary drug use goes undetected and unchecked, the resulting changes in the brain can ultimately erode a person's ability to control the impulse to take addictive drugs.

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369

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Principles of Addiction Medicine Text Book, ASAM 2018

Chapter #117: Clinical, Ethical, and Legal Considerations in Prescribing Drugs With Potential for Non-medical Use and Addiction

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Neurocircuitry of Addiction

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Drug addiction is a chronically relapsing disorder that has been characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (eg, dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented. Drug addiction has been conceptualized as a disorder that involves elements of both impulsivity and compulsivity that yield a composite addiction cycle composed of three stages: 'binge/intoxication', 'withdrawal/negative affect', and 'preoccupation/anticipation' (craving). Animal and human imaging studies have revealed discrete circuits that mediate the three stages of the addiction cycle with key elements of the ventral tegmental area and ventral striatum as a focal point for the binge/intoxication stage, a key role for the extended amygdala in the withdrawal/negative affect stage, and a key role in the preoccupation/anticipation stage for a widely distributed network involving the orbitofrontal cortex–dorsal striatum, prefrontal cortex, basolateral amygdala, hippocampus, and insula involved in craving and the cingulate gyrus, dorsolateral prefrontal, and inferior frontal cortices in disrupted inhibitory control. The transition to addiction involves neuroplasticity in all of these structures that may begin with changes in the mesolimbic dopamine system and a cascade of neuroadaptations from the ventral striatum to dorsal striatum and orbitofrontal cortex and eventually dysregulation of the prefrontal cortex, cingulate gyrus, and extended amygdala. The delineation of the neurocircuitry of the evolving stages of the addiction syndrome forms a heuristic basis for the search for the molecular, genetic, and neuropharmacological neuroadaptations that are key to vulnerability for developing and maintaining addiction.
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CONCEPTUAL FRAMEWORK

Addiction Definitions: Drug Use, Abuse, and Dependence Addiction Cycle

Drug addiction is a chronically relapsing disorder that has been characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (eg, dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented (defined as Substance Dependence by the *Diagnostic and Statistical Manual of Mental Disorders* [DSM] of the American Psychiatric Association; Koob and Le Moal, 1997; Table 1). The occasional but limited use of an abusable drug is clinically distinct from escalated drug use, loss of control over limiting drug intake, and the emergence of chronic compulsive drug-seeking that characterizes addiction. The

critical nature of the distinction between drug use, abuse, and dependence has been illuminated by data showing that approximately 15.6% (29 million) of the US adult population will go on to engage in nonmedical or illicit drug use at some time in their lives, with approximately 2.9% (5.4 million) going on to substance dependence on illicit drugs (Grant and Dawson, 1998; Grant *et al*, 2004). For alcohol, 51% (120 million) of people over the age of 12 were current users, and of these current users, 7.7% (18 million) met the criteria for Substance Abuse or Dependence on Alcohol. For nicotine, in 2007, approximately 28.6% (70.9 million) Americans aged 12 or older were current (past month) users of a tobacco product, and of these current users, 24.2% (60.1 million) were current cigarette smokers; 5.4% (13.3 million) smoked cigars; 3.2% (8.1 million) used smokeless tobacco; and 0.8% (2.0 million) smoked tobacco in pipes (Substance Abuse and Mental Health Services Administration, 2008).

Although much of the initial study of the neurobiology of drug addiction focused on the acute impact of drugs of abuse (analogous to comparing no drug use to drug use), the focus now is shifting to chronic administration and the acute and long-term neuroadaptive changes in the brain

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Table 1 Definitions

Addiction	Assumed to be identical to the syndrome of Substance Dependence (as currently defined by the *Diagnostic and Statistical Manual of Mental Disorders*; American Psychiatric Association, 1994), and Substance Dependence on Alcohol is assumed to be identical to alcoholism. In this paper, we favor the term 'addiction' rather than dependence to avoid confusion with 'physical dependence,' which refers to the physical adaptations that result in largely somatic withdrawal symptoms when drugs such as alcohol, heroin, and benzodiazepines are abruptly discontinued. The adaptations associated with physical drug withdrawal are distinct from the motivational changes of acute withdrawal and protracted abstinence.
Impulsivity	Defined behaviorally as 'a predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others' (Moeller *et al*, 2001). Impulsivity is often measured in two domains: the choice of a smaller, immediate reward over a larger, delayed reward (Rachlin and Green, 1972) or the inability to inhibit behavior by changing the course of action or to stop a response once it is initiated (Logan *et al*, 1997). Impulsivity is a core deficit in substance abuse disorders (Allen *et al*, 1998).
Compulsivity	Defined as elements of behavior that result in perseveration in responding in the face of adverse consequences, perseveration in responding in the face of incorrect responses in choice situations, or persistent reinitiation of habitual acts (Everitt and Robbins, 2005). The elements of compulsivity are represented in many of the symptoms outlined in the DSM-IV: continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem and a great deal of time spent in activities necessary to obtain the substance (American Psychiatric Association, 2000).
Positive reinforcement	Defined as the process by which presentation of a stimulus, usually pleasant (eg, the drug itself), increases the probability of a response.
Negative reinforcement	Defined as the process by which removal of an aversive stimulus (eg, negative emotional state of drug withdrawal) increases the probability of a response (eg, dependence-induced drug intake).
Automaticity	Defined as behaviors that occur without conscious awareness of intentionality.
Motivation	Defined as a 'tendency of the whole animal to produce organized activity' (Hebb, 1972).
Intracranial self-administration	A procedure whereby drugs injected directly into the brain in minute amounts serve as positive reinforcers.
place conditioning	A procedure whereby drugs directed into the brain are paired with a specific environment and vehicle with another environment. Subsequently, the animal is tested for its preference for the paired environment or the nonpreferred environment.
Second-order schedule of reinforcement	A procedure in which an animal is trained to work for a drug under conditions of two components. In the first component, a previously neutral stimulus such as a light or tone is delivered under certain requirements (eg, each stimulus is delivered after 10 lever presses). In the second component, the drug is delivered after the last 10th response after 15 min has elapsed (Arroyo *et al*, 1998).

that result in relapse. The purpose of current neurobiological drug abuse research is to understand the genetic/epigenetic, cellular, and molecular mechanisms that mediate the transition from occasional, controlled drug use to the loss of behavioral control over drug-seeking and drug-taking and to chronic relapse even after protracted abstinence which is a hallmark of addiction.

A psychiatric-motivational framework that provides sources of both positive and negative reinforcement for drug-taking is the conceptualization that drug addiction has aspects of both impulse control disorders and compulsive disorders (Table 1). Impulse control disorders are characterized by an increasing sense of tension or arousal before committing an impulsive act and pleasure, gratification, or relief at the time of committing the act. Impulse control disorders are largely associated with positive reinforcement mechanisms (American Psychiatric Association, 1994). In contrast, compulsive disorders are characterized by anxiety and stress before committing a compulsive repetitive behavior and relief from the stress by performing the compulsive behavior. Compulsive disorders are largely associated with negative reinforcement mechanisms and automaticity.

Collapsing the cycles of impulsivity and compulsivity yields a composite addiction cycle composed of three stages—binge/intoxication, withdrawal/negative affect, preoccupation/anticipation—in which impulsivity often dominates at the early stages and impulsivity combined with compulsivity dominates at the later stages. As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behavior to negative reinforcement and automaticity driving the motivated behavior (Koob, 2004; Table 1). These three stages are conceptualized as interacting with each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Le Moal, 1997; Table 2). The transition from occasional drug use to addiction involves neuroplasticity in all of these elements and may begin with initial drug use in vulnerable individuals or individuals at particularly vulnerable developmental periods (eg, adolescence; Koob *et al*, 2008b). The present review focuses on the brain neurocircuitry that is engaged at each stage of the addiction cycle, how it changes with increasing engagement with drugs of abuse, and how it interacts to produce the pathological state known as addiction.

Sources of Reinforcement: Motivation, Opponent Process, Incentive Salience

Changes in the motivation for drugs and natural rewards are a key component of addiction (Table 1). Early work by Wikler (1952) stressed the function of changes in drive states associated with dependence (herein referred to as

Table 2 Animal Laboratory Models of The Different Stages of The Addiction Cycle

Stage of addiction cycle	Animal models	Reference
Binge/Intoxication	Drug/alcohol self-administration	Collins et al, 1984
	Conditioned place preference	Sanchis-Segura and Spanagel, 2006
	Brain stimulation reward thresholds	Kornetsky and Bain, 1990
Withdrawal/ Negative affect	Anxiety-like responses	Sarnyai et al, 1995; Schulteis et al, 1998; Baldwin et al, 1991
	Conditioned place aversion	Tzschentke, 1998
	Elevated reward thresholds	Markou et al, 1998
	Increased motivation for self-administration in dependent animals	Ahmed and Koob, 1998; Ahmed et al, 2000; Roberts et al, 2000; Kitamura et al, 2006; O'Dell and Koob, 2007; Tornatzky and Miczek, 2000; Ahmed and Koob, 1998; Deroche-Gamonet et al, 2004; Vanderschuren and Everitt, 2004
Preoccupation/ Anticipation	Drug-induced reinstatement	Sanchis-Segura and Spanagel, 2006
	Cue-induced reinstatement	Sanchis-Segura and Spanagel, 2006
	Stress-induced reinstatement	Sanchis-Segura and Spanagel, 2006

Taken with permission from Koob et al (2009).

addiction. Subjects described withdrawal changes as a 'hunger' or primary need and the effects of morphine on such a state as 'satiation' or gratification of the primary need (Wikler, 1952). Although Wikler argued that positive reinforcement was retained even in heavily dependent subjects (eg, thrill of the intravenous opioid injection), addiction produced a new source of gratification, that of negative reinforcement (Table 1).

The concept of motivation was linked inextricably with hedonic, affective, or emotional states in the transition to addiction by Solomon's opponent process theory of motivation. Solomon and Corbit (1974) postulated that hedonic, affective, or emotional states, once initiated, are automatically modulated by the central nervous system with mechanisms that reduce the intensity of hedonic feelings. Positive hedonic responses in drug use occur shortly after presentation of a stimulus, correlate closely with the intensity, quality, and duration of the reinforcer, and show tolerance and affective or hedonic withdrawal (abstinence). In contrast, negative hedonic responses follow the positive hedonic responses, are sluggish in onset, slow to build up to an asymptote, slow to decay, and get larger with repeated exposure. The role of opponent processes begins early in drug-taking, reflects changes in the brain reward and stress systems, and later forms one of the major motivations for compulsivity in drug-taking in the form of a motivational withdrawal syndrome.

In this formulation, manifestation of a withdrawal syndrome after removal of chronic drug administration, either acute or protracted, is defined in terms of motivational aspects of dependence such as the emergence of a negative emotional state (eg, dysphoria, anxiety, irritability) when access to the drug is prevented (Koob and Le Moal, 2001), rather than on the physical signs of dependence, which tend to be of short duration. Indeed, some have argued that the development of such a negative affective state can define dependence relative to addiction (Russell, 1976; Baker et al, 1987) and that such a negative affective state contributes to compulsivity through negative reinforcement mechanisms (Koob and Le Moal, 2005).

Another conceptualization of the motivational changes associated with addiction is derived from early work on conditioned reinforcement, incentive motivation, behavioral sensitization, and maladaptive stimulus–response learning, all of which are subsumed under the motivational conceptualization of incentive salience. Drugs are hypothesized to usurp systems in the brain that are put in place to direct animals to stimuli with salience for preservation of the species. The incentive salience hypothesis has significant heuristic value as a common element of drug addiction because it narrows the focus to drug-seeking at the expense of natural rewards. The clinical observation that individuals with substance use disorders have an unusual focus on drug-seeking to the exclusion of natural rewards fits the incentive salience view.

The increase in incentive salience produced by psychostimulant drugs has early roots in the facilitation of conditioned reinforcement and drug-seeking (Robbins, 1976; Hill, 1970). Here, drug-seeking is controlled by a succession of drug-associated discriminative stimuli that can also function as conditioned reinforcers when presented as a consequence of instrumental responses (Everitt et al, 2008). Many have argued that by means of associative learning, the enhanced incentive salience state becomes oriented specifically toward drug-related stimuli, leading to escalating compulsion for seeking and taking drugs (Hyman et al, 2006; Kalivas and Volkow, 2005). The underlying activation of neural structures involved in maintaining the incentive salience state persists, making addicts vulnerable to long-term relapse.

Another view of incentive salience involved behavioral sensitization, usually measured as increased locomotor responses to repeated administration of a drug. The behavioral sensitization paradigm has provided a major impetus to exploring not only the neurocircuitry of addiction but also a model of the neuroplasticity that may occur during the transition from drug use to addiction. Here, a shift in an incentive salience state, described as 'wanting' linked to compulsive use, as opposed to 'liking' linked to hedonic responses, was hypothesized to be progressively increased by repeated exposure to drugs of abuse (Robinson and Berridge, 1993).

Transition to Addiction: Patterns of Drug-Taking, Animal Models

Different drugs produce different patterns of neuroadaptations with chronic drug exposures. For example, opioid-addicted subjects meet most of the DSM criteria for addiction, including dramatic tolerance and withdrawal (classic symptoms associated with physical dependence) and most of the symptoms associated with motivational withdrawal. A pattern of intravenous or smoked drug-taking evolves, including intoxication, tolerance, escalation in intake, and profound dysphoria, physical discomfort, and somatic withdrawal signs during abstinence. Intense preoccupation with obtaining opioids (craving) develops that often precedes the somatic signs of withdrawal and is linked not only to stimuli associated with obtaining the drug but also to stimuli associated with withdrawal and the aversive motivational state. A pattern develops in which the drug must be obtained to avoid the severe dysphoria and discomfort of abstinence. Other drugs of abuse follow a similar pattern but may involve more the binge/intoxication stage (psychostimulants) or less binge/intoxication and more withdrawal/negative affect and preoccupation/anticipation stages (nicotine and cannabinoids).

Much of the recent progress in understanding the neurobiology of addiction has derived from the study of animal models of addiction to specific drugs such as stimulants, opioids, alcohol, nicotine, and Δ^9-tetrahydrocannabinol (Δ^9-THC). Although no animal model of addiction fully emulates the human condition, animal models do permit investigation of specific elements of the process of drug addiction. Such elements can be defined by models of different stages of the addiction cycle (see above; Table 2).

A progressive increase in the frequency and intensity of drug use is one of the major behavioral phenomena characterizing the development of addiction and has face validity with the DSM criteria: 'The substance is often taken in larger amounts and over a longer period than was intended' (American Psychiatric Association, 1994). Two animal models, one involving experimenter-administered drug, and the other involving self-administered drug, have been used to explore the effects of repeated drug administration on neuroplasticity in the neurocircuits identified

above. Behavioral sensitization typically involved repeated administration by the experimenter of a drug, usually a psychostimulant, in a specific environmental context and the dependent measure was usually locomotor activity. Here, animals that received drug showed a much more dramatic increase in locomotor activity to a challenge dose of drug (sensitization) than controls that had received only repeated measures of vehicle injections.

A framework, perhaps with more face validity with which to model the transition from drug use to drug addiction, can be found in animal models of prolonged access to self-administration of drugs. Here, using intravenous drug self-administration, extended access to drugs is associated with an escalation in intake over days (Koob, 2009a). Such increased self-administration also has been observed with alcohol in which rats drink excessively during acute and protracted withdrawal from dependence induction using either chronic liquid diet or chronic vapor exposure (Gilpin and Koob, 2008). Animals made dependent on alcohol reliably obtain blood alcohol levels in the 100–150 mg% range, which are equivalent to the levels abused by moderate to heavy alcohol abusers. Changes in the reinforcing and incentive effects of the drug have been observed following extended access and induction of dependence and include increased progressive-ratio responding (Koob, 2009a), increased drug-induced reinstatement after extinction, decreased latency to goal time in a runway model for drug reward (Deroche-Gamonet et al, 2004), and increased resistance to punishment in which the animal will sustain higher aversive punishment to obtain drug (Vanderschuren and Everitt, 2004). Whether the enhanced drug-taking with extended access reflects a sensitization of reward (or of incentive motivation) or a reward-deficit state, or both, remains under discussion (Vezina, 2004).

NEUROCIRCUITRY OF ADDICTION: NEUROPSYCHOPHARMACOLOGICAL EVIDENCE FROM ANIMAL STUDIES

Binge/Intoxication Stage

Our understanding of the neurobiological substrates for the reinforcing effects of drugs of abuse can be traced to early work on the identification of a reward system in the brain with the discovery of electrical brain stimulation reward or intracranial self-stimulation by Olds and Milner (1954). Brain stimulation reward involves widespread neurocircuitry in the brain, but the most sensitive sites defined by the lowest thresholds involve the trajectory of the medial forebrain bundle that connects the ventral tegmental area (VTA) to the basal forebrain (Olds and Milner, 1954). All drugs of abuse, when administered acutely, decrease brain stimulation reward thresholds (ie, increased reward; Kornetsky and Esposito, 1979) and when administered chronically increase reward thresholds during withdrawal (ie, decreased reward; see below). Although much emphasis

was focused initially on the role of the ascending mono-amine systems in the medial forebrain bundle in reward, first norepinephrine (Stein, 1962) and then dopamine (Crow, 1973; Wise, 1978), other nondopaminergic systems in the medial forebrain bundle clearly have a key role in mediating brain stimulation reward (Hernandez *et al*, 2006). Indeed, much work suggests that activation of the midbrain dopamine system has multiple roles to give incentive salience to stimuli in the environment (Robinson and Berridge, 1993) to promote performance of goal-directed behavior (Salamone *et al*, 2007) or activation in general (Le Moal and Simon, 1991). More recently, the hypothesis has been raised that the time course of dopamine signaling is a key factor, with the fastest time course predominantly having a preferential role in reward and valuation of predicted outcomes of behavior and steady activation of dopamine release having a preferential role in providing an enabling effect on specific behavior-related systems (Schultz, 2007). Work in the domain of the acute reinforcing effects of drugs of abuse supports this hypothesis in which the mesolimbic dopamine system is critical for the acute rewarding effects of psychostimulant drugs but has a more enabling function for all drugs of abuse.

The acute rewarding properties of psychostimulant drugs have long been known to depend on activation of the mesolimbic dopamine system, but activation of this system is not necessarily critical for the acute reinforcing effects of other drugs of abuse (Koob, 1992; Nestler, 2005; Hnasko *et al*, 2005). Neurotoxin-selective lesions of the mesocorti-colimbic dopamine system block the reinforcing effects of cocaine and D-amphetamine (McGregor and Roberts, 1993). In contrast, neurochemically specific lesions of dopamine in the nucleus accumbens with 6-hydroxydopamine failed to block heroin or ethanol self-administration, supporting this hypothesis (Koob and Le Moal, 2006).

Using the technique of intracranial self-administration (Table 1) and intracranial place conditioning (Table 1), opioids and alcohol have been shown to be directly self-administered into the VTA. Opioids also produce condi-tioned place preference when injected into the VTA. Opioids, phencyclidine, and psychostimulants are directly self-administered into the nucleus accumbens, and psy-chostimulants produce a conditioned place preference when injected into the nucleus accumbens. Cocaine and phency-clidine are directly self-administered into the frontal cortex (McBride *et al*, 1999). The mesolimbic dopamine system is activated by acute administration of opioids, ethanol, nicotine, and Δ^9-THC (Di Chiara and Imperato, 1988).

Intravenous nicotine self-administration is blocked by neurotoxin-specific lesions of the mesocorticolimbic dopa-mine system, and the neuropharmacological action has been hypothesized to be through nicotinic receptor activa-tion of release of dopamine primarily in the VTA and also presynaptically in the nucleus accumbens (Watkins *et al*, 2000). However, nicotine reward measured by conditioned place preference appears to be independent of the mesocorticolimbic dopamine system (Laviolette *et al*,

2002). Other substrates implicated in nicotine reward include cholinergic inputs to the pedunculopontine nucleus (Yeomans and Baptista, 1997). In the VTA, activation of the $\beta2$ subunit of nicotinic receptors appears to be critical for nicotine activation of dopamine neurons (Mameli-Engvall *et al*, 2006). Neuropharmacological studies on cannabinoids have implicated both cannabinoid and opioid mechanisms. Opioid and cannabinoid CB_1 antagonists block intravenous self-administration of Δ^9-THC in squirrel monkeys (Justi-nova *et al*, 2003). Similar to other drugs of abuse, Δ^9-THC administration activates dopamine release in the nucleus accumbens shell (Tanda *et al*, 1997).

Thus, all drugs of abuse activate the mesolimbic dopamine system, but much evidence suggests that dopamine-independent reinforcement occurs at the level of the nucleus accumbens, suggesting multiple inputs to the activation of critical reinforcement circuitry in these brain regions (Koob, 1992; Nestler, 2005).

The central nucleus of the amygdala (CeA) also has a key function in the acute reinforcing actions of drugs of abuse. Microinjections of dopamine D_1 receptor antagonists into the CeA block cocaine self-administration (Caine *et al*, 1995; McGregor and Roberts, 1993). The most sensitive site for γ-aminobutyric acid (GABA) and opioid antagonism of oral alcohol self-administration in nondependent rats was the CeA (Hyytia and Koob, 1995; Heyser *et al*, 1999). Lesions of the CeA block oral self-administration of alcohol (Moller *et al*, 1997). Serotonin-3 antagonists injected into the CeA block oral ethanol self-administration in nondependent rats, an effect hypothesized to possibly involve the ability of serotonin-3 receptor antagonists to block drug-induced dopamine release (Dyr and Kostowski, 1995).

A major output from the nucleus accumbens is to the ventral pallidum/substantia innominata. Consistent with the nucleus accumbens as a key substrate for drug reward, lesions of the ventral pallidum are particularly effective in blocking the motivation to work for intravenous cocaine and intravenous heroin (Hubner and Koob, 1990; Robledo and Koob, 1993). In addition, blockade of dopamine and $GABA_A$ receptors in the ventral pallidum blocks the reinforcing effects of alcohol (Melendez *et al*, 2004; June *et al*, 2003). Thus, elements of the ventral pallidum may not only be critical for further processing of the drug reward signal but may also be directly modulated by drugs of abuse.

The dorsal striatum does not appear to have a major role in the acute reinforcing effects of drugs abuse but appears to be recruited during the development of compulsive drug-seeking (Everitt *et al*, 2008). 6-Hydroxydopamine lesions of the dorsal striatum do not block cocaine-induced locomotor activity or cocaine self-administration (Roberts, 1992) but do block amphetamine-induced stereotyped behavior (Kelly and Iversen, 1976; Creese and Iversen, 1974). Using a second-order schedule (Table 1), lesions of the nucleus accumbens and basolateral amygdala blocked the acquisition of cocaine-seeking (Whitelaw *et al*, 1996). Similarly, when the nucleus accumbens core was selectively lesioned on one side of the brain and combined with

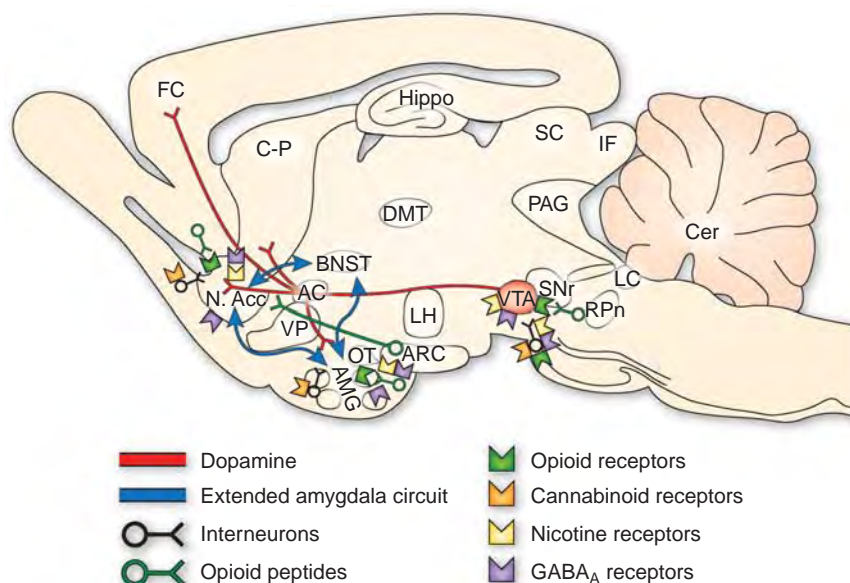Neurochemical neurocircuits in drug reward

Figure 1. Sagittal section through a representative rodent brain illustrating the pathways and receptor systems implicated in the acute reinforcing actions of drugs of abuse. Cocaine and amphetamines activate the release of dopamine in the nucleus accumbens and amygdala through direct actions on dopamine terminals. Opioids activate opioid receptors in the VTA, nucleus accumbens, and amygdala through direct or indirect actions via interneurons. Opioids facilitate the release of dopamine in the nucleus accumbens by an action either in the VTA or the nucleus accumbens, but also are hypothesized to activate elements independent of the dopamine system. Alcohol activates γ-aminobutyric acid-A (GABA$_A$) receptors or GABA release in the VTA, nucleus accumbens, and amygdala by either direct actions at the GABA$_A$ receptor or through indirect release of GABA. Alcohol is hypothesized to facilitate the release of opioid peptides in the VTA, nucleus accumbens, and central nucleus of the amygdala. Alcohol facilitates the release of dopamine in the nucleus accumbens through an action either in the VTA or the nucleus accumbens. Nicotine activates nicotinic acetylcholine receptors in the VTA, nucleus accumbens, and amygdala, either directly or indirectly, through actions on interneurons. Cannabinoids activate cannabinoid CB$_1$ receptors in the VTA, nucleus accumbens, and amygdala. Cannabinoids facilitate the release of dopamine in the nucleus accumbens through an unknown mechanism either in the VTA or the nucleus accumbens. The blue arrows represent the interactions within the extended amygdala system hypothesized to have a key function in drug reinforcement. The medial forebrain bundle represents ascending and descending projections between the ventral forebrain (nucleus accumbens, olfactory tubercle, septal area) and the ventral midbrain (VTA) (not shown in figure for clarity). AC, anterior commissure; AMG, amygdala; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; Cer, cerebellum; C-P, caudate-putamen; DMT, dorsomedial thalamus; FC, frontal cortex; Hippo, hippocampus; IF, inferior colliculus; LC, locus coeruleus; LH, lateral hypothalamus; N Acc., nucleus accumbens; OT, olfactory tract; PAG, periaqueductal gray; RPn, reticular pontine nucleus; SC, superior colliculus; SNr, substantia nigra pars reticulata; VP, ventral pallidum; VTA, ventral tegmental area (taken with permission from Koob, 2005).

dopamine receptor blockade in the contralateral dorsal striatum, no effect was observed in animals immediately after acquisition, but greatly decreased cocaine-seeking was observed in rats with stable responding on a second-order schedule (Belin and Everitt, 2008). These results suggest that the dorsal striatum may have a minor role in the acute reinforcing effects of psychostimulant drugs but a key role in the transition to compulsive use (Everitt et al, 2008).

Data with knockout mice also provide key insights into the role of dopamine in the rewarding effects of drugs of abuse. Genetically altered mice homozygous with a lack of the dopamine D$_1$ receptor do not self-administer cocaine (Caine et al, 2007). Although the initial report that dopamine transporter (DAT) knockout mice continued to self-administer cocaine (Rocha et al, 1998) questioned the function of the DAT in cocaine's reinforcing effects, a recent study showed that transgenic animals that expressed DAT that did not bind cocaine but that was functional as a dopamine reuptake carrier did not show cocaine reward measured by conditioned place preference (Chen et al,

2006a). These results support the hypothesis of a crucial role of the DAT in cocaine's reinforcing effects.

On the basis of this synthesis, an early neurobiological circuit for drug reward was proposed (Koob, 1992) that has been elaborated and expanded (Koob and Nestler, 1997; Figure 1). The starting point for the reward circuit was the medial forebrain bundle, composed of myelinated fibers connecting bidirectionally the olfactory tubercle and nucleus accumbens with the hypothalamus and VTA (Nauta and Haymaker, 1969) and including the ascending monoamine pathways such as the mesocorticolimbic dopamine system.

The initial action of drug reward was hypothesized to depend on dopamine release in the nucleus accumbens for cocaine, amphetamine, and nicotine; opioid peptide receptor activation in the VTA (dopamine activation) and nucleus accumbens (independent of dopamine activation) for opiates; and GABA$_A$ systems in the nucleus accumbens and amygdala for alcohol. The nucleus accumbens is situated strategically to receive important limbic information

from the amygdala, frontal cortex, and hippocampus that could be converted to motivational action through its connections with the extrapyramidal motor system. Thus, an early critical role for the nucleus accumbens was established for the acute reinforcing effects of drugs, with a supporting role for the CeA and ventral pallidum (Figures 1 and 2a).

Withdrawal/Negative Affect Stage

The neuroanatomical entity termed the extended amygdala (Heimer and Alheid, 1991) may represent a common anatomical substrate integrating brain arousal–stress systems with hedonic processing systems to produce the negative emotional states that promote negative reinforcement mechanisms associated with the development of addiction. The extended amygdala is composed of the CeA, bed nucleus of the stria terminalis (BNST), and a transition zone in the medial (shell) subregion of the nucleus accumbens (Figure 2b). Each of these regions has cytoarchitectural and circuitry similarities (Heimer and Alheid, 1991). The extended amygdala receives numerous afferents from limbic structures such as the basolateral amygdala and hippocampus and sends efferents to the medial part of the ventral pallidum and a large projection to the lateral hypothalamus, thus further defining the specific brain areas that interface classical limbic (emotional) structures with the output of extrapyramidal motor system (Alheid et al, 1995). The extended amygdala has long been hypothesized to have a key role not only in fear conditioning (Le Doux, 2000) but also in the emotional component of pain processing (Neugebauer et al, 2004).

Within-system neuroadaptations to chronic drug exposure include decreases in function of the neurotransmitter systems in the neurocircuits implicated in the acute reinforcing effects of drug of abuse. One prominent hypothesis is that dopamine systems are compromised in crucial phases of the addiction cycle, such as withdrawal, and lead to decreased motivation for nondrug-related stimuli and increased sensitivity to the abused drug (Melis et al, 2005; see brain imaging studies below). Psychostimulant withdrawal in humans is associated with fatigue, decreased mood and psychomotor retardation, and in animals is associated with decreased motivation to work for natural rewards (Barr and Phillips, 1999) and decreased locomotor activity (Pulvirenti and Koob, 1993), behavioral effects that may involve decreased dopaminergic function. Animals during amphetamine withdrawal show decreased responding on a progressive-ratio schedule for a sweet solution, and this decreased responding was reversed by the dopamine partial agonist terguride (Orsini et al, 2001), suggesting that low dopamine tone contributes to the motivational deficits associated with psychostimulant withdrawal. Decreases in activity of the mesolimbic dopamine system and decreases in serotonergic neurotransmission in the nucleus accumbens occur during acute drug withdrawal

from all major drugs of abuse in animal studies (Rossetti et al, 1992; Weiss et al, 1992, 1996).

A second component of the withdrawal/negative affect stage is a between-system neuroadaptation in which different neurochemical systems involved in stress modulation also may be engaged within the neurocircuitry of the brain stress and aversive systems in an attempt to overcome the chronic presence of the perturbing drug to restore normal function despite the presence of drug. Both the hypothalamic–pituitary–adrenal axis and the brain stress/aversive system mediated by corticotropin-releasing factor (CRF) are activated during withdrawal from chronic administration of all major drugs with abuse potential, with a common response of elevated adrenocorticotropic hormone, corticosterone, and amygdala CRF during acute withdrawal (Koob, 2008; Koob and Kreek, 2007). Acute withdrawal from all drugs of abuse also produces an aversive or anxiety-like state in which CRF and other stress-related systems (including noradrenergic pathways) have key roles.

The aversive stimulus effects of drug withdrawal can be measured using place aversion (Hand et al, 1988), and the opioid partial agonist buprenorphine dose dependently decreased the place aversion produced by precipitated opioid withdrawal. Systemic administration of a CRF_1 receptor antagonist and direct intracerebral administration of a peptide CRF_1/CRF_2 antagonist also decreased opioid withdrawal-induced place aversions (Stinus et al, 2005; Heinrichs et al, 1995). Functional noradrenergic antagonists administered directly into the BNST blocked opioid withdrawal-induced place aversion, implicating the importance of noradrenergic stimulation in the stress responses that follow acute drug withdrawal (Delfs et al, 2000). Indeed, classical medications used to treat physical withdrawal in heroin abusers and alcoholics include α-adrenergic drugs (eg, clonidine) that inhibit noradrenergic release and decrease some symptoms of alcohol and heroin withdrawal.

Another candidate for the aversive effects of drug withdrawal is dynorphin. Much evidence shows that dynorphin is increased in the nucleus accumbens in response to dopaminergic activation and, in turn, that overactivity of the dynorphin systems can decrease dopaminergic function. κ-Opioid agonists are aversive, and cocaine, opioid, and ethanol withdrawal is associated with increased dynorphin in the nucleus accumbens and/or amygdala (Koob, 2008). An exception is salvidorin A, which is a κ-agonist abused by humans, but this may reflect its hallucinogenic effects rather than any pleasurable properties (Gonzalez et al, 2006).

Another common between-system response to acute withdrawal and protracted abstinence from all major drugs of abuse is the manifestation of anxiety-like responses. For example, withdrawal from repeated administration of cocaine produces an anxiogenic-like response in the elevated plus maze and defensive burying test, both of which are reversed by CRF antagonists. Similarly, ethanol withdrawal produces anxiety-like behavior that is reversed
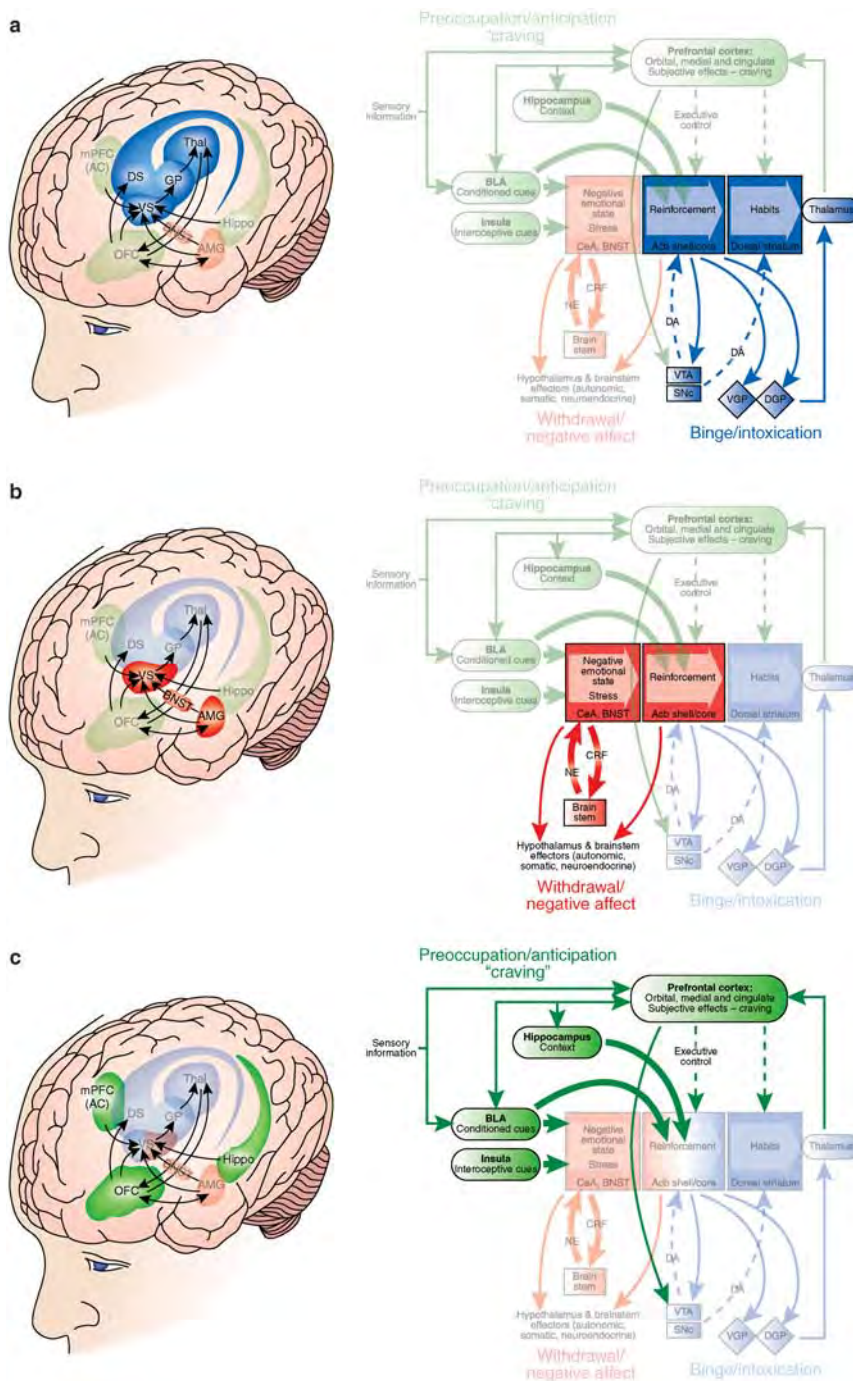
Figure 2. Neural circuitry associated with the three stages of the addiction cycle. (a) Binge/intoxication stage. Reinforcing effects of drugs may engage reward neurotransmitters and associative mechanisms in the nucleus accumbens shell and core and then engage stimulus–response habits that depend on the dorsal striatum. Two major neurotransmitters mediating the rewarding effects of drugs of abuse are dopamine and opioid peptides. (b) Withdrawal/negative affect stage. The negative emotional state of withdrawal may engage the activation of the extended amygdala. The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly a transition zone in the medial portion (or shell) of the nucleus accumbens. Major neurotransmitters in the extended amygdala hypothesized to have a function in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. Major projections of the extended amygdala are to the hypothalamus and brainstem. (c) Preoccupation/anticipation (craving) stage. This stage involves the processing of conditioned reinforcement in the BLA and the processing of contextual information by the hippocampus. Executive control depends on the prefrontal cortex and includes representation of contingencies, representation of outcomes, and their value and subjective states (ie, craving and, presumably, feelings) associated with drugs. The subjective effects termed drug craving in humans involve activation in functional imaging studies of the orbital and anterior cingulate cortices and temporal lobe, including the amygdala. A major neurotransmitter involved in the craving stage is glutamate localized in pathways from frontal regions and the BLA that project to the ventral striatum. Green/blue arrows, glutamatergic projections; orange arrows, dopaminergic projections; pink arrows, GABAergic projections; Acb, nucleus accumbens; BLA, basolateral amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; VGP, ventral globus pallidus; DGP, dorsal globus pallidus; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; NE, norepinephrine; CRF, corticotropin-releasing factor; PIT, Pavlovian instrumental transfer (modified with permission from Koob *et al*, 2008a).

by intracerebroventricular administration of CRF$_1$/CRF$_2$ peptidergic antagonists, systemic administration of a small molecule CRF$_1$ antagonist, and microinjection of a peptidergic CRF$_1$/CRF$_2$ antagonist into the amygdala (Funk *et al*, 2006; Koob, 2008). CRF antagonists injected intracerebroventricularly or systemically also block the potentiated anxiety-like responses to stressors observed during protracted abstinence from chronic ethanol, and the effects of CRF antagonists have been localized to the CeA (Koob, 2008). Precipitated withdrawal from nicotine produces anxiety-like responses that are also reversed by CRF antagonists (Tucci *et al*, 2003; George *et al*, 2007).

Thus, acute withdrawal is associated with within-system changes reflected in a decrease in dopaminergic activity in the mesolimbic dopamine system and with between-system recruitment of neurotransmitter systems that convey stress and anxiety-like effects such as CRF and dynorphin. Other neurotransmitter systems known to be involved in emotional dysregulation of the motivational effects of drug withdrawal include norepinephrine, substance P, vasopressin, neuropeptide Y (NPY), endocannabinoids, and nociceptin (Koob, 2008).

Preoccupation/Anticipation (Craving) Stage

The preoccupation/anticipation or craving stage of the addiction cycle has long been hypothesized to be a key element of relapse in humans and defines addiction as a chronic relapsing disorder. Although often linked to the construct of craving, craving *per se* has been difficult to measure clinically (Tiffany *et al*, 2000) and often does not correlate well with relapse. Nevertheless, the stage of the addiction cycle in which the individual reinstates drug-seeking behavior after abstinence remains a challenging focus for neurobiological mechanisms and medications development for treatment. Animal models of craving can be divided into two domains: drug-seeking induced by drug or stimuli paired with drug-taking, and drug-seeking induced by an acute stressor or a residual negative emotional state, often a state of stress, termed protracted abstinence (see Transition to addiction: patterns of drug-taking, animal models section).

Much evidence from animal studies suggests that drug-induced reinstatement is localized to the medial prefrontal cortex/nucleus accumbens/ventral pallidum circuit mediated by the neurotransmitter glutamate (McFarland and Kalivas, 2001). In contrast, cue-induced reinstatement appears to involve the basolateral amygdala as a critical substrate with a possible feed-forward mechanism through the prefrontal cortex system involved in drug-induced reinstatement (Everitt and Wolf, 2002; Weiss *et al*, 2001). The association of previously neutral stimuli paired with precipitated opioid withdrawal (conditioned withdrawal) also depends critically on the basolateral amygdala (Schulteis *et al*, 2000), and such stimuli may have motivational significance (Kenny *et al*, 2006). Neurocircuitry changes associated with drug- and cue-induced reinstatement after

extinction have been linked to a glutamatergic pathway from the prefrontal cortex to the nucleus accumbens core, the dopamine projection from the VTA to the medial prefrontal cortex, and the GABA projection from the nucleus accumbens to the ventral pallidum (Kalivas and O'Brien, 2008).

In contrast, stress-induced reinstatement of drug-related responding in animal models appears to depend on the activation of both CRF and norepinephrine in elements of the extended amygdala (both the CeA and BNST; for reviews, see Shaham *et al*, 2003; Shalev *et al*, 2002). Protracted abstinence, largely described in alcohol dependence models, appears to involve overactive glutamatergic and CRF systems, presumably in the extended amygdala, although to a large extent this remains to be explored (de Witte *et al*, 2005; Valdez *et al*, 2002).

Human subjects with cocaine addiction show impaired performance in tasks involving attention, cognitive flexibility, and delayed reward discounting that are mediated by the medial and orbital prefrontal cortices, as well as spatial, verbal, and recognition memory impairments that are mediated by the hippocampus, and these deficits can predict poor treatment outcomes (Aharonovich *et al*, 2006; Bolla *et al*, 2003). Parallel animal studies of the orbitofrontal, prefrontal cortex, and hippocampus in addiction using animal models have begun to show some of the deficits reflected in human studies. Experimenter-administered cocaine produced impairments in reversal learning (an orbital frontal task) in rats and monkeys (Jentsch *et al*, 2002; Schoenbaum *et al*, 2004; Calu *et al*, 2007). Perhaps even more compelling, animals allowed extended access, but not limited access, to cocaine showed deficits in working memory (a prefrontal-cortex-dependent task), sustained attention task (a prefrontal-cortex-dependent task), and an object recognition task (a hippocampus-dependent task; Briand *et al*, 2008a, b; George *et al*, 2008). In one study (Briand *et al*, 2008a), these deficits were associated with a significant decrease in dopamine D$_2$ receptor mRNA in the medial and orbital prefrontal cortices, an observation also consistent with human imaging studies. Thus, animal studies using models of compulsive stimulant administration are beginning to show deficits associated with human cocaine addiction (see Human studies: imaging and neuropsychopharmacology).

HUMAN STUDIES: IMAGING AND NEUROPSYCHOPHARMACOLOGY

As noted above, evidence from preclinical and clinical studies suggests that addiction represents sequential neuroadaptations. As a result, an initial impulsive action turns compulsive and becomes (eventually) chronic and relapsing. Work from imaging studies has provided evidence that this transition involves reprogramming of neuronal circuits that process (1) reward and motivation; (2) memory, conditioning, and habituation; (3) executive
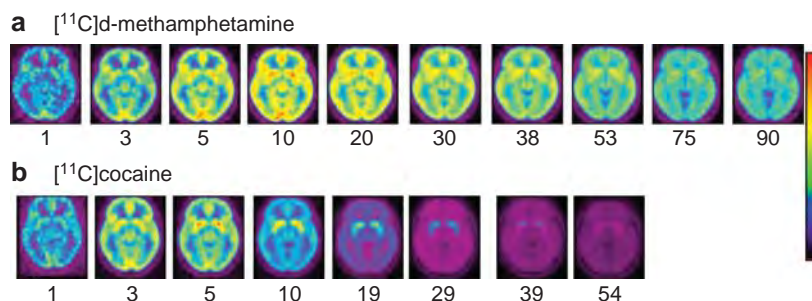
a [^{11}C]d-methamphetamine

1 3 5 10 20 30 38 53 75 90

b [^{11}C]cocaine

1 3 5 10 19 29 39 54

Figure 3. Brain images obtained at different times after administration for [^{11}C]D-methamphetamine and for [^{11}C]cocaine ($n = 19$ for each drug) showing axial planes at a level that transects the basal ganglia. Note the fast uptake of both drugs in the brain and the much slower clearance for [^{11}C]D-methamphetamine than for [^{11}C]cocaine (taken with permission from Fowler *et al*, 2008).

function and inhibitory control; (4) interoception and self-awareness; and (5) stress reactivity. This transition is heavily influenced by genetic, developmental, and environmental factors and their dynamic interactions, which will determine the course and severity of the addiction.

Similar to preclinical investigations, distinguishing the three stages in the recurring course of addiction in humans (intoxication, withdrawal, and craving/relapse) has been useful. The following sections describe these stages and some of the relevant neuronal circuits that underlie them.

Binge/Intoxication Stage

Most cases of addiction are initiated by the abuse of substances that are sought because of their hedonic properties. However, drug experimentation also results from the reinforcing effects of conforming to social groups (peer pressure) with the eventual subsequent transfer of motivation to taking the drug for its reinforcing effects. Infrequently, the first use of a drug may be related to its therapeutic properties (such as opiate analgesics for pain or stimulants for attention-deficit hyperactivity disorder). As shown by preclinical studies, a key element of the reinforcing effects of drugs is broadly accepted to involve their ability to trigger large increases in extracellular dopamine in limbic regions (including the nucleus accumbens). Although acute drug self-administration is a good animal model for drug intoxication, using animal models to assess the subjective correlates of drug-induced dopamine increases is difficult. Brain imaging studies in humans have been instrumental in showing that drug-induced increases in dopamine in the striatum (including the ventral striatum where the nucleus accumbens is located) are associated with subjective descriptors of reward (eg, pleasure, high, euphoria; Volkow *et al*, 1996b). Moreover, these studies have shown that fast dopamine changes are associated with the subjective perception of reward, whereas slow and stable dopamine increases do not induce these subjective responses (Grace, 2000; Volkow and Swanson, 2003).

The pharmacokinetic properties of drugs, which influence the speed of delivery into the brain as well as the duration of their actions, are key elements of their addiction potential. Pharmacokinetic properties determine the doses, routes of

administration, and frequency of drug use within a given binge episode. For example, comparison of the brain pharmacokinetics of cocaine and of methamphetamine reveals that both reach the brain very rapidly (although cocaine is somewhat faster than methamphetamine) but that cocaine clears out of the brain much faster than methamphetamine (Figure 3). This difference helps explain why cocaine is taken every 30–60 min during a binge, whereas methamphetamine is taken every couple of hours (Fowler *et al*, 2008). The importance of pharmacokinetics also helps explain why most abused drugs (with the exception of alcohol) are injected, smoked, or snorted. These routes allow for a much faster delivery of the drug to the brain than when taken orally (Volkow *et al*, 2000). Pharmacokinetics also help explain why stimulant drugs such as methylphenidate or amphetamine, which also increase dopamine, are not typically perceived as reinforcing when taken orally as prescribed therapeutically (Chait, 1994; Volkow *et al*, 2001b).

Clinical studies have also shown that the expectation of the drug's effects significantly influences the rewarding responses to drugs, such that the behavioral as well as regional brain activation response of the brain to the drug tends to be more intense when a rewarding drug is expected compared with when the same drug is received unexpectedly (Volkow *et al*, 2003). The dependency of the drug's rewarding effects on context and expectation suggests the importance of other neurotransmitters such as glutamate, which modulates the reactivity of dopamine cells and dopamine release in the nucleus accumbens, in the rewarding effects of drugs of abuse (Kalivas and Volkow, 2005).

Withdrawal/Negative Affect Stage

The response that follows the stage of drug intoxication differs markedly across drugs and is influenced by the chronicity and frequency of its abuse. For some drugs such as opiates, alcohol, and sedative hypnotics, drug discontinuation in chronic drug users can trigger an intense, acute physical withdrawal syndrome that, if not properly managed and when severe, can sometimes be fatal. All drugs of abuse are associated with a motivational withdrawal syndrome characterized by dysphoria, irritability, emotional

distress, and sleep disturbances that persist even after protracted withdrawal. The neurobiology of acute withdrawal is distinct from protracted or motivational withdrawal, and both contribute to relapse. Few imaging studies have been carried out during acute withdrawal. One such study that measured changes in dopamine during heroin withdrawal failed to document the dopamine decreases in the nucleus accumbens that had previously been reported with microdialysis in the rodent brain (Wang et al, 1997). From this study, it is unclear whether the results reflect the lack of involvement of striatal dopamine during acute withdrawal in heroin abusers or the limited sensitivity of the positron emission tomography (PET) technology.

The mechanisms underlying acute withdrawal are likely to be drug specific and reflect adaptations in the molecular targets of these drugs. For example, during the first few days of cocaine withdrawal, enhanced sensitivity of the brain to the effects of GABA-enhancing drugs occurs that may reflect the downregulation of this neurotransmitter with chronic cocaine use (Volkow et al, 1998). Similarly, brain imaging studies have also revealed decreases in endogenous opioids during cocaine withdrawal, which may contribute to the irritability, malaise, and dysphoria that occur during this phase of motivational withdrawal (Zubieta et al, 1996).

During protracted withdrawal, once the signs and symptoms of acute withdrawal have subsided, imaging studies have documented hypofunction in dopamine pathways, demonstrated by decreases in D_2 receptor expression and decreases in dopamine release, which may contribute to the anhedonia (ie, decreased sensitivity to rewarding stimuli) and amotivation reported by drug-addicted subjects during protracted withdrawal (Volkow et al, 1997b, 2007; Martinez et al, 2004, 2005). The decreased reactivity of dopamine to reinforcing stimuli is also present after protracted withdrawal from alcohol when acute physical withdrawal has subsided. In contrast to the decreased sensitivity to rewards (including drug rewards), imaging studies have reported that during detoxification, enhanced sensitivity to conditioned cues also occurs. Abstinence from smoking, for example, can dramatically potentiate neural responses to smoking-related cues (McClernon et al, 2009). These conditioned responses sustain the cycle of abstinence and relapse that characterizes substance use disorders (Childress et al, 1988).

In addition, imaging studies evaluating markers of brain function have shown that drug abusers tested during protracted detoxification show evidence of disrupted activity of frontal regions, including dorsolateral prefrontal regions, cingulate gyrus, and orbitofrontal cortex, which is hypothesized to underlie their impaired inhibitory control and impulsivity and contribute to relapse (see the following section for discussion).

Preoccupation/Anticipation (Craving) Stage

The enhanced sensitivity to conditioned cues, which include emotional states, triggers the latent preoccupation/ anticipation (craving) stage, which is characterized by an increase in drug craving. Indeed, stress is a powerful trigger of relapse to drug-taking behaviors through the activation of brain circuits involved in reward processing and in the attentional and mnemonic bias for drug use reminders (Duncan et al, 2007). This chronic relapse phenomenon is broadly recognized as one of the most challenging problems in fighting drug addiction. Addicted subjects are liable to return to compulsive drug-taking long after experiencing acute withdrawal symptoms (Langleben et al, 2008). The gradual reorganization of reward and memory circuits, brought about by chronic drug abuse, is hypothesized to be crucial to the mounting of these responses. Both dopamine and glutamate have been identified in preclinical studies as contributing to the neuroplastic changes associated with conditioned responses. Moreover, plastic changes in CRF and glucocorticoid receptors likely participate in the enhanced sensitivity to stressors. In humans, the lack of suitable radiotracers to assess glutamate neurotransmission and the lack of ligands for CRF or glucocorticoid receptors have limited the studies of craving mostly to the dopamine system.

NEUROCIRCUITRY DYNAMICS IN THE TRANSITION TO ADDICTION

The neurocircuitry outlined above forms the basis for the neuroplasticity associated with the development of addiction. Summarized below are neuroadaptive changes engaged within the circuits that represent the stages of the addiction cycle outlined above. Five circuits are hypothesized to be engaged in succession, including (1) mesolimbic dopamine system, (2) ventral striatum, (3) ventral striatum/ dorsal striatum/thalamus circuits, (4) dorsolateral frontal cortex/inferior frontal cortex/hippocampus circuits, and (5) extended amygdala (Figure 4). The relative weighting and direction of these neuroadaptive changes is illustrated in the circuit diagram of the addicted state (Figure 5).

Mesolimbic Dopamine System: Incentive Salience Pathways, Salience Attribution

One major hypothesis guiding the neuroplasticity associated with addiction is focused on the mesolimbic dopamine system. The hypothesis is that drugs of abuse, particularly cocaine and amphetamine, increase dopamine release in a more prolonged and unregulated manner than natural stimuli, resulting in changes in synaptic plasticity both within the dopamine system and in dopamine-receptive neurons (Wolf, 2002). These changes ultimately usurp normal learning mechanisms to shift neurocircuitry to associations or a form of habit-learning that persists in the face of significant adverse consequences (a component of compulsivity; Everitt and Wolf, 2002; Hyman et al, 2006).

Animal models of behavioral sensitization have focused largely on the increased locomotor-activating effects of psychomotor stimulant drugs in animals with a history of

stimulant exposure. Such studies have revealed a rich neuroplasticity associated with mesolimbic dopamine systems and its terminal projection to the ventral striatum (where the nucleus accumbens is located). Drugs of abuse induce short- and long-term modifications of firing of dopamine neurons in the VTA (Bonci *et al*, 2003). Studies
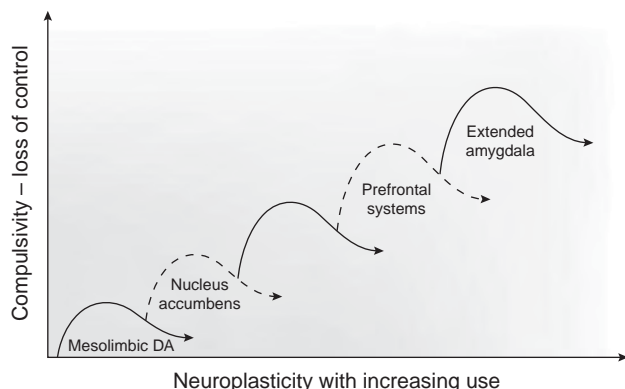

Figure 4. Schematic drawing describing the sequential and cumulative effects of neuroadaptive changes hypothesized to contribute to the neuroplasticity that promotes compulsive drug-seeking. An early neuroadaptation, common to all drugs of abuse and observed after a single injection of cocaine, is increased excitability of the mesolimbic dopamine system reflected in long-term potentiation dependent on changes in glutamate activity. Subsequently, the activation of dopamine contributes to increased excitability of the ventral striatum with decreased glutamatergic activity during withdrawal and increased glutamatergic activity during drug-primed and cue-induced drug-seeking. The engagement of ventral striatal-pallidal-thalamic loops is hypothesized to translate to the dorsal striatum to contribute to engagement of habits and automaticity that resemble compulsive-like behavior. As compulsivity evolves into full-blown addiction, loss of function occurs in the frontal cortex systems that control executive function, contributing to poor decision-making and gain of function in the brain stress systems but contributing to incentive salience for drugs over natural reinforcers.

have shown that burst firing of dopamine neurons in the VTA appears to be correlated with an orienting response to a sensory stimulus (Freeman *et al*, 1985). A single *in vivo* exposure to cocaine or amphetamine induces long-term potentiation (LTP) of AMPA-mediated excitatory neurotransmission in dopamine neurons (Ungless *et al*, 2001). The potentiation of synaptic AMPA responses has been hypothesized to increase the incidence of burst firing (Jones and Bonci, 2005). Persistent LTP lasting for 3 months of abstinence was induced in the VTA in rats that actively self-administered cocaine but not in passively injected rats (Chen *et al*, 2008). Similar effects of induction of LTP of glutamate transmission on dopamine neurons have been observed with morphine and nicotine (Saal *et al*, 2003).

However, more chronic repeated administration of psychostimulants failed to produce sensitization of mesolimbic dopamine activity as measured by *in vivo* microdialysis (Maisonneuve *et al*, 1995). In addition, extended access to cocaine fails to produce locomotor sensitization (Ben-Shahar *et al*, 2004) but does produce a sensitized stereotyped behavior response (Ferrario *et al*, 2005). Moreover, human cocaine abusers showed attenuated dopamine responses when challenged with a stimulant drug, which is opposite to that predicted by the enhanced sensitization of mesolimbic dopamine activity (Volkow *et al*, 1997b; Martinez *et al*, 2007).

Ventral Striatum: Incentive Salience Pathways, Salience Attribution

Another plasticity associated with behavioral sensitization is a persistent potentiation of nucleus accumbens excitatory synapses that is observed after repeated drug exposure followed by an extended drug-free period (Kourrich *et al*, 2007). Repeated cocaine administration increases glutamate
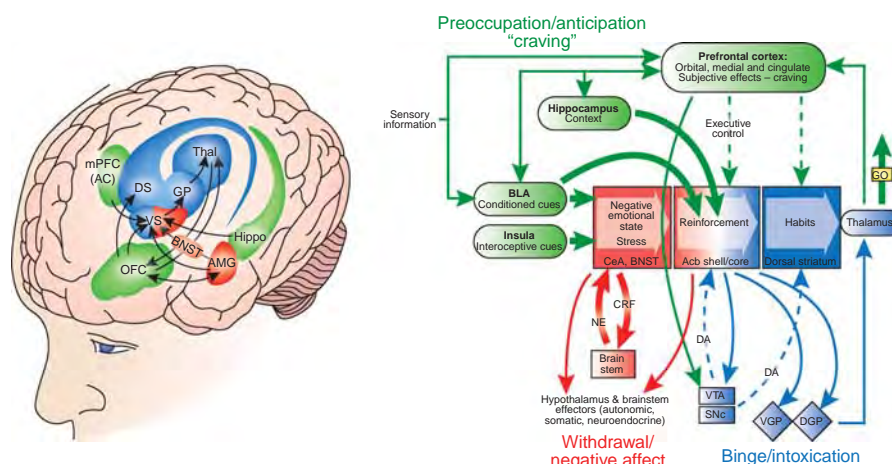

Figure 5. Neurocircuitry schematic illustrating the combination of neuroadaptations in the brain circuitry for the three stages of the addiction cycle that promote drug-seeking behavior in the addicted state. Note the activation of the ventral striatum/dorsal striatum/extended amygdala driven by cues through the hippocampus and basolateral amygdala and stress through the insula. The frontal cortex system is compromised, producing deficits in executive function and contributing to the incentive salience of drugs compared to natural reinforcers. Dopamine systems are compromised, and brain stress systems such as CRF are activated to reset further the salience of drugs and drug-related stimuli in the context of an aversive dysphoric state (modified with permission from Koob *et al*, 2008a).

neurotransmission only in rats that showed behavioral sensitization (Pierce *et al*, 1996). In addition, cocaine-sensitized mice showed an enhancement of LTP in nucleus accumbens slices during withdrawal, presumably reflecting increased activity of glutamatergic activity (Yao *et al*, 2004). An increased surface-to-intracellular ratio of glutamate-1 receptors (GluR1) has been observed 21 days after the last injection of cocaine, suggesting a slowly developing redistribution of AMPA receptors to the surface of nucleus accumbens neurons, particularly in those lacking GluR2 (Boudreau and Wolf, 2005; Conrad *et al*, 2008). The increases in cell-surface AMPA receptors depends on activation of dopamine D_1 receptors and subsequent protein kinase A signaling (Chao *et al*, 2002). Functionally, overexpression of GluR1 in the nucleus accumbens facilitated extinction of cocaine-seeking responses (Sutton *et al*, 2003) and increased brain stimulation reward thresholds, reflecting decreased reward and possibly decreased motivated behavior (Todtenkopf *et al*, 2006). However, a single reexposure to cocaine during extended withdrawal produced synaptic depression, which may reflect the enhanced glutamate release during cocaine reexposure (Kourrich *et al*, 2007). Curiously, the increase in AMPA receptor expression observed with cocaine does not occur in amphetamine-sensitized rats, leading to the hypothesis of different functional effects of glutamate projections to the nucleus accumbens during cocaine *vs* amphetamine withdrawal (Nelson *et al*, 2009).

Consistent with the results of altered glutamate neurotransmission in cocaine-sensitized rats, microdialysis and microinjection studies have shown that following chronic cocaine, decreased basal release of glutamate occurs but sensitized synaptic glutamate release during reinstatement of extinguished drug-seeking in rats (Kalivas and O'Brien, 2008; McFarland *et al*, 2003). This glutamate dysregulation has been hypothesized to be caused by decreased function of the cystine–glutamate exchanger (Baker *et al*, 2003) and desensitization of the metabotropic glutamate mGlu2/3 receptor. Lower basal levels of glutamate, combined with increased release of synaptic glutamate from activation of prefrontal cortex afferents to the nucleus accumbens, are hypothesized to result in a drive to engage in drug-seeking (Kalivas, 2004).

These long-lasting synaptic effects produce both a decrease in glutamate neurotransmission during chronic administration of the drug and a persistent increase in the efficacy of glutamatergic synaptic neurotransmission during reinstatement following withdrawal. These dynamic changes may promote cellular excitation, which has been hypothesized to be an important substrate for sensitization and drug-related learning in the addictive state (Kauer and Malenka, 2007; Wolf *et al*, 2004).

As previously suggested by animal models, the magnitude of striatal dopamine release (particularly in its ventral aspect) in humans correlates positively with the hedonic response to most drugs of abuse, including amphetamine (Drevets *et al*, 2001), cocaine (Volkow *et al*, 1997a), methylphenidate (Volkow *et al*, 2002), and nicotine (Sharma and Brody, 2009). The drug-dependent, fast, and supraphysiological increases in dopamine are likely to mimic the dopamine changes induced by the phasic dopamine cell firing that occurs in response to salient stimuli, thus categorizing the drug experience as one that is highly salient, an experiential outcome that commands attention and promotes arousal, conditioned learning, and motivation (Volkow *et al*, 2004b). On the basis of findings in laboratory animals, the frequent exposure to these drug responses in drug abusers is postulated to result in the recalibration of dopamine-activating (reward) thresholds for natural reinforcers.

Thus, one can envision the development of a change in firing in mesolimbic dopamine neurons that begins with one administration of the drug, develops into LTP first in the VTA then nucleus accumbens, and via feedback loops subsequently engages the dorsal striatum. Moreover, long-term changes in the CeA and medial prefrontal cortex may follow, and combined with dysregulation of the brain stress systems (see below) may provide a powerful drive for drug-seeking behavior even months after drug withdrawal (Figure 4 and 5).

Ventral Striatum/Dorsal Striatum/Thalamus: Voluntary to Habitual Drug-Seeking

The hypothesis that dorsal striatal circuitry has a key role in the development of habitual compulsive cocaine use is supported by data showing the importance for the dorsal striatum in stimulus–response habit learning (Yin *et al*, 2005) and microdialysis studies showing that prolonged cocaine-seeking increased dopamine release in the dorsal striatum but not ventral striatum (Ito *et al*, 2002). Disconnection of the ventral striatum from the dorsal striatum in rats self-administering cocaine on a second-order schedule only showed a deficit in animals with well-established 'compulsive' intake but not in animals that recently acquired the second-order schedule (Belin and Everitt, 2008). Thus, the hypothesis is that drug addiction represents changes in associative structures to become automatic or habitual and involves a gradual engagement of dorsal striatal mechanisms.

Animal studies have strongly suggested that with repeated drug exposure neutral stimuli that are associated with the drug can eventually acquire the ability to increase dopamine by themselves. Brain imaging studies confirmed this in addicted humans (Volkow *et al*, 2008a; Heinz *et al*, 2004). These studies showed that drug-associated cues induced dopamine increases in the dorsal striatum (caudate and putamen), an effect that correlated with self-reports of craving. The fact that the magnitude of the dopamine increases triggered by the cues was associated with the degree of addiction severity highlights the importance of these conditioned dopamine responses in the process of drug addiction in humans.

Clinical studies have also shown that the striatal slow dopamine increases induced by acute administration of oral methylphenidate do not elicit craving in cocaine abusers unless they are coupled to drug-associated cues (Volkow et al, 2008a). This most likely reflects the fact that the craving results from fast dopamine increases achieved with phasic dopamine firing, as opposed to slow dopamine increases achieved with tonic dopamine firing and in the experiment with oral methylphenidate. In fact, intravenous administration of methylphenidate, which results in fast dopamine increases, induces intense craving.

Brain imaging studies have also shown that, in drug-addicted subjects, these processes involve the orbitofrontal cortex, a brain region implicated in salience attribution and motivation, disruption of which results in compulsivity, and is a brain region with heavy projections to the dorsal striatum. The cingulate gyrus is also involved and is a brain region implicated in inhibitory control and conflict resolution, disruption of which results in impulsivity (Volkow et al, 2004b). Moreover, in cocaine-addicted, but not nonaddicted, subjects, the intravenous administration of methylphenidate, which cocaine abusers report has effects similar to those of cocaine, activated the orbital and medial prefrontal cortices, and this activation was associated with cocaine craving (Volkow et al, 2005). Similarly, in marijuana-addicted subjects, but not in nonaddicted individuals, acute administration of Δ^9-THC activated the obitofrontal cortex (Volkow et al, 1996a). Activation of the obitofrontal cortex and cingulate gyrus is also triggered by conditioned cues that predict reward and trigger craving (McClernon et al, 2009). Interestingly, these are regions that regulate dopamine cell firing and release, which have been postulated to be necessary for the enhanced incentive motivational values of drugs in addicted individuals (mirroring a hypothesis based on animal studies; Volkow et al, 1999). When combined, these observations strongly suggest that the dopamine increases associated with conditioned cues are not primary responses, but rather the result of feedback stimulation of dopamine cells, most likely glutamatergic afferents from the prefrontal cortex and/or amygdala. On the basis of these findings, the activation of the obitofrontal cortex, with concomitant increases in dopamine produced by the drug, has been hypothesized to contribute to the compulsive drug consumption that characterizes drug bingeing in addicted individuals (Volkow et al, 2007).

Indeed, human neuroimaging studies show that the prefrontal cortex (orbitofrontal, medial prefrontal, prelimbic/cingulate) and the basolateral amygdala are critical in drug- and cue-induced craving in humans (Franklin et al, 2007). In prefrontal regions (eg, cingulate gyrus and obitofrontal cortex), these changes have been associated with a reduction in striatal dopamine D_2 receptor availability observed in addicted subjects (Heinz et al, 2004; Volkow et al, 1993, 2001a, 2007). These associations could either reflect a disruption of frontal brain regions secondary to changes in striatal dopamine activity, or alternatively they could reflect a primary disruption of frontal regions that regulate dopamine cell activity. Indeed, a recent PET study provided evidence that prefrontal brain regions regulate the value of rewards by modulating dopamine increases in the ventral striatum, a regulatory mechanism that becomes dysfunctional in addicted individuals (Volkow et al, 2007).

Thus, concomitant dopamine and glutamate neurotransmission in the dorsal striatum, a region implicated in habit learning and action initiation, is involved in cue/context-dependent craving. As such, the dorsal striatum may be a fundamental component of addiction (Volkow et al, 2006). Research on novel strategies to inhibit cue-conditioned dopamine and glutamate responses is a major focus of current medications development efforts.

The thalamus has not been studied as extensively in the context of addiction. However, because of its integrative function in the regulation of arousal and attentional modulation, this region has been increasingly implicated in the addiction process. For example, intravenous administration of a stimulant drug in cocaine abusers, but not in controls, increased dopamine neurotransmission in the thalamus, an effect associated with craving (Volkow et al, 1997a). In contrast, compared with controls, cocaine abusers show hypoactivation of the thalamus, possibly reflecting noradrenergic and/or dopaminergic deficits, when performing a cognitive task (Tomasi et al, 2007b). Similarly, the thalamus was reported to show attenuated activation while performing a visual cognitive task in smokers exposed to nicotine (Sharma and Brody, 2009). These results suggest that thalamic abnormalities in cocaine abusers may contribute not only to impairments in sensory processing and attention but also to craving. Interestingly, changes in dopamine transmission in the thalamus and striatum appear to be involved in the deterioration of cognitive performance (eg, visual attention and working memory) that inexorably follows a period of sleep deprivation (Volkow et al, 2008b). Thus, more research that builds upon the available preliminary data is warranted.

Dorsolateral Frontal Cortex, Inferior Frontal Cortex, Hippocampus: Cognitive Control, Delayed Gratification, and Memory

Addiction also entails perturbations in cortically regulated cognitive and emotional processes, which cause the overvaluing of drug reinforcers at the expense of the undervaluing of natural reinforcers, and deficits in inhibitory control of drug responses (Goldstein and Volkow, 2002). As a result, an underperforming prefrontal system is widely believed to be crucial to the addiction process.

One of the components in such a system is impulse control, which is among the most robust cognitive risk factors for substance use disorders. Cocaine appears to have a direct effect on the neurobiology underlying impulse control. After an intravenous injection of cocaine, cocaine

users actually showed an improvement in a motor response inhibition task and concomitant increased activation in their right dorsolateral and inferior frontal cortices (Garavan *et al*, 2008). Because these areas are considered to be important in impulse control, this observation suggests that some of the acute effects of cocaine could in fact mediate a transient reversal of the chronic hypofunction in impulse control circuitry.

Another important function that resides in frontocortical areas is the ability to choose between small and immediate rewards compared to large but deferred rewards, which can be measured using a delayed discounting task. A recent study found that both the dorsolateral and inferolateral frontal cortex gray matter volumes inversely correlated with preference for immediate gratification during decision-making (Bjork *et al*, 2009). This finding suggests that abnormalities in frontocortical regions may underlie the inability to delay gratification, a trait that is characteristic of addiction and other psychiatric disorders.

The neural substrates of memory and conditioned learning are among the major circuits undergoing aberrant neuroadaptations in response to chronic drug exposure (Volkow *et al*, 2004a). Different memory systems have been proposed to be involved in drug addiction, including conditioned-incentive learning (via the nucleus accumbens and amygdala), habit learning (via the caudate and putamen), and declarative memory (via the hippocampus; White, 1996), which is the focus of this section.

Over the past decade, many provocative animal studies have suggested that addictive drugs can disrupt neurogenesis in the adult hippocampus (Canales, 2007). Damage to the ventral subiculum of the hippocampus was shown to affect cocaine self-administration in rats (Caine *et al*, 2001). Such observations have provided insights into the possible involvement of a dysregulated hippocampus in human addiction. This hypothesis is an extension of current knowledge because the hippocampus is broadly viewed as important in contextual conditioning, namely in the processing of contextual cues by which memories can be accessed and retrieved. In fact, declarative memory has been long recognized to be involved in learning and the linking of affective conditions or circumstances with drug-taking experiences. Studies with PET and functional magnetic resonance imaging have shown that cue-elicited craving, as well as acute intoxication, activates the hippocampus and amygdala (Volkow *et al*, 2004a). For example, the craving that cocaine users experience while exposed to drug-related stimuli is accompanied by blood flow increases in a distributed region implicated in several forms of memory, including the amygdala (Childress *et al*, 1999; Grant *et al*, 1996; Kilts *et al*, 2001) and hippocampus (Kilts *et al*, 2001).

Therefore, new approaches to disrupt memory reconsolidation may help erode the strong associations between context and drug (Lee, 2008; Lee *et al*, 2005). Interestingly, *β*-blockers have already shown a promising capacity to inhibit conditioned responses to both natural reinforcers and aversive stimuli (Miranda *et al*, 2003). Moreover, results from a more recent study suggest that drug-induced conditioned responses may also be sensitive to *β*-blockade treatment (Milton *et al*, 2008). Similarly, further research on GABA-enhancing drugs also seems warranted. GABAergic stimulation, which can attenuate Pavlovian conditioning, appears to disrupt the response to drugs of abuse in animals (Volkow *et al*, 2004a) and may be a useful strategy to treat addiction in humans (Dewey *et al*, 1998).

Extended Amygdala: Negative Reinforcement Pathways

Compulsive drug use defined by increased intake of drug with extended access is accompanied by a chronic perturbation in brain reward homeostasis using measures of brain stimulation reward thresholds. The differential exposure to drug self-administration has dramatic effects on reward thresholds that progressively increase (ie, decreased reward) in extended-access, but not in limited-access, rats across successive self-administration sessions (Ahmed *et al*, 2002; Kenny *et al*, 2006; Wee *et al*, unpublished results). Animals with extended access to cocaine are more sensitive to the blockade of self-administration by dopamine antagonists and partial agonists (Ahmed and Koob, 2004; Wee *et al*, 2007), and the opioid partial agonist buprenorphine dose dependently decreased heroin self-administration in extended-access, opioid-dependent rats (Chen *et al*, 2006b), suggesting that reversal of reward deficits can blunt the motivational drives of drug addiction. This mechanism could underlie the benefit of methadone and buprenorphine treatment in heroin addiction.

As noted above, CRF antagonists blocked the anxiogenic- and aversive-like effects of drug withdrawal, and withdrawal from all drugs of abuse activated CRF in the CeA. These observations led to the hypothesis that activation of CRF, specifically extrahypothalamic CRF in the CeA, contributed to the motivational state driving compulsivity from the negative reinforcement perspective (Koob and Le Moal, 2008). Thus, one would predict that blockade of the brain stress systems in animal models of extended access to drugs may block the motivation for excessive drug intake. CRF antagonists selectively blocked the increased self-administration of drugs associated with extended access to intravenous self-administration of cocaine, nicotine (Koob, 2008), heroin (Greenwell *et al*, 2009), and alcohol (Koob, 2008). A particularly dramatic example of the motivational effects of CRF in the extended amygdala in dependence can be observed in animal models of ethanol self-administration in dependent animals in which a $CRF_{1/2}$ peptide antagonist injected into the amygdala blocked the increase in ethanol self-administration during withdrawal (Funk *et al*, 2006; Koob, 2008).

Although less well developed, evidence suggests involvement of norepinephrine systems in the extended amygdala in the negative motivational state and increased self-administration associated with dependence (Koob, 2009b). Consistent with the

role of the dynorphin-κ opioid system in the aversive effects of drug withdrawal, a κ-opioid antagonist blocked the excessive drinking associated with ethanol withdrawal in dependent rats and selectively blocked the increased progressive-ratio performance in rats with extended access to cocaine (Koob, 2009b; Wee *et al*, 2009).

Neuropeptide Y has dramatic anxiolytic-like properties localized to the amygdala and has been hypothesized to have effects opposite to CRF in the negative motivational state of withdrawal from drugs of abuse (Heilig *et al*, 1994; Heilig and Koob, 2007). NPY administered intracerebroventricularly blocked the increased drug intake associated with ethanol dependence (Thorsell *et al*, 2005a, b). Injection of NPY into the CeA (Gilpin *et al*, 2008) and viral vector-enhanced expression of NPY in the CeA also blocked the increased drug intake associated with ethanol dependence (Thorsell *et al*, 2007).

Thus, the CRF increases in the CeA that occur with acute withdrawal from drugs have motivational significance not only for the anxiety/aversive-like effects of acute withdrawal but also for the increased drug intake associated with dependence. Acute withdrawal also may increase the release of norepinephrine in the BNST and dynorphin in the nucleus accumbens, both of which may contribute to the negative emotional state associated with dependence. Decreased activity of NPY in the CeA also may contribute to the anxiety-like state associated with ethanol dependence. Activation of brain stress systems (CRF, norepinephrine, dynorphin), combined with inactivation of brain antistress systems (NPY) in the extended amygdala may elicit powerful emotional dysregulation with motivational significance to addiction. A number of other neurotransmitter systems have been hypothesized to modulate the extended amygdala both from the stress-induction domain (vasopressin, substance P, orexin) and the antistress domain (nociceptin, endocannabinoids; for review, see Koob, 2008). Such dysregulation may be a significant contribution to the between-system opponent processes that help maintain dependence and also sets the stage for more prolonged state changes in emotionality such as protracted abstinence.

Research on negative reinforcement mechanisms in human addiction has been very limited. With cocaine, for example, the amygdala and lateral orbitofrontal cortex were shown to be activated by unexpected but not expected cocaine infusions in active cocaine abusers (Kufahl *et al*, 2008), but cocaine abstinence was associated with large reductions in the activity of dopamine projection regions, including the amygdala (Tomasi *et al*, 2007a). In apparent contrast, smoking abstinence was associated with increased cerebral blood flow in the extended amygdala, among other regions (Wang *et al*, 2007), whereas a nasal nicotine spray reduced regional cerebral blood flow in the right amygdala and left anterior temporal cortex of habitual smokers subjected to 12 h of smoking deprivation (Zubieta *et al*, 2001).

The amygdala may be equally important for processing positive reward (Murray, 2007) and reward expectancy (Holland and Gallagher, 2004), similar to processing negative reward. Particularly interesting in the context of brain imaging research will be to understand the function of the amygdala in generating the anxiety and negative emotion frequently seen during abstinence.

A recent report highlighted the importance in addiction of the interoceptive circuit that most likely interfaces with the extended amygdala and ventral striatum. The study showed that smokers with damage to their insula (but not smokers with extrainsular lesions) were able to stop smoking easily and without experiencing either cravings or relapse (Naqvi *et al*, 2007). The insula, particularly its more anterior regions, is reciprocally connected to several limbic regions (eg, ventromedial prefrontal cortex, amygdala, and ventral striatum) and appears to have an interoceptive function, integrating the autonomic and visceral information with emotion and motivation and providing conscious awareness of these urges (Naqvi and Bechara, 2009). Indeed, brain lesion studies suggest that the ventromedial prefrontal cortex and insula are necessary components of the distributed circuits that support emotional decision-making (Clark *et al*, 2008). Consistent with this hypothesis, many imaging studies show differential activation in the insula during craving (Naqvi and Bechara, 2009). The reactivity of this brain region has been suggested to serve as a biomarker to help predict relapse.

MOLECULAR TARGETS FOR NEUROPLASTICITY: BINGE/INTOXICATION, WITHDRAWAL/NEGATIVE AFFECT, AND PREOCCUPATION/ANTICIPATION (CRAVING)

The focus of the present review is on the neurocircuitry of addiction. However, parallel to the neuroplasticity of the neurocircuitry are the molecular changes that occur in these same structures. Chronic exposure to opiates and cocaine leads to activation of cyclic adenosine monophosphate response-element binding protein (CREB) in the nucleus accumbens and CeA (Shaw-Lutchman *et al*, 2002; Edwards *et al*, 2007). CREB can be phosphorylated by protein kinase A and by protein kinase regulated by growth factors, putting it at a point of convergence for several intracellular messenger pathways that can regulate gene expression. Activation of CREB in the nucleus accumbens with psychostimulant drugs is linked to the motivational symptoms of psychostimulant withdrawal, such as dysphoria, possibly through induction of the opioid peptide dynorphin, which binds to κ-opioid receptors and has been hypothesized to represent a mechanism of motivational tolerance and dependence (Nestler, 2005). Repeated CREB activation promotes dynorphin expression in the nucleus accumbens, which in turn decreases dopaminergic activity, both of which can contribute to negative emotional states. Extracellular signal-regulated kinase is another key element of intracellular signaling considered a key component in the plasticity associated with repeated administration of cocaine, specifically behavioral sensitization, cocaine reward,

and time-dependent increases in cocaine-seeking after withdrawal (ie, incubation effect; Lu *et al*, 2006; Li *et al*, 2008).

Another molecular target for regulating the plasticity that leads to addiction is dysregulation of cystine–glutamate exchange, which is hypothesized to promote pathological glutamate signaling related to several components of the addiction cycle. Here, repeated administration of cocaine blunts cystine–glutamate exchange, leading to reduced basal and increased cocaine-induced glutamate in the nucleus accumbens that persists for at least 3 weeks after the last cocaine treatment (Baker *et al*, 2003). Most compelling is the observation that treatment with *N*-acetylcysteine, by activating cystine–glutamate exchange, prevented cocaine-induced escalation and behavioral sensitization, restored the ability to induce LTP and long-term depression in the nucleus accumbens, and blunted reinstatement in animals and conditioned reactivity to drug cues in humans (Moussawi *et al*, 2009; LaRowe *et al*, 2007; Madayag *et al*, 2007).

CREB and other intracellular messengers can activate transcription factors, which can change gene expression and produce long-term changes in protein expression, and, as a result, neuronal function. Although acute administration of drugs of abuse can cause a rapid (within hours) activation of members of the Fos protein family, such as c-*fos*, FosB, Fra-1, and Fra-2 in the nucleus accumbens, other transcription factors, isoforms of ΔFosB, a highly stable form of FosB, have been shown to accumulate over longer periods of time (days) with repeated drug administration (Nestler, 2005). Animals with activated ΔFosB have exaggerated sensitivity to the rewarding effects of drugs of abuse, and ΔFosB may be a sustained molecular 'switch' that helps to initiate and maintain a state of addiction (McClung *et al*, 2004). Whether (and how) such transcription factors influence the function of the brain stress systems, such as CRF and those described above, remains to be determined.

SUMMARY AND CONCLUSIONS

In summary, multiple brain regions and circuits are disrupted in drug addiction and are likely to contribute differentially to the complex phenotype observed in addicted individuals (Figure 5). Although some of these functional abnormalities may be present to a greater or lesser extent across all classes of drug addictions, some of the changes may be specific to certain types of drugs. For example, long-lasting decrements in the DAT in the striatum are observed in methamphetamine but not in alcohol or cocaine addictions. Conversely, decrements in dopamine D_2 receptors in the striatum are observed in subjects addicted to all of the drugs of abuse that have been investigated, and increased activation of brain stress systems such as CRF has been observed in animal models during acute withdrawal for all types of drugs. Importantly, the neuronal abnormalities that become manifest in an addicted individual and that can be uncovered by imaging and/or neuropsychopharmacological studies are a reflection of not only a given chronic drug exposure trajectory, but also an individual's specific constellations of genetic, developmental, and environmental characteristics.

FUTURE RESEARCH DIRECTIONS

The advances outlined above point the way to future directions for research in the neurocircuitry of addiction in the same conceptual framework of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. The rich resources of modern neurosciences applied to the neurobiology of addiction offer an opportunity to not only understand the neurocircuitry of the addiction process but also to provide the keys to understanding vulnerability and providing treatment for this devastating disease.

In the binge/intoxication stage of the addiction cycle, how neuroplasticity that begins with a change in firing in mesolimbic dopamine neurons during initial drug exposure is translated to engagement of the dorsal striatum, disruption of frontal system function, and recruitment of brain stress systems and results in a residual powerful drive for drug-seeking behavior even months after withdrawal remains to be determined. For example, what is the relationship between vulnerability to impulsivity and subsequent compulsivity in the neuroplasticity of the circuits described above? Such future studies may involve molecular genetic approaches that range from selective breeding to upregulation or knockdown of molecular mechanisms within specific brain circuits using short-hairpin RNA technology.

In the withdrawal/negative affect stage, engagement of the brain stress systems, such as CRF, in animal models needs to be extended to other interactive brain stress systems and explored in human studies. Numerous other neurotransmitter systems that interact with the brain stress system are only now being explored, such as dynorphin, NPY, substance P, nociceptin, and orexin. Virtually unexplored at this stage are human imaging studies of this component of the addiction cycle and human imaging of brain neurotransmitter systems implicated in motivational aspects of drug withdrawal. The development of novel radioactive ligands for human imaging studies that bind to the receptors of the above neurotransmitter systems would be a great boost to the field.

In the preoccupation/anticipation stage, human neuroimaging studies show that the prefrontal cortex (orbitofrontal, medial prefrontal, prelimbic/cingulate) and the basolateral amygdala are critical in drug- and cue-induced craving. Whether such associations reflect a disruption of frontal brain regions secondary to changes in striatal dopamine activity, or alternatively reflect a primary disruption of frontal regions that regulate dopamine cell activity, remains to be determined. New approaches to the study of memory reconsolidation may help elucidate the

strong associations between context and drug. The importance in addiction of the interoceptive circuit involving the insula and other regions that most likely interface with the extended amygdala and ventral striatum remains to be determined. The reactivity of these brain circuits may serve as a biomarker to help predict relapse and help predict treatment efficacy. Human post-mortem studies, human laboratory studies, and neurocircuitry studies in parallel animal models will likely yield promising results in this domain.

Finally, molecular and genetic changes that convey the changes in activity of the neurocircuits in all three stages of the addiction cycle described above are only now being elucidated. Changes in transmitter regulatory systems, transcription factors, and even gene regulation at the epigenetic level may explain how circuits are dysregulated, stay dysregulated, and provide vulnerability to dysregulation initially or long into abstinence. Ultimately, neurobiological targets elucidated through the framework of the neurocircuitry of addiction will provide targets for identifying genetic vulnerability in the human population, and genetic vulnerability in the human studies may identify novel targets to be explored at the mechanistic level in animal studies.

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DISCLOSURE

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Impact of quitting smoking and smoking cessation treatment on substance use outcomes: An updated and narrative review

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HIGHLIGHTS

- Quitting smoking/smoking cessation has a positive effect on substance use outcomes.
- Improvement in a range of alcohol and drug use outcomes was reported.
- Smoke-free policy nor cessation intervention worsened SUD treatment outcomes.
- Smoking cessation aid should be offered to any individual who reports substance use.
- Not offering smoking cessation in SUD treatment is tantamount to increased harm.

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ABSTRACT

Background: Historically, smoking cessation was thought to negatively impact substance use outcomes among smokers who use other substances. We sought to synthesize recent reports on this association.
Methods: Google Scholar, PubMed, and Cinahl were searched for studies published from 2006 to March 29, 2016 that reported impact of smoking cessation treatment or quitting smoking on substance use or substance use disorder treatment outcomes in the general population and among those in substance abuse treatment. Studies were grouped by reported impact as follows: "positive" (i.e. improved), "null" (i.e. no change), or "negative" (i.e. worsened).
Results: Twenty-four studies were included. Eighteen reported the impact of quitting smoking and six reported the impact of smoking cessation treatment intervention, independent of quitting, on substance use outcomes. Eleven studies (46%) reported solely positive impact; four (17%) reported solely null impact; eight (33%) reported mixed positive and null impact by analysis (combined and subgroup, $n = 1$); substance ($n = 4$); length of follow-up ($n = 2$); and comparison group ($n = 1$). One study (4%) reported mixed negative and null impact by ethnic group. No studies reported increased substance use.
Conclusion: Smoking cessation does not appear to have a negative effect, and often has a positive effect on substance use outcomes. Smoking cessation advice should be offered, without hesitation, to smokers who report substance use and those in treatment for substance use disorder.

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Contents

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1. Introduction

Smoking rates are two to four times higher among adolescents and adults with substance use disorders (SUD) compared to the general population (Compton et al., 2007; Guydish et al., 2015; Kalman et al., 2005). Still, smoking cessation treatment is not included in most SUD treatment settings (Dawson et al., 2013; Piper et al., 2013) and there is a dearth of reporting on the impact of quitting smoking on substance use behaviors in non-treatment seeking populations. Smoking has had a steady, long-term relationship with both clinicians and patients in substance use and mental health treatment settings, making these settings less receptive to smoking cessation treatment and less supportive of quitting than providers in general medical facilities or the community (Metrik et al., 2011; Tsoh et al., 2011). Historically, smoking was allowed and even encouraged in addiction treatment programs and in mental health units, the pervasive rationale being that tobacco was a lower treatment priority and/or a less harmful alternative to other substance use (Piper et al., 2013; Brown et al., 2009; de Dios et al., 2009). Arguments proffered by treatment providers included if their patients quit tobacco they would relapse on other substances of abuse, their depression would recur and/or they would otherwise decompensate (Myers et al., 2007). Meanwhile, just below the surface, the tobacco industry was marketing cigarettes to persons with mental illness and providing tax-free cigarettes to treatment facilities (Satre et al., 2007) where cigarettes were provided to patients, facilitating smoking initiation, while hospitalized, for some formerly nonsmoking patients (Alessi & Petry, 2014; Kahler et al., 2010). Finally, many staff and clinicians in the fields of drug abuse treatment and mental health are smokers, which serves to both perpetuate the habit and stem implementation of smoking cessation programs and smoke free policies in these settings (Callaghan et al., 2007; Rohsenow et al., 2015; Lisha et al., 2014; Reitzel et al., 2014).

Many adults and adolescents attend 12-step fellowship meetings such as Alcoholics Anonymous or Narcotics Anonymous to achieve abstinence or as a form of relapse prevention upon completion of formal SUD treatment (Winhusen et al., 2014; Stahre et al., 2013). The 12-step philosophy, which teaches that the first and primary responsibility is sobriety from alcohol, illegal drugs, and non-prescription medications (Campbell et al., 2009; Myers & Prochaska, 2008; Prochaska et al., 2008) can further perpetuate continued smoking by recommending members focus and not make too many additional changes (i.e. quitting smoking) (Myers & Prochaska, 2008; Prochaska et al., 2008; Brook et al., 2007). Meetings often allow or encourage smoking as a form of "fellowshipping" to enhance recovery, thereby helping to maintain smoking and nicotine dependence among individuals who report use of other substances (Caldwell & Cutter, 1998; Laudet et al., 2006).

Evidence is mounting that the harms of tobacco use far outweigh any perceived benefit in the context of substance use or SUD treatment. For example, adolescent substance users who smoke are more likely to continue smoking in adulthood (Orlando et al., 2005) and far more deaths among adults reporting alcohol and drug use are due to smoking than to alcohol and all other drugs combined (Baca & Yahne, 2009). In 2004, a meta-analysis of smoking cessation intervention studies conducted among individuals in SUD treatment or recovery found that cessation interventions offered concurrently with addictions treatment

were associated with a 25% increased likelihood of long-term drug and alcohol abstinence (Prochaska et al., 2004). Thus, fears associated with smoking cessation among people with SUD may be unwarranted.

Studies have increasingly addressed smoking cessation in the context of SUD treatment over the last decade. Strategies for promoting smoking cessation have included delivering cessation programs to individuals in SUD treatment and implementing and enforcing smoking bans in adult and adolescent treatment facilities (Brown et al., 2009; Callaghan et al., 2007; Lawn & Campion, 2013.) In 2010, two literature reviews summarized the evidence on the effects of smoking cessation in the context of SUD treatment: one among those in treatment for or in early remission from alcohol dependence (Kalman et al., 2010); and one in addiction and mental health treatment settings (Myers et al., 2007). Both studies found improved rather than worsened substance use treatment outcomes related to smoking cessation intervention. In 2015, a systematic review of randomized controlled trials that included impact of smoking cessation treatment on substance use outcomes among those in early recovery from or in treatment for SUD reported either no impact on or improvement in substance use treatment outcomes (Thurgood et al., 2015). With limited extant research, no reviews among adolescent populations were identified. One study (2007) conducted in adolescent residential substance use treatment programs assessed the relationship between program-level policies and client-level smoking, and showed increases in stringency of smoke-free policy were associated with decreases in smoking prevalence (Chun et al., 2007). These findings suggest addressing tobacco use in the context of addiction treatment and recovery may afford patients multiple health benefits now and in the future.

Here, we provide an updated review and interpretation of the most current knowledge by reviewing reports from the last decade (January 2006 through March 2016) on the impact of formalized smoking cessation treatment or of quitting smoking/former smoker status on substance use outcomes. By synthesizing recent findings and including studies with adolescents, reports from epidemiological studies, and results from pilot studies and secondary analyses, we fill important gaps in the extant literature. Whereas reports from 2010 (Kalman et al., 2010) and 2015 (Thurgood et al., 2015) have addressed solely formal smoking cessation treatment interventions among those in treatment for or recovery from substance use (including alcohol) this report includes findings among non-SUD treatment seeking populations including reports published from 2015 through March 2016 as well. This allows for a broader, more inclusive view of the overarching impact of smoking cessation and quitting smoking on substance use outcomes.

2. Methods

Articles published in print or online between January 1, 2006 and March 29, 2016 were identified through electronic searches of Google Scholar, PubMed, and Cinahl. Google Scholar was chosen for breadth and as a more novel search tool; PubMed as a standard search engine; and Cinahl for its inclusion of peer-reviewed nursing and nursing practice journals not easily identified elsewhere. Search criteria combined the terms "smoking" "cessation" "substance" "drug," and "alcohol." Study title, abstracts, and bodies were reviewed by KM and JT to determine study inclusion. Selection was restricted to English language

studies that: (a) established temporality (i.e. cross sectional studies were excluded), (b) listed at least one outcome related to substance use, SUD, or SUD treatment, and (c) identified quitting smoking ("former smoker status") or a smoking cessation treatment intervention as an independent variable. To avoid duplicative reporting and in light of the similarity in conclusions drawn by the three reviews conducted over the past decade (Prochaska, 2010; Kalman et al., 2010; Thurgood et al., 2015) the reviews and the studies included within were omitted.

Titles of the first 100 citations in Google Scholar were scanned and 35 unique and potentially relevant citations were identified. Google Scholar has been found to have recall and precision comparable or superior to more traditional databases when the first 100 citations are considered (over 84,000 citations were identified in the instant search). (Walters, 2009) PubMed and Cinahl were then searched using the same search terms and resulted in 50 unique citations (35 and 15, respectively). No additional studies were identified through bibliographic searches. The 85 articles identified were read by JT and KM to ascertain if they met inclusion criteria and 24 studies were included in the review.

As the 24 selected studies showed considerable heterogeneity in terms of measurement of smoking cessation intervention or quit status, outcome variables, and analyses, it was not feasible to conduct a meta-analysis focused on effect size (Moher et al., 2009). In accordance with the "principle of best evidence" (Slavin, 1995), we did not discard studies without the information necessary for formal quantification since they still provide valuable and relevant evidence. We then appraised each study for overall impact on substance use outcomes as positive, null, mixed, or negative. Within each study, impact was assessed for each reported substance use outcome. Overall impact was deemed "positive" if only improvements were reported on all substance-related outcomes assessed (e.g. increased length of time to relapse, decreased number of days using drugs). "Null" impact was assigned if no change in any substance use outcomes was reported. A "negative" impact was assigned if worse substance use outcomes were found (e.g. shorter term of abstinence). A "mixed" impact was assigned if there were differences in the direction of individual outcomes within a study.

3. Results

Twenty-four studies (25 study populations as one study (Lisha et al., 2014) included two samples) reported the impact of quitting smoking ($n = 18$) or of smoking cessation treatment intervention, independent of quitting smoking ($n = 6$), on substance use outcomes (Table 1). Fourteen studies were among SUD treatment samples (five among adolescents); two in household survey samples, one in a school-based survey sample (among adolescents); four among samples seeking smoking cessation treatment; and one each of high-needs population samples: HIV positive patients, homeless smokers, and smokers in mental health outpatient and inpatient (adolescent) treatment (Fig. 1).

3.1. Positive findings

Eleven of 24 studies (46%) reported positive findings regarding the impact of quitting smoking ($n = 9$) (Berg et al., 2015; Cavazos-Rehg et al., 2014; Dawson et al., 2013; Piper et al., 2013; Tsoh et al., 2011; de Dios et al., 2009; Myers et al., 2007; Satre et al., 2007; Magee & Winhusen, 2015) and of smoking cessation treatment interventions ($n = 2$) (Brown et al., 2009; Metrik et al., 2011) on substance use outcomes. Of these, five were among patients in SUD treatment - (Tsoh et al., 2011; de Dios et al., 2009; Myers et al., 2007; Satre et al., 2007; Magee & Winhusen, 2015) of which two targeted adolescents (de Dios et al., 2009; Myers et al., 2007) four were among participants delivered smoking cessation interventions (Brown et al., 2009; Berg et al., 2015; Piper et al., 2013; Metrik et al., 2011), of which one study targeted adolescents during psychiatric hospitalization (Brown et al., 2009), and two were among adult general population samples (Cavazos-Rehg et al., 2014; Dawson et al., 2013) (Fig. 2).

Of the 11 studies with positive findings, eight (73%) found improved alcohol-specific outcomes of fewer drinks per day (Berg et al., 2015), fewer drinks per week (Metrik et al., 2011), decreased likelihood of relapse (de Dios et al., 2009), increased abstinence for 12 months (Dawson et al., 2013; Tsoh et al., 2011) and for 30 days (Satre et al., 2007), increased likelihood of "alcohol-abstainer" trajectory membership (Myers et al., 2007), and decreased likelihood of being diagnosed with alcohol use disorder (Cavazos-Rehg et al., 2014). Five studies (45%) reported drug-specific outcomes or general "drug" outcomes that excluded alcohol; one found increased likelihood of past year abstinence from drugs (Tsoh et al., 2011), one found decreased likelihood of being diagnosed with a drug use disorder (Cavazos-Rehg et al., 2014), two found improved marijuana-specific outcomes of reduced percent of using days (Metrik et al., 2011) and decreased likelihood of relapse and longer time to relapse (de Dios et al., 2009) and one found reduced stimulant craving (Magee & Winhusen, 2015). Finally, among studies that reported improved combined (e.g. alcohol and other drugs) substance use outcomes ($n = 4$; 36%), findings of decreased likelihood of SUD diagnosis (Piper et al., 2013), past-year remission (Tsoh et al., 2011), decreased escalation of use post-treatment (Brown et al., 2009), and increased likelihood of past 30-day abstinence and lower addiction severity index (ASI) scores (Satre et al., 2007) were found.

3.2. Null findings

Four studies (17%) reported an overall null impact on substance use outcomes. Study designs varied (pro- and retrospective cohort studies and RCT) as did outcomes: drinking and drug use behavior, treatment enrollment and completion, study attendance and adherence. Sample populations also varied widely: general population adults, and adolescents, adults in SUD treatment, adolescents in SUD treatment, and adults seeking smoking cessation treatment. The studies investigated quitting smoking as well as effects of different smoking cessation interventions (implementation of a smoking ban, contingent vs. non-contingent vouchers crossed with motivational interviewing or brief advice, contingency management vs. behavioral support).

One study reported no change in the alcohol-specific outcomes of binge- and overall drinking frequency (Kahler et al., 2010). Another found no difference in SUD treatment enrollment or completion (Callaghan et al., 2007). The third study showed no difference in reported number of heavy drinking days, number of drug use days, and instances of reported relapse (Rohsenow et al., 2015). The fourth study found no differences in study attendance and adherence and no difference in reported and verified substance use abstinence (Alessi & Petry, 2014). Given the sample sizes of 45 (Alessi & Petry, 2014), 54 (Myers & Prochaska, 2008), and 184 (Rohsenow et al., 2015), it is possible (but not likely) that the null findings were due to small sample sizes and thus low power to detect an effect.

3.3. Mixed findings

Nine studies (38%) reported mixed findings: eight studies (89%) reported mixed positive and null impact by analysis (combined and subgroup, $n = 1$) (Lisha et al., 2014); type of substance ($n = 4$) (Prochaska et al., 2008; Reitzel et al., 2014; Winhusen et al., 2014; Campbell et al., 2009); length of follow-up ($n = 2$) (Stahre et al., 2013; Myers & Prochaska, 2008); and comparison group ($n = 1$). (Brook et al., 2007) Six studies (Prochaska et al., 2008; Lisha et al., 2014; Reitzel et al., 2014; Winhusen et al., 2014; Campbell et al., 2009; Brook et al., 2007) addressed quitting smoking and three were smoking cessation treatment interventions (Stahre et al., 2013; Myers & Prochaska, 2008; Fu et al., 2008). Five were among SUD treatment seeking samples (Lisha et al., 2014; Winhusen et al., 2014; Campbell et al., 2009; Myers & Prochaska, 2008; Fu et al., 2008), three were among adolescents (Campbell et al., 2009; Myers & Prochaska, 2008; Brook et al., 2007), two in general population samples (Stahre et al., 2013; Brook et

Table 1
Studies examining the effect of tobacco cessation or quitting smoking on substance use outcomes (N = 24).

Authors (year)	Study design	Sample description*	Smoking variable assessed	SU outcome of interest	Cessation/treatment	Synopsis of findings
Positive impact						
Berg, Piper, Smith, Fiore, Jorenby (2015)	Secondary analysis of RCT, bupropion, NRT, counseling	N = 1301, mean age 45, 59% female, 84% white, 48% history alcohol abuse, 10% history of alcohol dependence, smokers	N/A, investigated changes pre and post target quit date	Mean number of drinks per day 2 weeks pre and post target quit date	Smoking cessation	*Positive* Generally, alcohol use decreased post-target quit date. Smokers who reported less pre-quit alcohol use, as well as smokers who were female, non-white, and had a history of alcohol dependence tended to use less alcohol post-quit
Magee, Winhusen (2015)	Secondary analysis of multi-site RCT, SUD treatment with or without smoking cessation treatment, counseling, bupropion, contingency management	N = 538, mean age 36, 48% female, adults with cocaine or methamphetamine SUD	N/A, investigated impact of smoking cessation intervention	Stimulant craving	Smoking cessation	*Positive* Smoking cessation eliminated coupling between nicotine craving and stimulant craving, $\gamma = -0.07$, $p = 0.39$. Conclusions: Contrary to concerns about nicotine abstinence during substance dependence treatment, increases in nicotine craving may be associated with later reductions in stimulant craving and use
Cavazos-Rehg, Breslau, Hatsukami, Krauss, Spitznagel, Grucza, Salyer, Hartz, Bierut (2014)	Prospective cohort, NESARC	N = 4853, adults, 48% female, 77% white	Usual number of cigarettes per day, self-report	Past year diagnosis DSM-IV alcohol use disorder or drug use disorder	Smoking cessation	*Positive* Among daily smokers who had current or lifetime history diagnosis of the outcome of interest at Wave 1, quitting by Wave 2 predicted a decreased risk of mood/anxiety disorder (aOR 0.6, 95% CI 0.4, 0.9) and alcohol disorder (aOR 0.7, 95% CI 0.5, 0.99) at Wave 2. Among daily smokers with no lifetime history diagnosis of the outcome of interest at Wave 1, quitting smoking by Wave 2 predicted a decreased risk of drug use disorder at Wave 2 aOR 0.3, 95% CI 0.1, 0.9).
Dawson, Goldstein, Grant (2013)	Prospective cohort	N = 14,885, adult past-year ≥ monthly drinkers	Smokers at baseline but not during year preceding follow-up, self-report	One year alcohol abstinence	Smoking cessation	*Positive* Smoking cessation associated with drinking cessation over follow-up, OR = 2.82 (95% CI = 1.62–4.92) to 3.45 (2.20–5.39)
Piper, Rodock, Cook, Schlam, Fiore, Baker (2013)	RCT, bupropion, NRT, counseling	N = 1470, mean age 45, 58% female, 84% white, smokers	7-Day point prevalence abstinence, biochemically verified (breath CO)	Past year SUD diagnosis	Smoking cessation	*Positive* Participants who were smoking at the Year 3 follow-up were more likely to have developed and maintained a substance use or major depressive disorder by that time than were individuals who were abstinent at Year 3
Metrik, Spillane, Leventhal, Kahler (2011)	RCT, counseling, NRT, brief alcohol intervention	N = 216, mean age 42, 45% female, 91% white, heavy drinkers seeking smoking cessation treatment	N/A, investigated impact of smoking cessation intervention	Number of drinks/week, percent of marijuana use days	Smoking cessation treatment intervention	*Positive* All participants made large reductions in weekly alcohol consumption during the trial, with weekly marijuana users also reducing their marijuana use. Frequent marijuana smokers may benefit from smoking cessation even when not explicitly discussed
Tsoh, Chi, Mertens, Weisner (2011)	Retrospective cohort/chart review	N = 1951, adults, 39% female, 75% white, Kaiser patients from 1994 to 98	Current cigarette smoking, self-report	1 year alcohol or drug abstinence at 5, 7, and 9 years; past-year remission SUD	Smoking cessation	*Positive* Stopping smoking during the first year after substance use treatment intake predicted better long-term substance use outcomes through 9 years after intake
Brown, Strong, Abrantes, Myers, Ramsey, Kahler (2009)	RCT, motivational interviewing, brief advice	N = 191, adolescents mean age 15, 62% female, 95% white, mental hospital inpatients	N/A, investigated impact of smoking cessation intervention	Percentage of days with substance use (alcohol and illicit drugs)	Smoking cessation treatment intervention	*Positive* The results of this study suggest that MI for smoking cessation had a significant effect in preventing an increase in substance use during

						the first 6 months following hospitalization
de Dios, Vaughan, Stanton, Niaura (2009)	Multi-site prospective cohort	$N = 1779$, adolescents mean age 16, 30% female, 57% white, in SUD treatment	Current cigarette smoking, self-report	Relapse to alcohol and marijuana; time to relapse to alcohol and marijuana	Smoking cessation	*Positive* Persistent smokers and smoking initiators had significantly greater odds of alcohol and marijuana relapse and shorter periods to marijuana relapse at follow-up compared with quitters
Myers, Doran, Brown (2007)	Prospective cohort, secondary analysis	$N = 123$, adolescents, mean age 16, 41% female, 81% white, in SUD treatment	Smoking abstinence for >1 year, self-report	Alcohol use trajectory (abstainers, infrequent drinkers, worse over time, frequent drinkers)	Smoking cessation	*Positive* Larger proportion of quitters (v. persistent smokers) were alcohol abstainers compared to frequent drinkers
Satre, Kohn, Weisner (2007)	Prospective cohort	$N = 598$, smokers: $n = 315$, mean age 36, 44% female, 76% white, non-smokers: $n = 283$, mean age 40, 42% female, 71% white, Kaiser, CA, admitted 1997–1998, health plan members	Current cigarette smoking, self-report	Addiction Severity Index scores, 30 day abstinence from alcohol and drugs	Smoking cessation	*Positive* Smokers were less likely to be abstinent from alcohol and drugs in the prior 30 days (48.3% vs. 64.0%), and had higher Addiction Severity Index scores
Null impact						
Alessi and Petry (2014)	RCT, frequent monitoring and behavioral support or that plus contingency management	$N = 45$ - behavioral support: $N = 21$, 100% male, mean age 37, 43% Black, 48% European American; contingency management: $N = 24$, 100% male, mean age 38, 17% Black, 79% European American	Percent of days CO-negative (biochemically validated)	Study attendance, study adherence, days of self-reported drug use (biochemically validated)	Smoking cessation treatment intervention	*Null* No study withdrawals, no difference by treatment arm for adherence, days of self-reported substance use, or drug-positive urine tests.
Kahler, Borland, Hyland, McKee, O'Connor, Fong, Cummings (2010)	Prospective cohort	$N = 3614$, mean age 42, 47% female, 95.8%, adult daily smokers from AU, CA, UK, US	Smoking abstinence for >6 months, self-report	Drinking frequency, number of drinks per day and heavy or "binge" drinking frequency	Smoking Cessation	*Null* No difference in reduction in drinking by quitters compared to non-quitters
Callaghan, Brewster, Johnson, Taylor, Beach, Lentz (2007)	Retrospective cohort, NRT available on request	$N = 520$, adolescents mean age 17, 57% female, 39% Aboriginal ancestry, in SUD treatment	N/A, investigated impact of smoking ban at SUD treatment facility	SUD treatment enrollment and treatment completion	Smoking cessation	*Null* The total smoking ban was not associated with a lower proportion of adolescent smokers seeking treatment or a lower treatment completion rate among smokers compared to nonsmokers
Rohsenow, Tidey, Martin, Colby, Sirota, Swift, Monti (2015)	RCT, contingent vouchers, motivational interviewing, brief advice	$N = 184$, mean age 35, 55% female, 83% white, smokers in SUD treatment	N/A, investigated impact of smoking cessation intervention	Number of heavy drinking days and biochemically verified number of drug use days at each follow up and relapse at 1 year	Smoking cessation treatment intervention	*Null* No differential effects on drug use
Mixed impact (*positive and null*)						
Lisha, Carmody, Humfleet, Delucchi (2014)	Secondary analysis of 2 RCTs, smoking cessation interventions, NRT, counseling, estimated both synchronous (within day) and lagged (across day) forecasts between smoking and alcohol use	$N = 302$, mean age 48, 9% female, 50% white, adults with HIV & adults in alcohol use disorder treatment	Number of cigarettes, timeline follow-back, 7-day point prevalence abstinence, biochemically verified (breath CO)	Alcohol use number of drinks	Smoking cessation	*Positive & null by subgroup/null overall* In the overall sample, there was no difference in alcohol use between those who stopped smoking (even for 1 day) and those who never stopped ($t(300) = 0.08$, $p = 0.93$). When broken up by study there was a significant reduction in the alcohol dependent sample: $t(137) = 2.88$, $p < 0.0001$. The mean number of drinks was 29.76 ($SD = 90.9$) for those who stopped v. 131.7 ($SD = 324.5$) for those who did not.
Reitzel, Nguyen, Eischen, Thomas, Okuyemi (2014)	Secondary analysis of RCT, NRT, self-help guide, counseling	$N = 427$, mean age 44, 25% female, 35% white, homeless adult daily smokers interested in quitting smoking	7-Day point prevalence abstinence, biochemically verified (breath CO)	Number of drinking days of 30; drinks per drinking day; number of heavy drinking days; number of days cocaine or mj/hash or heroin and any drug	Smoking cessation	*Positive* (*alcohol*)/*null* (*drugs*) Smoking abstinence (CO-verified) was associated with fewer drinking days ($P = 0.03$), fewer drinks consumed on drinking days ($P = 0.01$), and lower odds of heavy drinking ($P = 0.05$), but not with differences in the number of days of cocaine, marijuana/hashish, heroin or any drug use

Table 1 (continued)

Authors (year)	Study design	Sample description*	Smoking variable assessed	SU outcome of interest	Cessation/treatment	Synopsis of findings
Winhusen, Kropp, Theobald, Lewis (2014)	Secondary analysis of multi-site RCT, SUD treatment with or without smoking cessation treatment, counseling, bupropion, contingency management	N = 249, baseline demographics reported by follow-up smoking status, continued smoking: N = 174, mean age 38, 49% female, 61% white, smoking abstinent: N = 75, mean age 36, 37% female, 55% white, adults with cocaine or methamphetamine SUD	7-Day point prevalence abstinence, biochemically verified (breath CO)	Stimulant abstinence (biochemically verified)	Smoking cessation	*Positive (cocaine)/null (methamphetamines)* A significant effect was found for the cocaine-dependent subsample (N = 147) in which participants who stopped smoking were abstinent for illicit stimulants an average of 78.2% of the post-smoking-quit weeks (weeks 4–10) relative to 63.6% in participants who continued smoking ($\chi^2(1) = 8.55$, $p < 0.01$, d = 0.36). No significant effects were found for the sample as a whole (N = 249) or for the methamphetamine-dependent subsample (N = 102).
Stahre, Toomey, Erickson, Forster, Okuyemi, Ahluwalia (2013)	RCT, counseling	N = 755, mean age 45, 67% female, African American adults	7-Day point prevalence abstinence, self-report	Prevalence and frequency of past 30-day binge drinking and average daily alcohol consumption	Smoking cessation	*Positive (short term)/null (long term)* Individuals who quit smoking within the first 8 weeks of the study reported lower past 30-day binge drinking prevalence at week 8 than those who did not quit during the first 8 weeks (P = 0.035), but the effect was not sustained at the end of the study (week 26)
Campbell, Chi, Sterling, Kohn, Weisner (2009)	Prospective cohort	N = 419, adolescents mean age 16, 34% female, 49% white, recruited when entering SUD treatment	Abstinence for previous 6 or 12 months, self-report	SU self-report follow-up data validated on subsample at 12 months w/urinalysis, abstinence from drugs and alcohol	Smoking cessation	*Positive (drugs)/null (alcohol)* Self-initiated tobacco cessation at 6 months, and at both 6 and 12 months, were related to higher odds of drug abstinence but not alcohol abstinence
Myers, Prochaska (2008)	RCT, group counseling	N = 54, adolescents mean age 16, 22% female, 69% white, outpatient SUD treatment in Southern California	N/A, investigated impact of smoking cessation intervention	Total days of substance use at the 3-and 6-month follow-up time points	Smoking cessation treatment intervention	*Positive (short term)/Null (long term)* Participants who received smoking cessation intervention had significantly fewer days of substance use than controls at the 3-months, but not at 6-months follow-up
Prochaska, Hall, Tsoh, Eisendrath, Rossi, Redding, Rosen, Meisner, Humfleet, Gorecki (2008)	RCT, smoking cessation intervention, computer-based intervention, counseling	N = 322, depressed smokers in mental health outpatient treatment	7-Day point prevalence abstinence, biochemically verified (breath CO)	Alcohol, mj, stimulant, opiate use (y/n) between follow-ups		*Positive (alcohol)/null (drugs)* Participants who successfully stopped smoking reported less alcohol use than did participants who continued smoking. No difference in drug use
Brook, Balka, Ning, Brook (2007)	Prospective cohort	N = 473, adolescents mean age 14, 51% female, 51% black, 49% Puerto Rican	Current cigarette smoking, self-report	Alcohol dependence, illicit drug dependence, alcohol and illicit drug dependence	Smoking cessation	*Positive (quitters v. early starters & continuous) Null (quitters v. late starters)* Early starting continuous smokers more likely than quitters report alcohol dependence (OR 3.72) and illicit drug dependence (3.21). There was no difference between late-starting smokers and quitters
Mixed impact (negative and null)						
Fu, Kodl, Willenbring, Nelson, Nugent, Gravely, Joseph (2008)	Secondary analysis of RCT, smoking cessation intervention, NRT, counseling (concurrent or delayed smoking cessation treatment)	N = 459, mean age 40, 30% female, 83% white, adults in alcohol use disorder treatment	7-Day point prevalence abstinence, self-report (25% subsample biochemically verified)	6-Months alcohol abstinence @ 6, 12, 18 months; time to first alcohol use; black/white differences	Smoking cessation treatment intervention	For whites: alcohol abstinence outcomes were consistently worse in concurrent group than delayed group, but not for blacks

al., 2007), one among a smoking-cessation treatment-seeking (but not SUD treatment seeking) sample, and three among high-needs populations (an HIV clinic sample (of HIV + patients), a homeless smokers sample, and a sample of smokers in mental health outpatient treatment). While all nine reported at least one substance use outcome that was not impacted, eight reported at least one substance use outcome that was positively impacted (Prochaska et al., 2008; Lisha et al., 2014; Reitzel et al., 2014; Winhusen et al., 2014; Campbell et al., 2009; Stahre et al., 2013; Myers & Prochaska, 2008; Brook et al., 2007), and only one reported a negatively impacted substance use outcome (Fu et al., 2008).

Considering substance use outcomes, six reported alcohol-specific outcomes (either alone or in combination with other substance use outcomes), three of which had findings both positive and null for the same alcohol-specific outcomes, two had findings of positive impact, and one reported no impact. Both positive and no impact was reported regarding number of drinks (Lisha et al., 2014), prevalence of binge drinking (Stahre et al., 2013), and odds of reporting alcohol (or illicit drug) dependence (Brook et al., 2007). The direction of these findings depended on the group analyzed, length of follow-up, and comparison group, in that order. Two studies reported impacts resulting solely in positive alcohol-related outcomes of decreased use (Satre et al., 2007) and decreased number of drinks and drinking days as well as lower odds of heavy drinking (Reitzel et al., 2014). These same studies, however, found no impact on drug use or number of days using drugs, respectively. One study reported no impact on odds of reporting alcohol abstinence and positive impact/increased odds of reporting abstinence from drugs (Campbell et al., 2009).

Only one study did not separate alcohol from other drug outcomes and instead reported on "substance use" outcomes (Myers & Prochaska, 2008). Here, the positive impact of decreased number of substance use days at 3 months follow-up was not found at 6 months (no impact). There was also a single study that reported higher average percent of abstinent weeks among cocaine dependent (positive impact), but not methamphetamine dependent (no impact), individuals (Winhusen et al., 2014). Finally, one study reported decreased alcohol abstinence (negative impact) for Caucasian participants who received smoking cessation treatment concurrent with alcohol use treatment compared to those who received smoking cessation treatment 6 months after alcohol use treatment, the same was not true for African American participants (no impact) (Fu et al., 2008).

4. Discussion

We reviewed the published evidence from the last decade reporting the impact of quitting smoking and/or smoking cessation treatment intervention on substance use outcomes. Across 24 studies, both quitting smoking and smoking cessation treatment intervention had either a positive impact or no impact on substance use outcomes. Positive impact was reported for a range of alcohol use outcomes (e.g., number of drinks, alcohol abstinence, and alcohol use disorder diagnosis) as well as drug use outcomes (e.g., using days, relapse, remission, SUD diagnosis). Importantly, for those in SUD treatment, neither forced quit attempt (smoke-free policy) nor smoking cessation treatment intervention type (e.g. brief advice to quit, motivational interviewing, and offering vs. not offering nicotine replacement) affected treatment outcomes. Results support the broad delivery of smoking cessation intervention in accordance with clinical practice guidelines (Fiore et al., 2008) (offering advice to quit, using medications, and enrollment in smoking cessation counseling) to any individual that reports alcohol or other drug use (whether recreational, disordered, or otherwise). Further, if patients are able to quit smoking, it may make it easier for them to change other substance use for a variety of reasons.

Only one study reported a negative impact of smoking cessation on a substance use outcome (Fu et al., 2008). A secondary analysis of data from a 2004 study by Joseph and colleagues (Joseph et al., 2004) found smoking cessation treatment delayed by 6 months was associated with longer alcohol abstinence than smoking cessation treatment implemented concurrently with alcohol treatment, but only for Caucasian (not African-American) participants (Fu et al., 2008). Results cannot be generalized to the general population of smokers with alcohol use disorders.

It is evident that neither quitting smoking nor smoking cessation treatment-intervention results in worsening substance use outcomes (e.g. increased rates of relapse to alcohol or other drugs), even absent direct comparisons. For example, one study found participants who quit smoking reported less craving for stimulants (elimination of craving coupling) (Magee & Winhusen, 2015) while two others (an RCT and analysis of a large prospective cohort) found those who quit smoking were less likely to have incident SUD diagnoses (Thurgood et al., 2015; Walters, 2009). Further, if patients are able to quit smoking, it may make it easier for them to change other substance use.

Some limitations of this review bear noting. First, review was restricted to studies published in English. Second, findings in reviewed studies were limited to those the authors chose to publish. Third, meta-analysis was not conducted due to heterogeneity of outcomes, measurements, and sample characteristics. Fourth, studies reporting the impact of quitting smoking, or of "former smoker" status did not differentiate between former smokers who quit on their own and those who may have participated in a formal smoking cessation treatment intervention.
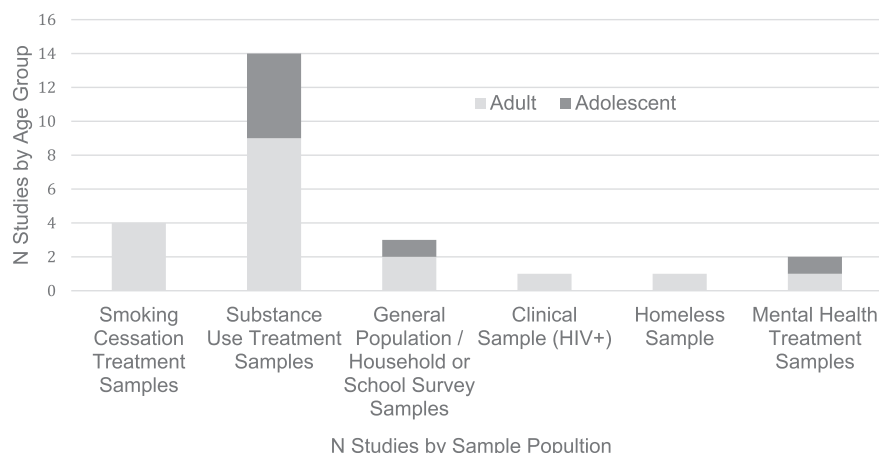

Fig. 1. Overview of included studies by sample populations and age group ($N = 24^*$). *Chart adds to 25 study sample populations as one study included two samples (Lisha et al., 2014).
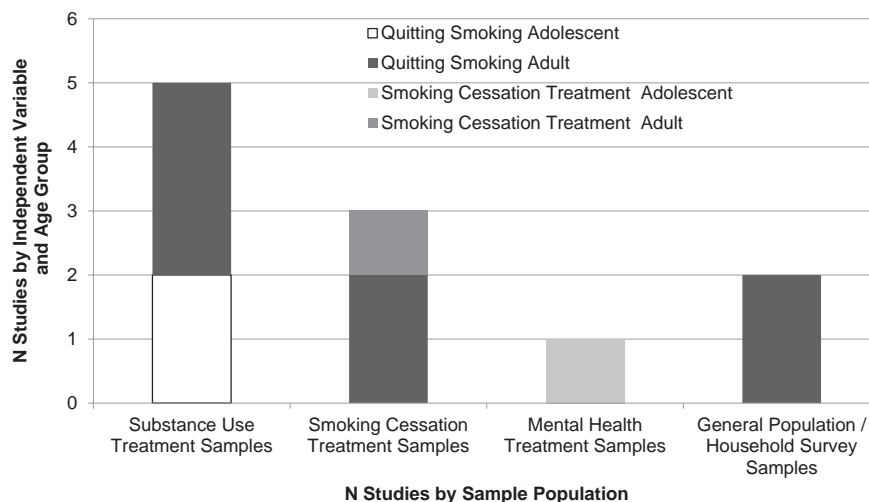
Fig. 2. Positive findings by sample population, independent variable (quitting smoking or smoking cessation treatment intervention), and age group ($n = 11$).

5. Conclusions

When considered in conjunction with the known, undisputed harms of smoking (US Department of Health and Human Services, 2014), this review provides support for policies encouraging quitting among smokers in SUD treatment settings and the offering of formal smoking cessation treatment or advice to quit, including cessation aids, to smokers who report use of other substances, whether or not they are seeking SUD treatment. Additionally, since provider barriers to offering smoking cessation treatment options and strategies to patients is often cited (Blumenthal, 2007; Bowman & Walsh, 2003), this review also provides support for broad delivery of clinician training in smoking cessation treatment and support. The integration of such practices and policies will improve the health and wellbeing not only of substance using populations, but also of their families and friends - now and for future generations. Failing to do so is tantamount to increased harm.

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Cigarette smoking is associated with increased risk of substance use disorder relapse: A nationally representative, prospective longitudinal investigation

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Abstract

Objective—Little is known about the relationship between cigarette smoking and long-term substance use disorder (SUD) outcomes. The current study examined the association between smoking and SUD relapse among adults with remitted SUDs.

Method—Analyses were conducted on respondents who completed Waves 1 and 2 of the National Epidemiologic Survey on Alcohol and Related Conditions and met DSM-IV criteria for substance abuse and/or prior to but not during the year before the Wave 1 interview (n=5,515). Relationships between smoking status (Wave 2 smoking versus non-smoking among Wave 1 smokers; Wave 2 smoking versus non-smoking among Wave 1 non-smokers) and Wave 2 substance use and SUD relapse were examined using logistic regression analyses. Analyses were adjusted for demographics; psychiatric and alcohol use disorders; nicotine dependence; and SUD severity.

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Results—In the fully adjusted models, among Wave 1 smokers, continued smoking at Wave 2 was associated with significantly greater odds of substance use (OR=1.56, 95% CI=1.10-2.20) and SUD relapse (OR=2.02, 95% CI=1.65-2.47) compared to Wave 2 non-smoking. In the fully adjusted model, among Wave 1 non-smokers, smoking at Wave 2 was associated with significantly greater odds of SUD relapse compared to Wave 2 non-smoking (OR=4.86, 95% CI=3.11-7.58).

Conclusion—Continued smoking for smokers and smoking initiation for non-smokers was associated with greater odds of SUD relapse. More research is needed to examine the timing of SUD relapse in relation to smoking behaviors. Incorporating smoking cessation and prevention efforts into substance abuse treatment may improve long-term substance use outcomes for adult smokers with SUDs.

INTRODUCTION

Illicit substance use and substance use disorders are growing public health concerns in the United States (U.S.). In 2011, an estimated 22.5 million Americans, roughly 8.7% of the population aged 12 or older were current or past-month users of illicit drugs including marijuana/hash, cocaine (including crack), heroin, hallucinogens, inhalants, or prescription medicine used non-therapeutically.[1] One hundred and thirteen people die from drug overdose every day in the U.S. and over 6,700 people are treated in emergency departments for drug misuse or abuse.[1] In the U.S., opioid abuse accounts for nearly $55.7 billion divided up among attributable workplace costs, healthcare costs and criminal justice costs.[2, 3] Further, illicit drug abuse is growing in popularity as demonstrated by 118% increase since 1992 to 2011.[1]

While the use of illicit drugs is increasing, the use of cigarettes in the U.S. has been declining. The prevalence of smoking among U.S. adults has declined from 42% in 1964, the year of the surgeon general's first report about the health consequences of smoking, to 18% in 2012 although the decline has slowed down in recent years[4]. Cigarette smoking causes more than 480,000 deaths each year in the U.S.,[4, 5] roughly 20% of all yearly deaths, [4] and smoking cigarettes leads to an increased number of deaths when combined with illicit substance abuse.[6–8]

Illicit substance use and smoking behaviors are highly comorbid. Cross-sectional epidemiologic data from the U.S. adult population suggest that more than half (53.6%) of adults with a lifetime SUD diagnosis and two-thirds (66.7%) of adults with a past-year SUD diagnosis are current smokers.[9] Rates of lifetime smoking among adults with lifetime or past-year SUDs reach three-quarters or more (75.4% and 77.6%, respectively[9]). Further, clinical data consistently report smoking prevalences ranging from 77% to 88% among patients in treatment for substance use problems.[10–12]

While smoking is common among the vast majority of people who enter treatment for SUD, and nicotine dependence itself is an SUD, smoking cessation therapy is neither a standard

part of care, nor required as a component of SUD treatment. Tobacco use disorder is the sole SUD for which treatment is not consistently integrated into treatment programs for other SUDs. Further, required abstinence from cigarettes may not be actively discouraged or theoretically linked with recovery or the "drug-free" lifestyle in many cases. Clinical lore has been that quitting both illicit substances and cigarettes may be "too difficult," all at once, yet data is beginning to suggest that not doing so may lead to poorer outcomes. For example, data from clinical samples of adults in treatment for SUDs suggest that quitting smoking does not harm SUD treatment outcomes[13, 14] while continued use of cigarettes after cannabis treatment was associated with relapse to cannabis use in adolescents.[15] Cross-sectional epidemiological data has suggested that nicotine dependence is associated with an increased likelihood of cocaine dependence remission.[16] While many people with SUDs will quit using substances for varying lengths of time, a primary feature of substance use disorders is that attempts to cut down or stop using substances are unsuccessful,[17] so it is critical that research on SUDs examine not just quit attempts but also long-term success at avoiding relapse. To our knowledge, no prior epidemiologic study has prospectively examined the relationship between cigarette smoking over time and the risk of relapse to SUDs among adults in remission from an SUD.

The current study used longitudinal data from a representative sample of U.S. adults who completed two assessments that occurred three years apart in order to compare the risk of SUD relapse among respondents with remitted SUDs by smoking status using data on smoking from both assessment time-points. The first aim of the study was to examine the risk of (1) substance use and (2) SUD relapse among adults with remitted SUDs at the end of the three year study period for two distinct populations: those who initiated smoking compared to those who reported never smoking among respondents who were not smoking at Wave 1, and those who continued smoking compared to those who quit smoking among respondents who were smoking at Wave 1. The second aim of the study was to examine the relationships between smoking status and risk of substance use and SUD relapse after controlling for demographics; mood, anxiety, and personality disorders; alcohol use disorders; nicotine use disorder; and severity of remitted SUD.

METHODS

Data source and study population

Study data were taken from a subsample of the National Epidemiological Study of Alcohol Use and Related Disorders (NESARC), an assessment of substance use, SUDs, and related physical and psychiatric conditions in a representative sample of the U.S. population of civilian non-institutionalized adults. The study was a two-wave multistage stratified design in which primary sampling units, housing units, and group-quarter units were stratified to collect data on certain under-represented socio-demographic criteria. Specifically, non-Hispanic Black, Hispanic, and young adult (ages 18–24) units were selected at higher rates than other housing units. The final data were weighted according to the demographic distribution of the US population based on the 2000 census. Experienced lay interviewers completed Wave 1 interviews 43,093 respondents in 2001-2002. Wave 2 interviews occurred three years later with 34,653 (80%) of the Wave 1 respondents. Study design and

administration details have been described in elsewhere.[18, 19] The original data sets for the NESARC was obtained from the National Institute on Alcohol Abuse and Alcoholism (NIAAA, http://www.niaaa.nih.gov) and researchers can currently request specific analyses of the data sets through the NIAAA. Our subsample included respondents who completed both waves of data collection and reported a history of any substance use, abuse, or dependence prior to but not during the year before Wave 1 interview (N=5,515; 12.8% of the original Wave 1 sample).

Measures

Substance use status—The two primary outcomes under investigation were substance use and SUD relapse (i.e., diagnoses of substance abuse and/or dependence) as measured at the Wave 2 follow-up assessment. The SUD diagnoses assessed in the Wave 2 NESARC included DSM-IV substance-specific abuse and dependence for ten substance types: sedatives, tranquilizers, opioids, heroin, amphetamines, cannabis, cocaine, hallucinogens, inhalants/solvents, and other drug categories.[20] Disorder diagnosis was determined by using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule–Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Version (AUDADIS-IV), a fully structured diagnostic interview instrument.[21] The reliability of the AUDADIS has been shown to be good to excellent for the assessment of SUDs in the general population (κs=0.63-0.99)[22] and in a clinical sample of adults in outpatient and inpatient treatment for SUDs (κs=0.57-0.83)[23]. A respondent who endorsed any type of substance use, abuse, or dependence was classified as having a positive outcome. Those with no reported substance use behaviors were classified as having no substance use. Participants who endorsed the use of any substance and did not meet criteria for abuse or dependence for any substance were classified as positive for substance use at Wave 2. Participants who met criteria for abuse or dependence for at least one substance at Wave 2 were classified as positive for SUD relapse at Wave 2. The relapse of substance abuse and substance dependence were modeled as separate outcomes, but because the reported prevalence of substance dependence was low, the SUD relapse outcome included participants who met criteria for either substance abuse or dependence (or both). The categories of substance use and SUD relapse were mutually exclusive and compared to the reference group of respondents who reported no substance use at Wave 2. In order to accurately capture the temporality of the relapse, the baseline study sample was limited to respondents with a lifetime history of SUD but who reported no substance use or SUD remission for at least one year prior to Wave 1. We also considered three measures of SUD severity: the duration of the longest episode of substance abuse (in months), the number of episodes of abuse, and the age of onset of abuse, in order to investigate if our association of interest was due solely to a smaller sub-population of the most severe cases of SUDs.

Tobacco use and nicotine dependence—Tobacco use was assessed for five tobacco products: cigarettes, cigars, pipe tobacco, snuff, and chewing tobacco. Smoking status was classified using data on cigarette smoking from both the Wave 1 and Wave 2 assessments and was defined as two dichotomous variables based on definitions used by the U.S. Department of Health and Human Service's Centers for Disease Control and Prevention[24]. Wave 2 non-smoking was defined as smoking fewer than 100 lifetime cigarettes at Wave 1

(i.e., did not meet criteria for lifetime smoking) and no past-year smoking at Wave 2. Wave 2 initiated smoking included those who reported smoking fewer than 100 lifetime cigarettes at Wave 1 and past-year use of cigarettes at Wave 2. Wave 2 quit smoking was defined as a report of lifetime smoking of 100 or more cigarettes at Wave 1 and a report of no past-year smoking at the Wave 2 follow-up. Wave 2 continued smoking was defined as a report of lifetime smoking of 100 or more cigarettes at Wave 1 and past-year cigarette smoking at Wave 2. To accurately measure the association of cigarette use and substance use relapse, participants who reported use of other forms of tobacco (e.g. cigars, pipes, snuff, chewing tobacco) were included in the sample only if respondents also reported cigarette use. Lifetime nicotine dependence diagnosis was based on meeting four criteria from the AUDADIS module on nicotine dependence disorder: experiencing withdrawal, giving up activities in favor of nicotine use, spending a great deal of time using nicotine, and using nicotine more than intended.[25] The AUDADIS has been shown to be good reliability in the general population for the assessment of smoking behavior (ICCs=0.60-0.92) and nicotine dependence (κ=0.60-0.63).[26]

Socio-demographic covariates and other potential confounders—Socio-demographic covariates were considered in the analysis and added to a series of multivariable-adjusted models. Variables included gender, age, education, race/ethnicity groups (Asian/Pacific Islander, non-Hispanic Black, Hispanic, Native American/Alaskan, and non-Hispanic White), marital status (married/living with someone as married, widowed, divorced/separated, single), and income. Gender, race/ethnicity, and marital status were added as discrete variables, while age, education, and income were continuous.

A summary dichotomous variable was also created to adjust for a range of lifetime psychiatric disorders reported at Wave 2 including major depression, bipolar disorder, dysthymia, hypomania, panic disorder with/without agoraphobia, agoraphobia, social and specific phobia, generalized anxiety disorder, posttraumatic stress disorder, attention deficit-hyperactivity disorder, antisocial personality disorder, borderline personality disorder, schizotypal personality disorder, and narcissistic personality disorder. Two binary alcohol use covariates were also considered in our models: one adjusted for any lifetime alcohol abuse or dependence as reported at Wave 2 and one adjusted for non-disordered alcohol use (i.e., participants who reported alcohol use but did not meet criteria to receive a diagnosis of either abuse or dependence). In addition, covariates related to the severity of the outcome were considered, including the disorder duration, frequency, and age of onset.

Statistical Analysis

Sample frequencies—The Rao Scott chi-square test, which accounts for the complex survey design, was used to test if the demographics were statistically significantly among smoking status groups. The Rao-Scott chi-square test was also used to test for significant differences between the Wave 2 smoking statuses (Wave 2 smoking versus non-smoking among Wave 1 smokers; Wave 2 smoking versus non-smoking among Wave 1 non-smokers) and the three possible Wave 2 substance use outcome groups (No Substance Use, Substance Use, SUD Relapse).

Regression modeling—Two separate sets of logistic regression models were created to address the second study aim. The first set of models included a sample of only non-smokers at Wave 1. In this population, we examined the association between past-year smoking at Wave 2 (i.e., initiated smoking) vs. no past-year smoking (i.e., non-smoking) at Wave 2 and (1) Wave 2 substance use and (2) Wave 2 SUD relapse. The second set of models included a sample of those who reported current smoking at Wave 1. In this population, we examined the association between no past-year smoking (i.e., quit smoking) at Wave 2 vs. past-year smoking at Wave 2 (i.e., continued smoking) and (1) Wave 2 substance use and (2) Wave 2 SUD relapse. Outcomes were analyzed as a three-level categorical variable using those with no substance use as the reference group. Models were run to determine the unadjusted odds ratio of (1) substance use and (2) SUD relapse by the smoking status groups (Wave 1 smokers: Wave 2 continued smoking versus quit smoking; Wave 1 non-smokers: Wave 2 initiated smoking versus non-smoking). Then, four additional models were run for each of the two outcome variables (substance use, SUD relapse) to adjust for the potential confounders and covariates. The first adjusted model adjusted for socio-demographic covariates. A second model adjusted for lifetime history of psychiatric disorders. The third model adjusted for non-disordered alcohol use, lifetime history of alcohol abuse or dependence, and nicotine dependence. The fourth model was adjusted for all covariates in models 1-3 and the three measures of SUD severity (duration, frequency, age of onset). Results from all five models are presented with unadjusted odds ratios (ORs), adjusted ORs (AORs), and 95% confidence intervals (CIs).

Sensitivity analyses—In order to further examine the specificity and robustness of our study associations, several sensitivity analyses were completed. To examine any dose-response effect of smoking on the study outcomes, a supplementary set of models tested the association between the quantity of cigarettes reported by Wave 1 smokers who reported smoking at Wave 2 and Wave 1 non-smokers who reported smoking at Wave 2 and the odds of substance use or SUD at Wave 2. A second sensitivity analysis limited the outcome variable to only those who reported substance dependence at Wave 2 (i.e., excluding respondents who reported substance abuse) in order to test the specificity of our results to the respondents with the most clinically problematic use of substances.

All tests were completed in STATA using weighted analysis (StataCorp, 2011) to account for residual differences between the sample and the population profile, according to the 2000 United States Population Census, as well as to account for nonresponse and sample attrition. The weighted Wave 2 data represent the same baseline population as represented in Wave 1.

RESULTS

Demographic characteristics (Table 1)

Among the analytic sample of Wave 1 non-smokers (n=3,458), 4.9% reported initiating smoking at Wave 2. Among the sample of Wave 1 smokers, (n=2,057), 81.7% reported continued smoking at Wave 2. The analytic sample identified primarily as Non-Hispanic White and currently married. Approximately half of the sample was female, and the majority of the sample had a high school degree or more. See Table 1 for the complete demographic

frequencies by Wave 2 smoking status (Wave 1 non-smoker, Wave 1 smoker) and by Wave 2 smoking classification.

Substance use and SUD relapse at Wave 2 (Table 2)

See Table 2 for the prevalences of no substance use, substance use, and SUD relapse at Wave 2 by smoking status. Among Wave 1 non-smokers, prevalences of Wave 2 substance use and SUD relapse were significantly higher for Wave 1 non-smokers who initiated smoking at Wave 2, compared to Wave 1 non-smokers who were also Wave 2 non-smokers. Among Wave 1 smokers, the prevalence of Wave 2 substance use and SUD relapse were significantly higher for Wave 1 smokers who had continued smoking at Wave 2, compared to Wave 1 smokers who had quit smoking at Wave 2. The highest prevalence of Wave 2 SUD relapse was found for adults who were lifetime non-smokers at Wave 1 and had engaged in past-year smoking by Wave 2 (10.9%).

Wave 2 substance use and SUD relapse by smoking status (Table 3)

In the fully adjusted model (labeled AOR[8]), Wave 1 non-smokers who had initiated smoking at Wave 2 had 4.86 times the odds of reporting Wave 2 SUD relapse (95% CI=3.11-7.58) compared to Wave 2 non-smokers. Wave 1 non-smokers who had initiated smoking at Wave 2 reported no greater odds of reporting substance use (OR=0.92; 95% CI=0.75-1.12) compared to Wave 2 non-smokers. Among Wave 1 smokers, those who continued smoking at Wave 2 reported 1.56 times greater odds of substance use (95% CI=1.10-2.10) and 2.02 times greater odds of SUD relapse (95% CI=1.65-2.47) compared to smokers who did not report smoking at Wave 2 in the fully adjusted models. Unadjusted odds ratios were slightly larger, but the resulting changes to the model parameters were slight after adjusting for demographics; lifetime mood, anxiety, or personality disorders; lifetime alcohol use disorder; nicotine use disorder; and severity of substance use. Complete model results are presented in Table 3.

Sensitivity analyses

The fully adjusted models were also re-run with an additional covariate for the number of daily cigarettes smoked in a sensitivity analysis to examine if the quantity of cigarettes smoked was associated with an increase in the odds of substance use or SUD at Wave 2. Those who reported smoking at Wave 1 smoked an average of 17.7 (SE=0.19) cigarettes per day, while those who initiated smoking at Wave 2 smoked an average of 13.1 (SE=0.15) cigarettes per day. The odds of Wave 2 SUD relapse increased by 2.4% with each additional daily cigarette smoked by non-smokers at Wave 1 who reported smoking at Wave 2 (95% CI=1.8-2.9%), while the odds of Wave 2 SUD relapse increased by 0.7% with each additional daily cigarette smoked by smokers at Wave 1 who also reported smoking at Wave 2 (95% CI=0.2-1.1%). The odds of Wave 2 substance use did not significantly increase with the number of daily cigarettes smoked in either group.

In order to examine whether the results would change when the definition of "SUD relapse" was defined as substance dependence alone rather than those reporting substance abuse and dependence, models were re-run limiting the outcome to relapse to substance dependence.

Effect estimates were slightly larger but were similar to the models combining substance abuse and dependence disorders (data not shown).

DISCUSSION

This study examined the association between smoking and relapse to substance use and SUD three years later among adults in the U.S. with remitted SUDs. Among respondents who were smoking at Wave 1, those who were smoking at Wave 2 were significantly more likely to report substance use and relapse to SUDs three years later compared with respondents who did not report smoking at Wave 2. Among respondents who were not smoking at Wave 1, those who were smoking at Wave 2 were significantly more likely to relapse to SUDs three years later compared with respondents who did not report smoking at Wave 2. These relationships remained significant after controlling for demographics; mood, anxiety, and personality disorders; alcohol use disorders; nicotine dependence; and severity of past SUD. These relationships were also significant when SUD relapse was defined by the more severe category of substance dependence rather than a variable that combined both substance dependence and abuse. Further, after these adjustments, sensitivity analyses suggested that a higher number of cigarettes consumed by Wave 1 smokers who smoked at Wave 2 and Wave 1 non-smokers who smoked at Wave 2 was associated with a greater likelihood of SUD relapse. To our knowledge, no prior study has shown that cigarette smoking–both continued smoking and new-onset smoking—is associated with an increase the likelihood of relapse to SUD among adults with past SUDs. More research is needed to clarify whether quitting smoking (for smokers) or not initiating smoking (for non-smokers) would reduce relapse to SUDs and lead to better long-term abstinence outcomes.

There are several reasons that smoking may increase the likelihood of relapse to SUDs. Smoking often occurs in combination with the use of other drugs and cigarettes may become a cue for use of illicit drugs. Preclinical and laboratory research has shown a link between nicotine and increased cravings and administration of stimulants and opiates.[27–29] Also, combined use of nicotine with other substances (e.g., cannabis) is associated with greater psychiatric and personality disorders[30, 31] which are associated with difficulty quitting smoking[32] and dropping out of substance abuse treatment.[33] Research on the reasons why adults who smoke are more likely to relapse to SUDs can provide important information that can be incorporated into SUD treatment programs.

It has been suggested that addressing smoking among adults with SUDs is important for treating SUDs.[34] The majority of adults with SUDs are interested in quitting smoking and motivated to quit at rates consistent with the general population.[35] While there are concerns about whether quitting smoking would make it difficult to remain abstinent from illicit drugs, studies in clinical treatment settings have found that smoking abstinence does not appear to lead to a compensatory increase in other drug use and may even improve drug abstinence.[36–39][13, 14, 40, 41] The conversation about providing smoking services for adults with SUDs has typically focused on smoking cessation services; however, our results suggest that efforts related to preventing smoking initiation could be beneficial as well since adults with past SUDs who initiated smoking demonstrated the greatest odds of SUD relapse.

If research continues to show a relationship between smoking and SUD relapse, then incorporating smoking prevention efforts and smoking cessation treatments into substance abuse treatment may be important services to provide to adults with SUDs to help sustain long-term substance treatment outcomes. The balance of research suggests that providing smoking treatment concurrently with treatment for other drugs improves smoking outcomes in the short-term and does not appear to harm drug treatment outcomes.[35, 40, 42] Relapse to smoking is common among smokers attempting to quit,[43] including adults with SUDs.[40] Few studies have tested effective smoking treatments for adults with SUDs[29] but there are promising preliminary results with pharmacotherapies for nicotine dependence.[29, 44, 45] More research is needed to determine what treatments will best help the greatest number of adults with SUDs to achieve abstinence from both cigarettes and illicit drugs over the long-term. In addition, little is known about smoking initiation among adults with past SUDs. It would be useful for future studies to examine factors that have been shown to play a role in smoking initiation for younger or older adults (e.g., demographics, stress, psychiatric symptoms and disorders, temperament, environment[46–50]) to determine which factors may play a significant role in the smoking initiation of adults with SUDs. Additional research on the timing of and reasons for cigarette smoking initiation would aid in determining what prevention efforts could help adults with SUDs to avoid smoking initiation.

It should also be noted that more information is needed to determine how to aid SUD treatment programs in developing and incorporating smoking-related services. A minority of treatment centers report that they have a designated leader or formalized procedures related to smoking cessation services, the ability to prescribe smoking cessation pharmacotherapies, the financial capacity to provide medication or counseling, and staff training on smoking treatments.[51] Further, an absence of barriers (e.g., being hospital-based, having a lower number of clinicians who smoked) and the availabilities of incentives (e.g., reimbursement for smoking services) are associated with incorporating pharmacotherapies[52] while support from administrators and building staff expertise have been found to be important for continued success of active smoking cessation services within SUD treatment sites.[53] While more information is needed to build on the research related to SUD treatment programs providing smoking services, research on all aspects of smoking prevention efforts is needed (e.g., the degree to which efforts to prevent smoking initiation are already included in SUD treatment programs, how administrators and staff can develop or build prevention efforts, the most useful content or form of prevention efforts). Improving the ability of SUD treatment programs to provide patients who smoke with treatment access and support and to provide patients who do not smoke with support to remain smoke-free may lead to not just better smoking outcomes but also better outcomes related to illicit drug use.

A number of limitations to this study must be noted. These results may have limited generalizability to those who were not part of the NESARC sample, such as adults outside of the U.S. and persons under the age of 18. Also, the survey excluded institutionalized and incarcerated populations who may exhibit unique or elevated patterns of risk for SUD relapse. It should also be noted that the reliability for some modules of the AUDADIS (e.g., smoking behavior) was determined using the full NESARC participant sample which differs from the analytic sample for the current analyses. Smoking and drug use was documented by self-report without biochemical confirmation and therefore may have been underreported. In

addition, due to sample sizes and power issues, it was not possible to determine whether the SUD relapse reported by participants at Wave 2 was the same substance for which they had initially reported use or abuse/dependence at Wave 1. Similarly, the sample sizes were small for several groups (i.e., those who quit smoking and reported SUD relapse and those who began smoking and reported substance use or SUD relapse) which may have affected the precision of our effect estimates.

It was also not possible to determine the timing of SUD relapse in relation to the timing of smoking initiation or smoking cessation which limits the ability to determine causality and the sequence of events in the relationship between smoking and SUD relapse. Studies of clinical samples would be useful to more closely examine the timing, context, and details of changes in drug behavior in association with smoking, as would longitudinal datasets with multiple follow-up periods which would allow for an investigation into this association using methods to account for time-varying variables and correlated measures (e.g., cross-lagged structural equation modeling). While outside the scope of the current investigation, it would also be important for future studies to examine potential mechanisms (i.e. mediators, effect modifiers, etc.) through which cigarette smoking is associated with SUD relapse. It would also be useful for future investigations to examine potential moderators of the relationship between smoking and SUD relapse (e.g., gender, race, psychiatric disorders).

Finally, it must be noted that cigarette smoking is just one potential factor associated with SUD relapse. Our data suggests that continued smoking and smoking initiation are related to statistically significant increases in the odds of SUD relapse compared to those who quit smoking; however, more data are needed to determine the clinical significance of these relationships. The treatment of SUDs is extremely challenging and even if smoking is just modestly associated with improvements in sustained abstinence this may be useful in treatment programs. Smoking is modifiable and is relatively easily evaluated. Attention to smoking in illicit drug treatment programs would also be in line with the Clinical Practice Guideline on Treating Tobacco Use and Dependence[54] which recommends that all patients in various clinical settings be assessed for smoking and given aid with regard to smoking cessation treatments. In addition to the impact that smoking cessation could have on SUD treatment outcomes, smoking is causally associated with a wide range of illnesses[4] and therefore both smoking cessation and the avoidance of smoking initiation would potentially be associated with improved overall health.

Relapse is common among the majority of people with past illicit substance use disorders and identifying factors associated with relapse to SUDs after stopping the use of illicit drugs may improve long-term outcomes of SUDs. Continuing or initiating cigarette use after stopping the use of illicit drugs was associated with an increased likelihood of relapse to SUDs. Incorporating smoking cessation treatments and smoking prevention efforts into substance abuse treatment may be one way to improve long-term substance use outcomes for adult smokers with SUDs.

Acknowledgments

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Clinical Points

-Historically in clinical settings, it has been suggested that quitting cigarette smoking while also addressing drug treatment would be too difficult, and that continued smoking has no impact on long term outcomes of substance use treatment or abstinence. While a majority of persons in treatment for substance use disorders also use cigarettes, smoking cessation treatments are not routinely offered in the same treatment setting.

-We found that among adults with remitted substance use disorders, those who were smokers and reported continued smoking three years later had increased odd of substance use and relapsing to substance use disorders compared to those who were no longer smoking. Those who were non-smokers and reported smoking three years later were had increased odd of relapsing to substance use disorders compared to those who continued to be non-smokers.

-Future research should examine how the inclusion of smoking prevention and cessation programs in substance use treatment impacts long-term abstinence from illicit substance use.

TABLE 1

Sample frequencies of demographic categories by Waves 1 and 2 smoking status.

		Wave 1 non-smoking				Wave 1 current smoking		
	Total	W2 Non-smoker (%)[1]	W2 Initiated smoking (%)[2]	p	Total	W2 Quit smoking (%)[3]	W2 Continued smoking (%)[4]	p
Total (n; %)	n=3458	3291; 95.1%	167; 4.9%		n=2057	397; 18.3%	1660; 81.7%	
Gender								
Men	51.5	50.9	64.4	<0.0001	57.6	56.6	57.8	0.489
Women	48.5	49.1	35.6		42.4	43.4	42.2	
Age								
18-29	11.7	11.2	22.2	<0.0001	19.1	22.3	18.4	<0.0001
30-44	40.0	39.8	44.3		41.9	45.7	41.0	
45-64	43.1	43.7	31.8		37.4	29.8	39.1	
65+	5.1	5.3	1.6		1.6	2.2	1.5	
Race/Ethnicity								
NH White	77.4	77.4	78.5	0.115	79.2	74.0	80.3	<0.0001
NH Black	9.5	9.6	9.0		8.6	8.5	8.6	
NH Native American/AK Native	2.4	2.4	3.3		3.7	2.5	4.0	
NH Asian/Pacific Islander	2.0	1.9	2.9		1.6	1.4	1.7	
Hispanic	8.6	8.8	6.3		6.9	13.6	5.4	
Marital status								
Current	71.7	71.8	70.3	0.033	59.8	61.6	59.4	<0.0001
Previous	14.4	14.5	13.0		22.2	17.5	23.2	
Never	13.9	13.7	16.7		18.0	20.8	17.4	
Personal income								
$0-19,999	29.8	29.7	31.5	0.010	36.7	34.0	37.3	<0.0001
$20-34,999	19.9	19.7	24.5		25.5	23.1	26.0	
$35-69,999	32.1	32.3	27.5		29.2	29.1	29.3	
$70,000+	18.2	18.3	16.6		8.6	13.8	7.5	
Education								
Less than HS degree	6.1	6.0	7.6	0.001	13.4	10.0	14.2	<0.0001
High school degree	41.7	41.3	48.9		56.6	49.3	58.2	

	Wave 1 non-smoking				Wave 1 current smoking			
	Total	W2 Non-smoker (%)[1]	W2 Initiated smoking (%)[2]	p	Total	W2 Quit smoking (%)[3]	W2 Continued smoking (%)[4]	p
More than HS	52.2	52.7	43.5		30.0	40.6	27.6	_6
Current use of each tobacco product at Wave 1[5]								
Cigarettes	0.0	0.0	0.0	_6	100.0	100.0	100.0	_6
Cigars	0.0	0.0	0.0	_6	7.1	6.4	7.3	0.356
Pipe	0.0	0.0	0.0	_6	1.1	1.1	1.1	0.821
Snuff	0.0	0.0	0.0	_6	5.6	4.8	5.8	0.455
Chewing tobacco	0.0	0.0	0.0	_6	1.9	1.3	2.0	0.349
Lifetime nicotine dependence[7]	1.33	0.0	27.4	<0.0001	65.6	52.6	68.5	_6

Key: NH, non-Hispanic; AK, Alaska; HS, high school; PY, past year; SE, standard error

[1] A report of smoking fewer than 100 lifetime cigarettes at Wave 1 and no past-year smoking at Wave 2

[2] A report of lifetime smoking of 100 or more cigarettes at Wave 1 and no past-year smoking at Wave 2

[3] A report of lifetime smoking of 100 or more cigarettes at Wave 1 and past-year smoking at Wave 2

[4] A report of smoking fewer than 100 lifetime cigarettes at Wave 1 and past-year smoking at Wave 2

[5] Smoker sample includes those who report smoking cigarettes, with or without other tobacco use, percentages are the number of respondents reporting use of the product out of the full analytic sample

[6] P values could not be calculated due to 0 frequency cells

[7] Assessed at Wave 2

TABLE 2

Wave 2 substance use and substance use disorder relapse by smoking status between Waves 1 and 2, among individuals with a history of illicit substance use, abuse, or dependence prior to Wave 1.

	Wave 1 non-smoking: Wave 2 non-smoking vs. initiated smoking (n=3458)					
W2 substance use status	Total n, (%)		W2 Non-smoking[1] n, (%)		W2 Initiated smoking[2]; n, (%)	p
Wave 2 no substance use	3167	(91.2)	3033	(91.7)	134	(80.3)	<0.0001
Wave 2 substance use	226	(6.7)	210	(6.6)	16	(8.8)	
Wave 2 SUD relapse[5]	65	(2.1)	48	(1.7)	17	(10.9)	

	Wave 1 smoking: Wave 2 quit smoking vs. continued smoking (n=2057)					
W2 substance use status	Total n, (%)		W2 Quit smoking[3] n, (%)		W2 Continued smoking[4]; n, (%)	p
Wave 2 no substance use	1765	(85.5)	357	(90.3)	1408	(84.5)	<0.0001
Wave 2 substance use	210	(10.4)	32	(7.5)	178	(11.0)	
Wave 2 SUD relapse[5]	82	(4.1)	8	(2.2)	74	(4.5)	

Key: W2=Wave 2; SUD=substance use disorder

[1] A report of smoking fewer than 100 lifetime cigarettes at Wave 1 and no past-year smoking at Wave 2

[2] A report of smoking fewer than 100 lifetime cigarettes at Wave 1 and past-year smoking at Wave 2

[3] A report of lifetime smoking of 100 or more cigarettes at Wave 1 and past-year smoking at Wave 2

[4] A report of lifetime smoking of 100 or more cigarettes at Wave 1 and no past-year smoking at Wave 2

[5] Met criteria for abuse or dependence of at least one substance at Wave 2

TABLE 3

Odds of Wave 2 substance use and substance use disorder relapse by smoking status between Waves 1 and 2, among individuals with a history of illicit substance use, or abuse/dependence prior to Wave 1

	OR Wave 2 initiated smoking vs. Wave 2 non-smoking (n=3,458)[1]														
W2 substance use status	**OR (95% CI)**			**AOR[5]**			**AOR[6]**			**AOR[7]**			**AOR[8]**		
Wave 2 no substance use	1.0			1.0			1.0			1.0			1.0		
Wave 2 substance use[3]	1.36	1.16	1.60	1.09	0.96	1.25	1.28	1.10	1.49	1.28	1.08	1.51	0.92	0.75	1.12
Wave 2 SUD relapse[4]	7.17	5.50	9.35	5.30	3.70	7.58	5.97	4.51	7.89	6.90	5.28	9.01	4.86	3.11	7.58

	OR Wave 2 continued smoking vs. Wave 2 quit smoking (n=2,057)[2]														
W2 substance use status	**OR (95% CI)**			**AOR[5]**			**AOR[6]**			**AOR[7]**			**AOR[8]**		
Wave 2 no substance use	1.0			1.0			1.0			1.0			1.0		
Wave 2 substance use[3]	1.52	1.14	2.03	2.03	1.76	2.34	1.48	1.11	1.97	1.55	1.15	2.10	1.56	1.10	2.20
Wave 2 SUD relapse[4]	2.11	1.87	2.37	1.40	1.04	1.90	1.91	1.69	2.15	2.17	1.93	2.45	2.02	1.65	2.47

Key: OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; SUD, substance use disorder

[1] Comparing past-year smoking at Wave 2 to no past-year smoking at Wave 2, among those who reported smoking fewer than 100 lifetime cigarettes at Wave 1

[2] Comparing past-year smoking at Wave 2 to no past-year smoking at Wave 2, among those who reported smoking more than 100 lifetime cigarettes at Wave 1

[3] Reported substance use below the threshold for abuse or dependence status at Wave 2

[4] Met criteria for abuse or dependence of at least one substance at Wave 2

[5] Adjusted for age, gender, income, race, education, marital status

[6] Adjusted for any lifetime mood, anxiety, or personality disorders

[7] Adjusted for non-disordered alcohol use, any lifetime alcohol use disorders, and nicotine dependence

[8] Adjusted for all previous model covariates, duration of the longest episode of substance abuse, number of episodes of substance abuse, and the age of onset of substance abuse

Cigarette Smoking and Risk of Alcohol Use Relapse Among Adults in Recovery from Alcohol Use Disorders

Andrea H. Weinberger, Jonathan Platt, Bianca Jiang, and Renee D. Goodwin

Background: Individuals in recovery from alcohol use disorders (AUDs) frequently continue to smoke cigarettes. The purpose of this study was to examine the relationship between cigarette smoking status and risk of AUD relapse in adults with remitted AUDs among adults in the United States.

Methods: Data were drawn from Wave 1 (2001 to 2002) and Wave 2 (2004 to 2005) of the National Epidemiologic Survey on Alcohol and Related Conditions. Analyses included the subsample of respondents who completed both waves of data collection reported a history of alcohol abuse and/or dependence prior to Wave 1 ($N = 9,134$). Relationships between Wave 1 cigarette smoking status (nonsmoker, daily cigarette smoker, and nondaily cigarette smoker) and Wave 2 alcohol use, abuse, and dependence were examined using logistic regression analyses. Analyses were adjusted for Wave 1 demographics; mood, anxiety, and substance use disorders; nicotine dependence; and AUD severity.

Results: Both daily and nondaily cigarette smoking at Wave 1 were significantly associated with a lower likelihood of alcohol use and a greater likelihood of alcohol abuse and dependence at Wave 2 compared to Wave 1 nonsmoking. These relationships remained significant after adjusting for demographics, psychiatric disorders, substance use disorders, AUD severity, and nicotine dependence.

Conclusions: Among adults with remitted AUDs, daily and nondaily use of cigarettes was associated with significantly decreased likelihood of alcohol use and increased likelihood of alcohol abuse and alcohol dependence 3 years later. Concurrent treatment of cigarette smoking when treating AUDs may help improve long-term alcohol outcomes and reduce the negative consequences of both substances.

Key Words: Smoking, Nicotine Dependence, Alcohol Use Disorders, Relapse, Epidemiology.

ALCOHOL USE AND smoking, both major public health concerns associated with illness and mortality, are strongly correlated with each other. Smoking is associated with a greater likelihood of an alcohol use disorder (AUD) diagnosis (alcohol abuse or alcohol dependence), greater hazardous or binge drinking, more severe alcohol dependence, and greater alcohol-related problems (see McKee and Weinberger, 2013). Conversely, adults who consume alcohol or meet criteria for an AUD are more likely to report current and former smoking and to meet criteria for tobacco use disorders (Lasser et al., 2000; McKee et al., 2007). Further, while each substance has potentially serious health effects on its own, comorbid smoking and alcohol use demonstrate multiplicative effects on disease (Kalman et al.,

2010). Because of the strong and reciprocal relationship between alcohol use and smoking, it is important to understand how one behavior impacts changes in the other behavior, especially the ability to successfully abstain or avoid problematic use.

Epidemiologic data have shown that AUDs have a significant, and detrimental, impact on transitions in smoking behavior. Compared to those without AUDs, adult never smokers with AUDs are more likely to initiate smoking (Goodwin et al., 2013) and current smokers with AUDs are less likely to report successful smoking cessation (Breslau et al., 1996; Lasser et al., 2000; Weinberger et al., 2013). Further, former smokers with AUDs are more likely to report smoking relapse (Weinberger et al., 2013). Results from a clinical trial show that smoking after attempting to quit was more likely to occur on occasions of heavy drinking (Leeman et al., 2008).

While the epidemiologic data described above have shown a relationship between AUDs and smoking outcomes, less is known about the relationship between smoking and changes in alcohol behavior (e.g., relapse to AUDs) at a population level. One previous study used 2 waves of longitudinal data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to examine relapse to AUD symptoms or diagnosis over a 3-year period for adults who had met criteria for past alcohol dependence at Wave 1 (Dawson et al., 2007). In analyses of potential covariates of AUD relapse,

being a past-year cigarette smoker at the time of the Wave 1, assessment was significantly associated with recurrence of both AUD symptoms and diagnosis at Wave 2. While the study was not designed to examine the association of smoking and relapse to AUDs as a primary aim, these preliminary findings suggest that a more detailed investigation of the association of smoking behavior and relapse to AUDs is warranted. Also, given that nicotine dependence, psychiatric disorders, and illicit drug use disorders are highly comorbid with AUDs and/or cigarette smoking (Goodwin et al., 2008; Grant et al., 2004a,b; Lasser et al., 2000), an observed relationship between smoking and alcohol relapse may be confounded with these comorbid disorders.

Against this background, the goal of the proposed study was to better understand the potential impact of cigarette smoking on risk of alcohol use relapse among those with remitted AUDs, compared with that of nonsmokers. First, the study investigated the relationship between current daily and nondaily cigarette smoking and alcohol relapse 3 years later. Second, the study examined the potentially confounding role of mood, anxiety, and illicit drug use disorders; nicotine dependence; and AUD severity in the relationship between smoking and alcohol use and AUD relapse.

MATERIALS AND METHODS

Data Source and Study Population

Study data were taken from Waves 1 and 2 of the NESARC which assessed substance use, substance use disorders, and related physical and psychiatric disabilities in a representative sample of the adult U.S. population. Wave 1 interviews took place from 2001 to 2002 and included 43,093 U.S. civilian noninstitutionalized adult respondents. Wave 2 interviews occurred 3 years later with 34,653 of the Wave 1 respondents, a follow-up rate of 80%. The study design and administration has been described in detail elsewhere (Grant and Kaplan, 2005; Grant et al., 2003b).

To accurately characterize relapse to alcohol, the sample for this study was restricted to individuals who (i) completed both the Wave 1 and Wave 2 assessments, (ii) reported having alcohol abuse, alcohol dependence, or both more than 1 year prior to the Wave 1 assessment, and (iii) reported being in remission from alcohol abuse or dependence for at least 1 year prior to Wave 1 data collection ($N = 9,134$; 26.4% of the original Wave 1 sample). These criteria were developed to ensure that individuals were free of the outcome behavior at the beginning of data collection. Respondents were still considered in remission if they endorsed any criteria for alcohol abuse or dependence below DSM-IV (American Psychiatric Association, 1994) diagnostic thresholds.

Measures

Alcohol Use, Abuse, and Dependence. The primary study outcomes were defined as relapse to alcohol use, abuse, or dependence assessed during the Wave 2 follow-up interview. In the NESARC, AUD status was determined using the National Institute on Alcohol Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV version (AUDADIS-IV), a fully structured diagnostic interview instrument designed for experienced lay interviewers (Grant et al., 2001). The reliability and validity of this measure are good-to-excellent (Grant et al., 1995).

Alcohol use at Wave 2 was defined as having consumed at least 1 drink at any time in the previous year. Additionally, to be given this label, a respondent must not have also met criteria for a diagnosis of alcohol abuse or dependence in the past year. A diagnosis of past-year alcohol abuse at Wave 2 was assessed by DSM-IV criteria and required the report of a pattern of alcohol use leading to clinically significant impairment or distress, as demonstrated by meeting at least 1 of the 4 abuse criteria (failure to complete major responsibilities at work, school, or at home; use of alcohol in hazardous situations such as driving a car or operating machinery; alcohol-related legal problems; the continued use of alcohol despite social or interpersonal problems; American Psychiatric Association, 1994) in the previous 12 months. A DSM-IV diagnosis of past-year alcohol dependence at Wave 2 required that a respondent report at least 3 of the 7 dependence criteria (tolerance, withdrawal, use of alcohol in larger amounts or over a longer period of time than planned, inability to cut down alcohol use, significant amount of time obtaining alcohol or recovering from alcohol use, reduction or cessation of important activities due to alcohol use, continued use despite recognition of alcohol-related problems; American Psychiatric Association, 1994) in the previous 12 months. A person who met criteria for both abuse and dependence was classified as dependent. Each of these outcomes (abuse, dependence) was considered as a dichotomous variable.

Smoking Behavior and Nicotine Dependence. The NESARC assessment included measurements of use of a range of tobacco products (e.g., cigarettes, cigars, pipes, snuff, chewing tobacco). Smoking behavior at Wave 1 was defined as a 3-category independent variable: (i) nonsmokers: participants who reported no use of any cigarettes in the year prior to the Wave 1 assessment, (ii) daily smokers: participants who reported cigarette use every day in the year prior to the Wave 1 assessment, and (iii) nondaily smokers: participants who reported smoking cigarettes 6 or fewer days per week in the year prior to the Wave 1 assessment. To isolate the association of cigarette use on alcohol relapse, participants who reported the use of other forms of tobacco (e.g., cigars, pipes, snuff, chewing tobacco) were included in the sample only if respondents also reported cigarette use.

A diagnosis of past-year nicotine dependence at Wave 1 was assessed in the AUDADIS using DSM-IV criteria: experiencing withdrawal, giving up activities in favor of nicotine use, spending a great deal of time using nicotine, and using nicotine more than intended (Grant et al., 2004a). A previous test of reliability of the AUDADIS in the assessment of smoking behavior found excellent test–retest reliability for the diagnosis of past-year nicotine dependence (intraclass correlation = 0.77, 95% confidence interval (CI) = 0.70, 0.82; Grant et al., 2003b). Each participant who reported Wave 1 past-year smoking (daily or nondaily) was classified as either meeting criteria for past-year nicotine dependence or not meeting criteria for past-year nicotine dependence.

Statistical Analysis

Sample Frequencies. The Rao–Scott chi-squared test, which accounts for the complex survey design, was used to test whether the proportion of individuals experiencing alcohol use relapse was statistically significantly different, first among the relevant socio demographic covariates, as well as among Wave 1 daily and nondaily smokers versus nonsmokers more broadly. To measure potential changes in the smoking exposure between interviews, correlations between alcohol use status and smoking status at Wave 1 and Wave 2 were tested for significance using the Rao–Scott chi-squared statistics. Sample attrition between waves was tested for significant differences in the frequency of loss to follow-up among respondents with and without AUDs at Wave 1.

Regression Modeling. Multiple regression modeling was used to examine the association between Wave 1 smoking status and the odds of alcohol use, abuse, or dependence at Wave 2. First, a model was run to determine the unadjusted odds ratio (OR) for smoking status and alcohol use relapse. Results from this model are presented ORs and 95% CIs.

Then, 5 additional models were run to control for potential confounders and covariates. Results from these 5 adjusted models, described in more detail below, are presented using adjusted ORs (AORs) and 95% CIs. The first adjusted model examined the association between smoking status and alcohol use relapse controlling for key socio demographic covariates: gender, race, age, education, marital status (married/living with someone as married, widowed, divorced/separated, single), and income. A second model was adjusted for a wide selection of mood and anxiety disorders reported at Wave 1 including history of major depression, manic depression, dysthymia, hypomania; history of anxiety disorders including panic disorder with/without agoraphobia, agoraphobia, social and specific phobia, generalized anxiety disorder, post traumatic stress disorder, attention deficit–hyperactivity disorder, antisocial personality disorder, borderline personality disorder, and schizotypal or narcissistic personality disorder. One dichotomous variable was created for the occurrence of any mood/anxiety disorder (1 = yes, 0 = no). The third model adjusted for any other illicit substance use disorder reported at Wave 1, including sedatives, tranquilizers, opiates (other than heroin or methadone), stimulants, hallucinogens, cannabis, cocaine (including crack cocaine), inhalants/solvents, heroin, and other drugs. One dichotomous variable was created for any reported illicit drug use disorder (1 = yes, 0 = no). The model also adjusted for the potential interaction by lifetime history of nicotine dependence. A fourth model adjusted for nondisordered alcohol use (any alcohol use with no disorder) and 8 separate measures of AUD severity using Wave 1 data and based on previous similar analyses (Dawson et al., 2007). Criteria included the initiation of drinking before age 15, the interval from first drink to onset of dependence, duration of dependence, duration of remission, the number of relapse episodes, number of lifetime symptoms prior to the year preceding Wave 1, the volume of alcohol consumed during the period of heaviest drinking, and ever having obtained either formal or informal help for alcohol problems. A fifth model was created to fully adjust for all of the above covariates simultaneously.

Adjusted models were restricted to complete cases only. Due to the interview skip patterns (e.g., only those who met criteria for alcohol dependence were asked certain questions), a large proportion of responses for 4 covariates were missing: interval from first drink to onset of dependence (n = 3,652), number of relapse episodes (n = 3,537), duration of dependence (n = 3,588), and duration of remission (n = 1,719). Because inclusion of these covariates led to large sample size reductions in the regression models, we removed them as a variable in our final models in order to maintain a nearly complete analytic sample in adjusted models 4 and 5.

All tests were completed in STATA using weighted analysis (StataCorp, 2011) to account for residual differences between the sample and the population profile, according to the 2000 U.S. Population Census, as well as to account for nonresponse and sample attrition. The weighted Wave 2 data represent the same baseline population as represented in Wave 1.

RESULTS

Sample Demographic Characteristics

Of the respondents in our sample with remitted AUDs, 18.6% were lost to follow-up at Wave 2, while of the respondents without remitted AUDs, 19.5% were lost to follow-up at Wave 2. Therefore, we restricted our analytical sample to only those who were not lost to follow-up at Wave 2, assuming minimal risk for selection bias from attrition.

See Table 1 for Wave 1 demographic frequencies of the full analytic sample and by smoking status. Among the full analytic sample (n = 9,134), 36.1% were daily smokers, 7.0% were nondaily smokers, and 56.9% were nonsmokers. The daily smokers reported smoking an average of 19.6 cigarettes per day (95% CI = 19.3 to 19.9) and the nondaily smokers reported smoking an average of 5.0 cigarettes on a days that they smoked (95% CI = 4.7 to 5.3). The nondaily smokers reported smoking an average of 1 to 2 days per week. The highest rates of daily smoking were reported by respondents who were men (37.5%), ages 18 to 29 (43.7%), Native American (46.6%), widowed, separated, or divorced (47.7%), those who reported earning $0 to 19,999 (44.4%), and those with less than a high school (HS) degree (53.8%). Among nondaily smokers, the highest percentages of use of cigarettes were reported among men (7.2%), ages 18 to 29 (14.2%), Native American (9.6%), never married (10.3%), those with an income greater than $70,000+ (8.2%), and more than a HS degree (8.0%). The most commonly reported noncigarette tobacco products used by Wave 1 daily and nondaily cigarette smokers were cigars, snuff, and chewing tobacco. A majority of daily smokers met criteria for lifetime nicotine dependence, while just under half of nondaily smokers met these criteria.

Alcohol Use Frequencies

Across the Wave 1 study sample, 57.7% participants reported nondisordered, subthreshold alcohol use at Wave 1. Forty-nine percent of respondents reported at least 1 abuse and/or dependence symptom. At the Wave 2 assessment, 61.2% of participants reported alcohol use in the previous year, while 12.1% of participants reported alcohol abuse, and 10.8% of participants reported alcohol dependence. Among both daily and nondaily smokers, rates of alcohol abuse and dependence were significantly higher than rates among nonsmokers, while the rate of nonproblematic alcohol use was higher among nonsmokers compared to smokers (see Table 2). Smoking status and alcohol use status variables were statistically correlated for all 3 outcomes. The changes in correlation coefficients between Waves 1 and 2 were minimal, suggesting that smoking prevalence paralleled changes in alcohol use behaviors, and lending support that smoking is a proximal risk factor for AUDs (see Table 2).

Relapse to Alcohol Use and AUDs by Wave 1 Smoking Status

Compared with nonsmokers, those who reported either daily or nondaily smoking at Wave 1 had statistically significantly higher odds of reporting recurrent alcohol abuse and dependence at Wave 2 (Table 3). These relationships persisted after controlling in subsequent models for demographic variables, any mood or anxiety disorder, any illicit

Table 1. Demographic Covariates by Wave 1 Smoking Status (n = 9,134)

Variable	Total	Wave 1 Nonsmokers	Wave 1 Nondaily smokers	Wave 1 Daily smokers	p
Total (%)		56.9	7.0	36.1	<0.0001
Gender (%)					<0.0001
Male	64	62.2	65.9	66.5	
Female	36	37.8	34.1	33.5	
Age					
18 to 29	13.1	9.7	26.6	15.9	<0.0001
30 to 44	35.7	35.2	43.3	35	
45 to 64	40.3	41.2	26.4	41.7	
65+	10.8	13.9	3.8	7.4	
Race/Ethnicity (%)					
NH White	81	81	79.6	81.3	<0.0001
NH Black	7.1	6.9	5.4	7.8	
NH Native American/AK Native	3	2.3	4	3.8	
NH Asian/Pacific Islander	1.5	1.4	1.8	1.6	
Hispanic	7.4	8.5	9.2	5.5	
Marital status (%)					
Current	65.7	71.6	59.8	57.5	<0.0001
Widowed, separated, divorced	18.3	14.8	16.8	24.2	
Never	16	13.6	23.4	18.3	
Personal income (%)					
$0 to 19,999	32.8	28.5	28.9	40.4	<0.0001
$20 to 34,999	23.2	22.2	21.5	25.3	
$35 to 69,999	29.8	31.5	33.1	26.5	
$70,000+	14.1	17.8	16.5	7.8	
Education (%)					
Less than HS degree	11.1	8.3	6.4	16.6	<0.0001
High school degree	48.7	42.2	47.9	59.1	
More than HS	40.2	49.5	45.7	24.3	
Use of tobacco products[a] (%)					
Cigarettes	67.8	n/a	100	100.0	<0.0001
Cigars	13.2		22.5	19.8	
Pipe	10.2		11.2	12.8	
Snuff	9.1		22.4	15.8	
Chewing tobacco	9.6		21.8	16.4	
Lifetime nicotine dependence	36.1		42.8	70.6	
Nondisordered alcohol use at Wave 1 (%)					
Subthreshold use[b]	57.7	62.4	52.5	51.5	<0.0001
At least 1 abuse/dependence symptom[b]	49.0	42.3	71.5	55.0	<0.0001

NH, non-Hispanic; AK, Alaska; HS, high school.
[a]Includes those who report smoking cigarettes, with or without other tobacco use.
[b]Reported as column percents (i.e., among those who report daily cigarette use, XX% report subthreshold alcohol use).

substance use disorder, nondisordered alcohol use, and AUD severity (Table 3). The interaction term for nicotine dependence was statistically significant for alcohol use (β = 0.082; p = 0.023) and dependence (β = 0.398; p < 0.0001), but not alcohol abuse (β = 0.014; p = 0.798) and was included in the final models. Only 1 relationship was no longer significant after adjusting for covariates and that comparison was for daily smokers versus nonsmokers for Wave 2 alcohol use when all covariates were included in the model (AOR[5] in Table 3).

In the fully adjusted model (model 5), Wave 1 daily smokers had 17% greater odds of relapsing to alcohol abuse (95% CI: 1.02 to 1.34), and 54% greater odds of relapsing to alcohol dependence (95% CI: 1.38 to 1.71) compared to Wave 1 nonsmokers. Nondaily smokers had 87% greater odds of relapsing to alcohol abuse (95% CI: 1.65 to 2.12), and 95% greater odds of relapsing to alcohol dependence (95% CI: 1.53 to 2.49) compared to Wave 1 nonsmokers. Complete results are presented in Table 3.

Additionally, pairwise tests were completed to determine whether the odds of alcohol use and AUDs were statistically significantly different between nondaily and daily smokers. Nondaily smokers were not significantly more likely to report alcohol use at Wave 2, compared with daily smokers (OR: 0.901; 95% CI: 0.74 to 1.10), nor did they report significantly greater alcohol dependence (OR: 1.19; 95% CI: 0.89 to 1.58). However, nondaily smokers were significantly more likely to report alcohol abuse than daily smokers (OR: 1.46; 95% CI: 1.1 to 1.93) at Wave 2 (data not shown).

DISCUSSION

The purpose of this study was to examine the relationship between smoking status and risk of relapse 3 years later among adults with remitted AUDs using a representative sample of the adult U.S. population. Among adults with remitted AUDs, daily and nondaily use of cigarettes at Wave 1 was associated with significantly increased likelihood of

Table 2. Prevalence and Correlation of Wave 2 Alcohol Use Status by Waves 1 and 2 Smoking Status

Wave 2 Alcohol: (%, SE)	Wave 1 (%, SE)						Wave 2 (%, SE)					
	Nonsmoker	Nondaily smoker	Daily smoker	p^a	r^2	p^b	Nonsmoker	Nondaily smoker	Daily smoker	p^a	r^2	p^b
None (18.2%; 0.26)	18.8 (0.32)	8.8 (0.77)	19.3 (0.47)	<0.0001	0.087	<0.0001	18.1 (0.56)	9.7 (1.08)	18.9 (0.29)	<0.0001	−0.027	0.0087
Use (61.2%; 0.30)	65.0 (0.38)	56.9 (1.14)	56.0 (0.52)	<0.0001	−0.076	<0.0001	64.8 (0.36)	48.3 (1.41)	55.1 (0.51)	<0.0001	−0.086	<0.0001
Abuse (12.1%; 0.18)	10.6 (0.19)	21.3 (1.17)	13.1 (0.34)	<0.0001	0.038	0.0006	10.5 (0.23)	28.0 (1.22)	13.9 (0.44)	<0.0001	0.054	<0.0001
Dependence (10.8%; 0.22)	7.1 (0.23)	20.2 (1.25)	15.1 (0.37)	<0.0001	0.139	<0.0001	7.2 (0.23)	25.2 (1.40)	17.0 (0.40)	<0.0001	0.159	<0.0001

SE, standard error.
[a] p-Value represents the comparison of the prevalence of the Wave 2 alcohol use statuses among the 3 smoking statuses (nonsmoker, nondaily smoker, daily smoker).
[b] p-Value represents the correlation of the smoking status and the alcohol use status.

alcohol abuse and dependence 3 years later, compared with nonsmoking. Wave 1 daily and nondaily smoking were both associated with a decreased likelihood of alcohol use at Wave 2 compared to Wave 1 nonsmoking. These relationships remained significant after adjusting for demographics, psychiatric disorders, substance use disorders, nondisordered alcohol use, severity of AUDs, and nicotine dependence.

Smokers who smoke cigarettes every day compared to those who do not smoke every day differ with regard to smoking behavior. For example, nondaily smokers smoke fewer cigarettes on smoking days, are less likely to report dependence on nicotine, and are more likely to report motivation to quit smoking although nondaily smokers also appear to be similar to daily smokers with regard to having trouble quitting smoking (Rubinstein et al., 2014; Tindle and Shiffman, 2011). Little is known about the association of smoking and alcohol for smokers who consume cigarettes every day versus some days. One study of adolescents found that daily and nondaily smokers were equally likely to report smoking when they consumed alcohol (Rubinstein et al., 2014). Similarly, the current study found that daily and nondaily smoking was similarly related to AUD relapse. Further, nondaily smokers were not less likely than daily smokers to report Wave 2 alcohol use and dependence and were actually more likely to report alcohol abuse.

The results of the current analyses are consistent with preclinical and clinical trial data. In preclinical studies, nicotine facilitates the acquisition of alcohol self-administration (Smith et al., 1999) and reinstates previously extinguished alcohol-seeking behavior (Lê et al., 2003). Adults reported increased urges to consume alcohol after smoking cigarettes (Cooney et al., 2007) and use of alcohol and nicotine together leads to greater cravings for both substances (Piasecki et al., 2011). In adults who completed treatment for both alcohol and tobacco use, there was an association between high urges to smoke cigarettes and relapse to alcohol consumption (Cooney et al., 2007). In a recent study of adults with alcohol dependence and smoking (Cooney et al., 2015), days when participants did not smoke, compared to days when participants did smoke, were associated with decreased alcohol consumption, lower urges to drink, and higher levels of self-efficacy and motivation to remain abstinent from alcohol. Secondary analysis from Project MATCH (Friend and Pagano, 2005), a clinical trial of behavioral treatments for AUDs, reported that participants who decreased their cigarette consumption during the course of treatment were less likely to relapse to alcohol consumption compared to participants who consumed the same or more than their baseline number of cigarettes. Together, there is evidence across multiple methodologies (i.e., preclinical, clinical, epidemiologic) that cigarette smoking is associated with relapse to alcohol.

Smoking may facilitate relapse to AUDs for a number of reasons. Adults who smoke cigarettes report greater reinforcement from alcohol (McKee et al., 2004) and there is preclinical and clinical evidence for cross-tolerance between

Table 3. Odds of Wave 2 Alcohol Use Disorder Relapse by Wave 1 Smoking Status Among Individuals with a History of Alcohol Use Disorders Prior to Wave 1

Wave 2 alcohol use status	OR (95% CI)	AOR[1]	AOR[2]	AOR[3]	AOR[4]	AOR[5]
Nondaily smokers versus nonsmokers						
None	ref.	ref.	ref.	ref.	ref.	ref.
Use	0.71 (0.65 to 0.78)	0.74 (0.67 to 0.82)	0.72 (0.65 to 0.79)	0.78 (0.70 to 0.86)	0.84 (0.74 to 0.95)	0.81 (0.71 to 0.92)
Abuse	2.30 (2.00 to 2.60)	1.67 (1.47 to 1.90)	2.32 (2.02 to 2.66)	2.27 (1.97 to 2.62)	2.45 (2.17 to 2.76)	1.87 (1.65 to 2.12)
Dependence	3.30 (2.79 to 3.96)	2.19 (1.84 to 2.61)	3.19 (2.65 to 3.84)	2.89 (2.41 to 3.46)	2.88 (2.30 to 3.60)	1.95 (1.53 to 2.49)
Daily smokers versus nonsmokers						
None	ref.	ref.	ref.	ref.	ref.	ref.
Use	0.69 (0.65 to 0.72)	0.86 (0.82 to 0.91)	0.70 (0.66 to 0.74)	0.74 (0.68 to 0.81)	0.84 (0.78 to 0.91)	0.97 (0.91 to 1.04)
Abuse	1.30 (1.19 to 1.37)	1.13 (1.05 to 1.22)	1.31 (1.22 to 1.4)	1.34 (1.21 to 1.47)	1.27 (1.16 to 1.40)	1.17 (1.06 to 1.29)
Dependence	2.30 (2.17 to 2.53)	1.70 (1.55 to 1.86)	2.20 (2.04 to 2.39)	1.51 (1.29 to 1.77)	1.99 (1.81 to 2.19)	1.54 (1.38 to 1.71)

OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval.
AOR[1]—age, gender, income, race, education, marital status.
AOR[2]—any mood or anxiety disorders at Wave 1.
AOR[3]—any illicit substance use disorders at Wave 1, including interaction by nicotine dependence.
AOR[4]—nondisordered alcohol use and alcohol use disorder severity.
AOR[5]—fully adjusted for all covariates in models 1 to 4.

nicotine and alcohol (e.g., Drobes, 2002; Kouri et al., 2004). Preclinical, clinical, and epidemiologic data have linked smoking to difficulty remaining abstinent from alcohol and smoking and alcohol show strong behavioral and neurochemical links to each other (McKee and Weinberger, 2013). Further, smoking has detrimental effects on neurocognition (e.g., executive function, memory, processing speed; Durazzo et al., 2012; Wagner et al., 2013) and is associated with greater impairments in cognition and altered brain structure in active and recently abstinent drinkers (Durazzo et al., 2007, 2013; Glass et al., 2006) and with decreased cognitive recovery in adults with AUDs in early recovery (Durazzo et al., 2006; Pennington et al., 2013). Together these data suggest that smoking cessation may provide benefits for continued abstinence from alcohol/remission from AUDs and may therefore be an important target for interventions to improve long-term alcohol outcomes.

Many adult smokers with AUDs report motivation to quit smoking (Ellingstad et al., 1999; Zullino et al., 2000) and the majority believe that quitting smoking will not make it difficult to resist urges to drink or harm their remission from AUDs (Kalman et al., 2010). While some studies have reported that current and past AUDs are associated with a decreased likelihood of quitting smoking, other data report that smokers with past AUDs quit smoking at similar rates as adults without AUDs (Breslau et al., 1996; Hughes and Kalman, 2006; Weinberger et al., 2013). Concerns have been raised about the potential harmful effects of providing concurrent smoking and alcohol treatment on alcohol outcomes. Overall, the balance of studies has found no detrimental impacts on alcohol outcomes when smoking cessation treatments are provided to adults in treatment for AUDs (e.g., Baca and Yahne, 2009; Cooney et al., 2009; Kalman et al., 2010; for reviews, see Kodl et al., 2006; Prochaska et al., 2004). Of note, smoking treatments have been given at different points during alcohol treatment (Kodl et al., 2006), and a greater length of abstinence from alcohol at the start of treatment is associated with greater smoking cessation success (Prochaska et al., 2004). This suggests that, even with "concurrent" alcohol and smoking treatment, better outcomes may be found for patients who stop using alcohol prior to stopping the use of cigarettes. More research is needed to understand how timing of smoking treatment at different points during concurrent alcohol treatment (e.g., at a point during treatment that coincides with the start of sobriety vs. at a point in treatment after sobriety has begun) relates to alcohol and smoking outcomes. Further, it should be noted that some patients prefer treatment for smoking after, rather than concurrently with, alcohol treatment (Kodl et al., 2006) and clinicians should consider patient preferences when developing treatment plans.

Long-term smoking cessation outcome studies of adults in treatment for AUDs were low, regardless of whether smoking treatment was concurrent or delayed, similar to low rates of long-term successful cessation in the general smoking population (Centers for Disease Control and Prevention, 2011; Fiore et al., 2008). There is a need for continued research on improving cessation outcomes and reducing relapse rates. To facilitate the most favorable alcohol and smoking outcomes, additional research is also needed to identify optimal ways to motivate adults with AUDs to quit smoking, treatments that yield the best short- and long-term outcomes, and variables to target within treatments. For example, a study of lapses to alcohol consumption and smoking suggested the benefits of targeting mood, abstinence-related self-efficacy, and urges to smoke (Holt et al., 2012). Alcohol relapse behaviors were related to both daily and nondaily smoking, highlighting the need to target intermittent smoking as well as daily smoking in adults with AUDs.

It should be noted that a large number of Wave 1 participants with past AUDs, smokers and nonsmokers, reported that they consume alcohol without any current problems. There are several possibilities for reasons for the large rate of nonproblem alcohol use in this sample. First, participants

with past AUDs may be underreporting problems related to current alcohol use. Second, participants may have learned to drink at a level or manner that no longer leads to problems. Third, participants may have resumed drinking, but their behavior has not yet reached the point where it has begun to cause problems. While some suggest that former problematic drinkers can consume alcohol without problems (Hodgins, 2005), other research shows that relapse to AUDs in adults with former AUDs is associated with more frequent alcohol consumption (Moos and Moos, 2006) or alcohol consumption relative to abstinence (Dawson et al., 2007). Adults with past AUDs should be monitored by clinicians over time to assess whether drinking that is reported to be nonproblematic remains that way to intervene as quickly as possible should problems begin to occur.

Nicotine dependence was a significant effect modifier of the association between cigarette use and alcohol use and dependence. This finding is consistent with other studies that have also demonstrated a strong comorbidity or parallel risk between AUDs and nicotine dependence. AUDs are associated with higher rates of nicotine dependence compared to the general U.S. population (12.8% vs. 22.8%; Grant et al., 2004a) and incident nicotine dependence (Goodwin et al., 2013). One previous study found that adults with a diagnosis of nicotine dependence were >3 times more likely to transition from alcohol use to alcohol dependence than adults without nicotine dependence (hazard ratio = 3.29, 95% CI = 2.9 to 3.7; Lopez-Quintero et al., 2011). Our results suggest that nicotine dependence is also associated with a greater likelihood of transition from past AUDs to recurrent AUDs. Just as clinicians should be aware the smoking is associated with AUD relapse, clinicians should also be aware that the endorsement of nicotine dependence may represent an even higher risk factor for their patients.

Limitations of this study must be noted. First, the NESARC sample included persons in the United States who were 18 years and older and noninstitutionalized. These results would have limited generalizability to other groups including adolescents and adults outside of the United States. Second, data for the analyses were taken from 2 time points that were 3 years apart and were limited to the information assessed in the 2 interviews. Information that could not be examined includes the timing of or context related to relapse to alcohol use or AUDs. Future studies would benefit from examining the contexts of relapse to AUDs in cigarette smokers versus nonsmokers. Third, the alcohol use outcomes were assessed 3 years after baseline, and therefore, relapse to AUDs could only be captured within this time frame. It would be useful for future studies to examine the role of smoking in alcohol relapse over longer periods of time. Fourth, data from the NESARC relied on self-report and there was no biochemical verification of smoking or alcohol consumption. The reliance on self-report may have led to either the underreporting (e.g., problematic alcohol use, smoking) or over reporting (e.g., nonproblematic alcohol use) of addiction-related behaviors.

Alcohol consumption and cigarette use are frequently co-occurring behaviors that can have negative impacts on the health of adults. The current data suggest that both daily and nondaily cigarette smoking are associated with a greater risk of relapse to AUDs among adults in the United States, which is consistent with data from clinical treatment settings. Treatments for AUDs that include simultaneous treatment for smoking cessation and nicotine dependence may help improve long-term outcomes and reduce the negative consequences of both substances.

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#7 Bachhuber MA, Saloner B, Cunningham CO, Barry CL. 2014. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States 1999-2010. JAMA Internal Medicine.

"Results: Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999. Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) enacted medical cannabis laws between 1999 and 2010. States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; $P = .003$) compared with states without medical cannabis laws. Examination of the association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law showed that such laws were associated with a lower rate of overdose mortality that generally strengthened over time: year 1 (−19.9%; 95% CI, −30.6% to −7.7%; $P = .002$), year 2 (−25.2%; 95% CI, −40.6% to −5.9%; $P = .01$), year 3 (−23.6%; 95% CI, −41.1% to −1.0%; $P = .04$), year 4 (−20.2%; 95% CI, −33.6% to −4.0%; $P = .02$), year 5 (−33.7%; 95% CI, −50.9% to −10.4%; $P = .008$), and year 6 (−33.3%; 95% CI, −44.7% to −19.6%; $P < .001$). In secondary analyses, the findings remained similar."

Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study☆

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Highlights: • Prescription opioid dependent patients were followed post-treatment for 42 months. •Long-term outcomes demonstrated clear improvement from baseline. • 61% were abstinent from illicit opioids, including 29% on agonist therapy. • Agonist therapy was associated with a greater likelihood of Month-42 abstinence. • 10% initiated heroin use, and 10% initiated injection heroin use post-treatment.

Abstract: Despite the growing prevalence of prescription opioid dependence, longitudinal studies have not examined long-term treatment response. The current study examined outcomes over 42 months in the Prescription Opioid Addiction Treatment Study (POATS). Methods: POATS was a multi-site clinical trial lasting up to 9 months, examining different durations of buprenorphine-naloxone plus standard medical management for prescription opioid dependence, with participants randomized to receive or not receive additional opioid drug counseling. A subset of participants (N = 375 of 653) enrolled in a follow-up study. Telephone interviews were administered approximately 18, 30, and 42 months after main-trial enrollment. Comparison of baseline characteristics by follow-up participation suggested few differences. Results: At Month 42, much improvement was seen: 31.7% were abstinent from opioids and not on agonist therapy; 29.4% were receiving opioid agonist therapy, but met no symptom criteria for current opioid dependence; 7.5% were using illicit opioids while on agonist therapy; and the remaining 31.4% were using opioids without agonist therapy. Participants reporting a lifetime history of heroin use at baseline were more likely to meet DSM-IV criteria for opioid dependence at Month 42 (OR = 4.56, 95% CI = 1.29–16.04, p < .05). Engagement in agonist therapy was associated with a greater likelihood of illicit-opioid abstinence. Eight percent (n = 27/338) used heroin for the first time during follow-up; 10.1% reported first-time injection heroin use. Conclusions: Long-term outcomes for those dependent on prescription opioids demonstrated clear improvement from baseline. However, a subset exhibited a worsening course, by initiating heroin use and/or injection opioid use.

CrossMark

REVIEW

Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage

Yasmin L. Hurd[1] · Michelle Yoon[1] · Alex F. Manini[2] · Stephanie Hernandez[2] ·
Ruben Olmedo[2] · Maria Ostman[3] · Didier Jutras-Aswad[4]

Abstract Multiple cannabinoids derived from the marijuana plant have potential therapeutic benefits but most have not been well investigated, despite the widespread legalization of medical marijuana in the USA and other countries. Therapeutic indications will depend on determinations as to which of the multiple cannabinoids, and other biologically active chemicals that are present in the marijuana plant, can be developed to treat specific symptoms and/or diseases. Such insights are particularly critical for addiction disorders, where different phytocannabinoids appear to induce opposing actions that can confound the development of treatment interventions. Whereas Δ^9-tetracannabinol has been well documented to be rewarding and to enhance sensitivity to other drugs, cannabidiol (CBD), in contrast, appears to have low reinforcing properties with limited abuse potential and to inhibit drug-seeking behavior. Other considerations such as CBD's anxiolytic properties and minimal adverse side effects also support its potential viability as a treatment option for a variety of symptoms associated with drug addiction. However, significant research is still needed as CBD investigations published to date primarily relate to its effects on opioid drugs, and CBD's efficacy at different phases of the abuse cycle for different classes of addictive substances remain largely understudied. Our paper provides an overview of preclinical animal and human clinical investigations, and presents preliminary clinical data that collectively sets a strong foundation in support of the further exploration of CBD as a therapeutic intervention against opioid relapse. As the legal landscape for medical marijuana unfolds, it is important to distinguish it from "medical CBD" and other specific cannabinoids, that can more appropriately be used to maximize the medicinal potential of the marijuana plant.

Keywords THC · Cannabis · Heroin · Human · Rat · Craving

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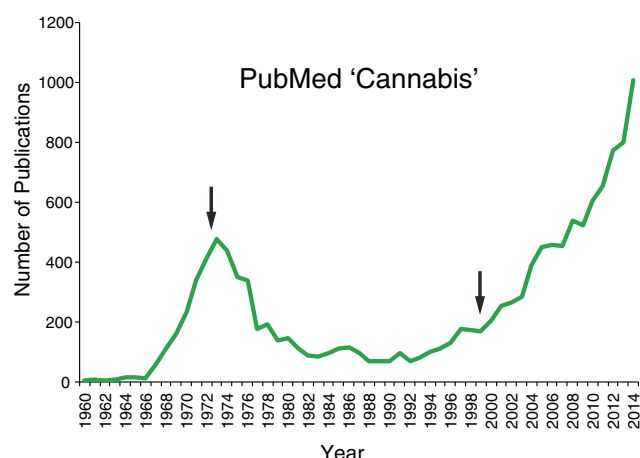
Introduction

With debates about so-called *medical marijuana* and the widespread media coverage on the subject, the call for the legalization of marijuana (*Cannabis sativa*) both for recreational and medical purposes has gained considerable momentum in recent years. While much attention has been given to the medicinal promises that the marijuana plant might possess, the spotlight on marijuana has also raised awareness about the remarkable dearth of scientific studies that have been conducted on this plant's therapeutic potential. As shown in Fig. 1, the number of research studies published on cannabis has coincided temporally with major changes in the social and political climates of the time such as in the early 2000s after states such as California legalized marijuana. Unfortunately, many scientific and medical questions remain with respect to the potential or actual benefits and risks of medicinal and recreational marijuana use. Although the public and the media use the term "medical marijuana" liberally, few acknowledge or are even aware of the complex nature of the plant, which consists

Fig. 1 The number of publications based on PubMed search for the term "cannabis". Patterns coincides with governmental policy and societal changes (some denoted by arrows), such as cannabis becoming a Schedule I drug in the USA in 1970, in the 1970s state laws and local regulations begin to ban possession or sale of cannabis, in 1996 California voters passed Proposition 215 that legalized medical cannabis, and in 2000 there were increased attempts for decriminalization and legalized marijuana use around the USA. No other cannabinoid-related PubMed search term showed the same temporal pattern

of >400 chemicals, with approximately 70 cannabinoids [1, 2]. The truth is, there is growing evidence that not all components of marijuana are medically beneficial and it is still unclear as to what specific medical disorders are best treated by this plant. Which cannabinoids mediate what specific beneficial or adverse effects remains an important question when one considers the complexity of the marijuana plant, and there is now growing research interest in answering such questions in the hopes of identifying and developing medicinal cannabinoids targeted for specific medical symptoms and diseases.
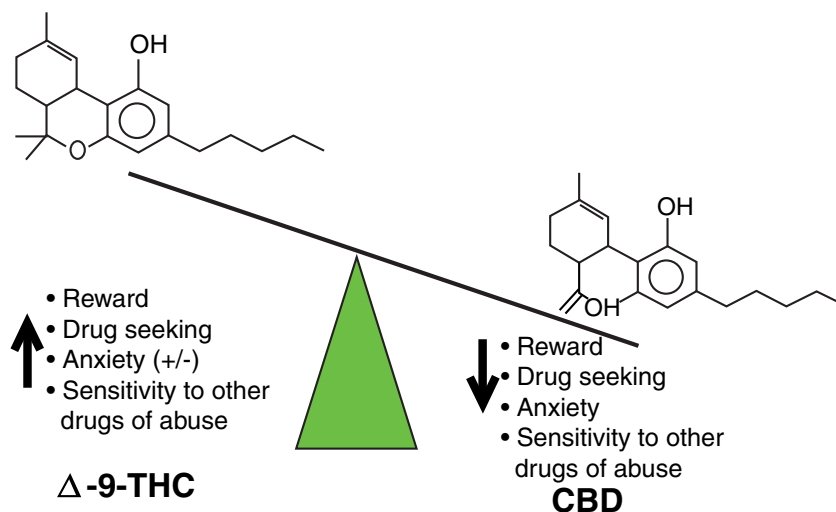
Most scientific studies to date have focused on Δ^9-tetrahydrocannabinol (THC), the most prominent psychoactive constituent of the plant and the cannabinoid that leads to the rewarding effects of cannabis. Another prominent phytocannabinoid is

cannabidiol (CBD) [2], which has extremely low concentrations in the marijuana strains commonly used recreationally in which the THC potency has dramatically increased [3]. Plants more recently cultivated with a high CBD content (and low THC levels) are thought to have potential benefit in treating various diseases; in particular, CBD as an antiepileptic agent in children has received much public interest, even though the evidence to date has been mostly anecdotal, with active clinical trials now underway [4, 5]. In this article, we focus on CBD's potential therapeutic potential in addiction disorders based on evidence from preclinical studies that suggest a "yin/yang" relationship between 2 components of the cannabis plant where one enhances substance abuse risk (THC) and the other inhibits drug relapse (CBD) (Fig. 2). The information below provides a foundation for the development of CBD as a potential treatment for addiction to specific drug classes.

Overview of Addiction and Current Treatment Challenges

Individuals who suffer from addictive disorders go through various stages in their illnesses (Fig. 3), each of which is characterized by specific neurobiological states. Substance use and intoxication produce psychoactive and addictive effects by acting on the brain's reward system—a set of interconnected regions that control pleasure and motivation [6]. During the intoxication phase, drugs modulate a number of neurotransmission systems such as dopamine, opioid, serotonin, and norepinephrine. These biochemical events are responsible for the physiological and behavioral effects observed in abusers (e.g., euphoria, restlessness, and tachycardia). Early abstinence in dependent patients results in pharmacological and clinical effects that are opposite to those found during the intoxication phase. Acute withdrawal may include symptoms that vary according to the type of drug, including

Fig. 2 Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have opposing "yin/yang" effects on addiction-related behaviors. In contrast to THC that is rewarding and promotes drug use, CBD has low hedonic property and inhibits drug seeking

sleep disturbances, anxiety, dysphoria, and fatigue [7]. Most importantly, this phase is associated with low stress tolerance and recurrent episodes of craving (an intense desire to use), which persist for months, often resulting in relapse [8, 9]. In the long term, addiction becomes characterized by compulsive substance use and, most strikingly, repetitive urges to consume the drug can persist even after sustained periods of abstinence.

While substance use remains the most obvious direct outcome of addiction, there is now growing interest among scientists to focus on other core symptoms of this disorder. In the recently published *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, craving—the most prominent symptom and long-lasting sequel of drug dependence—has been added to the criteria of substance use disorders, a direct reflection of its clinical relevance in addictive disorders. Craving has become a subject of great interest as it is a reliable intermediate phenotype of relapse and the most distressing and long-lasting symptom experienced by dependent individuals between uses. Indeed, even after a period of abstinence, dependent individuals remain vulnerable to stress and other craving-inducing stimuli [10], which, in turn, leads to intense physiological responses and various negative feelings such as anger and sadness [11]. Real-time daily monitoring of craving and drug use has shown that craving reliably predicts relapse among dependent individuals [9, 12–15]. The data suggest that improving the treatment of craving could not only help prevent relapse, but could also reduce patient distress on the emotional, cognitive, and physiological levels.
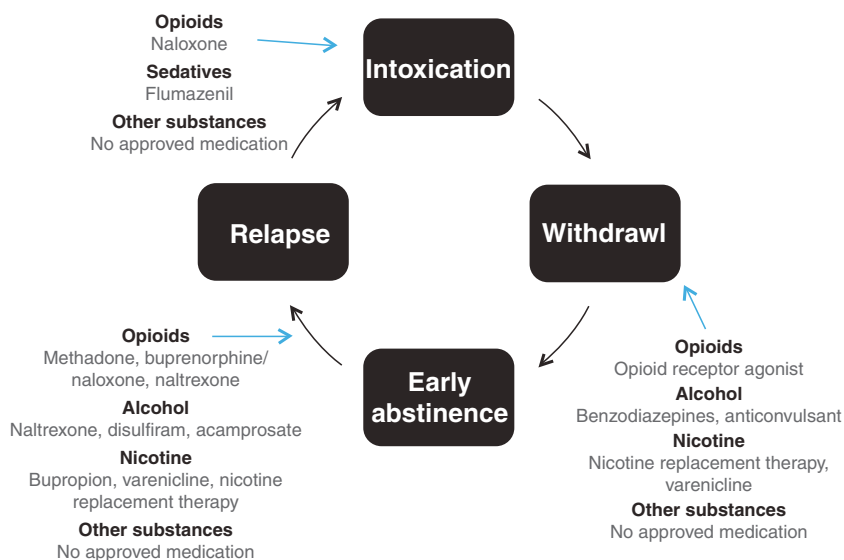
While significant scientific efforts have been deployed over the last few decades in the development of interventions that target craving and different phases of the addiction cycle (Fig. 3), their success rates have been limited. Psychosocial approaches have been widely used to help patients achieve improved outcomes after drug cessation; however, the literature indicates that these strategies alone are at times insufficient to induce significant behavioral changes or a reduction in rates of drug consumption [16]. In addition, most of the available medication for treating addiction (e.g., alcohol and nicotine dependence) have had low-to-moderate effects on relapse outcomes. Even more concerning is the fact that no pharmacological treatment for substance abuse have yet been proven completely effective in preventing relapse for a number of substances including cocaine, amphetamine, and cannabis. The treatment options that have been explored, which include trials of medications known to regulate monoamine neurotransmission such as antidepressants, anticonvulsants, and antipsychotics, have been the subject of several systematic reviews but they have not demonstrated their efficacy in improving outcomes [17–19]. Although an immunotherapeutic vaccine strategy to hinder the passage of drugs through the blood–brain barrier is currently underway, its efficacy and realistic implementation appear unclear thus far [20, 21]. With these developments and challenges in mind, a rightful sense of urgency persists within the scientific community for the identification of new compounds that will help patients initiate abstinence and avoid relapse.

The Endocannabinoid System as a Treatment Target for Addiction

Among potential emerging neurobiological targets for treating craving and addiction, the endogenous cannabinoid receptors and ligands that constitute the endocannabinoid (eCB) system have been the subject of growing interest. The eCB has tight neurobiological interaction with other neurotransmission systems that have important implications for the neural adaptations induced by drug use. For example, type 1 cannabinoid receptors (CB$_1$R) are co-localized with opioid μ opioid

Fig. 3 Cycle of addiction and currently available medications for substance use disorders at each stage of the cycle

Intoxication
Opioids Naloxone
Sedatives Flumazenil
Other substances No approved medication

Withdrawl
Opioids Opioid receptor agonist
Alcohol Benzodiazepines, anticonvulsant
Nicotine Nicotine replacement therapy, varenicline
Other substances No approved medication

Early abstinence

Relapse
Opioids Methadone, buprenorphine/naloxone, naltrexone
Alcohol Naltrexone, disulfiram, acamprosate
Nicotine Bupropion, varenicline, nicotine replacement therapy
Other substances No approved medication

receptors (which mediate the actions of opioid drugs) in striatal output projection neurons of the nucleus accumbens and dorsal striatum that modulate reward, goal-directed behavior, and habit formation relevant to addiction [22]. Type 2 cannabinoid receptors (CB$_2$R) have very low expression in the brain generally, but recently they have been shown to be expressed in dopamine neurons of the midbrain ventral tegmental area and modulate the functional excitability of dopamine neurons central to addiction related behaviors such as drug reinforcement [23]. Stimulation of CB$_2$R in mice models has an inhibitory influence on cocaine and alcohol self-administration and related conditioned place preference, as well as nicotine place preference behavior [23, 24].

CBD and Neurobiological Targets/Effects

Interestingly, different cannabinoids that target the eCB system exhibit distinct properties on addictive behavior. It is generally well known that THC, the predominant psychoactive cannabinoid in the cannabis plant, has high affinity at the CB$_1$R, where it acts as a partial agonist to elicit potent rewarding effects. We focus this review on CBD as it is a cannabinoid that has not been extensively studied to date and is currently being explored for its potential antiaddiction properties. CBD has long been recognized as a nonpsychotropic constituent of cannabis and is generally the second most abundant cannabinoid present in the plant [2, 3]. Contrary to previous beliefs that CBD did not bind directly to cannabinoid receptors, recent findings indicate that CBD acts as an inverse agonist at CB$_1$R and CB$_2$R [25, 26]. CBD stimulates the transient receptor potential vanilloid 1/2 proteins [27], which serve as so-called ionotropic cannabinoid receptors. In addition, CBD inhibits fatty acid amide hydrolase, a catabolic enzyme that alters the hydrolysis of the endogenous cannabinoid neurotransmitter anandamide [28]. Perhaps the largest body of evidence pertains to the modulation and activation of 5-hydroxytryptamine 1A serotoninergic receptors [29–35]. CBD also has low potency for inhibiting the uptake of striatal dopamine [36]; it modulates allosterically μ and δ opioid receptors [37] and enhances adenosine signaling through uptake inhibition [36, 38]. Although more studies are needed to further understand the impact of CBD on glutamatergic neurotransmission, its protective effects on glutamate toxicity and its pharmacologic interaction with ketamine [39, 40], an *N*-methyl-ᴅ-aspartate receptor (NMDA) antagonist, are also well documented.

By virtue of its 5-hydroxytryptamine 1A receptor-modulating properties, CBD consistently decreases stress vulnerability and exhibits anxiolytic-like effects [29, 32–34, 41–44]. Indeed, CBD's antianxiety properties have been substantiated by elevated plus-maze and rat Vogel conflict tests [41–43]. The reduction of fear-related behaviors evoked by the prey/

predator paradigm also suggests some panicolytic properties [45]. CBD improves performance in numerous animal models of cognitive impairments [30, 46–48]. It acts as an antidepressant in animal models of depression and decreases compulsive behaviors in rodents [35, 49]. These actions are hypothesized to be linked to CB1-related mechanisms [50, 51]. CBD has also been proven to be protective against a number of drug-induced adverse outcomes in animals. For example, CBD was shown to prevent cocaine-induced hepatotoxicity [52], reverse binge ethanol-induced neurotoxicity [53], and even mitigate the cardiac effects of THC [54, 55]. In addition, CBD administration is known to attenuate amphetamine-induced hyperlocomotion [56].

Human studies on CBD corroborate preclinical findings on its therapeutic effects on nausea, inflammation, and cerebral ischemia. CBD also possesses antipsychotic properties [2, 57–61]. Not surprisingly, and as witnessed in the aforementioned preclinical data, CBD has been shown to reduce anxiety in patients with social phobia and generalized social anxiety disorders [62–64]. CBD decreases autonomic arousal and subjective anxiety [65]; these anxiolytic effects were found to be linked to the modulation of limbic and paralimbic structures [57, 62]. It remains to be determined if these properties translate in the attenuation of symptoms for other anxiety disorders than social phobia (e.g., post-traumatic stress disorder, panic disorder) [66]. There are contradictory results as to CBD's effect on sleep (similar to results from animal studies) as it has been associated with both wake-inducing and hypnotic properties in humans [11, 67, 68]. Altogether, many pharmacological, preclinical, and clinical properties (e.g., antipsychotic, anxiolytic) of CBD that had been demonstrated over roughly the last decade all point towards a potential role for CBD in alleviating behaviors relevant to addiction disorder. As described below, recent animal and human studies have provided supporting evidence that these properties do, indeed, translate into the modulation of addiction-related outcomes.

CBD in Preclinical Addiction Models

An important consideration in the development of any new antiaddiction medication is its relative abuse liability, which, ideally, should be low. Different animal models have confirmed the low psychotropic nature of CBD [69–71], suggesting that in contrast to what is normally observed for THC, CBD does not have hedonic property on its own, that is, it is not rewarding and does not induce drug-seeking behavior. Such studies have demonstrated that CBD does not promote conditioned place preference [69, 70] or increase the reinforcing efficacy of brain stimulation [71], which are both definitive characteristics of addictive substances.

Our own research efforts have emphasized CBD's low capacity to potentiate the rewarding effects of other addictive drugs. We specifically focused on evaluating CBD's effects in relation to opioids as multiple lines of our research had already established that THC potentiates heroin self-administration in rats controlling their own drug intake, whereas the question as to whether other cannabinoids in the cannabis plant also exhibited similar properties remained unanswered. Our results showed that repeated CBD administration (5–20 mg/kg) did not alter heroin self-administration, but clearly inhibited cue-induced heroin-seeking behavior [72]; Fig. 4). Intriguingly, CBD's effects were prolonged, lasting two or more weeks after administration in its efficacy to reduce heroin reinstatement behavior triggered by drug-specific environmental cues. Moreover, even when administered during active heroin intake, the ability of CBD to inhibit relapse behavior was still apparent weeks after the last exposure, suggesting that CBD could impact the course of heroin dependence even following a potential lapse condition after a period of abstinence. This highlights a property unique to CBD, one that is not found in the medications currently used for the treatment of heroin abuse. Importantly, no physical side effects were noted in the animals with respect to gross effects on motor function.

Research is currently ongoing to delineate the neurobiological mechanisms by which CBD mediates its long-term effects on heroin-seeking behavior, but initial data suggest that CBD normalizes heroin-induced impairment on the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor (AMPA) GluR1, as well as the CB_1R expression within the nucleus accumbens [72]. The glutamatergic system and particularly GluR1 receptors are known to contribute to neuroplasticity underlying drug-seeking behavior [67, 73], and treatments targeting glutamates are being developed for addiction intervention.

Corroborating our own investigations, other animal studies have also suggested beneficial effects of CBD in relation to clinical symptoms associated with opioid exposure. One line of evidence particularly relevant to opioid abuse is the consistent findings that 1) CBD reduces morphine withdrawal symptoms (e.g., wet shakes, diarrhea, abnormal posture, ptosis, chewing, or teeth chattering) [74–77], and 2) even in combination with THC, CBD is capable of reducing abstinence scores to a greater extent than THC alone [74, 75].

Although significant preclinical animal data are accumulating with regard to CBD and opioid drugs, information regarding CBD and its effects on other substances of abuse are currently still very limited. Findings to date suggest minimal CBD impact on apparent positive subjective effects induced by psychostimulants or THC [70, 71, 78]. Moreover, no animal studies have been published to date regarding CBD's effects on nicotine or alcohol. Clearly, more research is needed. Importantly, most studies have predominantly evaluated CBD in models designed to only assess its immediate actions on other drugs, and have yet to fully evaluate its potential protracted effects on drug-seeking behavior and withdrawal symptoms. Of note, Parker et al. [69] found that CBD potentiated the extinction of cocaine and amphetamine-induced conditioned place preference learning, but had no impact on the establishment of conditioned place preference. The implementation of studies using animal models of relapse will be critical to inform human investigations considering the possibility of CBD as a long-lasting therapeutic agent for addiction.

CBD and Human Translational Studies

Human studies regarding CBD's potential impact on the abuse of other drugs are even more limited than preclinical animal investigations. Thus far, there has only been 1 report with cigarette-dependent participants, and CBD was observed to reduce the number of cigarettes consumed by active users[79]. The same investigative team has also evaluated CBD in relation to cannabis abuse. In naturalistic studies conducted with cannabis users, the concentration of CBD in smoked cannabis did not attenuate psychomimetic symptoms in participants when they were acutely intoxicated [80]; however, CBD reduced "wanting" and "liking" of cannabis-related stimuli [81]. Additionally, a case report in 1 patient indicated that CBD might reduce withdrawal symptoms and the amount of cannabis smoked upon resumption of cannabis use, but no systematic study has been conducted in relation to CBD and cannabis relapse behavior.

Based on the animal data supporting the effect of CBD on opioid-seeking behavior, we initiated pilot human clinical
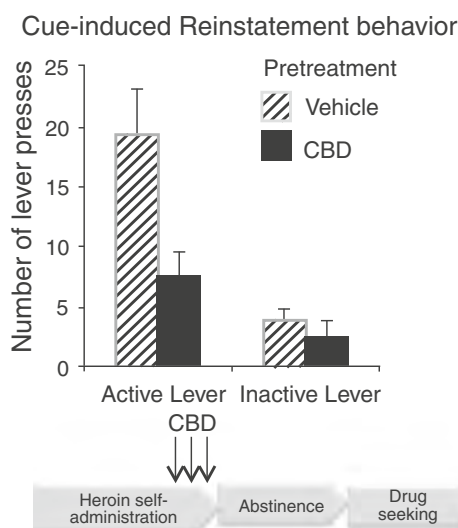

Fig. 4 Cannabidiol (CBD) effects on heroin self-administration and cue-induced heroin reinstatement behavior in rats showing CBD reduces heroin reinstatement behavior. Modified from Ren et al. [72]

laboratory studies to begin to explore the potential of this cannabinoid as a medication for opioid craving. A critical first step was to document that CBD, if combined with a potent opioid, would be safe as there was always the chance for a lapse in abstinent heroin abusers. Our double-blind, placebo-controlled cross-over phase I study in healthy subjects demonstrated that CBD (400 mg and 800 mg; approximately 10–15 mg/kg) co-administered with intravenous fentanyl is well tolerated and does not exacerbate adverse effects associated with intravenous fentanyl administration such as respiratory depression or cardiovascular complications [82]. Measurements of CBD plasma levels showed the time to peak CBD concentration occurred at 3 h (C_{max} 181.2±39.8 μg/l and 221.1±35.6 μg/l, respectively, for the 400-and 800-mg doses; Fig. 5). Exploratory analysis of subjective measures scales [Positive and Negative Affect Schedule and Opioid Visual Analog Scale], as well as anxiety visual analog scale (VAS) scores suggested that CBD at the doses examined did not significantly alter their affective states, which was consistent with other reports [83].

The next pilot phase was to evaluate CBD as a potential treatment for heroin craving by assessing its effects in heroin abusers. A small double-blind design was conducted in opioid-dependent individuals (no dependence on any other drug than heroin *according to the Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition) who, based on urine toxicology screening and the Clinical Opioid Withdrawal Scale, had been abstinent for at least 7 days. As the preclinical animal study had evaluated CBD effects following the administration of a single dose of CBD for 3 consecutive days [72], the human study design for the pilot experiment also had a similar design. As such, individuals were randomized to 3 consecutive days of CBD or placebo treatment before participating in laboratory sessions. The craving paradigm consisted of cue-induced craving test sessions where opioid-related and neutral video cues were presented at 1 h after a single CBD/placebo administration, 24 h after a single CBD/placebo administration, and 7 days following the final CBD/placebo administration. The
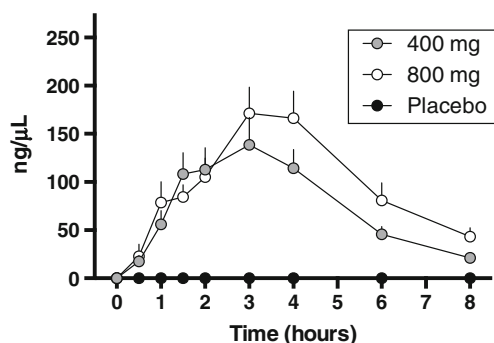
a Cue-induced craving

b General craving difference from baseline

c Cue-induced anxiety

Fig. 6 The effect of cannabidiol (CBD) on craving and anxiety in abstinent heroin-dependent subjects. (**a**) Cue-induced craving (visual analog scale; VAS) induced by heroin video cue was blunted by a single administration of CBD (400 mg or 800 mg combined) in comparison with placebo. Craving calculated as the change scores between pre- and postexposure to neutral or heroin cue videos. (**b**) General craving (heroin craving questionnaire) tended to decrease 24 h after a single administration of CBD that remained 7 days after 3 daily administrations of CBD in comparison with placebo. Craving calculated as change scores from pre-CBD administration (session 1) score. (**c**) Cue-induced anxiety induced by heroin cue was blunted 1 h after a single administration of CBD (400 mg or 800 mg combined) in comparison with placebo. Anxiety calculated as the change scores between pre- and postexposure of neutral or heroin cue videos (n=3–6). Data are mean±SD

Fig. 5 Time course of plasma concentrations of 400 mg and 800 mg cannabidiol and placebo in combination with a potent opioid fentanyl in healthy individuals. Modified from Manini et al. [82]
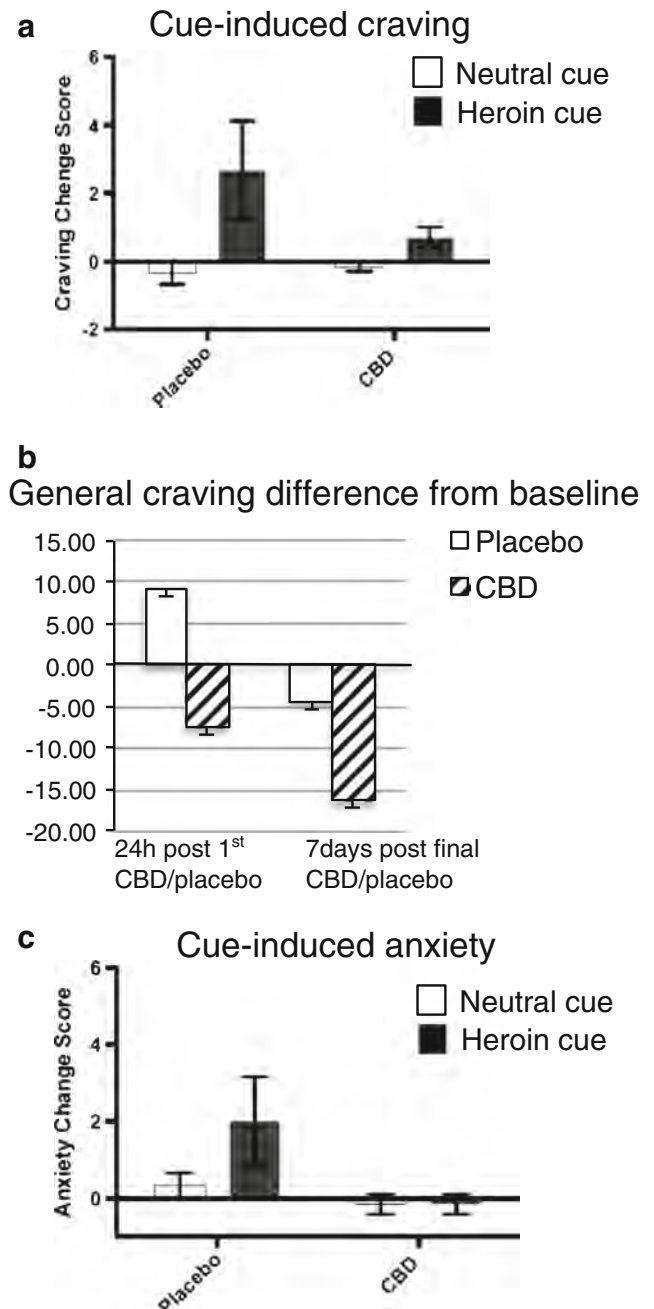
results showed that a single administration of CBD, in comparison to placebo, attenuated subjective cue-induced craving measured after 1 h using the VAS craving scale (Fig. 6a). The single administration of CBD even maintained a decrease of general craving 24 h later, assessed using a heroin-craving questionnaire (Fig. 6b). Furthermore, the effect of CBD in reducing craving persisted even 7 days after the last treatment. Interestingly, the effects of CBD were also evident on anxiety in which there was an effective reduction in VAS anxiety measures (Fig. 6c). These preliminary pilot human study findings support the preclinical evidence and clinical studies that have evaluated anxiety, suggesting a potential therapeutic efficacy of CBD to reduce negative states in opioid-dependent individuals, which may, in turn, predict reduced craving and hence reduce the likelihood of relapse behavior.

An investigation with a larger number of participants is currently being conducted, but it is clear more studies are necessary to confirm these preliminary findings, as well as to evaluate different treatment schedules in order to fully evaluate the spectrum of CBD's effects. Nevertheless, the current human data are consistent with results from the rat models, suggesting that CBD attenuates cue-induced and general craving in opioid-dependent individuals and that the effects are protracted even after the acute exposure to the cannabinoid [62–64]. Overall, the pilot human and preclinical animal laboratory studies provide a foundation for continued exploration of CBD in treating opioid dependence.

Conclusion

Despite its long history of pervasive recreational use in society, the understanding of medicinal aspects of cannabinoids is only in its infancy. Significant research efforts are still necessary to evaluate fully the development of CBD as a potential therapy for addiction disorders. To date, the evidence appears to at least support a potential beneficial treatment for opioid abuse. The fact that patients with substance use disorders often present with various psychiatric and medical symptoms that are reduced by CBD—symptoms such as anxiety, mood symptoms, insomnia, and pain—also suggests that CBD might be beneficial for treating opioid-dependent individuals. Currently most medications for opioid abuse directly target the endogenous opioid system. CBD could thus offer a novel line of research medication that indirectly regulate neural systems modulating opioid-related behavior, thus helping to reduce side effects normally associated with current opioid substitution treatment strategies.

The fact that CBD and THC have divergent effects on behaviors linked to addiction vulnerability emphasizes the important need to educate the general public. Medical marijuana represents a complex chemical mixture, all of which may not be an appropriate treatment for substance use disorders; while one cannabinoid constituent in the plant can alleviate negative symptoms, another may exacerbate them. As such, it is important to make a distinction in the nomenclature and emphasize that it is specific cannabinoids, such as "CBD", that may hold the psychiatric therapeutic promise, not the general marijuana plant. As more research efforts are directed towards cannabinoids, we will soon be able to understand how best to leverage the potentially beneficial properties of cannabinoids to develop more targeted treatment interventions.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

Medications for Opioid Use Disorder Save Lives

Released: March 20, 2019 National Academies of Medicine

REVIEW ARTICLE:

Treatment of Opioid-Use Disorders. Marc A. Schuckit, M.D.

July 28, 2016, N Engl J Med 2016; 375:357-368

67 References

This article provides an overview of the current treatment of opioid-related conditions, including treatments provided by general practitioners and by specialists in substance-use disorders. The recent dramatic increase in misuse of prescription analgesics, the easy accessibility of opioids such as heroin on the streets, and the epidemic of opioid overdoses underscore how important it is for physicians to understand more about these drugs and to be able to tell patients about available treatments for substance-use disorders.

Neurological Review, November 2007.

Dopamine in Drug Abuse and Addiction - Results of Imaging Studies and Treatment Implications

Nora D. Volkow, MD; Joanna S. Fowler, PhD; Gene-Jack Wang, MD; et al James M. Swanson, PhD; Frank Telang, MD.

Articles

Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States

[Mark Olfson](#), M.D., M.P.H., [Melanie M. Wall](#), Ph.D., [Shang-Min Liu](#), M.S., [Carlos Blanco](#), M.D., Ph.D.

Abstract

Objective:

The authors sought to determine whether cannabis use is associated with a change in the risk of incident nonmedical prescription opioid use and opioid use disorder at 3-year follow-up.

Method:

The authors used logistic regression models to assess prospective associations between cannabis use at wave 1 (2001–2002) and nonmedical prescription opioid use and prescription opioid use disorder at wave 2 (2004–2005) of the National Epidemiologic Survey on Alcohol and Related Conditions. Corresponding analyses were performed among adults with moderate or more severe pain and with nonmedical opioid use at wave 1. Cannabis and prescription opioid use were measured with a structured interview (the Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV version). Other covariates included age, sex, race/ethnicity, anxiety or mood disorders, family history of drug, alcohol, and behavioral problems, and, in opioid use disorder analyses, nonmedical opioid use.

Results:

In logistic regression models, cannabis use at wave 1 was associated with increased incident nonmedical prescription opioid use (odds ratio=5.78, 95% CI=4.23–7.90) and opioid use disorder (odds ratio=7.76, 95% CI=4.95–12.16) at wave 2. These associations remained significant after adjustment for background characteristics (nonmedical opioid use: adjusted odds ratio=2.62, 95% CI=1.86–3.69; opioid use disorder: adjusted odds ratio=2.18, 95% CI=1.14–4.14). Among adults with pain at wave 1, cannabis use was also associated with increased incident nonmedical opioid use (adjusted odds ratio=2.99, 95% CI=1.63–5.47) at wave 2; it was also associated with increased incident prescription opioid use disorder, although the association fell short of significance (adjusted odds ratio=2.14, 95% CI=0.95–4.83). Among adults with nonmedical opioid use at wave 1, cannabis use was also associated with an increase in nonmedical opioid use (adjusted odds ratio=3.13, 95% CI=1.19–8.23).

Conclusions: *__Cannabis use appears to increase rather than decrease the risk of developing nonmedical prescription opioid use and opioid use disorder.__*

Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study

Gabrielle Campbell, Wayne D Hall, Amy Peacock, Nicholas Lintzeris, Raimondo Bruno, Briony Larance, Suzanne Nielsen, Milton Cohen, Gary Chan, Richard P Mattick, Fiona Blyth, Marian Shanahan, Timothy Dobbins, Michael Farrell, Louisa Degenhardt

Summary

Background Interest in the use of cannabis and cannabinoids to treat chronic non-cancer pain is increasing, because of their potential to reduce opioid dose requirements. We aimed to investigate cannabis use in people living with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis; associations between amount of cannabis use and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time; and potential opioid-sparing effects of cannabis.

Methods The Pain and Opioids IN Treatment study is a prospective, national, observational cohort of people with chronic non-cancer pain prescribed opioids. Participants were recruited through community pharmacies across Australia, completed baseline interviews, and were followed up with phone interviews or self-complete questionnaires yearly for 4 years. Recruitment took place from August 13, 2012, to April 8, 2014. Participants were asked about lifetime and past year chronic pain conditions, duration of chronic non-cancer pain, pain self-efficacy, whether pain was neuropathic, lifetime and past 12-month cannabis use, number of days cannabis was used in the past month, and current depression and generalised anxiety disorder. We also estimated daily oral morphine equivalent doses of opioids. We used logistic regression to investigate cross-sectional associations with frequency of cannabis use, and lagged mixed-effects models to examine temporal associations between cannabis use and outcomes.

Findings 1514 participants completed the baseline interview and were included in the study from Aug 20, 2012, to April 14, 2014. Cannabis use was common, and by 4-year follow-up, 295 (24%) participants had used cannabis for pain. Interest in using cannabis for pain increased from 364 (33%) participants (at baseline) to 723 (60%) participants (at 4 years). At 4-year follow-up, compared with people with no cannabis use, we found that participants who used cannabis had a greater pain severity score (risk ratio 1·14, 95% CI 1·01–1·29, for less frequent cannabis use; and 1·17, 1·03–1·32, for daily or near-daily cannabis use), greater pain interference score (1·21, 1·09–1·35; and 1·14, 1·03–1·26), lower pain self-efficacy scores (0·97, 0·96–1·00; and 0·98, 0·96–1·00), and greater generalised anxiety disorder severity scores (1·07, 1·03–1·12; and 1·10, 1·06–1·15). We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation.

Interpretation Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect. As cannabis use for medicinal purposes increases globally, it is important that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain.

Funding National Health and Medical Research Council and the Australian Government.

Introduction

The use of prescribed opioids in the treatment of chronic non-cancer pain is controversial because of insufficient evidence for their long-term effectiveness[1,2] and increased harms as opioid prescribing for chronic non-cancer pain has increased.[3,4]

Alternatives to opioids are increasingly being debated and considered. Reviews of cannabinoids suggest they might have efficacy in some chronic non-cancer pain conditions.[5–7] In the USA,[8] Canada,[9] and the Netherlands,[10] chronic non-cancer pain is the most commonly cited reason for use of cannabis for medicinal purposes.

Research in context

Evidence before this study

The potential use of cannabinoids in chronic non-cancer pain has raised substantial interest. We did a literature review by searching MEDLINE, Embase, PsycINFO, CENTRAL, and ClinicalTrials.gov in July, 2017, with no language restrictions, for randomised controlled trials (RCTs) and observational studies relating to all cannabinoid types and specific chronic non-cancer pain conditions and pain-related outcomes. We used the following search terms: "Cannabinoids", "Cannabis", "cannab*", "marijuana", "marinol", "dronabinol", "nabilone", "levonantradol", "tetrahydrocannabinol", "cesamet", "delta-9-THC", "delta-9-tetrahydrocannabinol", "nabiximols", "sativex", "cannabidiol", "therapeutic use", "analgesics", "medical marijuana", "medicinal cannabis", "pain", "chronic pain", "Neuralgia", and "neuropathic pain". We identified 91 publications, containing 104 studies, which included 47 randomised control trials and 57 observational studies. We found the pooled change in pain intensity (standardised mean difference –0·14, 95% CI –0·20 to –0·08) was equivalent to 3 mm on a 100 mm visual analogue scale greater than placebo. We graded the quality of evidence as moderate using an adapted version of the standard Grades of Recommendation, Assessment, Development and Evaluation tool. Existing clinical studies of the effects of cannabinoids on chronic non-cancer pain mainly consisted of RCTs done using a restricted range of cannabinoids in a small range of chronic non-cancer pain conditions and lacked clarity in reporting of pain outcomes.

Added value of this study

To our knowledge, our study is one of the longest, in-depth, prospective studies of a community cohort of people with various types of chronic non-cancer pain that examined the effects of cannabis use on pain and prescribed opioid use during 4 years of follow-up. Cannabis use was common in our cohort, patients reported that it reduced their pain, and interest in using cannabis for pain doubled in the cohort during the 4-year follow-up. Nonetheless, patients who had used cannabis had greater pain severity and interference, lower pain self-efficacy, and greater generalised anxiety disorder severity than did patients who had not used cannabis. Unlike recent reviews that suggested a positive effect of cannabinoids on pain and a reduction in opioid use, we found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation.

Implications of all the available evidence

Previous systematic reviews suggested there is moderate evidence that cannabinoids are effective for certain types of pain. Previous evidence has been scarce because of studies with short duration and exclusion of participants with complex clinical profiles. In our 4-year prospective cohort of people prescribed opioids for chronic non-cancer pain, we did not find evidence supporting claims that cannabis and cannabinoids improved outcomes in chronic non-cancer pain, nor that they reduced prescription opioid use. To date, evidence that cannabinoids are effective for chronic non-cancer pain and aid in reducing opioid use is lacking. Large, well designed clinical trials are required to evaluate in which patients cannabinoids might be effective in reducing pain severity, interference, and opioid doses.

Furthermore, there is increasing discussion about the potential opioid-sparing effects of cannabinoids.[11] Changes in regulations mean that there could be an increase in use of cannabinoid products for chronic non-cancer pain.

Longitudinal studies of cannabis use among people with chronic non-cancer pain are scarce. Randomised controlled studies typically exclude individuals with complex physical, substance use, and mental health comorbidities, who represent a substantial proportion of people living with chronic non-cancer pain.[12] Evidence on efficacy in the most common causes of chronic non-cancer pain—namely, back or neck problems, arthritis, and migraine, is scarce.[7,13] Long-term follow-up in prospective studies is insufficient, with most being 12 months or less.[14–16] Discussion about the opioid-sparing effects of cannabinoids has often been confined to ecological studies or cross-sectional surveys, which are poorly suited for testing causal hypotheses.

We used the Pain and Opioids IN Treatment (POINT) study, a national cohort of people with chronic non-cancer pain who had been prescribed opioids, to examine cannabis use and pain outcomes over 4 years. We aimed to investigate the following: cannabis use during a 4-year period in people with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis; associations between amount of cannabis use in the past month and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time, controlling for potential confounding of demographic and clinical variables; and potential opioid-sparing effects of cannabis, controlling for potential confounding variables.

Methods

Study design and participants

Full details of the study design and measures included have been published elsewhere.[12,17] POINT participants were recruited through community pharmacies across Australia (appendix). We did not have a planned period of recruitment, but aimed to recruit until we reached 1500 participants. Recruitment took place from August 13, 2012, to April 8, 2014. Participants were aged 18 years or older, living with chronic non-cancer pain (defined in this

study as pain lasting longer than 3 months), taking prescribed schedule 8 opioids (including fentanyl, morphine, oxycodone, buprenorphine, methadone, and hydromorphone) for chronic non-cancer pain for longer than 6 weeks, competent in English, mentally and physically able to participate in telephone and self-complete interviews, and did not have any serious cognitive impairments, as determined by the interviewer at the time of screening. A history of injecting drug use was not an exclusion criterion, but people currently prescribed pharmaceutical opioids for opioid substitution therapy for heroin dependence or cancer were not eligible for inclusion.

Written informed consent was obtained from participants. This study was approved by the Human Research Ethics Committee of the University of New South Wales (reference #HC12149 and #HC16916).

Measures

The measures, tools, and data domains were based on recommendations made by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[18,19] Details of the interview procedure are provided in the appendix. Baseline interviews comprised a phone interview and self-complete survey and were done from Aug 20, 2012, to April 14, 2014. 3-month self-complete surveys were done as close to 3 months after baseline interview as possible and occurred from Nov 15, 2012, to Nov 1, 2014. The 3-month self-complete questionnaire was a reduced questionnaire with a smaller number of measures included and is therefore not included in the current analysis as many of the measures used, such as Pain Self-Efficacy Questionnaire (PSEQ) and questions regarding cannabis use, were not included. Furthermore, for consistency in analyses, we used interviews which were 12 months apart. 12-month self-complete questionnaires occurred 12 months after baseline interviews, between Aug 28, 2013, and Dec 4, 2015. 2-year interviews were done from Aug 12, 2014, to March 23, 2016. The 3-year interview was part of a new funding grant and all participants were interviewed annually by calendar year. 3-year interviews took place between Jan 11, 2016, and Jan 3, 2017. 4-year follow-ups were done from Jan 9, 2017, to Dec 12, 2017.

We collected data on age, sex, relationship status, and current work status. Relationship status and work status data were collected at all timepoints. Sex and age data were collected only at baseline.

Participants were asked about chronic pain conditions in their lifetime and during the past year, and duration of chronic non-cancer pain. As pain is only one of several core outcomes to consider when evaluating interventions for chronic non-cancer pain,[18] we used the pain severity and interference (how pain affects sleep, daily living, working ability, and social interaction) subscales of the Brief Pain Inventory (BPI),[20] with higher scores indicating greater pain severity or interference (score range 0–10).

Pain self-efficacy relates to an individual's beliefs about the extent to which they can do daily activities despite their pain; this was measured using the PSEQ[21] (score out of 60, higher scores indicating greater self-efficacy). Participants were asked at baseline "Is your pain neuropathic? That is, pain that burns or tingles (either diagnosed by self or doctor)."

Daily oral morphine equivalent doses of opioids, in mg per day, were estimated using conversion units established through synthesis of clinical references,[22] using a medication diary. At each follow-up, we confirmed whether participants were still taking a schedule 8 opioid.

Participants were asked about lifetime and past 12-month use of cannabis, and number of days used in the past month, in general and for pain specifically. Frequency of cannabis use in the past month was categorised as no use (0 days), less frequent use (1–19 days), and near-daily or daily use (≥20 days of cannabis use, approximately five times a week or more).
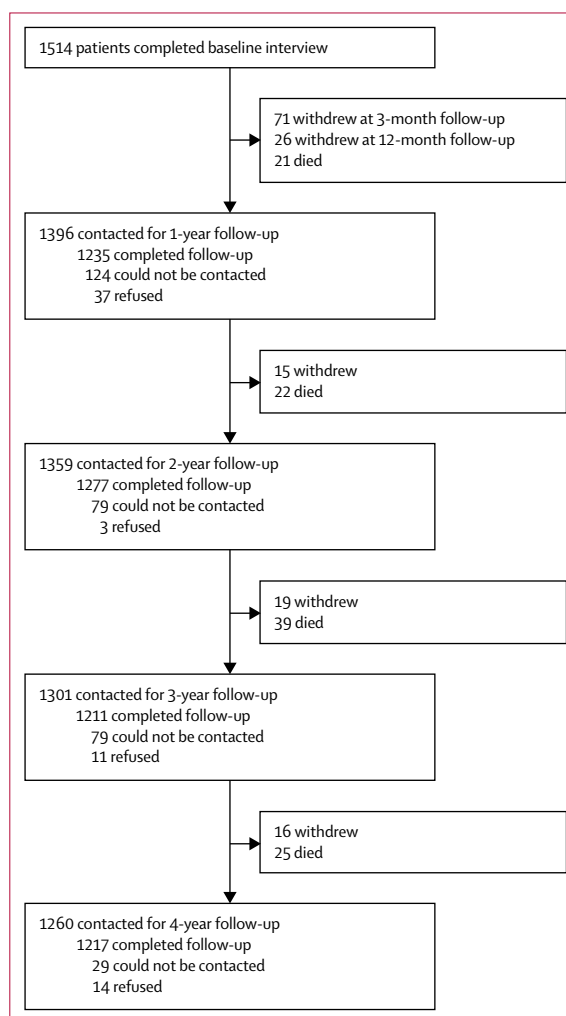

Figure: Study flow chart
Patient flow and reasons for exclusion between study referral and baseline interview are provided in the appendix.

Participants who reported lifetime use of cannabis for pain but had discontinued use were asked their reasons for doing so. Those who reported past 12-month cannabis use were asked further questions about reasons for use (appendix). All participants were asked "If you had access to cannabis, would you want to use it?" at each wave (excluding the 1-year follow-up). Based on a similar question in the BPI, we asked participants to rate the effectiveness of cannabis for their pain on a scale of 0 (no relief) to 10 (complete relief).

Current depression and generalised anxiety disorder were measured by the Patient Health Questionnaire 9 (PHQ-9) and Generalized Anxiety Disorder 7-Item Scale (GAD-7).[23,24] We defined moderate to severe depression as a PHQ-9 score of 10 or greater.[23] We defined moderate to severe anxiety as a GAD-7 score of 10 or greater.[24] We used the Composite International Diagnostic Interview

3.0 substance use module to assess lifetime International Statistical Classification of Diseases and Related Health Problems, Tenth Revision diagnostic codes for harmful use and dependence.[25]

Statistical analysis

We aimed to recruit 2000 participants, but then limited this number to 1500 because of funding and time constraints. For descriptive statistics, means and SDs were computed when data were normally distributed, and medians and IQRs when data were skewed.[26]

To investigate cross-sectional associations with cannabis use frequency, we used multinomial logistic regression models for univariate comparisons of people at each wave who reported less frequent cannabis use and near-daily or daily cannabis use (compared with people who had not used cannabis). Variables identified in previous research as related to the outcomes were included. For interpretability, risk ratios (RRs) for oral morphine equivalent doses are reported per 100 units. Additional analyses of the demographic and clinical associations between prevalent and incident cannabis use are presented and discussed in the appendix.

For prospective associations between cannabis use and outcomes, we used lagged mixed-effects models to examine temporal associations between cannabis use (the exposure) and pain severity, pain interference, and oral morphine equivalent doses (the outcomes), incorporating a random intercept for individuals to account for the repeated measures design and examining unadjusted and adjusted associations. We analysed data from baseline interviews and the four annual follow-up waves, with outcomes for the following year, and constructed four models. In the first model, we compared the outcome of interest in people who used cannabis (less frequent use, and near-daily or daily use) versus those who had never used cannabis. In the second, we adjusted for the outcome at the previous wave. In the third, we additionally adjusted for clinical covariates identified in previous research as related to the outcomes (age, sex, duration of pain, generalised anxiety disorder severity, and history of substance use).[26] Furthermore, for analysis of pain severity, we also adjusted for oral morphine, for pain interference, we adjusted for pain severity and oral morphine equivalent, and for oral morphine equivalent, we adjusted for pain severity. In the final model, we further adjusted for PSEQ results (we had some missing data as the PSEQ was not completed at the 1-year interview).

Analyses were done using Stata version 15.0. We used the Stata command margins (or mimrgns for multiple imputation) to obtain adjusted means. For details of sensitivity analyses see the appendix.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to

	Baseline (n=1514)	1-year follow-up (n=1235)	2-year follow-up (n=1277)	3-year follow-up (n=1211)	4-year follow-up (n=1217)
Demographics					
Age, years	58 (48–67)	58 (49–68)	59 (50–69)	60 (50–69)	60 (50–70)
Sex					
Male	672 (44%)	542 (44%)	555 (43%)	524 (43%)	524 (43%)
Female	842 (56%)	693 (56%)	722 (57%)	687 (57%)	693 (57%)
Pain					
BPI pain severity score	5·1 (1·79)	5·3 (1·9)	5·0 (1·9)	4·9 (1·9)	4·8 (1·9)
BPI pain interference score	5·7 (2·3)	5·7 (2·4)	5·4 (2·4)	5·5 (2·4)	5·4 (2·4)
Prescribed opioid use					
Oral morphine equivalent, mg/day	75 (36–150)	61 (24–135)	6 (25–135)	60 (22–126)	57 (15–125)
Discontinued opioids	··	131 (10·6%)	174 (13·6%)	202 (16·7%)	246 (20·2%)
Cannabis use					
Lifetime use	649 (43%)	··	··	··	··
Past 12 months	195 (13%)	135 (11%)	170 (13%)	173 (14%)	192 (16%)
Past month use	126 (8%)	112 (9%)	123 (10%)	132 (11%)	155 (13%)
Frequency of use in the past month*					
None	1319 (91%)	1085 (91%)	1151 (90%)	1078 (89%)	1047 (86%)
1–19 days (less frequent)	78 (5%)	65 (5%)	70 (5%)	70 (6%)	78 (6%)
20–31 days (near-daily or daily)	48 (3%)	47 (4%)	53 (4%)	62 (5%)	79 (6%)
Ever used for pain relief	237 (16%)	220 (18%)	260 (20%)	267 (22%)	295 (24%)
Used for pain relief in the past 12 months	··	123 (10%)	151 (12%)	145 (12%)	168 (14%)
Used for pain relief in the past month†	85 (6%)	··	111 (9%)	121 (10%)	134 (11%)
Effectiveness of cannabis for pain (out of 10)	6·5 (2·9)	5·0 (3·5)	7·3 (2·2)	7·0 (2·2)	7·2 (2·3)
Would use it if had access†	364 (33%)‡	··	562 (44%)	649 (54%)	723 (60%)

Data are median (IQR), n (%), or mean (SD). BPI=Brief Pain Inventory. *Data were missing for some patients. †Data not collected at 1-year timepoint. ‡Data missing for 396 patients.

Table 1: Sociodemographic characteristics, pain, prescribed opioid use, and cannabis use among the Pain and Opioids IN Treatment sample, by study wave

all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 2091 people we assessed for eligibility, 1873 (90%) were eligible for inclusion and 1514 (81%) completed the baseline interview (appendix p 7). At each follow-up wave, at least 80% of the original participants completed the assessment (figure).

At baseline, 44% of the cohort were male, and the median age was 58 years (IQR 48–67; table 1). 737 (49%) participants were unemployed and 469 (31%) had retired

	No cannabis use	Less frequent cannabis use (<20 days)	Daily or near-daily cannabis use (≥20 days)	Unadjusted			
				Less frequent cannabis use (<20 days) vs no cannabis use		Daily or near-daily cannabis use (≥20 days) vs no cannabis use	
				RR (95% CI)	p value	RR (95% CI)	p value
Duration of pain, years*	10·0 (4–20)	12·5 (6–21)	13·0 (5–22)	1·00 (0·99–1·02)	0·484	1·00 (0·98–1·02)	0·901
BPI pain severity score							
Baseline	5·1 (1·8)	5·3 (1·9)	5·1 (1·4)	1·09 (0·96–1·24)	0·19	1·00 (0·86–1·19)	0·906
1-year	5·3 (2·0)	5·4 (1·8)	5·6 (1·6)	1·03 (0·90–1·17)	0·703	1·09 (0·93–1·27)	0·27
2-year	5·0 (1·9)	5·4 (1·9)	5·6 (1·9)	1·12 (0·98–1·27)	0·090	1·20 (1·03–1·39)	0·020
3-year	4·8 (1·9)	5·4 (1·8)	5·5 (1·6)	1·19 (1·04–1·36)	0·011	1·21 (1·05–1·40)	0·0081
4-year	4·7 (1·9)	5·2 (1·9)	5·3 (1·8)	1·14 (1·01–1·29)	0·031	1·17 (1·03–1·32)	0·013
BPI pain interference score							
Baseline	5·6 (2·3)	6·0 (2·2)	6·2 (1·5)	1·08 (0·98–1·21)	0·13	1·13 (0·99–1·30)	0·078
1-year	5·6 (2·4)	6·2 (2·2)	6·4 (2·0)	1·11 (0·99–1·24)	0·076	1·15 (1·01–1·31)	0·039
2-year	5·3 (2·4)	6·2 (2·3)	6·2 (1·8)	1·18 (1·05–1·31)	0·0035	1·18 (1·04–1·33)	0·010
3-year	5·4 (2·4)	6·5 (2·0)	6·4 (2·0)	1·23 (1·10–1·38)	0·0003	1·22 (1·08–1·38)	0·0011
4-year	5·3 (2·4)	6·3 (2·3)	6·0 (2·3)	1·21 (1·09–1·35)	0·0004	1·14 (1·03–1·26)	0·0091
PSEQ score							
Baseline	29·7 (13·6)	26·4 (12·7)	25·6 (9·8)	0·98 (0·97–1·00)	0·039	0·98 (0·96–1·00)	0·048
1-year†	..	..	..	..	..	..	..
2-year	33·7 (13·4)	27·8 (11·2)	29·6 (11·4)	0·97 (0·95–0·99)	0·0004	0·98 (0·96–1·00)	0·029
3-year	34·4 (13·2)	28·1 (12·3)	28·6 (13·1)	0·96 (0·95–0·98)	0·0001	0·97 (0·95–0·99)	0·0008
4-year	34·2 (13·9)	30·2 (12·7)	30·6 (13·3)	0·97 (0·96–1·00)	0·015	0·98 (0·96–1·00)	0·026
Generalized Anxiety Disorder 7-item scale severity score							
Baseline	5·3 (5·3)	7·2 (5·5)	8·0 (5·5)	1·06 (1·02–1·10)	0·0023	1·09 (1·04–1·14)	0·0007
1-year	5·1 (5·3)	7·4 (5·3)	8·9 (7·2)	1·07 (1·03–1·12)	0·0012	1·11 (1·06–1·16)	<0·0001
2-year	4·5 (4·8)	7·5 (5·5)	6·9 (5·8)	1·11 (1·06–1·15)	<0·0001	1·09 (1·03–1·14)	0·0004
3-year	4·5 (4·8)	6·7 (5·5)	8·1 (5·9)	1·08 (1·03–1·13)	0·0004	1·12 (1·07–1·17)	<0·0001
4-year	4·3 (4·9)	6·4 (5·1)	7·3 (6·1)	1·07 (1·03–1·12)	0·0005	1·10 (1·06–1·15)	<0·0001
Oral morphine equivalent‡							
Baseline	70 (35–140)	84 (38–188)	90 (33–171)	1·21 (1·01–1·44)§	0·040	1·05 (0·80–1·37)	0·72
1-year	60 (23–135)	88 (44–152)	90 (31–240)	1·05 (0·85–1·30)	0·64	1·39 (1·18–1·63)	0·0001
2-year	60 (24–135)	87 (52–191)	80 (30–165)	1·12 (0·98–1·27)	0·082	1·14 (0·99–1·30)	0·063
3-year	60 (22–120)	71 (39–180)	60 (23–138)	1·15 (0·89–1·29)	0·072	1·07 (0·89–1·29)	0·47
4-year	55 (15–124)	63 (23–135)	49 (8–135)	1·04 (0·88–1·22)	0·65	1·01 (0·85–1·21)	0·89
Percentage that discontinued opioids, %							
1-year	10·8 (9·1–12·8)	9·2 (4·1–19·4)	10·6 (4·3–23·8)	0·59 (0·21–1·65)	0·31	0·88 (0·31–2·52)	0·81
2-year	13·8 (11·9–15·9)	7·1 (2·9–16·3)	18·9 (10·2–32·1)	0·48 (0·19–1·21)	0·12	1·44 (0·71–2·94)	0·304
3-year	16·8 (14·7–19·1)	15·7 (8·8–26·5)	16·1 (8·7–27·8)	0·92 (0·48–1·79)	0·81	0·95 (0·48–1·91)	0·89
4-year	20·9 (18·6–23·5)	9·0 (5·1–19·4)	21·5 (13·7–32·2)	0·38 (0·17–0·83)	0·016	1·05 (0·60–1·84)	0·85

Data are median (IQR) or mean (SD), unless otherwise indicated. RR=risk ratio. BPI=Brief Pain Inventory. PSEQ=pain self-efficacy questionnaire. *Only asked at baseline. †Data on PSEQ not collected at 1-year timepoint. ‡RR based on per 100 units.

Table 2: Bivariate cross-sectional associations between amount of cannabis use in the past month (days of use) and pain, anxiety, and medication use in the Pain and Opioids IN Treatment cohort, by study wave

	Current level of pain severity			
	Adjusted mean (SE)	β	95% CI	p value
Cannabis use at previous study wave				
No cannabis use (ref)	5·0 (0·05)	..	..	..
Less frequent use	5·1 (0·12)	0·16	−0·07 to 0·39	0·18
Near-daily or daily use	5·5 (0·13)	0·53	0·27 to 0·80	0·0001
Adjusted for pain severity at previous study wave				
No cannabis use (ref)	5·0 (0·02)	..	..	..
Less frequent use	5·0 (0·10)	0·06	−0·12 to 0·26	0·51
Near-daily or daily use	5·2 (0·10)	0·21	0·01 to 0·40	0·037
Adjusted for previous pain severity and clinical covariates*				
No cannabis use (ref)	4·9 (0·03)	..	..	..
Less frequent use	5·0 (0·13)	0·35	−0·01 to 0·71	0·061
Near-daily or daily use	5·1 (0·14)	0·45	−0·21 to 1·11	0·18
Adjusted for previous pain severity and clinical covariates* and Pain Self-Efficacy Questionnaire				
No cannabis use (ref)	4·9 (0·03)	..	..	..
Less frequent use	5·1 (0·13)	0·37	−0·01 to 0·75	0·056
Near-daily or daily use	5·2 (0·14)	0·43	−0·23 to 1·10	0·201

*Covariates were Brief Pain Inventory severity at previous study wave, age, sex, duration of pain, oral morphine equivalent, generalised anxiety disorder severity, baseline lifetime International Statistical Classification of Diseases and Related Health Problems, Tenth Revision substance use disorder, and time.

Table 3: Lagged mixed-effects linear regression examining the effect of cannabis use at the previous study wave on pain severity at the following wave (complete case analysis)

from work. Participants had been living with chronic non-cancer pain for a median of 10 years (IQR 4·5–20·0) and had been prescribed a strong opioid for a median of 4 years (1·5–10·0). The median oral morphine equivalent taken was 75 mg/day (36–150). The most common types of pain reported at baseline were back or neck pain (1159 [77%] participants), followed by arthritis (933 [62%] participants), and comorbid pain was common, with participants reporting a median of two (IQR 2–3) chronic pain conditions at baseline in the preceding 12 months. 937 (62%) participants reported neuropathic pain at baseline.

Using a random sample of 71 pharmacies, we compared the characteristics of all customers obtaining opioids during the 6-week recruitment window with the study cohort overall. Among 800 customers who recorded purchasing opioids in these pharmacies, 418 (52%) were female (*vs* 842 [55%] in the POINT cohort) and 58 (7%) were aged 18–34 years (*vs* 73 [5%]), 438 (55%) were aged 35–64 years (*vs* 952 [62%]), and 304 (38%) were aged 65 years or older (*vs* 489 [33%]). 500 (63%) people were prescribed oxycodone (*vs* 938 [62%] in the POINT cohort), 138 (17%) were prescribed morphine (*vs* 225 [15%]), and 190 (24%) were prescribed buprenorphine patches (*vs* 332 [21%]).

At baseline, two-fifths of the cohort reported ever using cannabis, 195 (13%) reported use in the past 12 months, and 126 (9%) reported use in the past month. Both past

12-month and past-month use increased from baseline to the 4-year timepoint (table 1).

At baseline, approximately one in six participants reported that they had used cannabis for pain in their lifetime. Past 12-month and past-month reporting of cannabis use for pain also increased over time. The proportion of participants reporting cannabis use on 1–19 days (categorised as less frequent use) in the month before interview remained relatively stable. The proportion reporting use on 20–31 days in the past month (categorised as near-daily or daily use) increased from 3% at baseline to 7% at 4-year follow-up (table 1).

At baseline, participants who had used cannabis for pain rated its mean effectiveness for their pain as 6·5 out of 10 (with 10 being extremely effective; table 1). The percentage of participants reporting that they would use cannabis if they had access to it increased from 33% at baseline to 60% at 4-year follow-up.

At the 3-year and 4-year follow-up waves, participants who reported cannabis use in the past month were asked whether it influenced their use of opioid medication. Most participants reported that cannabis had no effect on their use of opioid medication (3-year follow-up 103 [78%] of 132 participants; 4-year follow-up 105 [70%] of 151 participants). At 3-year follow-up, 29 (22%) of 132 participants, and at 4-year follow-up, 46 (30%) of 151 participants reported that they sometimes or regularly reduced their opioid medication when using cannabis (appendix). There were no differences in age, sex, pain severity or interference, or oral morphine equivalent between cannabis users who reported cannabis sometimes or regularly reduced their opioid use, compared with those who said it had no such effect (data not shown).

Of participants currently using cannabis, the most common reasons for use at both 3-year and 4-year follow-up were to relieve pain (3-year follow-up 142 [83%] of 174 participants; 4-year follow-up 157 [83%] of 190 participants) and pain-related distress (3-year follow-up 118 [68%] of 174 participants; 4-year follow-up 140 [73%] of 192 participants), to improve sleep (3-year follow-up 116 [67%] of 174 participants; 4-year follow-up 122 [64%] of 190 participants), and for general relaxation (3-year follow-up 126 [72%] of 175 participants; 4-year follow-up 124 [65%] of 192 participants; appendix). Participants who had previously used cannabis for pain, but were no longer doing so, were asked about their reasons for stopping. The most common reasons were side-effects (3-year follow-up 46 [28%] of 166 participants; 4-year follow-up 31 [23%] of 134 participants), legal concerns (3-year follow-up 43 [26%] of 166 participants; 4-year follow-up 24 [18%] of 134 participants), difficulties accessing cannabis (3-year follow-up 30 [18%] of 166 participants; 4-year follow-up 27 [20%] of 134 participants), and ineffectiveness in relieving pain (3-year follow-up 37 [22%] of 166 participants; 4-year follow-up 16 [12%] of 134 participants; appendix).

	Current amount of pain interference			
	Adjusted mean (SE)	β	95% CI	p value
Cannabis use in previous study wave				
No cannabis use (ref)	5·4 (0·06)	··	··	··
Less frequent use	5·8 (0·14)	0·38	0·11 to 0·66	0·0065
Near-daily or daily use	5·9 (0·15)	0·46	0·15 to 0·77	0·0034
Adjusted for pain interference in previous study wave				
No cannabis use (ref)	5·4 (0·03)	··	··	··
Less frequent use	5·8 (0·12)	0·32	0·08 to 0·55	0·0087
Near-daily or daily use	5·6 (0·11)	0·15	−0·08 to 0·37	0·20
Adjusted for previous oral morphine equivalent and clinical covariates*				
No cannabis use (ref)	5·3 (0·03)	··	··	··
Less frequent use	5·6 (0·14)	0·33	−0·23 to 0·89	0·25
Near-daily or daily use	5·2 (0·15)	−0·56	−1·41 to 0·28	0·19
Adjusted for previous oral morphine equivalent and clinical covariates* and Pain Self-Efficacy Questionnaire				
No cannabis use (ref)	5·4 (0·04)	··	··	··
Less frequent use	5·7 (0·16)	0·35	−0·22 to 0·92	0·23
Near-daily or daily use	5·2 (0·19)	−0·63	−1·46 to 0·19	0·13

*Covariates were Brief Pain Inventory interference at previous study wave, age, sex, duration of pain, Brief Pain Inventory severity score, oral morphine equivalent, generalised anxiety disorder severity, baseline lifetime International Statistical Classification of Diseases and Related Health Problems, Tenth Revision substance use disorder, and time.

Table 4: Lagged mixed-effects linear regression examining the effect of cannabis use at the previous study wave on pain interference at the following wave (complete case analysis)

	Current oral morphine equivalent use mg/day			
	Adjusted mean (SE)	β	95% CI	p value
Cannabis use in previous study wave				
No cannabis use (ref)	97·5 (2·77)	··	··	··
Less frequent use	100·7 (7·46)	3·31	−11·74 to 18·36	0·67
Near-daily or daily use	105·3 (13·44)	7·84	−18·75 to 34·44	0·56
Adjusted for oral morphine equivalent in previous study wave				
No cannabis use (ref)	96·3 (1·32)	··	··	··
Less frequent use	91·7 (5·15)	−4·56	−15·13 to 6·01	0·40
Near-daily or daily use	100·3 (7·43)	4·08	−10·79 to 18·95	0·59
Adjusted for previous oral morphine equivalent and clinical covariates*				
No cannabis use (ref)	91·2 (1·45)	··	··	··
Less frequent use	88·2 (6·78)	1·05	−31·25 to 33·35	0·95
Near-daily or daily use	91·5 (8·88)	27·64	−28·87 to 84·15	0·34
Adjusted for previous oral morphine equivalent and clinical covariates* and Pain Self-Efficacy Questionnaire				
No cannabis use (ref)	85·5 (1·74)	··	··	··
Less frequent use	95·1 (8·85)	7·00	26·97 to 40·96	0·69
Near-daily or daily use	97·1 (12·66)	32·76	−25·04 to 90·57	0·27

*Covariates were oral morphine equivalent at previous study wave, age, sex, duration of pain, Brief Pain Inventory severity score, generalised anxiety disorder severity, baseline lifetime International Statistical Classification of Diseases and Related Health Problems, Tenth Revision substance use disorder, and time.

Table 5: Lagged mixed-effects linear regression examining the effect of cannabis use at the previous study wave on amount of opioid use at the following wave (complete case analysis)

With a few exceptions, at each follow-up, people who were using cannabis (less frequent or daily or near-daily use) reported greater pain severity and pain interference, lower pain self-efficacy, and higher levels of generalised anxiety disorder than those not using cannabis (table 2). The associations were consistent for less frequent and near-daily users (table 2). For example, at the 4-year interview, compared with people with no cannabis use, those with less frequent and daily or near-daily use had greater pain severity scores, greater pain interference scores, lower pain self-efficacy scores, and greater generalised anxiety disorder severity scores.

Few differences were reported in oral morphine equivalent consumption or the proportion of participants who discontinued opioids between those using cannabis at different frequencies. However, people who reported less frequent cannabis use were less likely to discontinue opioids at 4 years (9%) than those reporting no use (21%), despite no difference in oral morphine equivalent at 4-year follow-up (table 2).

Using lagged-effects models, we examined the effect of past cannabis use on current pain severity (table 3), current pain interference (table 4), and current oral morphine equivalent consumption (table 5) in people using cannabis compared with those not using cannabis (complete case analysis; for multiple imputation analysis see appendix).

In the unadjusted model, near-daily or daily cannabis users had significantly greater pain severity than did people who had not used cannabis (difference of 0·5 on a 10-point scale; table 3). This difference, although still significant, was reduced by inclusion of previous pain severity score. In adjusted models that included clinical covariates and pain self-efficacy, we found no association between past cannabis use and current pain severity.

People who had reported use of cannabis at the previous wave had greater pain interference at subsequent follow-up than did those who had not used cannabis (table 4). In adjusted models, after controlling for age, sex, previous pain interference, pain factors (eg, duration of pain, pain severity, and pain self-efficacy), and oral morphine equivalent, previous cannabis use was not independently associated with current pain interference.

We did not detect an association between cannabis use in the previous wave and reduced oral morphine equivalent at subsequent follow-up; we found no association in the univariate model and no independent

association after controlling for other variables (table 5; for analysis based on multiple imputation see appendix).

We did sensitivity tests to examine the robustness of the findings. Sensitivity analyses using log transformations of oral morphine equivalent in categories (0 mg, 1–20 mg, 21–90 mg, 91–199 mg, and ≥200 mg) found similar results to those presented here (appendix). We ran post-hoc mixed-effects models among participants who self-reported neuropathic pain and adjusted for neuropathic pain and found no significant effect of past cannabis use on pain severity, interference, or oral morphine equivalent (appendix).

Discussion

To our knowledge, this is one of the longest, in-depth, prospective studies of a community cohort of people with chronic non-cancer pain, examining the effects of cannabis use on pain and prescribed opioid use. Cannabis use was common in our cohort, patients reported that it reduced their pain, and the proportion interested in using cannabis for pain doubled over the 4-year follow-up. We found that patients who had used cannabis had greater pain severity and interference, lower pain self-efficacy, and greater generalised anxiety severity than did patients who had not used cannabis.

We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased opioid discontinuation. The most common reasons for discontinuing cannabis use included side-effects, lack of efficacy, access difficulties, and legal concerns. Nonetheless, our data and other population surveys[27] highlight growing community interest in using cannabis for pain.

A legislative change on Oct 30, 2016, decriminalised medicinal use and supply of cannabis and cannabinoids;[13] perceptions of efficacy and safety of cannabis for medical use might therefore increase in Australia, as they have done in other jurisdictions.[28] Few data in our 4-year follow-up were collected after this change, and very few individuals nationally have accessed cannabinoids for medicinal purposes, so our cohort primarily used illicitly produced cannabis. Increased availability of medicinal cannabinoids might increase use among people living with chronic non-cancer pain in Australia, although access is still restricted and licensed cannabinoid medications are expensive. Additionally, in our study it is unlikely cannabis was consumed under the guidance of a medical practitioner. Expectations that cannabis will reduce pain and opioid use might differ for participants using medicinal cannabis compared with those using illicit cannabis. High-quality, double-blind, randomised, placebo-controlled trials examining expectancy effects, which are lacking for most chronic non-cancer conditions, might shed further light.

We found inconsistencies in our findings between what participants reported and our statistical assessment of associations. Although participants who used cannabis reported that the mean effectiveness of cannabis on pain was 7 out of a possible score of 10, in unadjusted cross-sectional and longitudinal analyses, people who used cannabis in the past month reported greater pain severity and interference than those who had not used cannabis in the past month. In adjusted longitudinal analyses, we found no association between cannabis and pain severity or interference. This finding is inconsistent with previous studies that have found cannabis reduced pain severity.[14–16]

In our cohort, patients with chronic non-cancer pain who used cannabis reported significantly greater pain severity than those not using cannabis, consistent with surveys of medicinal users who report using cannabis because of a failure of conventional treatments.[29,30] Those using cannabis with the intent of relieving their pain might represent a patient population with more distress and poorer coping mechanisms, as evidenced in our study by the lower pain self-efficacy scores for people who used cannabis. It could be that in the absence of cannabis use, pain severity and interference might have been worse. However, our study supports recent research that suggests cannabis use is associated with reduced self-efficacy in managing depression and anxiety.[31] Although previous reviews have found moderate support for cannabis use in reducing chronic non-cancer pain,[5–7,8] they have mainly relied on randomised controlled trials, in which people with complex comorbidities have been excluded. Considering recent findings[31] and our study, it is important that future research focuses on self-efficacy and complexity of patients to better understand what types of patients with chronic non-cancer pain might benefit from using cannabinoids.

Previous cross-sectional studies have suggested cannabis might have opioid-sparing effects in people with chronic non-cancer pain,[32,33] although a systematic review found a lack of high-quality clinical studies testing potential opioid-sparing effects.[11] In our study, using both cross-sectional and longitudinal analytic approaches, we found no evidence that cannabis use was associated with reduced opioid use or opioid cessation. This finding needs to be qualified as participants had access only to illicit cannabis and were not taking cannabis as part of structured pain management under medical supervision.

To our knowledge, our study was unique in exploring temporal associations between cannabis use, pain, and opioid use in a large cohort with multiple assessment waves and low attrition. There might be concern that we did not recruit a representative sample of people prescribed opioids for chronic non-cancer pain. To appraise the generalisability of the study cohort, we collected data from a random sample of 71 pharmacies on the characteristics of all customers obtaining opioids during their 6-week recruitment window. These data showed important similarities between the cohort we recruited and customers overall in sex, age, and type of opioid prescribed.

Although our data were self-reported, this method of collection is reasonably reliable,[34] particularly when there are no disincentives for being honest.[35] All participants were assured of confidentiality and that the data would be de-identified; however, we did no independent checks of participant reports of cannabis use. Because of the illegality of cannabis during the study period, it is possible that cannabis use has been under-reported. However, other epidemiological studies that have reported cannabis use associated with reduced opioid consumption have also depended on self-reported cannabis and opioid use.[32,33,36,37] Additionally, we recorded frequency of cannabis use, rather than quantity and type of cannabis, but there are major complexities in reliably measuring total cannabis consumption given variations in tetrahydrocannabinol content and amounts consumed in a session of use.[38,39] Finally, although we found no significant association between cannabis use and pain, it is difficult to completely understand the effects of cannabis on pain in an observational study.

In conclusion, cannabis use is common in people with chronic non-cancer pain who have been prescribed opioids, and interest in medicinal use of cannabis is increasing. We found no evidence that cannabis use improved patient outcomes; those who used cannabis had greater pain and lower self-efficacy in managing pain. Furthermore, we found no evidence that cannabis use reduced pain interference or exerted an opioid-sparing effect.

Contributors
GCa conceived the paper with LD, NL, WDH, and RB. GCa and GCh analysed the data. GCh, TD, and RB provided oversight for all statistical analyses. All authors made substantial contributions to critical review, editing, and revision of the manuscript, and all authors approved the final version.

Declaration of interests
GCa reports grants from Reckitt Benckiser outside the submitted work. WDH reports grants from Australian Therapeutic Goods Administration and personal fees as a Member of the Australian Advisory Council on Medical Uses of Cannabis, both outside the submitted work. AP reports grants from Mundipharma and an untied educational grant from Sequirus for studies of tapentadol, both outside the submitted work. NL has received research grant funding from Indivior, Braeburn, and NSW Health, and consultancies or advisory board participation from Indivior and Mundipharma, all outside the submitted work. RB reports grants from Indivior for the development of an opioid-related behaviour scale and a study of opioid substitution therapy uptake among patients with chronic non-cancer pain, all outside the submitted work. BL reports grants from Reckitt Benckiser for studies of the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among patients with chronic non-cancer pain; and Indivior for studies of buprenorphine-naloxone and buprenorphine depot; an untied educational grant from Sequirus for studies of tapentadol; and grants from Mundipharma, all outside the submitted work. SN reports grants from the National Drug and Alcohol Research Centre during the conduct of the study, and grants from Indivior outside the submitted work. MC reports personal fees from Mundipharma outside the submitted work. RPM reports National Health and Medical Research Council project grants during the conduct of the study. MF received investigator-initiated untied educational grants from Indivior for studies of buprenorphine depot and naloxone; and an untied educational grant from Sequirus for studies of tapentadol, all outside the submitted work. LD received grants from Indivior for studies of buprenorphine-naloxone, buprenorphine depot, and naloxone; and from Reckitt Benckiser for the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among patients with chronic non-cancer pain; an untied educational grant from Sequirus for studies of tapentadol; and a grant from the Australian Therapeutic Goods Administration, all outside the submitted work. GCh, FB, MS, and TD declare no competing interests.

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Review

An endocannabinoid mechanism in relapse to drug seeking: A review of animal studies and clinical perspectives

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ABSTRACT

Detoxification from drug abuse is strongly threatened by the occurrence of renewed episodes of drug intake. In human addicts, relapse to drug seeking may take place even after a considerably long period from the last drug consumption. Over the last decade, the endocannabinoid system has received remarkable attention due to its unique features, including its rewarding properties closely resembling those of the most commonly abused substances and its multiple therapeutic implications. Although limited at present, evidence is now emerging on a possible participation of the endogenous cannabinoid system in the regulation of relapsing phenomena. Both stimulation and blockade of the central cannabinoid CB-sub1 receptor have proved to play an important role in drug- as well as in cue-induced reinstatement of drug seeking behavior. Indeed, while CB-sub1 receptor stimulation may elicit relapse not only to cannabinoid seeking but also to cocaine, heroin, alcohol and methamphetamine, this effect is significantly attenuated, when not fully prevented, by pretreatment with the CB-sub1 receptor antagonist rimonabant. However, corroborating data on the involvement of the cannabinoid system in stress-induced reinstatement are still rather scarce. The present review attempts to collect data obtained from different laboratories using diverse experimental approaches, to provide a comprehensive picture of the recent evidence of a relationship between the cannabinoid system and the neurobiological mechanisms leading to relapse. For each class of abused drugs, the conspicuous progress made in delineating the role of the endocannabinoid system in relapse to drug seeking has been examined by placing particular emphasis on the findings obtained from behavioral studies. After summarizing findings and implications emerging from the reviewed studies, we conclude by briefly discussing what information is still missing and how missing information might be obtained.

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Abbreviations:
AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CB-sub1, type 1 cannabinoid receptor
CB-sub2, type 2 cannabinoid receptor
CP 55,940, (–)-*cis*-3-[2-hydroxy-4(1,1-dimethyl-heptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclo-hexanol
DA, dopamine
Δ^9-THC, delta9-tetrahydrocannabinol
GABA, gamma-aminobutyric acid
HU210, 3-(1,1-dimethylheptyl)-11-hydroxy-Δ^8-tetrahydro-cannabinol
METH, methamphetamine
NAcc, nucleus accumbens
NMDA, *N*-methyl-D-aspartate
SR 141716A, *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carbox-amide hydro-chloride
VTA, ventral tegmental area
WIN 55,212-2, R(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]-pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl)-methanone mesylate

Contents

1. Introduction

One of the major problems in the treatment of drug abuse is the reinitiating of drug craving and seeking after abstinence. A better understanding of the precise mechanisms triggering relapse strikes at the very core of pharmacological/psychological treatment of drug addiction and dependence. Clinical experience has reported the availability for specific drugs of abuse (i.e., heroin) of a few proven effective approaches for use in crisis intervention, detoxification, stabilization and harm reduction for addicted patients. That is, naloxone may be effective in treating respiratory depression and coma in patients with opioid overdose, detoxification can be achieved with opioid agonists (i.e., methadone, buprenorphine) or α2-adrenergic agonists (i.e., clonidine, lofexidine), and prevention of relapse may be supported by naltrexone.

The latter strategies however proved somewhat problematic due to low compliance and effectiveness as well as the manifestation of side effects, such as depression or anhedonia (Van den Brink and van Ree, 2003). Besides heroin, individuation of successful strategies aimed at preventing relapse to other drugs of abuse in abstinent individuals is still problematic, in view also of the fact that the former have proved beneficial only in strongly motivated subjects. Thus, recurrence of relapsing episodes in long-term abstinent patients represents one of the most significant and puzzling problems during disintoxication. In many ways, the problem is central to the whole enterprise of drug abuse and dependence research, in its attempt to provide a feasible scientific account of the brain circuits underlying relapse to drug seeking and drug taking.

The most commonly used approach to modeling human relapse to craving and drug seeking following abstinence in laboratory animals is the extinction/reinstatement paradigm, in which an animal is initially trained to operate (by lever-pressing or nose-poking) in order to self-administer the drug. Once the animal has learned this specific task, the drug is withheld even though the animal continues to operate to obtain the drug. After a while, the rat stops pressing the lever or making nose-poking responses, indicating the extinguishing of self-administration behavior. Following extinction, various stimuli may be acutely presented to assess whether they are able to reinstate drug seeking behavior, i.e., if they cause renewed operant responding even if the animal does not receive the drug. At least three types of stimuli can reinstate responding: (i) a single injection of the same previously experienced drug (i.e., drug priming), (ii) a conditioned stimulus that was contingently paired during the initial training sessions with the delivery of the drug and (iii) stress factors.

Among the neuronal systems involved in the resumption of drug seeking behavior following extinction particular attention has recently been paid to endogenous cannabinoid transmission. Our understanding of the endocannabinoid system has advanced enormously since the identification of the CB-sub1 and CB-sub2 cannabinoid receptors (Howlett et al., 1990; Matsuda et al., 1990; Munro et al., 1993; Gérard et al., 1991; Mailleux and Vanderhaeghen, 1992; Glass et al., 1997), the discovery of the endogenous ligands anandamide and 2-arachidonoylglycerol (Devane et al., 1992; Mechoulam et al., 1995; Sugiura et al., 1995) and the detection of their biosynthesis and degradation pathways (Di Marzo et al., 1994, Stella et al., 1997). Endocannabinoids have been proposed to act as retrograde signaling messengers in GABAergic and glutamatergic synapses (Wilson and Nicoll, 2001; Kreitzer and Regehr, 2002; Piomelli, 2003) and modulate post-synaptic transmission by interacting with many other neurotransmitters (Wilson and Nicoll, 2002). Although after repeated unsuccessful attempts, natural and synthetic exogenous cannabinoids are now well known to share with other drugs of abuse most of neurochemical and behavioral effects, among which the ability to enhance the mesolimbic dopaminergic transmission (French et al., 1997; Gessa et al., 1998; Wu and French, 2000; Cheer et al., 2004; Fadda et al., submitted for publication), reduce the threshold for electrical brain stimulation (Pradhan et al., 1978; Gardner et al., 1998;

Lepore et al., 1996) and sustain either intracerebroventricular or intravenous self-administration in laboratory animals (Martellotta et al., 1998; Fattore et al., 2001; Braida et al., 2001b; Justinova et al., 2003; Deiana et al., submitted for publication). In addition, exogenous administration of cannabinoids induces conditioned place preference (Lepore et al., 1995; Braida et al., 2001a, 2004; Valjent and Maldonado, 2000), even though conditioned place aversion or no effect have also been reported in this paradigm (McGregor et al., 1996; Sanudo-Pena et al., 1997; Chaperon et al., 1998; Mallet and Beninger, 1998; Hutcheson et al., 1998; Cheer et al., 2000).

A clear role for the CB-sub1 receptor in the neural circuitry regulating consumption of cocaine (Arnold, 2005), nicotine (Castañé et al., 2005; Cohen et al., 2002, 2004), alcohol (Mechoulam and Parker, 2003; Wang et al., 2003a; Hungund and Basavarajappa, 2004; Colombo et al., 2004; Gessa et al., 2005), opioids (Fattore et al., 2004, 2005a; Viganò et al., 2005) and 3,4-methylenedioxy-methamphetamine (Braida et al., 2005; Sala and Braida, 2005) has been clearly established. An involvement of the endocannabinoid system in relapsing episodes has also been reported, primings with CB-sub1 receptor agonists being able to resume extinguished operant behavior in rats (Yamamoto et al., 2004). Blockade of the CB-sub1 receptor by the specific antagonist rimonabant (SR 141716A) has also been shown to play an important role in the reinstatement of responding, thus confirming a cannabinoid mechanism in relapse to drug seeking behavior (Le Foll and Goldberg, 2005; De Vries and Schoffelmeer, 2005).

This review will analyse recent findings on the effect of either the CB-sub1 receptor stimulation or blockade on the resumption of drug seeking behavior following (1) primings with either the same previously self-administered drug (*drug-induced reinstatement*) or a different drug (*drug-induced cross-reinstatement*), (2) re-exposure to a drug-associated stimulus (*cue-induced reinstatement*) or (3) presentation of a stressor (*stress-induced reinstatement*). Experimental models (*between-* vs *within-sessions*), response-like procedures (*nose-poking* vs *lever-pressing*), schedules of reinforcement (*fixed* vs *progressive*) and animals (*rodents* vs *monkeys*) utilized in the different studies will be compared and discussed.

2. Effect of CB-sub1 receptor stimulation on drug seeking reinstatement

Similarly to other drugs of abuse such as alcohol, opiates and psychostimulants, cannabinoids might elicit relapse by interacting with nearly all neurotransmitter systems within the brain (Ameri, 1999; Chaperon and Thiebot, 1999). Mounting evidence indicates the endocannabinoid system as an essential neural substrate regulating many aspects of drug addiction including craving and motivation. The precise mechanisms underlying the resumption of drug taking following a period of drug abstinence (i.e., relapse) have not yet been identified; however, the idea of a pivotal role for CB-sub1 receptor stimulation in relapsing phenomena is currently acquiring robustness, as demonstrated by a growing list of evidence (Table 1).

Table 1 – Effect of the CB-sub1 receptor stimulation by natural or synthetic CB-sub1 receptor agonists on drug- and cue-induced reinstatement of drug seeking behavior in abstinent animals

Drug-induced reinstatement

SA	Procedure; training dose; reinforcement ratio; modus operandi; session length	Drug abstinence period (EXT); priming; dose (mg/kg); time before session	Effect	Animals	Ref
WIN	B; 12.5 μg/kg/inf; FR1; NP; 3 h	21 days; WIN, 0.25–0.5 (ip); immediately before starting the session	Drug seeking reinstatement	LE	Spano et al., 2004
WIN	B; 12.5 μg/kg/inf; FR1; NP; 3 h	21 days; Cocaine, 10.0 (ip); 10′	No effect	LE	Spano et al., 2004
WIN	B; 12.5 μg/kg/inf; FR1; NP; 3 h	21 days; Heroin, 0.5 (ip); 10′	Drug seeking reinstatement	LE	Spano et al., 2004
Cocaine	W; 0.5 mg/kg/inf; FR5; LP; 2 h	3 h; Δ^9-THC, 0.3–3.0 (ip); at the beginning of the 3rd phase of the session	No effect	SD	Schenk and Partridge, 1999
Cocaine	B; 0.5 mg/kg/inf; FR5; NP; 2 h	>14 days; HU, 0.02–0.1 (sc); 10′	Drug seeking reinstatement	WST	De Vries et al., 2001
Heroin	B; 30 μg/kg/inf; FR1; LP; 2 h	21 days; Δ^9-THC, 0.1–1.0; 10′	No effect	LH	Fattore et al., 2003
Heroin	B; 30 μg/kg/inf; FR1; LP; 2 h	21 days; WIN, 0.15–0.3 (ip); 10′	Drug seeking reinstatement	LH	Fattore et al., 2003
Heroin	B; 30 μg/kg/inf; FR1; LP; 2 h	21 days; CP, 0.05–0.1 (ip); 10′	Drug seeking reinstatement	LH	Fattore et al., 2003
Heroin	B; 50 μg/kg/inf; FR5/PR; NP; 3/4 h	21 days; HU, 0.020 (sc); 10′	Drug seeking reinstatement	WST	De Vries et al., 2003
Alcohol	B; 4.0% (v/v); VR10; TL; 30′	8 days; Δ^9-THC, 1.0 (ip); 10′	Alcohol seeking reinstatement	WST	McGregor et al., 2005
METH	B; 20 μg/kg/inf; FR1; LP; 2 h	6 days; Δ^8-THC, 0.32–3.2 (ip); 30′	No effect	WST	Anggadiredja et al., 2004
METH	B; 20 μg/kg/inf; FR1; LP; 2 h	6 days; Δ^8-THC 0.32 (ip) + METH 0.1 (ip); 30′	Drug seeking reinstatement	WST	Anggadiredja et al., 2004
METH	B; 20 μg/kg/inf; FR1; LP; 2 h	6 days; Δ^8-THC 0.32 (ip) + METH 0.1 (ip); 30′	Attenuation of METH-induced reinstatement of drug seeking	WST	Anggadiredja et al., 2004

Cue-induced reinstatement

SA	Procedure; training dose; schedule; modus operandi; session length	Drug abstinence period (EXT); primings; cue; CB1 agonist; time before session	Effect	Animals	Ref
METH	B/W; 20 μg/kg/inf; FR3; LP; 2 h	6 days; 20 s tone/cue light at the beginning of the cue-phase session; Δ^8-THC, 1.0 (ip); 30′	Enhancement of cue-induced reinstatement	WST	Anggadiredja et al., 2004

Abbreviations: SA: self-administration; B: between-session reinstatement procedure; W: within-session reinstatement procedure; FR: fixed ratio of reinforcement: PR: progressive ratio of reinforcement; VR: variable ratio of reinforcement; NP: nose-poking as operandum; LP: lever-pressing as operandum; TL: tube licking as operandum; EXT: extinction; LE: Long Evans rats; LH: Lister Hooded rats; SD: Sprague Dawley rats; WST: Wistar rats; WIN: WIN 55,212-2; CP: CP 55,940; HU: HU210.

2.1. Drug-induced reinstatement

Re-exposure to the experienced drug is generally accepted as the major trigger for relapse in abstinent addicts. Reinstatement of extinguished drug seeking behavior in laboratory animals by an acute priming with the same previously abused drug has been described for almost all drugs of abuse (Shaham et al., 2003).

The first extinction/reinstatement animal model of *cannabinoid seeking* behavior has been developed in Long Evans rats trained to intravenously self-administer the CB-sub1 receptor agonist WIN 55,212-2 as previously described by Fattore et al. (2001), i.e., at the unit dose of 12.5 μg/kg/inf and under a continuous (FR-1) schedule of reinforcement. By using a between-session protocol of relapse, Spano and colleagues have demonstrated how in these animals an acute intraperitoneal (ip) priming of the same CB-sub1 receptor agonist (WIN 55,212-2, 0.25 and 0.5 mg/kg) proved capable of reinstituting responding for the cannabinoid following long-term (21 days) extinction (Spano et al., 2004). Interestingly, a priming injection with cocaine (10 mg/kg ip) did not reinstitute responding in these animals, thereby attenuating the idea that cocaine may interfere with the endocannabinoid system in modulating relapsing events.

In line with results of Spano et al. (2004), it has been shown that *cocaine seeking* can be reinstated in Sprague-Dawley rats by drugs with primary dopaminergic mechanism such as cocaine, amphetamine, methylphenidate and caffeine, but

not delta9-tetrahydrocannabinol (Δ^9-THC, 0.3–3.0 mg/kg), morphine or nicotine (Schenk and Partridge, 1999). Conversely, De Vries and co-workers reported a cannabinoid mechanism in relapse to cocaine seeking by demonstrating that a subcutaneous (sc) priming with the potent CB-sub1 receptor agonist HU 210 (20 μg/kg) reinstates cocaine seeking in Wistar and Long Evans rats trained to self-administer cocaine at the unit dose of 0.5 mg/kg (De Vries et al., 2001). Several factors could account for such discrepant results, the first being the different cannabinoid agent (Δ^9-THC vs HU 210) used in the last two studies. The activity of Δ^9-THC as a partial agonist at the CB-sub1 receptor (Burkey et al., 1997; Petitet et al., 1998) might render its stimulus properties too weak for reinstating extincted responding in rats. Accordingly, even when tested in a wide range of doses and following different periods of withdrawal, Δ^9-THC primings fail to trigger heroin seeking (Fattore et al., 2003) and cannabinoid seeking (Spano MS, personal communication) behavior. Moreover, differences between the studies of Schenk and Partridge (1999) and De Vries et al. (2001) also concern (i) experimental design (*within-* vs *between-session*, respectively), (ii) modus operandi (*lever-pressing* vs *nose-poking*), (iii) duration of experimental sessions (*3–8* vs *2 h*), (iv) length of withdrawal period (*hours* vs *weeks*) after the last cocaine infusion and (v) rat strains used.

Whatever the intimate role played, the assumption that the endocannabinoid system might be involved in relapse to cocaine seeking is strengthened by the finding that exposure to exogenous cannabinoids may play a critical role in mediating the discriminative and rewarding properties of cocaine (Jarbe, 1984; Vlachou et al., 2003) as well as cocaine intake in both rats (Fattore et al., 1999) and humans (Foltin et al., 1993; Lukas et al., 1994). Accordingly, cocaine self-administration is significantly impaired in mice lacking the CB-sub1 receptor, i.e., CB-sub1 knockout mice (Soria et al., 2005) while Δ^9-THC affects the conditioned incentive properties of cocaine, being able to potentiate the extinction of cocaine-induced conditioned place preference (Parker et al., 2004). However, the question whether or not stimulation of CB-sub1 receptors influences the acquisition or maintenance of cocaine self-administration is still contentious, pharmacological inactivation or genetic absence of the CB-sub1 receptor failing to modulate cocaine self-administration in either rats (Fattore et al., 1999; De Vries et al., 2001), mice (Cossu et al., 2001; Lesscher et al., 2005) or squirrel monkeys (Tanda et al., 2000). The involvement of such receptors in the development of cocaine-induced behavioral sensitization also represents a currently controversial issue (Arnold et al., 1998; Martin et al., 2000; Lesscher et al., 2005).

With regard to reward-related events and addictive behavior, a clear functional cross-talk has been established between the cannabinoid and opioid systems (Fattore et al., 2000, 2004, 2005a; Navarro et al., 2001; Spano et al., in press). The role of the endocannabinoid system in relapse to *heroin seeking* is currently at the centre of attention in the scientific community, being to date the issue achieving the most consistent results. The two synthetic CB-sub1 receptor agonists WIN 55,212-2 (0.15 and 0.3 mg/kg, ip) and CP 55,940 (0.05 and 0.1 mg/kg, ip) have been shown to promptly elicit resuming of active lever-pressing behavior following a 3-week extinction period in Lister Hooded rats previously trained to self-administer

heroin at the unit dose of 30 μg/kg/inf under a continuous schedule of reinforcement (Fattore et al., 2003). Consistently, HU 210 (20 μg/kg, sc) reinstates active nose-poking responding after long-term (3 weeks) extinction in Wistar rats trained to self-administer heroin at the dose of 50 μg/kg/inf under both fixed (FR-5) and progressive (PR) schedules of reinforcement (De Vries et al., 2003). The unambiguous cannabinoid mechanism in relapse to heroin described in these studies well fits with the reported role for the opioid system in relapse to cannabinoid, as acute primings with heroin (0.5 mg/kg, ip) reinstate cannabinoid seeking behavior in Long Evans rats following prolonged drug-free periods (Spano et al., 2004). Noteworthy, the reinforcing properties of morphine and the severity of the withdrawal syndrome were strongly reduced in CB-sub1 knockout mice (Ledent et al., 1999), which do not display morphine-induced increase in dopamine release in the nucleus accumbens (Nacc) under conditions where this drug dose-dependently stimulates the release of dopamine in the corresponding wild-type mice (Mascia et al., 1999).

The role of cannabinoids in the reinstatement of *alcohol seeking* appears to be somewhat more intricate, the results from different laboratories being discrepant and often hard to interpret. For example, non-contingent chronic exposure to WIN 55,212-2 (0.4–10 mg/kg, sc) during alcohol deprivation is likely to enhance relapsing rate to alcohol (Lopez-Moreno et al., 2004), while acute administration of SR 141716A (0.3–3 mg/kg, ip) suppresses the extra intake of alcohol occurring in selectively bred alcohol-preferring sP rats after a period of alcohol abstinence (Serra et al., 2002), a finding recently replicated by the same group (Gessa et al., 2005) with the newly reported CB-sub1 receptor antagonist SR147778 (Rinaldi-Carmona et al., 2004). However, both CB-sub1 agonists (Δ^9-THC and CP 55,940) and antagonists (i.e., rimonabant) reduce ethanol intake in Wistar rats allowed to relapse after subsequent periods of alcoholization and alcohol deprivation (Gonzalez et al., 2004). The unfeasibility of distinguishing between the effects of CB-sub1 receptor stimulation and blockade leaves several questions on the specific contribution of the endocannabinoid system to relapse to alcohol seeking unanswered.

To further complicate the matter, Δ^9-THC (0.5 and 1 mg/kg ip) reinstates in Wistar rats extincted responding for alcoholic beverages, but also for near-beer and sucrose seeking behavior (McGregor et al., 2005). Finding that Δ^9-THC resumed responding for any of the caloric solutions tested regardless of the amount of alcohol (4.0% absolute ethanol in *beer* group, 0.5% in *near-beer* group and 0% in *sucrose* group) seems to implicate a specific effect of the cannabinoid priming on ingestive behavior. Notably, this study provides the only evidence to date for a reinstating effect of Δ^9-THC on *drug seeking* (and not *drug intake* as in the Gonzalez et al., 2004 study), as previous investigations failed to obtain positive results when testing Δ^9-THC on cocaine (Schenk and Partridge, 1999), heroin (Fattore et al., 2003) or WIN 55,212-2 (Spano MS, personal communication) seeking reinstatement, suggesting a selective effect of Δ^9-THC on relapse to alcohol rather than to other reinforcing drugs.

Finally, as cannabinoids are able to significantly attenuate *methamphetamine* (METH)-induced anxiety-related behaviors (Hayase et al., 2005) as well as the voluntary intake of METH in Wistar rats (Vinklerova et al., 2002), a role for cannabinoids in relapse to METH has also been investigated. It was found that

Table 2 – Effect of the CB-sub1 receptor blockade on drug-, cue- and stress-induced reinstatement of drug seeking behavior in abstinent animals

Drug-induced reinstatement

SA	Procedure; training dose; schedule; modus operandi; session length	Drug abstinence period (EXT); CB1 antagonist (mg/kg); time before session	Effect	Animals	Ref
WIN	B; 12.5 μg/kg/inf; FR1; NP; 3 h	21 days; SR 0.3 mg/kg (ip); 20′	Suppression of WIN (0.25–0.5 mg/kg ip)-induced reinstatement	LE	Spano et al., 2004
WIN	B; 12.5 μg/kg/inf; FR1; NP; 3 h	21 days; SR 0.3 mg/kg (ip); 20′	Suppression of heroin (0.3 mg/kg ip)-induced reinstatement	LE	Spano et al., 2004
Cocaine	B; 0.5 mg/kg/inf; FR5; NP; 2 h	≥14 days; SR 0.3–3.0 mg/kg (sc); 30′	Attenuation of cocaine (1.0 mg/kg iv)-induced reinstatement	WST	De Vries et al., 2001
Heroin	B; 30 μg/kg/inf; FR1; LP; 2 h	21 days; SR 0.3 mg/kg (ip); 20′	Suppression of heroin (0.5 mg/kg ip)-induced reinstatement	LH	Fattore et al., 2003
Heroin	B; 30 μg/kg/inf; FR1; LP; 2 h	21 days; SR 0.3 mg/kg (ip); 20′	Attenuation of WIN (0.15–0.3 mg/kg ip)-induced reinstatement	LH	Fattore et al., 2005b
Heroin	B; 30 μg/kg/inf; FR1; LP; 2 h	21 days; SR 0.3 (ip); 20′	Attenuation of CP (0.05–0.1 mg/kg ip)-induced reinstatement	LH	Fattore et al., 2005b
Heroin	B; 50 μg/kg/inf; FR5/PR; NP; 3/4 h	21 days; SR 3.0 mg/kg (sc); 30′	Attenuation of heroin (0.25 mg/kg sc)-induced reinstatement	WST	De Vries et al., 2003
Alcohol	B; 10% (v/v), two-bottle free choice regimen; 24 h/day for 4 weeks	15 days; SR 0.3–3.0 mg/kg (ip); 30′	Suppression of the alcohol deprivation effect (i.e. the extra amount of alcohol typically consumed after a period of alcohol deprivation)	sP	Serra et al., 2002
Alcohol	B; 10% (v/v), two-bottle free choice regimen; 24 h/day for 8 weeks	15 days; SR1 47778, 0.3–3.0 mg/kg (ip); 20′	Suppression of the alcohol deprivation effect	sP	Gessa et al., 2005
METH	B; 20 μg/kg/inf; FR1; LP; 2 h	6 days; SR 3.2 mg/kg (ip); 30′	Blockage of METH (1.0 mg/kg ip)-induced reinstatement)	WST	Anggadiredja et al., 2004

Cue-induced reinstatement

SA	Procedure; Training dose; schedule; modus operandi; session length	Drug abstinence period (EXT); primings: cue; CB1 antagonist; time before session	Effect	Animals	Ref
Cocaine	B; 0.5 mg/kg/inf; FR5; NP; 2 h	21 days; 15 s click + light signal; SR 1.0–3.0 mg/kg (sc), 30′	Dose-dependent attenuation of cue-induced reinstatement	WST	De Vries et al., 2001
Heroin	B; 50 μg/kg/inf; FR5/PR; NP; 2 h	21 days; 15 s click + light signal; SR 3.0 mg/kg (sc), 30′	Attenuation of cue-induced reinstatement	WST	De Vries et al., 2003
Nicotine	B; 30 μg/kg/inf; FR; LP; 1 h	1 month; 1 s tone/cue light; 15′ SR 1.0 mg/kg (ip), 15′	Attenuation of cue-induced reinstatement	SD	Cohen et al., 2004
METH	B/W; 20 μg/kg/inf; FR3; LP; 2 h	6 days; 20 s tone/cue light, at the beginning of the cue-phase session; SR 1.0 mg/kg (ip), 30′	Blockage of cue-induced reinstatement	WST	Anggadiredja et al., 2004
Alcohol	B; 10% w/v (0.1 ml/inf); FR1; LP; 30′	18 days; Orange extract odour/5 s house light; SR 0.3–3.0 mg/kg (ip), 30′	Reduction of cue-induced reinstatement	WST	Economidou et al., 2006
Alcohol	B; 10% v/v (0.1 ml/inf); FR1; LP; 30′	15 days; Orange extract odour/5 s house light; SR 0.3–3.0 mg/kg (ip), 30′	Reduction of cue-induced reinstatement	WST/ msP	Cippitelli et al., 2005

Table 2 (continued)

Stress-induced reinstatement

SA	Procedure; training dose; schedule; modus operandi; session length	Drug abstinence period (EXT); primings: stress; CB1 antagonist; time before session	Effect	Animals	Ref
Cocaine	B; 20 mg/kg/inf; FR5; NP; 2 h	14 days; Intermittent electric foot shock (0.6 mA, train length 0.5 s) for 15′; SR 1.0–3.0 mg/kg (ip); 30′	No effect	WST	De Vries et al., 2001
Alcohol	B; 10% w/v (0.1 ml/inf); FR1; LP; 30′	18 days; Intermittent electric foot shock (0.8 mA, train length 0.5 s) for 15′; SR 1.0–3.0 mg/kg (ip); 30′	No effect	WST	Economidou et al., 2006

Abbreviation: SA: self-administration; B: between-session reinstatement procedure; W: within-session reinstatement procedure; FR: fixed ratio of reinforcement: PR: progressive ratio of reinforcement; NP: nose-poking as operandum; LP: lever-pressing as operandum; EXT: extinction; LE: Long Evans rats; LH: Lister Hooded rats; SD: Sprague Dawley rats; sP: Sardinian alcohol-preferring rats; msP: Marchigian Sardinian alcohol-preferring rats; WST: Wistar rats; WIN: WIN 55,212-2; CP: CP 55,940; HU: HU210; SR: SR 141716A (Rimonabant).

the psychoactive ingredient of *Cannabis sativa* Δ^8-THC (0.1–0.32 mg/kg, ip) fails to reinstate METH seeking behavior by itself, but it dose-dependently attenuates drug seeking reinstatement induced by a priming injection of 1.0 mg/kg, ip, METH (Anggadiredja et al., 2004). However, when co-administered with a subthreshold dose of METH (0.1 mg/kg, ip), Δ^8-THC (0.32 mg/kg, ip) causes a significant increase in responding, an effect attributable to a non-specific effect (i.e., hyperactivity or stereotyped behavior) induced by the combination of the two drugs (Consroe et al., 1976).

2.2. Cue-induced reinstatement

Compelling theories of drug addiction attribute particular relevance to drug-associated environmental stimuli in inducing craving, supporting compulsive drug seeking and triggering relapse (Robinson and Berridge, 1993; Everitt et al., 2001; Vanderschuren and Everitt, 2005). These views are contingent on the finding that a drug-paired conditioned stimulus can maintain responding by acting as a conditioned reinforcer as it acquires emotional salience and motivational properties through predictive association with the self-administered drug. Exposure to drug-related cues in human addicts results in typical regional activation of central circuits that are known to mediate cue-induced reinstatement of drug seeking behavior in animal models of relapse (Childress et al., 1999; Ito et al., 2000; Ciccocioppo et al., 2001; Brody et al., 2002; Kelley et al., 2005). Accordingly, drug cues presented non-contingently to the infusion of the drug neither potentiate drug seeking activity nor reinstate extinguished responding in the rat (Kruzich et al., 2001; Di Ciano and Everitt, 2003). Epidemiological and anecdotic reports reveal that drug-related cues can sustain drug taking behavior in human addicts and enhance relapsing rate to drug seeking after even prolonged periods of drug abstinence. Comparably to the human situation, associated environmental stimuli can reinstate drug seeking behavior in laboratory animals under appropriate experimental conditions (Weiss et al., 2001; Shaham et al., 2003).

Very recently, a general role for the endocannabinoid system in modulating conditioned reinforcement or cue reactivity following extinction from self-administration of both drug and natural reinforcers has been proposed (De Vries and Schoffelmeer, 2005). However, to date, only one study has investigated the effect of CB-sub1 receptor stimulation on cue-induced reinstatement of drug seeking, reporting Δ^8-THC (0.1 mg/kg, ip) as being able to enhance the effect of re-exposure to a drug-associated cue on the reinstatement of METH seeking behavior (Anggadiredja et al., 2004).

2.3. Stress-induced reinstatement

Stress is known to aggravate craving and associated state of arousal in drug addicts and consequently to enhance the risk of perpetuating drug misuse and relapsing to drug seeking in abstinent individuals. A growing clinical literature indicates that a clear-cut linkage does exist between drug abuse and stress-related disorders, as many dually diagnosed patients make use of illicit drugs to cope with stressful life events (Sinha, 2001; Goeders, 2003). Exposure to a stressor, such as mild foot-shock or food-deprivation or cat odor for rodents, is recognized to elicit relapse to drug seeking behavior in laboratory animals (Shaham et al., 2000). The endocannabinoid system appears to be conspicuously involved in modulation of depression (Gobbi et al., 2005), stress (Hohmann et al., 2005; Viveros et al., 2005) and anxiety (Kathuria et al., 2003; Bortolato et al., 2006; Patel and Hillard, 2006), with the cannabinoid CB-sub1 receptor exerting an important function in the action of anxiolytics (Uriguen et al., 2004) while its absence results in a greater vulnerability to stress (Fride et al., 2005). Chronic stress downregulates CB-sub1 receptor expression and significantly reduces the content of the endocannabinoid 2-arachidonoylglycerol within the hippocampus (Hill et al., 2005). CB-sub1 receptor also plays a critical role in stress-stimulated ethanol drinking and alcohol withdrawal (Racz et al., 2003). Moreover, enhanced levels of corticotrophin-releasing factor in the central amygdala as well as activation of other stress-responsive nuclei have been described during precipitated cannabinoid withdrawal (Rodriguez de Fonseca et al., 1997).

However, the effect of CB-sub1 receptor activation on stress-induced reinstatement of drug seeking has not yet been investigated.

3.   Effect of CB-sub1 receptor blockage on drug seeking reinstatement

Undeniable evidence demonstrates the involvement of a cannabinoid mechanism in the modulation of appetitive motivation, incentive salience, craving and drug reward (Chaperon and Thiebot, 1999). Depending on behavioral protocols and specific experimental conditions, pharmacological inactivation of cannabinoid CB-sub1 receptors may reduce drug intake in several animal models of drug addiction by interfering with the reinforcing and/or incentive properties of cocaine (Vlachou et al., 2003), opioid (Navarro et al., 2001; Braida et al., 2001a,b; Fattore et al., 2002; Solinas et al., 2003), nicotine (Cohen et al., 2002, Forget et al., 2005), alcohol (Arnone et al., 1997; Colombo et al., 1998b, 2004; Freedland et al., 2001; Lallemand et al., 2004; Economidou et al., 2006) and amphetamine derivates (Vinklerova et al., 2002; Braida and Sala, 2002; Braida et al., 2005). Accordingly, genetic deletion of CB-sub1 receptors attenuates motivational effects of several classes of addictive substance in addition to Cannabis derivates (Ledent et al., 1999; Fattore et al., 2000; Soria et al., 2005), although opposite results have also been reported (Martin et al., 2000; Cossu et al., 2001). In addition, CB-sub1 knockout mice consistently display significantly lower levels of alcohol preference and intake than the wild-type littermates (Poncelet et al., 2003; Lallemand and De Witte, 2005; Naassila et al., 2004). On the other hand, suppression of food intake and food-reinforced behavior following pharmacological inactivation of cannabinoid CB-sub1 receptors has also been reported (Colombo et al., 1998a; Freedland et al., 2000; McLaughlin et al., 2003, 2006), with rimonabant affecting motivational processes in both the appetitive and consumatory phases of feeding behavior (Thornton-Jones et al., 2005). In line with these observations, CB-sub1 receptor knockout mice eat less than their wild-type littermates while rimonabant reduces food intake in wild-type but not knockout mice (Di Marzo et al., 2001), thus demonstrating a role for the CB-sub1 receptor in the regulation of feeding behavior. Intriguingly, rimonabant seems to selectively reduce feeding of a very highly palatable food (Simiand et al., 1998), implying a cannabinoid involvement in the incentive value of food. These observations are suggestive of a CB-sub1-related mechanism in the perception of the appetitive value of reinforcers, even when they do not interact directly with the endocannabinoid system. However, a role for the endocannabinoid system in the control of motivation to obtain natural reinforcers such as sucrose or food is still a matter of dispute (see De Vries et al., 2001; Navarro et al., 2001 but also Arnone et al., 1997; Higgs et al., 2003). Nevertheless, CB-sub1 antagonists do not affect operant responding for either sucrose (De Vries et al., 2001), food (Navarro et al., 2001) or cocaine (Fattore et al., 1999) and are devoid of any reinforcing effects per se (Beardsley et al., 2002).

Very recently, the possibility of using compounds with antagonistic activity at CB-sub1 receptors as pharmacological tool in the prevention of relapse to drug abuse has been vigorously proposed, based on the escalating evidence for an important role of rimonabant in reducing drug- and cue-induced reinstatement of drug seeking behavior (reviewed in Fowler, 2005; Carai et al., 2005; Le Foll and Goldberg, 2005; Beardsley and Thomas, 2005), as illustrated in Table 2.

3.1.   Drug-induced reinstatement

Rimonabant has been reported to block the reinstatement of cannabinoid seeking behavior in rats induced by a priming with the CB-sub1 receptor agonist WIN 55,212-2 following long-term extinction (Spano et al., 2004). Interestingly, at doses ranging from 0.3 to 3.2 mg/kg, the CB-sub1 antagonist has been found to significantly attenuate or even prevent the resumption of drug seeking behavior elicited by an acute priming with other abused substances in addition to cannabinoids. More specifically, rimonabant has proved capable of antagonizing cocaine (De Vries et al., 2001), heroin (Fattore et al., 2003; De Vries et al., 2003) and METH (Anggadiredja et al., 2004) seeking induced by a single priming with the same previously abused drug. Remarkably, all these effects were consistent regardless of differences in rat strain (Wistar, Long Evans, Lister Hooded), schedule of reinforcement (FR1, FR5), route of CB-sub1 antagonist administration (sc, ip) or experimental response-like operandum (lever-pressing, nose-poking) used. In addition, at the same range of doses, rimonabant abolishes the alcohol deprivation effect in alcohol-preferring sP rats (Serra et al., 2002) and reduced motivation for beer in Wistar rats (Gallate and McGregor, 1999; Gallate et al., 2004).

Notably, the antagonistic effect of CB-sub1 receptors blockade is extendable to the cross-reinstatement of drug seeking behavior, i.e., reinstatement of drug seeking behavior triggered by priming with a different drug. To this purpose, in light of the specific behavioral interactions between the endocannabinoid and the endogenous opioid systems (Fattore et al., 2004, 2005a), the findings that rimonabant (0.3 mg/kg, ip) significantly attenuates cannabinoid-induced reinstatement of heroin seeking (Fattore et al., 2005b) while completely antagonizing heroin-induced reinstatement of cannabinoid seeking (Spano et al., 2004) are of crucial importance. Hence, it emerges that blockade of the CB-sub1 receptors significantly prevents the reinstatement of drug seeking behavior induced by virtually all classes of drugs of abuse, thus pointing to a general role for the endocannabinoid system in modulating relapse phenomena.

3.2.   Cue-induced reinstatement

Environmental stimuli that previously accompanied voluntary drug taking are acknowledged to produce significant alterations in the brain underlying behavioral changes that characterise memory and addiction (Nestler, 2002). An increasing amount of evidence points to the inactivation/absence of CB-sub1 receptors as a relevant contributor to the central processes dampening cue-induced relapse to drug seeking behavior. Such a role was initially established for cocaine and heroin seeking, as rimonabant (1 and 3 mg/kg) is capable of attenuating the reinstatement triggered by a single re-exposure to a drug-associated cue (De Vries et al., 2001, 2003). More

recently, rimonabant has been found to attenuate in a dose-dependent manner the cue-induced reinstatement of alcohol seeking in Wistar rats and, to a greater extent, in genetically selected Marchigian Sardinian alcohol-preferring rats (Cippitelli et al., 2005). Similarly, it antagonizes cue-induced reinstatement of nicotine (Cohen et al., 2004; De Vries et al., 2005) and METH (Anggadiredja et al., 2004) seeking behavior in both Wistar and Sprague-Dawley rats. Finally, cue-induced reinstatement of sucrose seeking in Wistar rats is dose-dependently antagonized by rimonabant (De Vries et al., 2005).

3.3. Stress-induced reinstatement

Tonic endocannabinoid signaling has been thought to inhibit the activity of stress-responsive brain regions as rimonabant increases Fos expression in stress-responsive limbic forebrain regions, namely the prefrontal cortex, the NAcc shell, the ventro-lateral septum and the dorsal caudate putamen (Alonso et al., 1999; Patel et al., 2005). However, very little is known about its role in stress-induced reinstatement of drug seeking behavior following extinction.

At present, studies investigating a potential role of the CB-sub1 receptor blockade in stress-induced reinstatement described rimonabant as unable to affect relapse to both cocaine and ethanol seeking elicited by an intermittent exposure to mild foot-shock stressor, questioning the likelihood that the CB-sub1 receptor may also contribute to relapse triggered by an environmental stressor (De Vries et al., 2001; Economidou et al., 2006).

4. Clinical findings

Due to the high comorbidity among drug addicts, it is likely that many individuals undergoing detoxification from other drugs of abuse consume Cannabis. Recently, a prospective longitudinal study employing inpatients treated for alcohol and cocaine addiction demonstrated that Cannabis use following hospital discharge has a significant negative impact on remission and relapse (Aharonovich et al., 2005). These data are consistent with the aforementioned preclinical studies pointing to the endocannabinoid system as a possible modulator of the brain reward pathway capable of reinstating the use of the previously abused drug in abstinent individuals.

In clinical trials, rimonabant has proved capable of blocking acute physiological and psychological effects of smoked marijuana without altering Δ^9-THC pharmacokinetics (Huestis et al., 2001). Findings that subjective and rewarding effects of Δ^9-THC in humans are blocked by rimonabant correlate with animal data showing that positive reinforcing effects of either CB-sub1 receptor natural ligands or synthetic agonists are antagonized by pretreatment with rimonabant in both rodents (Martellotta et al., 1998; Fattore et al., 2001; Braida et al., 2004) and monkeys (Tanda et al., 2000; Justinova et al., 2005). Accordingly, the CB-sub1 receptor antagonist decreases sensitivity to the reinforcing effects of electrical brain stimulation in rats (Deroche-Gamonet et al., 2001), suggesting that the endocannabinoid system could be a target of interest in the treatment of psychopathologies implicating the rewarding substrates.

Early clinical trials with rimonabant were very promising in treating obesity and aiding smoking cessation. In particular, clinical studies reported that roughly one quarter out of the 261 smokers taking 20 mg of rimonabant enrolled in the 10-week study stopped smoking, a better quitting rate than that obtained with current nicotine replacement therapy (Anthenelli and Despres, 2004). However, despite these promising results, on February 2006, the American Food and Drug Administration (FDA) declined to approve rimonabant for smoking cessation while requiring further studies before final approval for weight management.

5. Possible neural targets of action

Irrespective of the growing evidence for an involvement of the endocannabinoid system in regulating relapse to many classes of abused drugs (i.e., psychostimulants such as cocaine, nicotine or methamphetamine, but also alcohol and opioids), the anatomical and neurochemical substrates responsible for the reinitiation of drug seeking behavior has only recently started to be unraveled. Considerable progress has been made in extricating the individual contribution of the neural systems involved in the three priming reinstatement modes discussed above, with the ventral tegmental area (VTA), the basolateral amygdala and the adrenergic innervation of the extended amygdala responsible for drug-, cue- or stress-induced relapse, respectively (Kalivas and McFarland, 2003). Accordingly, (i) 6-OHDA microinjected into VTA to damage the perikaryon of dopaminergic neurons completely abolished the drug-induced reinstatement of morphine CPP (Wang et al., 2003b), (ii) lesion or inactivation of the basolateral amygdala abolishes the ability of drug-associated cues to reinstate responding (Fuchs and See, 2002; McLaughlin and See, 2003), and (iii) infusion of noradrenergic antagonists into the bed nucleus of the stria terminalis or the central nucleus of the amygdala prevents footshock- but not cocaine-induced reinstatement of cocaine seeking (Leri et al., 2002). Actually, all these observations refer to reinstatement of cocaine or heroin seeking behavior (Shalev et al., 2002). However, as CB-sub1 receptors are well represented in such areas as well as in brain regions related to learning and memory processes (Herkenham et al., 1990; Mailleux and Vanderhaeghen, 1992), one could theorize that they may mediate drug seeking reinstatement by acting on the same neuronal circuitries.

The mesocorticolimbic dopaminergic system is a major neural substrate for the reinforcing effects of most drugs of abuse and is activated by exposure to pharmacological stimuli that promote relapse to drug seeking during withdrawal (Self, 1998; Spealman et al., 1999; Stewart, 2000; Shalev et al., 2002). Drug-induced neuroplasticity at excitatory synapses in both the VTA and the NAcc facilitates drug seeking behavior and the propensity for relapse (Self, 2004). Based on evidence for cannabinoid-DA functional interactions in several brain regions (French et al., 1997; Gessa et al., 1998; Wu and French, 2000; Cheer et al., 2004), it could be argue that stimulation of the CB-sub1 receptor might activate dopaminergic transmission, thus contributing towards drug seeking reinstatement. In line with this finding, it has been ascertained by cerebral

microdialysis (Cohen et al., 2002), electrophysiological (Cheer et al., 2003) and fast-scan cyclic voltammetry (Cheer et al., 2004) studies that rimonabant decreases the DA enhancing effect of drugs of abuse. However, endocannabinoid system might also act as an inhibitory feedback mechanism countering dopamine D2 receptor-induced facilitation of psychomotor activity (Giuffrida et al., 1999; Beltramo et al., 2000).

On the other hand, although dopaminergic transmission plays an essential role in conditioned responses associated with drug intake (Everitt et al., 2001), it might be expected that other neurotransmitters besides DA are involved in relapse. CB-sub1 receptors are widely distributed on axon terminals of GABAergic interneurons throughout the brain and have been reported to regulate GABA transmission in the NAcc (Manzoni and Bockaert, 2001), so that the stimulating effect of primings with cannabinoid agonists might result from an enhancement of mesolimbic DA release secondary to an inhibition of GABAergic synaptic transmission. Furthermore, it has been demonstrated that endocannabinoids act as retrograde messengers from depolarized postsynaptic neurons to presynaptic terminals (Maejima et al., 2001) and mediate presynaptic inhibition of glutamatergic transmission in VTA DA neurons through activation of CB-sub1 receptors (Melis et al., 2004a,b). Following the proposal whereby metabotropic, AMPA and NMDA glutamatergic receptors may take part in the regulation of discrete cue-induced reinstatement of drug seeking behavior (Bespalov et al., 2000, 2005; Bossert et al., 2004; Sanchis-Segura et al., 2006), it is possible that the attenuating effect of CB-sub1 receptor antagonists on cue-induced reinstatement of drug seeking behavior might be due, at least in part, to an inhibition of glutamatergic transmission.

6.   Concluding remarks

At the present, substantial data points to a role of the endocannabinoid system in triggering and/or preventing reinstatement of drug seeking behavior. We have here reviewed the striking progress made in this area, placing particular emphasis on the findings obtained from behavioral studies. The abovementioned results showing the stimulating and reducing effect of CB-sub1 activation and blockade, respectively, on drug seeking reinstatement have met with considerable consensus among numerous research groups using different protocols, animals and methodological procedures. Indeed, animal models have been extremely useful in demonstrating that, under certain conditions, CB-sub1 receptor stimulation may elicit relapse not only to cannabinoid seeking but also to cocaine, heroin, alcohol and METH. Remarkably, such an effect is significantly attenuated, when not fully prevented, by pretreatment with rimonabant, thus pointing to CB-sub1 receptor antagonists as a new class of promising medications capable of aiding maintenance of the drug-free state.

To date, it is not completely understood how blocking cannabinoid receptors should reduce the likelihood of relapse, but the cannabinoid system is closely linked to the reward pathways, possibly bearing crucial implications in particular for drugs of abuse, such as cocaine, that exert direct actions on the dopaminergic system. In view of the urgent need for medications to help prevent relapse in cocaine users, the finding that blockade of cannabinoid receptors prevents both drug- and cue-induced relapses to cocaine seeking is of obvious therapeutic significance. Moreover, as indicated by the preclinical studies reviewed here, the hypothetical therapeutic benefits of cannabinoid antagonists on relapse to cocaine might be extended to other substances of abuse, such as opiates and alcohol.

Indeed, rimonabant has been reported to be effective in significantly attenuating relapse to heroin, with primings with CB-sub1 receptor agonists causing relapse to heroin seeking (De Vries et al., 2003; Fattore et al., 2003, 2005b). Further support to the notion of a strict reciprocal relationship between the CB-sub1 and opioid receptors in modulating relapse is provided by the finding that the blockade of opioid receptor by naloxone prevents relapse to cannabinoids (Spano et al., 2004).

Moreover, important progress has recently been made in delineating the role of the CB-sub1 receptor in relapse to alcohol (Serra et al., 2002; Lopez-Moreno et al., 2004; Gessa et al., 2005; McGregor et al., 2005), particularly with specific regard to the brain areas possibly implicated in this phenomenon (Gonzalez et al., 2004). For example, an overactive endocannabinoid transmission (i.e., a decreased expression of the endocannabinoid-degrading enzyme fatty acid amidohydrolase) and a compensatory downregulation of CB-sub1 signaling has been described in the prefrontal cortex of alcohol-preferring rats (Hansson et al., 2006). A significant relationship between *Cannabis* use and relapse to alcohol has also been detected recently in a prospective clinical study (Aharonovich et al., 2005).

In addition, cannabinoids affect both the perception by animals of the motivational value of nicotine and the capacity of nicotine-paired conditioned stimuli to elicit approach behavior (Forget et al., 2005; Le Foll and Goldberg, 2005), thus implicating the CB-sub1 receptor in the motivational effects of nicotine. Once again, rimonabant was shown to be effective not only as an aid for drug use cessation but also in the maintenance of abstinence (Cohen et al., 2004, 2005). Finally, new perspectives on the involvement of the CB-sub1 receptor in the reinstatement of amphetamine and methamphetamine seeking behavior have also been provided (Schenk and Partridge, 1999; Anggadiredja et al., 2004), thus completing the scenario for a general role of the endocannabinoid system in relapse.

Importantly, CB-sub1 receptor blockade may also reduce the likelihood to relapse to drug seeking induced by drug-associated cues, although it does not seem to mediate brain response to emotional distress during withdrawal, which can also cause relapses to drug taking (De Vries et al., 2001; Economidou et al., 2006). Failure of the CB-sub1 receptor antagonist to block relapse triggered by stressors suggests that the neurobiological mechanisms of stress-induced reinstatement of drug seeking differ from those of drug- and cue-induced reinstatement. Accordingly, compounds that prevent the release or action of brain neurotransmitters that regulate the body's response to stressful situations have been shown to block stress-induced but not cue- or drug-induced reinstatement of drug seeking (Shaham et al., 2000). As it is reasonable

to expect that treatment of relapse will involve the use of more than one drug, as habitually occurs with other chronic diseases, one possible future step in research would be to evaluate whether a CB-sub1 antagonist can be used in combination with agents that block the release of stress-related neurotransmitters as relapse prevention medications.

Collectively, the preclinical and clinical studies available at present provide unequivocal evidence for an involvement of the endocannabinoid system in the resuming of drug seeking behavior. Much remains to be done before we fully understand how this system governs relapse central mechanisms. Future studies will need to extend the reviewed findings, i.e., by providing neuroanatomical, chemical and/or molecular correlates to behavioral data to precisely identify neural substrates and pathways through which cannabinoids regulate relapse-related mechanisms. Molecular, cellular, and electrophysiological events that mediate the learning of associations between drugs and the environment in which they are consumed should also be unravelled.

Acknowledgment

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Perspectives in Pharmacology

Cannabinoid CB$_1$ Receptor Antagonists as Promising New Medications for Drug Dependence

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ABSTRACT

This review examines the development of cannabinoid CB$_1$ receptor antagonists as a new class of therapeutic agents for drug addiction. Abused drugs [alcohol, opiates, Δ^9-tetrahydrocannabinol (Δ^9-THC), and psychostimulants, including nicotine] elicit a variety of chronically relapsing disorders by interacting with endogenous neural pathways in the brain. In particular, they share the common property of activating mesolimbic dopamine brain reward systems, and virtually all abused drugs elevate dopamine levels in the nucleus accumbens. Cannabinoid CB$_1$ receptors are expressed in this brain reward circuit and modulate the dopamine-releasing effects of Δ^9-THC and nicotine. Rimonabant (SR141716), a CB$_1$ receptor antagonist, blocks both the dopamine-releasing and discriminative and rewarding effects of Δ^9-THC in animals. Blockade of CB$_1$ receptor activity by genetic invalidation also decreases rewarding effects of opiates and alcohol in animals. Although CB$_1$ receptor blockade is generally ineffective in reducing the self-administration of cocaine in rodents and primates, it reduces the reinstatement of extinguished cocaine-seeking behavior produced by cocaine-associated conditioned stimuli and cocaine-priming injections. Likewise, CB$_1$ receptor blockade is effective in reducing nicotine-seeking behavior induced by re-exposure to nicotine-associated stimuli. Some of these findings have been recently validated in humans. In clinical trials, Rimonabant blocks the subjective effects of Δ^9-THC in humans and prevents relapse to smoking in exsmokers. Findings from both clinical and preclinical studies suggest that ligands blocking CB$_1$ receptors offer a novel approach for patients suffering from drug dependence that may be efficacious across different classes of abused drugs.

CB$_1$ Receptors Modulate the Brain Reward Pathway

Drug dependence is a chronic, relapsing disorder in which compulsive drug-seeking and -taking behavior persists despite serious negative consequences (American Psychiatric Association, 2000). Addictive substances, such as cannabinoids, opioids, ethanol, and psychostimulants, including nicotine, induce pleasant states or relieve distress, effects that contribute to their recreational use. After repeated exposure, adaptive changes occur in the central nervous system that lead to drug dependence (American Psychiatric Association, 2000). Although addictive drugs produce their effects through actions at various receptors in the brain, it is thought that their common effects on the activity of dopaminergic brain reward pathways is primarily responsible for their addictive properties (Koob, 1992a,b; Wise, 2004). Notably, the mesocorticolimbic system, which projects from the ventral tegmental area to the nucleus accumbens, cortical areas, and amygdala, is implicated in the rewarding effects of psychostimulants and other drugs of abuse, as well as the effects of nondrug natural rewards such as food (Wise, 1982). The involvement of dopamine in the rewarding effects of drugs of abuse is suggested by findings that most drugs abused by humans increase levels of dopamine in the nucleus

ABBREVIATIONS: Δ^9-THC, Δ^9-tetrahydrocannabinol; SR141716, Rimonabant; CPP, conditioned place preference(s); FR, fixed ratio; HU-210, (6aR)-*trans*-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol; AM-251, N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide.

accumbens (Imperato et al., 1986; Pidoplichko et al., 1997) and that blockade of dopamine transmission reduces the rewarding effects of psychostimulants (Koob, 1992a,b); however, the role of dopamine seems more complex than simply mediating the primary reinforcing effects of drugs of abuse (Salamone et al., 2003; Wise, 2004). Recent evidence suggests that dopamine is strongly implicated in learning and conditioning processes (Schultz et al., 1997; Schultz, 2002) and in drug-seeking behavior (Phillips et al., 2003).

Marijuana is the most widely used illicit drug in the United States. The main psychoactive ingredient in marijuana is Δ^9-tetrahydrocannabinol (Δ^9-THC). Two forms of cannabinoid receptors, CB_1 and CB_2, have been cloned (Matsuda et al., 1990; Gerard et al., 1991; Munro et al., 1993). The CB_1 receptor and its splice variant, the CB_{1A} receptor, are predominantly found in the brain, with the highest density in the hippocampus, cerebellum, cortex, and striatum, whereas CB_2 receptors are located peripherally, principally associated with the immune system (Howlett et al., 2002). New data suggest the existence of an additional cannabinoid receptor (non-CB_1/non-CB_2) (see Wilson and Nicoll, 2002). Δ^9-THC may produce its effects by duplicating the effects of natural ligands for CB_1 receptors (anandamide, 2-arachidonylglycerol, and, perhaps, noladin ether), which have a shorter duration of action than synthetic or plant-derived cannabinoids and are implicated in various nervous system functions such as reward, memory, cognition, and pain perception (Wilson and Nicoll, 2002). Central nervous system effects produced by Δ^9-THC have been linked to the cannabinoid CB_1 receptor. As with other drugs of abuse, Δ^9-THC also produces an elevation in dopamine levels in the nucleus accumbens of rats (Chen et al., 1990) that is blocked by SR141716, a cannabinoid CB_1 receptor antagonist (Tanda and Di Chiara, 1997).

The potential utility of cannabinoid CB_1 receptor antagonists for the treatment of drug dependence has recently received considerable attention. This approach has been tested for Δ^9-THC and other types of drugs of abuse. This review focuses on the development of cannabinoid CB_1 receptor antagonists for the treatment of drug dependence. We will first summarize the main animal models used to assess subjective and rewarding/reinforcing effects of drugs of abuse and then summarize in Table 1 the preclinical and clinical findings related to CB_1 receptor blockade and the subjective and rewarding/reinforcing effects of different drugs of abuse in these models. The results obtained with various drugs of abuse will be presented by drug class. The putative neurobiological mechanisms underlying these effects will also be discussed. Although some drugs of abuse, such as ecstasy, are sometimes used together with marijuana (Croft et al., 2001), the involvement of cannabinoid mechanisms in the effects of these drugs has seldom been studied (Braida and Sala, 2002), and these limited findings will not be reviewed here.

Animal Models for Studying Effects of Drugs of Abuse

A variety of animal models are available to study the cardinal features of drug dependence (Schuster and Woods, 1968; Goldberg, 1975; Goldberg et al., 1975, 1979, 1981; Spealman and Goldberg, 1978; Katz and Goldberg, 1988; Markou et al., 1993; Everitt and Robbins, 2000; Schindler et

al., 2002; Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). The effects of CB_1 blockade have been evaluated using animals models for the subjective effects of drugs (drug discrimination), their rewarding/reinforcing properties [intravenous drug self-administration, conditioned place preference (CPP), and intracranial self-stimulation procedures], the influence of environmental factors on drug-seeking behavior (CPP, second-order schedules of drug self-administration, reinstatement of extinguished drug-seeking behavior, and other relapse models), and the withdrawal states associated with the abrupt termination of drug action (administration of selective antagonists after chronic exposure). We will mainly review results obtained with the drug discrimination procedure and the two most widely used procedures assessing rewarding or reinforcing effects of drugs in experimental animals: intravenous drug self-administration and drug-induced CPP procedures.

Drug Discrimination

Humans that abuse psychoactive drugs report characteristic subjective effects, and drug discrimination procedures in rats and monkeys are extensively used as animal models for subjective reports of drug effects in humans. The organism's ability to perceive and identify the characteristic interoceptive effects of drugs is thought to play a role in drug seeking, encouraging the development of this behavior and directing it toward one substance rather than another on the basis of relative potencies and effects (Stolerman and Shoaib, 1991). These interoceptive subjective effects of drugs are most frequently assessed in humans through the use of performance-assessment tasks and subject-rating scales. In animals, the interoceptive effects of drugs can serve as discriminative stimuli to indicate how to obtain a reinforcer such as a food pellet or how to avoid an electric shock. For this purpose, animals are trained under a discrete trial schedule of food pellet delivery or stimulus-shock termination to respond on one lever after an injection of a training dose of a drug and on the other lever after an injection of vehicle. Once animals learn to reliably make this discrimination, the subjective effects of different drugs can be compared, and the modulation of subjective effects of drugs of abuse by various pharmacological ligands can be measured.

Intravenous Drug Self-Administration

Natural rewards, such as water or food, and drugs of abuse may serve as positive reinforcers. For example, to assess the reinforcing effects of food, a food-deprived animal can be placed in a sound-attenuating chamber containing stimulus lights, response levers, and a device for dispensing food pellets automatically. Lever-pressing responses will occur with increasing frequency when they result in delivery of the food pellets, which, therefore, serve as positive reinforcers under these conditions. With intravenous drug self-administration procedures, a catheter implanted in a jugular vein allows the animal to intravenously self-administer a small amount of drug by pressing a lever. The administration of drug constitutes the event that positively reinforces the lever-pressing behavior, and reward is inferred if the frequency of responding subsequently increases (thus defining reinforcement). With these behavioral procedures, a stimulus light is often associated with delivery of the reinforcer. This stimulus, or cue, progressively gains motivational value by Pavlovian con-

TABLE 1

Main effect of CB$_1$ blockade on the subjective, discriminative, and rewarding/reinforcing effects of drugs of abuse in animal and human subjects

Species	Model	Results	Reference
Δ^9-THC			
Squirrel monkeys	i.v. self-administration under an FR10 schedule	SR141716 decreased self-administration	Tanda et al. (2000)
Rats and monkeys	Drug discrimination	SR141716 blocked discrimination of Δ^9-THC	Wiley et al. (1995); Jarbe et al. (2001); Solinas et al. (2003)
Humans	Reports of subjective drug effects	SR141716 blocked subjective effects of Δ^9-THC	Huestis et al. (2001)
Cocaine			
Squirrel monkeys	i.v. self-administration under an FR10 schedule	No effect of SR141716	Tanda et al. (2000)
Rats	Cocaine self-administration at a low ratio requirement (FR5)	No effect of SR141716	De Vries et al. (2001)
Rats	Relapse to drug-seeking behavior	SR141716 prevented relapse induced by cues and drug priming	De Vries et al. (2001)
Mice	Cocaine self-administration	No effect of CB$_1$ receptor invalidation	Cossu et al. (2001)
Mice	Cocaine-induced CPP	No effect of CB$_1$ receptor invalidation	Martin et al. (2000)
Rats	Cocaine-induced CPP	SR141716 blocked acquisition, but not expression, of CPP	Chaperon et al. (1998)
Opiates			
Rats	Heroin self-administration at high ratio requirements (FR10 and progressive ratio schedules)	SR141716 decreased self-administration	De Vries et al. (2003); Solinas et al. (2003)
Rats	Heroin self-administration at low ratio requirements (FR1–5)	No effect of SR141716	De Vries et al. (2003); Solinas et al. (2003)
Rats	Morphine-induced CPP	SR141716 blocked acquisition of CPP	Chaperon et al. (1998)
Mice	Morphine self-administration at a low ratio requirement (FR1)	CB$_1$ receptor invalidation blocked opiate self-administration	Cossu et al. (2001)
Mice	Morphine-induced CPP	CB$_1$ receptor invalidation blocked acquisition of CPP	Martin et al. (2000)
Alcohol			
Rats and mice	Oral ethanol intake and ethanol preference	SR141716 decreased oral ethanol intake	Arnone et al. (1997); Colombo et al. (1998); Rodriguez de Fonseca et al. (1999); Rinaldi-Carmona et al. (2004)
Mice	Oral ethanol intake	CB$_1$ receptor invalidation decreased ethanol intake and the effects of SR141716	Hungund et al. (2003); Poncelet et al. (2003); Naassila et al. (2004)
Mice	Acquisition of ethanol-induced CPP	CB$_1$ receptor invalidation reduced ethanol CPP	Houchi et al. (2004)
Nicotine			
Humans	Smoking cessation trial	SR141716 increased smoking cessation rates	Anthenelli and Despres (2004)
Rats	Self-administration of i.v. nicotine at a low ratio requirement (FR4)	SR141716 decreased self administration	Cohen et al. (2002)
Rats	Expression of CPP (stimulus-controlled behavior)	SR141716 blocked preferences for nicotine-paired environment	Le Foll and Goldberg (2004a)
Rats	Nicotine discrimination	No effect of SR141716	Cohen et al. (2002); Le Foll and Goldberg (2004a)
Mice	Nicotine-induced CPP	No CPP for nicotine in CB$_1$-deficient mice	Castane et al. (2002)
Mice	Self-administration of i.v. nicotine at a low ratio requirement (FR1)	No effect of CB$_1$ receptor invalidation	Cossu et al. (2001)

ditioning and can induce and maintain drug-seeking behavior and also reinstate drug-seeking behavior after extinction (Goldberg, 1975; Goldberg et al., 1975, 1983; de Wit and Stewart, 1981; Stewart, 1983; Self and Nestler, 1988; Meil and See, 1996; Arroyo et al., 1999), providing useful measures of the motivational effects of drug-related stimuli. Various schedules of reinforcement of drug self-administration behavior have been developed.

Under a fixed ratio (FR) schedule of intravenous drug injection, a fixed number of lever presses is necessary to obtain each injection of drug (e.g., one lever press for a fixed ratio 1, i.e., FR1, schedule). In contrast, under a progressive ratio schedule, the number of lever-press responses necessary to obtain a drug injection increases after each drug injection (Hodos, 1961). Thus, the number of responses the subject must make for each successive drug injection (the ratio value) is increased progressively until the subject fails to emit the required number of responses; this highest ratio (the "breaking point") is thought to reflect the reinforcing effectiveness of the drug. Self-administration studies have repeatedly shown that most drugs considered to be addictive in humans can serve as positive reinforcers for laboratory rats and monkeys, whereas nonaddictive drugs

have given negative results in most cases (Katz and Goldberg, 1988; Balster, 1992). Once an animal has been trained to self-administer the drug, the influences of drug priming, stressors, or presentation of drug-associated cues on drug self-administration behavior or relapse to extinguished drug-seeking behavior provide useful measures for studying drug taking or relapse (Shalev et al., 2002).

Drug-Induced Conditioned Place Preferences

Another experimental animal model for exploring the rewarding effects of drugs of abuse is the CPP procedure. A distinctive environment (e.g., one compartment of a two- or three-compartment apparatus) is paired repeatedly with the administration of a drug, and a different environment is repeatedly associated with the administration of vehicle. CPP occurs when repeated administration of a drug in this particular environment results in the ability of that environment to elicit approach behavior and increased time contact (place preference) in the absence of the previously administered drug. It has been argued that CPP, like drug self-administration and a number of related phenomena, is an example of dopamine-mediated incentive learning and that

the approach behavior and increased time spent by animals in a drug-paired environment can be considered a measure of drug-seeking behavior (Bardo and Bevins, 2000; Le Foll and Goldberg, 2004a). CPP have been demonstrated for most drugs of abuse, as well as natural rewards such as food. The acquisition of a drug-induced CPP is likely to reflect the rewarding properties of a drug of abuse, whereas its expression reflects the influence on behavior of environmental stimuli previously associated with a drug's effects.

Effects of CB$_1$ Blockade on Effects of Drugs of Abuse

Δ^9-Tetrahydrocannabinol

Since the development of a rodent model of Δ^9-THC self-administration has so far been unsuccessful (Tanda and Goldberg, 2003), the drug discrimination model has been widely used to study cannabinoid effects in animals. Animals can learn to reliably discriminate Δ^9-THC from vehicle, and the cannabinoid CB$_1$ antagonist SR141716 produces reversible, dose-dependent antagonism of the discriminative stimulus effects of Δ^9-THC in rats (Wiley et al., 1995; Jarbe et al., 2001; Solinas et al., 2003) and monkeys (Wiley et al., 1995). When SR141716 was administered alone, it did not substitute for Δ^9-THC in rats (Wiley et al., 1995). Moreover, in humans, SR141716 (Rimonabant) was also able to block subjective effects induced by Δ^9-THC (Huestis et al., 2001). This selective cannabinoid antagonist also precipitated a withdrawal syndrome in cannabinoid-dependent animals (Tanda et al., 1999; Maldonado and Rodriguez de Fonseca, 2002). The precipitation of a physical withdrawal syndrome by SR141716 was associated with a reduction of dopamine levels in the shell of the nucleus accumbens in cannabinoid-dependent rats, but no such effects were found after the administration of SR141716 to saline-control rats (Tanda et al., 1999). Recently, a squirrel monkey model of Δ^9-THC intravenous self-administration has been developed (Tanda et al., 2000; Justinova et al., 2003). SR141716 almost entirely blocked the self-administration of Δ^9-THC in squirrel monkeys under an FR10 schedule of reinforcement (Tanda et al., 2000). These results suggest that blockade of cannabinoid CB$_1$ receptors may block both the subjective and rewarding effects of Δ^9-THC in humans.

Opiates

Functional interactions between cannabinoid and opioid neurotransmitter systems that are implicated in drug reinforcement/reward processes (Navarro et al., 2001; De Vries et al., 2003; Solinas et al., 2003) have been described previously (Manzanares et al., 1999). Notably, the discriminative (Solinas et al., 2004) and rewarding/reinforcing (Chen et al., 1990; Justinova et al., 2004) effects of Δ^9-THC are reversed by treatment with the opioid receptor antagonists naloxone and naltrexone. Selective μ-opioid receptor invalidation in mice also reduced the rewarding effects of Δ^9-THC, as assessed by the conditioned place preference procedure (Ghozland et al., 2002). These effects seem specific to the rewarding/reinforcing effects of Δ^9-THC, since naltrexone, an opiate antagonist, did not block the subjective effects of Δ^9-THC administration in humans (Wachtel and de Wit, 2000; Haney et al., 2003). Conversely, several studies have evaluated cannabinoid system modulation of the reinforcing effects of opiates. SR141716 treat-

ment prevented the development of morphine-induced CPP (Chaperon et al., 1998), and cannabinoid CB$_1$ receptor knockout mice did not self-administer morphine (Cossu et al., 2001) or develop morphine-induced CPP (Martin et al., 2000). In agreement, blockade of cannabinoid CB$_1$ receptors by SR141716 markedly reduced responding for intravenous heroin injections under an FR5 schedule of reinforcement and to a greater extent under a progressive ratio schedule of reinforcement in rats (De Vries et al., 2003; Solinas et al., 2003). The cannabinoid CB$_1$ receptor agonist HU-210 reinstated heroin-seeking behavior following a 2-week extinction period, whereas SR141716 dose-dependently attenuated heroin seeking produced by a priming injection of heroin or re-exposure to heroin-associated stimuli (De Vries et al., 2003). Although SR141716 markedly decreased responding for heroin by rats under a progressive ratio schedule across a wide range of heroin doses, it had little effect on responding for food under a similar progressive ratio schedule (Solinas et al., 2003). In contrast to effects under the progressive ratio schedule, when responding was continuously reinforced under an FR1 schedule, SR141716 only reduced responding for low 12.5- and 25-μg/kg injection doses of heroin. The fact that heroin self-administration was affected in a different manner under these schedules is consistent with a behavioral economic analysis (Bickel et al., 2000), where the price of drug is considered to be the amount of effort (ratio size) required to obtain a fixed amount of drug. Thus, the effects of SR141716 on drug self-administration were more pronounced under a progressive ratio schedule of reinforcement (high price of drug), weaker under an FR5 schedule of self-administration (lower price of drug), and null under an FR1 schedule of self-administration of heroin or cocaine injections (very low price of drug). The effectiveness of cannabinoid CB$_1$ receptor blockade seems to depend on the price of the drug, with self-administration at high drug prices being notably sensitive to disruption. It is interesting to note that SR141716 did not modify the dopamine-releasing effect of heroin in the nucleus accumbens (Tanda and Di Chiara, 1997; Caille and Parsons, 2003).

Psychostimulants (Cocaine-Amphetamine)

Several experiments do not support, at first sight, an involvement of cannabinoid systems in the reinforcing effects of psychostimulants. CB$_1$ receptor-deficient mice learned to self-administer cocaine and amphetamine, as did their wild-type littermate controls (Cossu et al., 2001). Moreover, SR141716 administration did not interfere with cocaine self-administration in rats (De Vries et al., 2001) or monkeys (Tanda et al., 2000) trained under fixed ratio schedules of reinforcement (Fig. 1). This lack of effect of SR141716 did not reflect an insufficient dosage, since the doses of SR141716 tested were able to dramatically reduce Δ^9-THC self-administration in monkeys (Tanda et al., 2000) (Fig. 1). In contrast, AM-251, another CB$_1$ receptor antagonist, decreased the frequency of methamphetamine self-administration under a fixed ratio schedule in rats (decreased drug intake), whereas anandamide and R-methanandamide, two cannabinoid receptor agonists, tended to increase the frequency of methamphetamine self-administration (Vinklerova et al., 2002). SR141716 was also effective in blocking the acquisition, but not the expression, of cocaine-induced CPP (Chaperon et al., 1998). However, CB$_1$ receptor invalidation did not prevent the development of cocaine-induced CPP (Martin et al., 2000). These studies suggest a weak modulatory role of en-
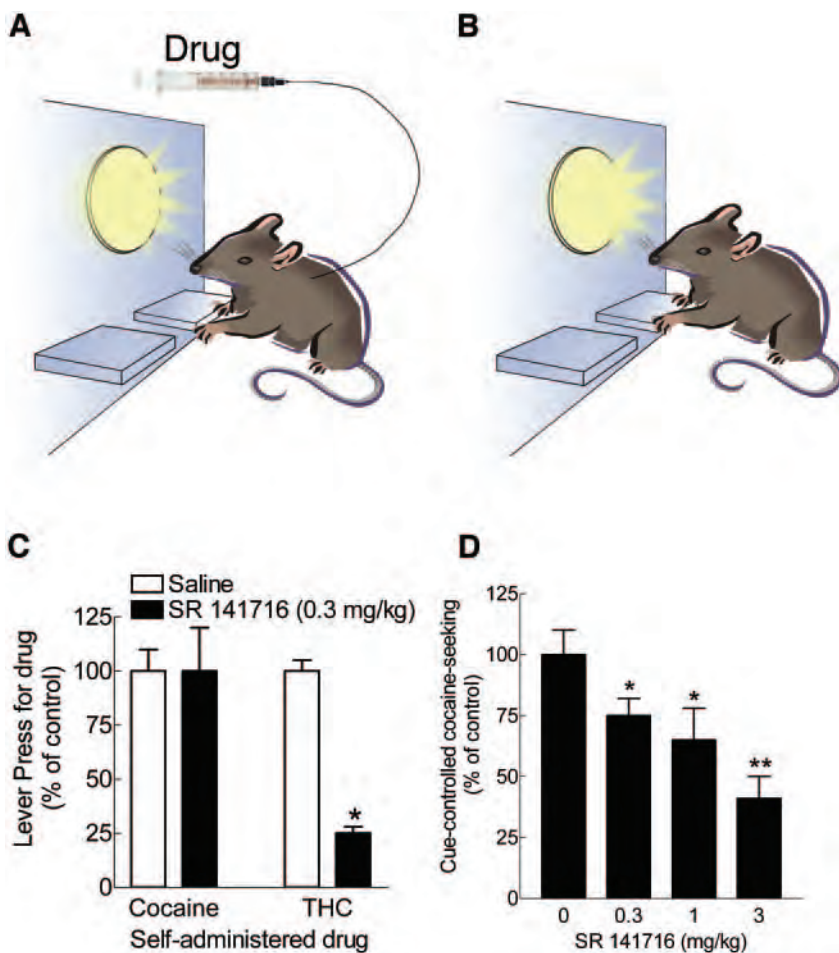
Fig. 1. SR141716 affects relapse in intravenous drug-self-administration studies. A, during repeated sessions, animals learned to press a lever to obtain intravenous injections of drug, and a brief light stimulus was associated with each drug injection. Through Pavlovian conditioning processes, this light stimulus progressively gained motivational properties. B, presentations of the brief light stimulus subsequently maintained drug-seeking behavior, even without drug delivery. C, SR141716 administration decreased Δ^9-THC self-administration, but not cocaine self-administration, in monkeys trained under an FR10 schedule of intravenous drug injection. Adapted from Tanda et al. (2000). D, SR141716 also did not affect cocaine self-administration in rats (data not shown), but it dose-dependently reduced relapse to cocaine-seeking behavior produced by cocaine-associated stimuli ("cues"). Adapted from De Vries et al. (2001).

docannabinoids on intake and, perhaps, on the rewarding/reinforcing effects of psychostimulants. The influence of the cannabinoid system on relapse has been demonstrated more clearly (De Vries et al., 2001). SR141716 reduced relapse to cocaine-seeking behavior produced by cocaine-paired stimuli (cues) (De Vries et al., 2001) (Fig. 1), whereas HU-210, a CB_1 receptor agonist, precipitated relapse to cocaine-seeking behavior (De Vries et al., 2001). Blockade of CB_1 receptors by SR141716 also was able to block relapse to cocaine-seeking behavior produced by a priming injection of cocaine but not by environmental stressors (De Vries et al., 2001). Likewise, SR141716 blocked the reinstatement of methamphetamine-seeking behavior in rats (Anggadiredja et al., 2004). Further experiments are needed to clarify the involvement of endogenous cannabinoid systems in the rewarding/reinforcing effects of psychostimulants.

Ethanol

Although the sites of actions for ethanol's effects in the brain are poorly understood, ethanol's reinforcing effects seem to involve dopamine pathways (Tabakoff and Hoffman, 1996). Recent evidence suggests that some of the pharmacological and behavioral effects of ethanol may also be mediated by endocannabinoid systems (Hungund et al., 2002). The expression of cannabinoid CB_1 receptors and their coupling to G proteins, as shown by the guanosine $5'$-O-(3-[^{35}S]thio)triphosphate binding assay, seems to be different between alcohol-preferring and -avoiding mice (Hungund

and Basavarajappa, 2000; Basavarajappa and Hungund, 2001). The pharmacological results obtained with SR141716 have been more pronounced with ethanol than with opiates and psychostimulants. Blockade of cannabinoid CB_1 receptors reduced alcohol intake (Arnone et al., 1997; Colombo et al., 1998; Rodriguez de Fonseca et al., 1999; Rinaldi-Carmona et al., 2004). The oral consumption of beer by rats, as assessed by a lick-based progressive ratio procedure, was decreased by CB_1 receptor blockade and increased by CB_1 receptor stimulation (Gallate and McGregor, 1999; Gallate et al., 1999, 2004). These effects have been reproduced in mice (Poncelet et al., 2003). The involvement of cannabinoid CB_1 receptors in the reinforcing/rewarding effects of ethanol is further indicated by findings that ethanol consumption is reduced in CB_1 receptor-deficient mice (Hungund et al., 2003; Poncelet et al., 2003; Naassila et al., 2004) and that the effects of SR141716 are abolished in these CB_1 receptor-deficient mice (Poncelet et al., 2003). Moreover, CB_1 receptor invalidation reduces ethanol-induced CPP (Houchi et al., 2004). All of these converging findings suggest that cannabinoid CB_1 receptor blockade may be an effective approach to the treatment of alcohol dependence in humans.

Nicotine

Nicotine and Δ^9-THC (in the form of marijuana) are often used in combination by humans. Several interactions have been described between nicotine and Δ^9-THC in animals (Valjent et al., 2002). Notably, the rewarding effects of these

two drugs measured by the CPP paradigm were additive when administered together; subthreshold doses of nicotine and Δ^9-THC, which were ineffective in inducing CPP by themselves, induced significant CPP when given together (Valjent et al., 2002). Interestingly, the cannabinoid CB_1 receptor antagonist SR141716 decreased nicotine self-administration in rats (Cohen et al., 2002), and nicotine was not able to induce conditioned place preferences in CB_1 receptor-deficient mice compared with their wild-type littermates (Castane et al., 2002). In contrast, CB_1 receptor knockout mice did seem to learn to self-administer nicotine (Cossu et al., 2001), suggesting that some of the actions of nicotine are not affected by cannabinoid CB_1 receptor blockade. Blockade of CB_1 receptors by SR141716 also did not block the discriminative stimulus effects of a high 0.4-mg/kg training dose of nicotine in one study (Cohen et al., 2002) and failed to change the discriminative stimulus effects of doses of nicotine ranging from 0.01 to 0.6 mg/kg in another study (Le Foll and Goldberg, 2004b). Interestingly, SR141716 dose-dependently blocked the dopamine-releasing effects of nicotine in the nucleus accumbens (Cohen et al., 2002) and the dopaminergic component of the nicotine discrimination (Cohen et al., 2002).

Since dopamine release in the nucleus accumbens is thought to play a major role in the positive reinforcing effects of nicotine, these findings support a role for cannabinoid CB_1 receptors in modulating the rewarding/reinforcing effects of nicotine.

The maintenance of nicotine self-administration behavior in rats and monkeys often seems to critically depend on associated environmental stimuli (Goldberg et al., 1981; Caggiula et al., 2001; Cohen et al., 2004), and persistent effects of conditioned environmental stimuli previously associated with the effects of nicotine in tobacco may be a major determinant of relapse to smoking behavior in exsmokers. Acute administration of SR141716 blocks the expression of nicotine-induced conditioned place preferences in rats (Le Foll and Goldberg, 2004b) (see Fig. 2) and the influence of environmental stimuli on nicotine-seeking behavior (Cohen et al., 2004). These findings suggest that cannabinoid CB_1 receptor blockade reduced the effectiveness of conditioned motivational stimuli associated with nicotine injection. In agreement with this hypothesis, SR141716 administration has been shown to reduce intravenous nicotine self-administration behavior in rats (Cohen et al., 2002).
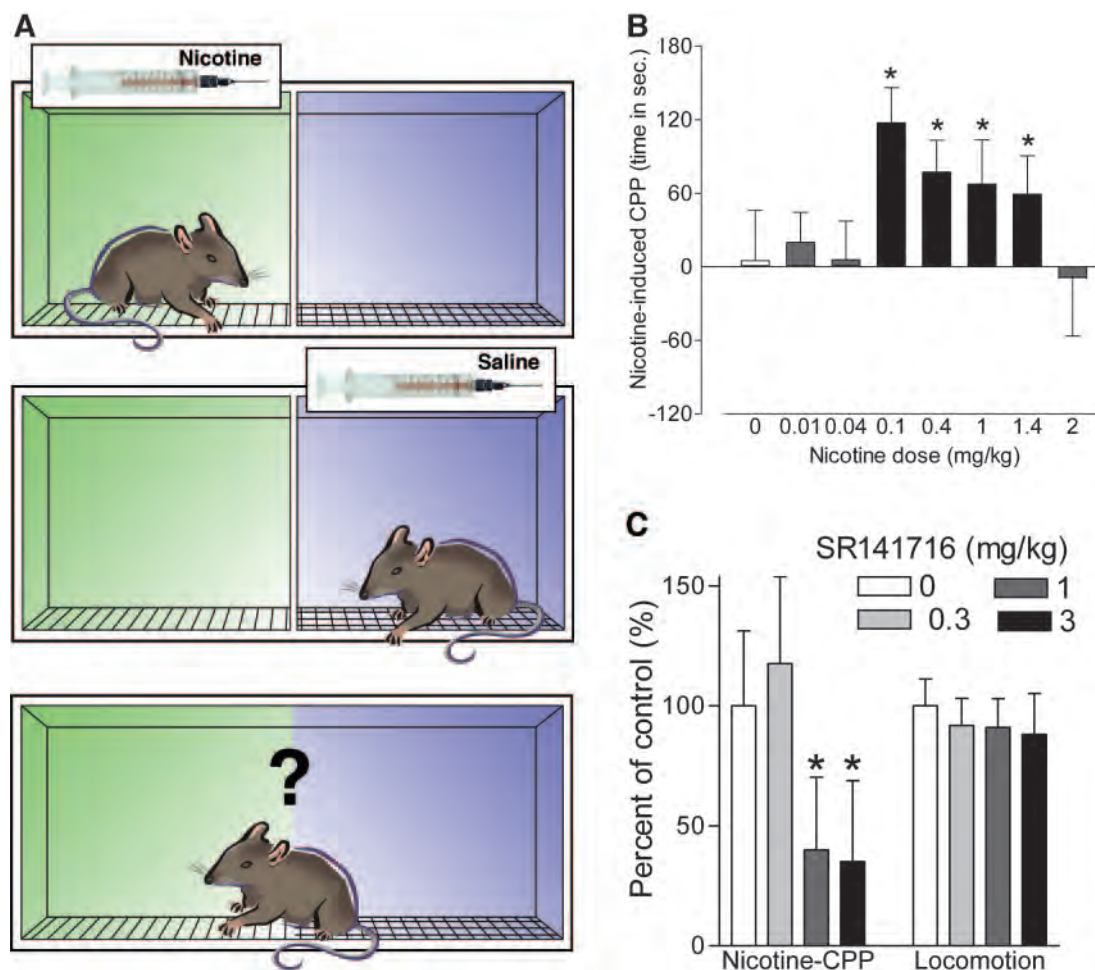

Fig. 2. SR141716 administration blocks nicotine-induced CPP. A, to induce CPP, a box with two discrete chambers, or environments, is used. Rats are repeatedly injected with nicotine before being placed in one environment and with saline before being placed in the other environment. Then, in a nicotine-free state, the animals are allowed access to both environments, and the amount of time spent in each environment is recorded. Adapted from Cami and Farre (2003) B, nicotine is able to induce significant conditioned place preferences over a large range of doses in rats. Results are expressed as the difference in time in seconds spent in the drug-paired side between the post- and preconditioning session. *, $P < 0.05$. Adapted from Le Foll and Goldberg (2004a). C, when SR141716 was administered acutely before the test session, it blocked the nicotine-induced conditioned place preference without interfering with the rat's locomotor activity. From Le Foll and Goldberg (2004b).

In human smokers, preliminary data from the STRATUS-US trial (smoking cessation in smokers motivated to quit) on the effects of SR141716 are promising (Anthenelli and Despres, 2004). This clinical study enrolled 787 smokers in 11 clinical trial sites in the United States. The participants were randomized to Rimonabant at a dose of 5 mg ($n = 262$) or 20 mg ($n = 261$) or a placebo. The study lasted 10 weeks, and the smokers were permitted to smoke during the first 2 weeks but were asked to abstain from smoking after this period. The quit rates for subjects in the 20-mg Rimonabant group were double that of the placebo group, and they showed a marked reduction in weight gain over the 10-week treatment (Anthenelli and Despres, 2004).

Neurobiological Pathways Affected by CB$_1$ Blockade

The mechanisms underlying the effects of CB$_1$ blockade on drug-induced reinforcement/reward and relapse to drug-seeking behavior remain unknown. Interestingly, SR141716 has been reported to block dopamine elevations in the nucleus accumbens produced by nicotine (Cohen et al., 2002) and Δ^9-THC (Tanda et al., 1997), and SR141716 is effective in decreasing the intravenous self-administration of these two drugs (Tanda et al., 1997; Cohen et al., 2002). In contrast, SR141716 is ineffective in blocking the dopamine-releasing effect of opiates in the nucleus accumbens (Tanda and Di Chiara, 1997) and is also ineffective in blocking opiate self-administration when the opiate is continuously available under an FR1 schedule of reinforcement (De Vries et al., 2003; Solinas et al., 2003). Further studies evaluating the effects of cannabinoid CB$_1$ receptor blockade on the dopamine-releasing effects of ethanol and cocaine are needed to confirm the putative relation between blockade of the dopamine-releasing effect of a drug in the nucleus accumbens and blockade of its reinforcing effects with self-administration procedures.

Environmental stimuli associated with drug self-administration can also produce dopamine elevations in the nucleus accumbens (Ito et al., 2000), and it is possible that SR141716 would also block such conditioned elevations in dopamine levels, which could result in a decreased efficacy of drug-paired stimuli and therefore reduce the tendency to relapse (De Vries et al., 2001, 2003; Cohen et al., 2004; Le Foll and Goldberg, 2004b). It is also likely that drug-priming effects that lead to relapse to drug-seeking behavior may be mediated through elevation of dopamine levels (Phillips et al., 2003). Further studies are needed to confirm the role of blockade of dopamine transmission in the behavioral effects of SR141716.

It is interesting to note that a profile similar to that described above with cannabinoid CB$_1$ receptor antagonists has been described with dopamine D$_3$ receptor ligands, which also reduce drug-seeking behavior induced by drug-associated stimuli (Pilla et al., 1999; Di Ciano et al., 2003) and block drug-induced conditioning processes (Le Foll et al., 2000, 2002, 2003a,b, 2004b; Vorel et al., 2002; Francès et al., 2004) but do not alter cocaine self-administration at a low fixed ratio value (Pilla et al., 1999). Some effects of SR141716 are diminished in dopamine D$_3$ receptor-deficient mice (Duarte et al., 2003), suggesting that dopamine D$_3$ receptors are involved in CB$_1$ receptor-mediated processes. Since dopamine D$_3$ receptors and cannabinoid CB$_1$ receptors are both expressed in the mesolimbic dopamine brain reward circuit (Mailleux and Vanderhaeghen, 1992; Diaz et al., 2000; Le Foll et al., 2002, 2003a,b), these two types of receptors may control the dopamine-releasing effect of drug-associated cues. These effects are probably mediated through the ventral tegmental area, the nucleus accumbens, or the amygdala (Le Foll et al., 2002, 2004a). An increase of monoaminergic neurotransmission in the medial prefrontal cortex may also be implicated in these behavioral effects (Lacroix et al., 2003; Tzavara et al., 2003).

Since cannabinoid CB$_1$ receptors are widely expressed throughout the brain, it seems likely that several different neurotransmitter systems are affected by cannabinoid CB$_1$ receptor blockade (Howlett et al., 2002). For example, CB$_1$ receptors are expressed in areas of the hypothalamus known to regulate appetite (Schwartz et al., 2000; Cota et al., 2003). Blockade of cannabinoid CB$_1$ receptors seems to decrease appetite and food intake, and CB$_1$ receptor antagonists are promising new medications for obesity (Black, 2004). Furthermore, blockade of cannabinoid CB$_1$ receptors by SR141716 prevents the development of food-induced CPP (Chaperon et al., 1998). Nevertheless, the neurobiological mechanisms underlying these effects are still unclear and may also involve dopaminergic transmission (Duarte et al., 2003). Further work is needed to determine whether similar or different neurotransmitter systems are involved in the effects of cannabinoid CB$_1$ receptor blockade on appetite and drug-seeking behavior.

Cannabinoid CB$_1$ Receptor Blockade: A Step Forward in Drug-Dependence Therapy?

Despite advances in the understanding of neurobiological and behavioral mechanisms that lead to drug dependence over the last 20 years, no effective treatment is yet available for cocaine or Δ^9-THC dependence. Moreover, medications available for ethanol, nicotine, or opioid dependence are ineffective in many subjects. For example, the rate of smoking cessation by subjects entering into clinical trials that combine effective medication and behavioral and cognitive therapy is around 30% at one year; most subjects relapse (Fiore, 2000). Cannabinoid CB$_1$ receptor antagonists represent a potentially useful tool not only for blocking the direct reinforcing effects of Δ^9-THC, nicotine, and ethanol, but also for preventing relapse to the use of various drugs of abuse, including cocaine, methamphetamine, and heroin. In addition, environmental stimuli seem to be one of the major factors that can trigger relapse to drug use in abstinent drug abusers. This process is not only critical for psychostimulant abuse, but also for nicotine and heroin abuse (Wikler, 1973; Childress et al., 1992; O'Brien et al., 1992, 1998), and probably for other drugs of abuse such as ethanol. By reducing the motivational effects of drug-related environmental stimuli, cannabinoid CB$_1$ receptor antagonists might, therefore, provide an effective means for preventing relapse to drug-seeking behavior in abstinent drug abusers, providing a promising new tool for the treatment of dependence on a wide range of abused drugs.

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Involvement of the endocannabinoid system in drug addiction

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Recent studies have shown that the endocannabinoid system is involved in the common neurobiological mechanism underlying drug addiction. This system participates in the primary rewarding effects of cannabinoids, nicotine, alcohol and opioids, through the release of endocannabinoids in the ventral tegmental area. Endocannabinoids are also involved in the motivation to seek drugs by a dopamine-independent mechanism, demonstrated for psychostimulants and opioids. The endocannabinoid system also participates in the common mechanisms underlying relapse to drug-seeking behaviour by mediating the motivational effects of drug-related environmental stimuli and drug re-exposure. In agreement, clinical trials have suggested that the CB$_1$ cannabinoid antagonist rimonabant can cause smoking cessation. Thus, CB$_1$ cannabinoid antagonists could represent a new generation of compounds to treat drug addiction.

Introduction

Drug addiction is a chronic relapsing brain disorder, characterized by neurobiological changes leading to compulsive drug seeking and drug taking despite serious negative consequences, and by loss of control over drug use [1]. Addiction includes complex behavioural and neurobiological processes. All the drugs of abuse produce reinforcing effects that are responsible for the initiation of the addictive disorder. However, other behavioural processes are also crucial for the maintenance of addiction, including the negative consequences of drug abstinence and the different stimuli leading to relapse (e.g. drug-associated cues, stressors and drug re-exposure) [2].

Several groups of compounds that produce different pharmacological effects can lead to addictive behaviour, including opioids, psychostimulants, cannabinoids, alcohol and nicotine. The initial mechanism of action of these drugs implicates different neurochemical targets [3]. However, all these compounds produce neural dysregulations involving similar neurochemical and neuroanatomical pathways [4]. Indeed, multiple studies support the existence of common neurobiological mechanisms for the addictive properties of most drugs of abuse. This information is based on findings showing the crucial role of the mesocorticolimbic dopaminergic pathways, the

endogenous opioid system, and the brain and pituitary stress system in the addictive processes. Drugs of abuse interact with these common brain circuits producing adaptive changes leading to a profound dysregulation of brain motivational and reward pathways [2]. The mesocorticolimbic system represents a common neuronal substrate for the reinforcing properties of drugs of abuse, where both dopamine and opioid transmission are crucial [5]. The major components of this drug reward circuit are the ventral tegmental area (VTA), which contains the dopaminergic cell bodies, and the terminal areas in the basal forebrain [the nucleus accumbens (NAc), olfactory tubercle, amygdala, and frontal and limbic cortices] [6]. These neurochemical circuits are also involved in the negative motivational consequences of drug withdrawal [2]. Mesolimbic dopaminergic neurons receive highly processed information from the cerebral cortex and other areas involved in cognitive functions, and dopamine release in the forebrain has been proposed to serve as a learning signal. Dopamine neurons in the NAc interact with glutamatergic projection neurons from the cerebral cortex, hippocampus and amygdala, providing information about external context and about internal emotional and physiological states. Hence, drug-induced plasticity in these NAc projections contributes to addiction by consolidating reward-driven behaviour [3,7]. Recruitment of brain stress pathways has also been reported as a common change during drug abstinence that seems be crucial in the reinstatement of drug seeking behaviour [8]. However, the common mechanisms involved in the development of the addictive processes have not been yet completely identified. This review focuses on the recent findings supporting participation of the endocannabinoid system in the common circuitry underlying drug addiction and proposes a mechanistic explanation for this physiopathological role.

Endocannabinoid system and brain reward circuitry

Knowledge of the endocannabinoid system has been largely improved since the cloning in 1990 of the CB$_1$ cannabinoid receptor, which is activated by Δ^9-tetrahydrocannabinol (THC), the main psychoactive component of *Cannabis sativa*. This system consists of cannabinoid receptors, endogenous ligands and several proteins responsible for their synthesis and degradation. To date, two subtypes of cannabinoid receptors, CB$_1$ and CB$_2$, have been characterized and cloned. CB$_1$ receptors are the most

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abundant G-protein-coupled receptor in the CNS and are also found in peripheral tissues. CB_2 receptors are mainly located in the cells of the immune system [9], but they have also been recently identified in brainstem, cortex and cerebellum neurons [10]. Several endogenous cannabinoids have been isolated from brain tissue, anandamide and 2-arachidonoylglycerol being the best characterized [9]. Endocannabinoids are thought to act as retrograde messengers in the CNS [11] and behave as neuromodulators in many physiological processes. Accordingly, endocannabinoids released from postsynaptic neurons upon depolarization activate presynaptic CB_1 cannabinoid receptors, resulting in inhibition of the release of both excitatory and inhibitory neurotransmitters. This endocannabinoid retrograde control has also been recently demonstrated after synaptic activation of group I metabotropic glutamate receptors [12] and D_2 dopamine receptors [13].

Several studies support the view that the endocannabinoid system represents a new candidate for the control of drug rewarding properties. Indeed, CB_1 cannabinoid receptors are abundant in the brain reward circuitry and participate in the addictive properties induced by different drugs of abuse. The dopaminergic neurons of the mesocorticolimbic pathway are controlled by excitatory and inhibitory inputs that are modulated by CB_1 cannabinoid receptors. Thus, endocannabinoids can be released following depolarization in the NAc [14] and from dopaminergic neurons in the VTA [13,15], and they modulate glutamatergic and GABAergic afferents by acting as retrograde messengers on CB_1 receptors. The presence of CB_1 receptors in other structures related to motivation and reward, such as the basolateral amygdala and the hippocampus, also contributes to this function of the endocannabinoid system [16]. In addition, endocannabinoids participate in synaptic plasticity in the mesolimbic system. The stimulation of prelimbic cortex afferents causes long-term depression (LTD) of NAc glutamatergic synapses that is mediated by endocannabinoid release and presynaptic CB_1 receptors [14,17]. Endocannabinoids also produce LTD of inhibitory synaptic transmission in the hippocampus and prepare excitatory synapses for facilitating subsequent induction of long-term potentiation (LTP) [18], which contributes to the plasticity mechanisms reported in the learning processes related to addictive behaviour.

The endocannabinoid system is certainly the primary site of action for the rewarding and pharmacological responses induced by cannabinoids [19,20]. However, this system plays an overall modulatory effect on the reward circuitry and also participates in the rewarding and addictive properties of all prototypical drugs of abuse.

Endocannabinoid system and nicotine addiction

Nicotine addiction is a complex neurochemical process that involves many neurotransmitters, and the endocannabinoid system is crucial in the addictive effects of this drug. Pharmacological studies revealed that non-effective doses of nicotine and THC produced significant conditioned place preference in mice when administered together [21]. Interestingly, the rewarding properties of nicotine, assessed in a place-conditioning paradigm, were absent in knockout mice lacking CB_1 receptors [22] (Table 1). By contrast, CB_1 knockout mice learned to self-administer nicotine using an acute paradigm in mice that were restrained to avoid their movement [23]. However, this acute paradigm fails to evaluate the maintenance of a stable operant self-administration response, and nicotine effects on anxiety-like behaviour could influence this self-administration response in restrained animals [23]. Pharmacological studies using the selective CB_1 receptor antagonist rimonabant (Box 1) have confirmed the involvement of these receptors in nicotine addiction (Table 2). Thus, rimonabant reduces

Table 1. Changes to the addictive properties of drugs observed in CB_1 cannabinoid receptor knockout mice

Drug	Model	Effect	Refs
Morphine	Conditioned place preference	Suppression	[45]
		No change	[46]
	Behavioural sensitization	Suppression	[45]
	Self-administration in restrained mice	Suppression	[19]
		Suppression	[23]
	Withdrawal syndrome	Attenuation	[19]
		Attenuation	[79]
Ethanol	Conditioned place preference	Attenuation	[40]
	Two-bottle choice (voluntary consumption)	Attenuation	[37]
		No change	[41]
		Attenuation	[38]
		Attenuation	[34]
	Withdrawal syndrome	Suppression	[41]
		Increase	[38]
	Extracellular dopamine levels (*in vivo* microdialysis)	Suppression	[37]
Nicotine	Conditioned place preference	Suppression	[22]
	Self-administration in restrained mice	No change	[23]
	Withdrawal syndrome	No change	[22]
Cocaine	Conditioned place preference	No change	[45]
		No change	[40]
	Behavioural sensitization	No change	[45]
	Self-administration in restrained mice	No change	[23]
	Self-administration	Attenuation	[63]
	Extracellular dopamine levels (*in vivo* microdialysis)	No change	[63]
Amphetamine	Self-administration in restrained mice	No change	[23]

nicotine operant self-administration [24] and nicotine-induced conditioned place preference in rats [25], although no effect was observed when nicotine place preference was evaluated 3 or 12 weeks after the initial conditioning phase [26]. Nicotine relapse induced by associated environmental stimuli is also mediated by activation of the endocannabinoid system. Thus, rimonabant attenuated the influence of these environmental stimuli on nicotine-seeking behaviour in rats [27,28]. CB_1 receptors do not seem to participate in the development of nicotine physical dependence because rimonabant did not precipitate a withdrawal syndrome in nicotine-dependent mice [29] and the severity of nicotine abstinence was not modified in CB_1 knockout mice [22]. The effects of the endocannabinoid system on the rewarding properties of nicotine are related to modulation of the extent to which nicotine activates the mesolimbic dopaminergic pathway. Thus, *in vivo* microdialysis studies revealed that rimonabant pre-treatment blocks nicotine-enhanced extracellular dopamine levels in the shell of the NAc and in the bed nucleus of the stria terminalis [24]. In agreement with these behavioural and biochemical results in rodents, Phase III clinical trials have revealed that rimonabant is significantly effective in obtaining smoking cessation

[Studies with Rimonabant and Tobacco Use in North America (STRATUS-North America)] and can produce a strong tendency for such cessation in a population with a more intense daily tobacco consumption (STRATUS-Europe) [30]. These results suggest that CB_1 cannabinoid receptors represent a promising target for new therapies to treat tobacco addiction.

Endocannabinoid system and alcohol addiction

Cannabinoids and alcohol activate similar reward pathways, and CB_1 receptors also seem to regulate the reinforcing properties of alcohol. Thus, the acute administration of cannabinoid agonists stimulates voluntary alcohol intake in Sardinian alcohol-preferring (sP) and Wistar rats [31,32]. In agreement, blockade of CB_1 receptors reduces alcohol consumption in C57BL/6 mice, and in Wistar and sP rats [33–35] (Table 2). However, part of this effect can be attributed to a more general suppression of food and fluid intake [36]. Genetic inactivation of CB_1 receptors has confirmed these pharmacological data (Table 1). Thus, a decrease of voluntary alcohol intake in CB_1 knockout mice has been shown using a two-bottle free-choice paradigm [34,37–39], and ethanol-induced place preference was reduced in these mutants [39,40]. A role of CB_1 receptors in stress-induced alcohol drinking and ethanol withdrawal has also been reported using knockout mice [41], although the same study showed normal ethanol drinking behaviour under non-stressful conditions in these animals. CB_1 receptors are also involved in the mechanisms mediating alcohol relapse. Accordingly, the exposure to the cannabinoid agonists WIN 55 212-2 (Box 1) or THC promotes the relapse of alcohol use in abstinent rats [42,43], and rimonabant reduces conditioned reinstatement of

Table 2. Effects of rimonabant on drug addictive properties

Drug	Model	Dose (mg kg^{-1})[a]	Effect	Animal	Refs
Morphine	Conditioned place preference	0.1 (ip)	Attenuation	Rat	[80]
		3.0 (ip)	Suppression	Rat	[47]
	Self-administration	0.25 (ip)	Suppression	Rat	[47]
Heroin	Self-administration	3.0 (ip)	Suppression	Rat	[47]
		3.0 (ip)	Suppression	Rat	[81]
		0.3–3.0 (ip)	Attenuation	Rat	[82]
		1.0 and 3.0 (ip)	Attenuation	Rat	[48]
	Self-administration (relapse)	0.3 (ip)	Suppression	Rat	[50]
		1.0 and 3.0 (ip)	Attenuation	Rat	[48]
	Extracellular dopamine levels (*in vivo* microdialysis)	0.3–3.0 (ip)	No change	Rat	[82]
		1.0 (sc)	No change	Rat	[53]
Ethanol	Two-bottle choice (voluntary consumption)	0.3–3.0 (sc)	Attenuation	Rat, mouse	[33]
		2.5–10.0 (ip)	Attenuation	Rat	[83]
		0.3–3.0 (ip)	Attenuation	Rat	[84]
		3.0 (ip)	Attenuation	Mouse	[34]
	Self-administration	0.3–3.0 (ip)	Attenuation	Rat	[35]
	Self-administration (relapse)	1.0 and 3.0 (ip)	Attenuation	Rat	[35]
	Extracellular dopamine levels (*in vivo* microdialysis)	3.0 (ip)	Attenuation	Rat	[24]
		3.0 (ip)	Suppression	Mouse	[37]
Nicotine	Conditioned place preference	1.0 and 3.0 (ip)	Suppression	Rat	[25]
	Self-administration	0.3 and 1.0 (ip)	Attenuation	Rat	[24]
	Self-administration (relapse)	1.0 and 3.0 (ip)	Attenuation	Rat	[28]
		1.0 (ip)	Attenuation	Rat	[27]
	Extracellular dopamine levels (*in vivo* microdialysis)	1.0 and 3.0 (ip)	Attenuation	Rat	[24]
Cocaine	Self-administration in restrained mice	1.0 (ip)	No change	Mouse	[85]
	Self-administration	1.0–3.0 (ip)	Attenuation	Mouse	[63]
	Self-administration (relapse)	0.3–3.0 (sc)	Attenuation	Rat	[64]

[a]Abbreviations: ip, intraperitoneal; sc, subcutaneous.

ethanol-seeking behaviour in rats [35]. The endocannabi-noid system seems to participate in alcohol rewarding properties by modulating its effects on the activation of mesolimbic dopamine transmission. *In vivo* microdialysis studies revealed that alcohol did not enhance extracellular levels of dopamine in the NAc in CB_1 knockout mice [37]. A similar result was obtained when wild-type mice were pre-treated with rimonabant before alcohol administration [37]. Clinical data on the possible efficacy of CB_1 receptor antagonists in the treatment of alcohol addiction are not still available.

Endocannabinoid system and opioid addiction

Several studies have revealed the existence of functional bidirectional interactions between cannabinoid and opioid systems, and both systems participate in the common circuits involved in the addictive properties of different drugs of abuse [44]. CB_1 cannabinoid receptors have an important role in the rewarding properties of opioids. Thus, morphine-induced conditioned place preference [45] and intravenous self-administration [19] were abolished in knockout mice lacking CB_1 receptors, although contra-dictory results have been reported on the place-condition-ing paradigm [46] (Table 1). In agreement, rimonabant reduced opioid self-administration and conditioned place preference in rodents [47,48] (Table 2). The effects of rimonabant on heroin self-administration were more pronounced when the effort required to obtain a heroin infusion was enhanced. Indeed, rimonabant markedly impaired heroin self-administration under a progressive ratio (PR) schedule of reinforcement, whereas this effect was attenuated under a fixed ratio (FR) schedule of 5 and almost disappeared at a FR1 [49] (Box 2). Rimonabant also prevented heroin-seeking behaviour after a long period of extinction, and the cannabinoid agonist HU-210 (Box 1) reinstated such a seeking behaviour [48–50]. Reciprocally, the rewarding effects induced by THC were suppressed in μ-opioid receptor knockout mice [51], and were attenuated by the opioid receptor antagonist naltrexone in monkeys [52]. Both opioid and cannabinoid rewarding responses are related to their facilitatory effects on mesolimbic dopamine transmission [5]. Rimonabant did not prevent the activation of dopamine transmission induced by heroin, although the opioid receptor antagonist naloxone prevented such a biochemical effect from being produced by cannabinoids [53,54].

Cross-dependence has also been reported between opioid and cannabinoid compounds. Thus, naloxone induced a withdrawal syndrome in THC-dependent rats,

whereas rimonabant precipitated abstinence in morphine-dependent animals [55,56]. In agreement, a robust attenuation in the severity of naloxone-precipitated morphine withdrawal was reported in CB_1 knockout mice [19]. Reciprocally, the expression of cannabinoid withdrawal was decreased in knockout mice lacking the gene encoding pre-proenkephalin and in double knockout mice deficient in μ and δ opioid receptors [54]. Both opioid and cannabinoid withdrawal syndromes have been associ-ated with compensatory changes in the cAMP pathway. Thus, enhanced activity of several components of the cAMP pathways has been reported during opioid and cannabinoid abstinence, although different brain struc-tures are involved in these compensatory mechanisms [4,54]. Changes in the cAMP pathway occur mainly in the locus coeruleus and some limbic structures, such as the NAc, during opioid withdrawal, whereas these alterations were selectively located in the cerebellum in the case of cannabinoid withdrawal [4,54]. Changes to the mitogen-activated protein (MAP) kinases cascade seem to be another common compensatory modification during the development of opioid and cannabinoid physical depen-dence [57]. Therefore, the endocannabinoid system is crucial not only in opioid-induced rewarding effects, but also in development of physical dependence during chronic opioid administration. The existence of bidirec-tional interactions between the endogenous cannabinoid and opioid systems provides neurobiological support for this role of the endocannabinoid system.

Endocannabinoid system and psychostimulant addiction

The mechanism of action of psychostimulants differs from that of other drugs of abuse in that they affect the mesolimbic dopaminergic terminals directly. Indeed, psychostimulants enhance activity of dopaminergic neur-ons by directly acting on the reuptake of monoamines, binding to one or multiple monoamine transporters [58]. This mechanism is important for understanding the particular involvement of the endocannabinoid system in psychostimulant rewarding effects. Several behavioural responses induced by acute and chronic administration of psychostimulants were not modified in CB_1 knockout mice (Table 1). Interestingly, cocaine-induced conditioned place preference and locomotor behavioural sensitization were not modified in these mice [45]. These knockout mice also learned to self-administer cocaine and amphetamine when using an acute paradigm in restrained animals [23], and rimonabant did not interfere with cocaine self-administration in rats [48] or monkeys [59] trained under FR schedules of reinforcement (Table 2). These results indicate that CB_1 receptors are not involved in the primary reinforcing effects of psychostimulants. By contrast, rimonabant decreased the acquisition but not the expression of conditioned place preference to cocaine [60], whereas the CB_1 antagonist AM-251 (Box 1) decreased methamphetamine self-administration under a FR schedule in rats [61]. In addition, THC and cannabidiol facilitated the extinction of place preference induced by cocaine and amphetamine, although this effect was not reversed by rimonabant [62]. A recent study using

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Box 2. Technical terms

Breaking points: the maximal numbers of operant responses that the animal achieves in order to obtain an injection of the drug.

Fixed ratio (FR) schedule: a FR schedule of drug self-administration requires a fixed number of operant responses to obtain a drug injection. Such schedules are used mainly to evaluate the acquisition and maintenance of drug self-administration.

Progressive ratio (PR) schedule: in a PR schedule of drug self-administration, the response requirement to earn a drug injection escalates progressively during the session. This provides infor-mation about the reinforcing strength of the drug.
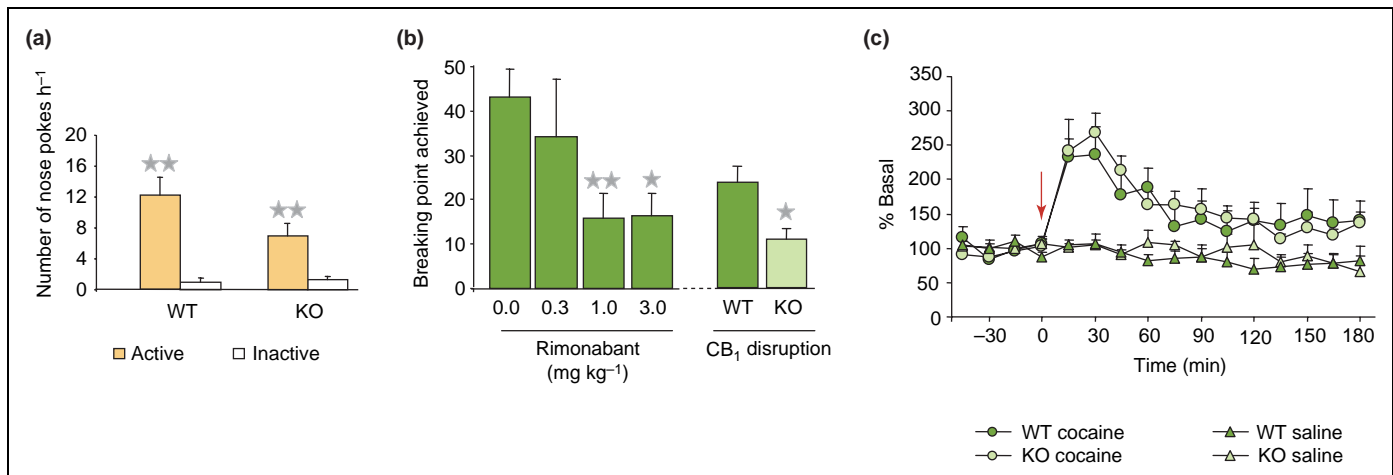
Figure 1. Suppression of CB_1 cannabinoid receptors impairs cocaine self-administration, but does not modify the effects of cocaine on extracellular dopamine levels in the nucleus accumbens (NAc). **(a)** CB_1 knockout (KO) and wild-type (WT) littermates self-administered cocaine (1 mg kg^{-1} per infusion) under a fixed ratio 1 schedule of reinforcement. Bars represent the average of the number of nose pokes into the active and inactive holes required to meet criteria for acquisition of the cocaine self-administration behaviour during three consecutive sessions. **(b)** Effects of rimonabant (0.3, 1.0 and 3.0 mg kg^{-1}, intraperitoneal administration) and genetic disruption of CB_1 receptors on the breaking points achieved under a progressive ratio schedule of reinforcement (Box 2). **(c)** Acute cocaine administration (20 mg kg^{-1}, intraperitoneal administration) enhanced extracellular dopamine levels in the NAc similarly in wild-type and CB_1 knockout mice. Effects on dopamine dialysate were determined by *in vivo* microdialysis from the NAc of wild-type and CB_1 knockout mice. The arrow indicates cocaine or saline administration at time 0. Values are expressed as mean $\pm$ SEM. One star indicates $P < 0.05$; two stars indicate $P < 0.01$. Adapted, with permission, from [63].

CB_1 knockout mice has provided new insights on these mechanisms [63]. Indeed, the acquisition of an operant response to self-administer cocaine was impaired in these mutants mainly when the effort required to obtain a cocaine infusion was enhanced. Thus, the breaking point achieved on a PR schedule of reinforcement was significantly reduced in CB_1 knockout mice, whereas self-administration behaviour was only slightly attenuated on a FR1 schedule (Figure 1). A similar result was obtained on the PR schedule after the blockade of these receptors using rimonabant in wild-type mice [63] (Figure 1). This impairment in cocaine self-administration indicates a decreased motivation for maintaining cocaine-seeking behaviour, providing a role for CB_1 receptors in consolidation of the psychostimulant addictive process. Furthermore, CB_1 receptors are also required to reinstate cocaine self-administration. Thus, the cannabinoid agonist HU-210 induced relapse to cocaine seeking after a prolonged withdrawal period, whereas rimonabant attenuated relapse induced by environmental cocaine-associated cues or cocaine re-exposure [64,65].

The precise mechanisms underlying the modulatory role of the endocannabinoid system on psychostimulant rewarding effects remain to be elucidated. These mechanisms seem to be independent from the activating effects on mesolimbic dopamine-mediated transmission. Thus, the enhancement of extracellular dopamine levels produced by cocaine in the NAc was not modified in CB_1 knockout mice [63] (Figure 1). Activation of the mesolimbic circuitry is essential for psychostimulants to induce feelings of reward, and CB_1 receptors are then not required to obtain the primary reinforcing effects of cocaine. Participation of CB_1 receptors in the motivation to maintain cocaine self-administration should therefore involve other neurochemical systems related to this complex addictive behaviour. Thus, amphetamine releases endocannabinoids in the amygdala to produce LTD by a dopamine-independent mechanism mediated by CB_1 receptors [66],

and these endocannabinoids participate in the synaptic plasticity produced by psychostimulants in mesocortico-limbic structures [67]. Hence, although the endocannabinoid system does not participate in the primary reinforcing effects of psychostimulants, it is important for maintaining psychostimulant seeking behaviour, probably by modulating synaptic processes induced by these drugs.

Mechanisms involved in modulation of the rewarding circuitry by endocannabinoids

CB_1 cannabinoid receptors are present in the different regions of the brain reward circuitry, including the VTA and the NAc, and also in several areas projecting to these two structures, such as the prefrontal cortex, central amygdala and hippocampus [68]. Acting as a retrograde messenger, endocannabinoids modulate the glutamatergic excitatory and GABAergic inhibitory synaptic inputs into the VTA and the glutamate transmission in the NAc (Figure 2). Thus, the activation of CB_1 receptors present on axon terminals of GABAergic neurons in the VTA would inhibit GABA transmission, removing this inhibitory input on dopaminergic neurons [15,69]. Glutamate synaptic transmission from neurons of the prefrontal cortex in the VTA and NAc is similarly modulated by the activation of CB_1 receptors [13,70]. The final effect on the modulation of VTA dopaminergic activity by endocannabinoids would depend on the functional balance between these inhibitory GABAergic and excitatory glutamatergic inputs, which are both inhibited by endocannabinoids under different physiological conditions.

The modulatory role of the endocannabinoid system on the primary rewarding effects of drugs of abuse might depend on endocannabinoid release in the VTA [69]. Thus, the endocannabinoid system seems to be involved in the primary rewarding effects of cannabinoids, opioids, nicotine and alcohol because these drugs increase dopaminergic neuron firing rates, thus making
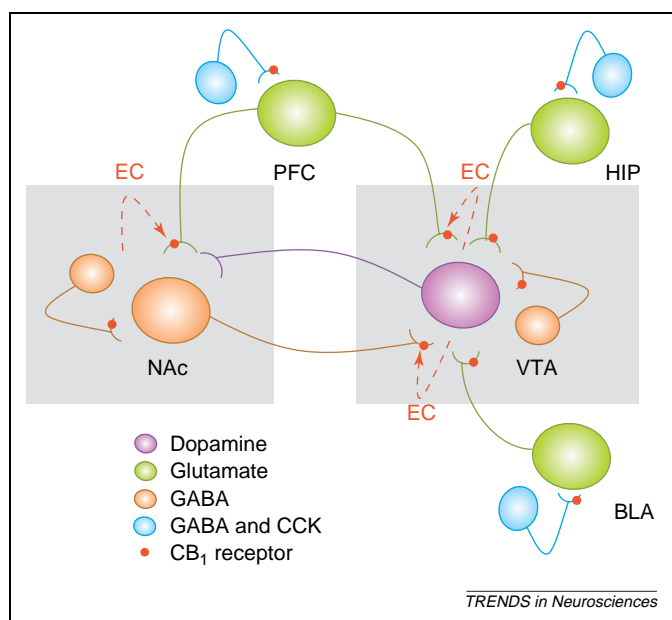
Figure 2. Possible sites of endocannabinoid action in modulation of drug rewarding effects. In the ventral tegmental area (VTA), CB_1 cannabinoid receptors are located on presynaptic glutamatergic and GABAergic neurons. By contrast, VTA dopaminergic neurons do not synthesize CB_1 cannabinoid receptors. Activation of CB_1 receptors in the VTA by endocannabinoids (EC; broken red arrows) produces inhibition of GABA release, thus removing the inhibitory effect of these GABAergic cells on dopaminergic neurons. In addition, the increase of dopaminergic neuron activity induces release from the dopaminergic cells of endocannabinoids that, acting in a retrograde manner on presynaptic CB_1 receptors, inhibit both inhibitory GABAergic and excitatory glutamatergic inputs to VTA dopaminergic neurons. Glutamatergic projections from the basolateral amygdala (BLA) and hippocampus (HIP), which are involved in motivation and memory processes related to drug rewarding effects, are also under the control of CB_1 receptors, through an inhibitory effect on presynaptic inhibitory neurons that release both GABA and cholecystokinin (CCK). In the nucleus accumbens (NAc), endocannabinoids behave as retrograde modulators acting mainly on CB_1 receptors on the axon terminals of glutamatergic neurons. The subsequent inhibition of glutamate release inhibits the GABAergic neurons that originate in the NAc and project to the VTA, thus indirectly activating VTA dopaminergic neurons. Endocannabinoids have also been demonstrated to participate in synaptic plasticity in the NAc. Thus, repetitive activation of prelimbic glutamatergic afferents to the NAc results in long-term depression (LTD) of this excitatory transmission that depends on endocannabinoids and CB_1 receptors [14]. Chronic [77] or even a single [78] THC exposure modifies this form of synaptic plasticity, which is important for the development of the addictive process. Endocannabinoid release in the VTA participates in the modulation of drug rewarding effects [69], which would explain the involvement of CB_1 receptors in the rewarding properties of opiates, ethanol, THC and nicotine. Hence, CB_1 receptors would not participate in the primary rewarding effects of psychostimulants because they essentially act on dopaminergic axon terminals in the NAc. Nevertheless, somatodendritic dopamine release induced by psychostimulants in the VTA could promote endocannabinoid release in this brain area [13]. Finally, CB_1 receptors on the glutamatergic projections from the prefrontal cortex (PFC) would be important to modulate motivation to seek the drug.

possible the release of endocannabinoids in the VTA. However, psychostimulants enhance dopamine levels in the NAc by directly acting on dopaminergic axon terminals. This mechanism of action avoids endocannabinoid release in the VTA and could explain the lack of alteration of primary psychostimulant rewarding effects in the absence of CB_1 receptors [69,71]. In addition, although chronic treatment with THC, nicotine or alcohol increases endocannabinoid content in the limbic forebrain, chronic cocaine reduces 2-arachidonoylglycerol content in these brain structures, indicating that psychostimulants and other drugs of abuse regulate endocannabinoid transmission differently [72]. Similarly, chronic administration of cocaine, but not ethanol or

nicotine, decreases mRNA levels for CB_1 receptors in several brain structures [73].

The endocannabinoid system also modulates the motivation to seek psychostimulants and opioids by a mechanism independent from release of dopamine in the NAc. CB_1 receptors are present in the prefrontal cortex, which constitutes a nexus for sensory integration, emotional processing and hedonic experience. This brain area is an important component in the addictive phenomenon because it processes the reward to become a 'hedonic experience' [74]. Hence, endocannabinoids could be involved in the motivation to obtain the drug by linking the reward to a 'hedonic experience' in the prefrontal cortex.

The mechanisms underlying the role of the endocannabinoid system in relapse to drug-seeking behaviour produced by drug-related environmental stimuli and drug re-exposure seem related to modulation of the impact of reward-related memories. Indeed, endocannabinoids acting as retrograde messengers mediate LTP and/or LTD of synaptic transmission in several addiction and memory-related brain areas, including the NAc, prefrontal cortex, amygdala and hippocampus [65]. These effects of endocannabinoids on synaptic plasticity might consolidate the reward-driven behaviour required to establish the addictive processes.

The recent identification of CB_2 receptors in the brain presents an alternative site of action for endocannabinoids [10]. These CB_2 receptors are functionally active because their stimulation, together with CB_1 receptor activation, inhibits morphine-6-glucuronide-induced vomiting at a central level. Therefore, CB_2 receptors are potentially involved in other CNS-mediated effects of cannabinoids that have previously been attributed to CB_1 receptors. Further studies are required to understand the precise role of central CB_2 receptors, and the possible alteration of their physiological activity during drug addictive processes. The possible involvement of other neurochemical circuits in the effects of the endocannabinoid system on reward function cannot be excluded. Thus, endocannabinoids facilitate the effects of orexin-releasing neurons in the hypothalamus, which also project to the NAc and the VTA. Interestingly, hypothalamic orexins, in addition to endocannabinoids, are directly involved in the rewarding effects of drugs of abuse and the relapse to drug-seeking behaviour [75].

Therefore, the endocannabinoid system represents a key component in the common neurobiological substrate of drug addiction, and the CB_1 receptor is a possible candidate to explain genomic variations that might determine human addiction vulnerability [76].

Concluding remarks

The endocannabinoid system participates in the addictive properties of all prototypical drugs of abuse by at least three complementary mechanisms. First, the system is directly involved in the primary rewarding effects of cannabinoids, nicotine, alcohol and opioids by acting on common cellular mechanisms and/or by permitting the effects of these drugs on mesolimbic transmission. Second, the endocannabinoid system is involved in the motivation

to seek the drug by a dopamine-independent mechanism; this has been demonstrated for psychostimulants and opioids and might also be the case for other drugs of abuse. Third, this system is implicated in relapse to drug-seeking behaviour participating in the motivational effects of drug-related environmental stimuli and drug re-exposure, probably by acting on the synaptic plasticity underlying memory processes. Further studies will be required to clarify the precise mechanisms involved in this physiological role of the endocannabinoid system, which has promising clinical consequences. Indeed, CB_1 cannabinoid antagonists might represent a new generation of compounds to treat a wide range of drug addictive processes, as clinical trials have already indicated for smoking cessation. Pharmaceutical companies have now focused the target of these new compounds in the treatment of tobacco dependence and other diseases such as obesity and cardiovascular risk. The possible application of CB_1 antagonists to other addictive processes remains to be demonstrated. Finally, the recent identification of CB_2 receptors in the brain has suggested that they might be a new therapeutic target for treatment of CNS disorders, and possible involvement of these receptors in drug addiction remains open.

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