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Substance use disorders: Psychoneuroimmunological mechanisms and new targets for therapy

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Abstract

An estimated 76.4 million people worldwide meet criteria for alcohol use disorders, and 15.3 million meet criteria for drug use disorders. Given the high rates of addiction and the associated health, economic, and social costs, it is essential to develop a thorough understanding of the impact of substance abuse on mental and physical health outcomes and to identify new treatment approaches for substance use disorders (SUDs). Psychoneuroimmunology is a rapidly expanding, multidisciplinary area of research that may be of particular importance to addiction medicine, as its focus is on the dynamic and complex interactions among behavioral factors, the central nervous system, and the endocrine and immune systems (Ader, 2001). This review, therefore, focuses on: 1) the psychoneuroimmunologic effects of SUDs by substance type and use pattern, and 2) the current and future treatment strategies, including barriers that can impede successful recovery outcomes. Evidence-based psychosocial and pharmacotherapeutic treatments are reviewed. Psychological factors and central nervous system correlates that impact treatment adherence and response are discussed. Several novel therapeutic approaches that are currently under investigation are introduced; translational data from animal and human studies is presented, highlighting immunotherapy as a promising new direction for addiction medicine.

Keywords

Addiction; Drug discovery; Inflammation; Psychoneuroimmunology; Substance use disorders; Treatment strategies

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Conflict of interest statement

The Department of Veterans Affairs and Oregon Health & Science University own a technology referenced in this review article (a partial MHC/neuroantigen peptide construct). The Department of Veterans Affairs, OHSU, Dr. Loftis, and Dr. Huckans have rights to the royalties from the licensing agreement with Artielle (the company that has licensed the technology). These potential conflicts of interest have been reviewed and managed by the Conflict of Interest Committees at the Portland VA Medical Center and Oregon Health & Science University.

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1. Introduction

An estimated 76.4 million people worldwide meet criteria for alcohol use disorders (AUDs) (World Health Organization [WHO], 2004), and 15.3 million meet criteria for drug use disorders (Anderson, 2006). Besides addiction, substance abuse and dependence are linked to a variety of medical disorders, including increased prevalence of infectious diseases [*e.g.*, HIV/AIDS (Kresina et al., 2004) and hepatitis C viral infection (HCV) (Klevens et al., 2012)], cancer, heart and liver disease, and others. The increased prevalence of medical disorders has been attributed, in part, to altered immune function in patients with a history of substance abuse (Arria et al., 1991; Liang et al., 2008; Loftis et al., 2006; Ye et al., 2008).

Substance abuse can also induce or exacerbate psychiatric symptoms such as depression, anxiety, posttraumatic stress disorder (PTSD), cognitive disorders (*e.g.*, due to traumatic brain injury), or insomnia. The Epidemiologic Catchment Area study, estimated that, within the community, 37% of adults with AUDs and 53% with drug use disorders have co-morbid psychiatric disorders (Regier et al., 1990). A more recent study found that within addiction treatment facilities, estimated rates of co-morbid psychiatric disorders were as follows: mood disorders (40%–42%), anxiety disorders (24%–27%), PTSD (24%–27%), severe mental illness (16%–21%), antisocial personality disorder (18%–20%), and borderline personality disorder (17%–18%) (McGovern et al., 2006). Among adults with schizophrenia in the community, lifetime SUD rates may approach 50% (Volkow, 2009). Substance abuse is also linked to homelessness, crime, and violence, and is costly to individuals and society (*e.g.*, motor vehicle accidents, domestic violence, and legal history). Were substance abuse a “budget category” it would rank the sixth biggest United States federal government expense (National Center on Addiction and Substance Abuse at Columbia University, 2009).

The WHO reports that there is significant need for better drug abuse treatment (as well as access to it) (Kuehn, 2012). In order to identify, develop, and disseminate improved treatments for SUDs, a more comprehensive understanding of the interplay between CNS and immune cell signaling is needed. Communication between the brain and the immune system is bi-directional, and immune-to-brain communication pathways induce a cascade of cellular and molecular events in the CNS, which have behavioral consequences. Thus, investigating addiction from a psychoneuroimmunological perspective may provide a more integrated view of the pathophysiological mechanisms associated with SUDs. This review summarizes: 1) the psychoneuroimmunologic effects of SUDs by substance type (*i.e.*, alcohol, stimulants, and opioids) and patterns of use (*i.e.*, acute *versus* chronic; periods of withdrawal/remission) and 2) the current and future treatment strategies, including the neuropsychiatric barriers that can impede successful outcomes.

2. Psychoneuroimmunological analysis of substance use disorders

Psychoneuroimmunology is a specialized field of research that studies the interactions between the nervous and immune systems, and the relationships between behavior and health. Psychoneuroimmunology researchers come from a number of disciplines including, but not limited to, psychology, psychiatry, neuroscience, immunology, infectious diseases, endocrinology, and behavioral medicine. A primary focus of this field has been on the immunological and psychological responses to stress. Substance abuse and, in particular, withdrawal from an abused substance can be significant stressors and result in immunological and neurological changes that negatively impact behavior and health outcomes. Both stress and substance abuse have measurable and reciprocal effects on immune system cytokines, which can be influential modulators of neuropsychiatric function. In addition to stress-induced effects on immune function, pre-clinical studies are beginning to link immune factor signaling with neural and behavioral aspects of addiction, such as

drug seeking and resilience to relapse (Schwarz et al., 2011; Zhang et al., 2012; Blednov et al., 2011; Blednov et al., 2012). Further, the immune effects of a substance may also affect its addictive properties, be additive or synergistic with those of other drugs of abuse (*e.g.*, in cases of polysubstance abuse), or be additive or interact with immune effects of co-morbid clinical disorders (*e.g.*, anxiety or depressive disorders) or chronic infections (*e.g.*, HIV, HCV). Other variables that can mediate or modulate the psychoneuroimmunological effects of abused substances include the influence of: 1) acute *versus* chronic substance use, 2) withdrawal and relapse patterns, 3) age (*e.g.*, early- *versus* late-onset exposure), 4) gender, 5) genetic factors, and 6) social and economic factors (Fig. 1).

Sections 2.1 – 2.4 and Tables 1–4 review pre-clinical and clinical studies that examine the psychoneuroimmune processes associated with exposure to alcohol, stimulants, and opioids. Collectively, these findings have led to a greater appreciation for the effects of addiction on immunological responses as well as on neurological function, behavior, and health.

2.1 Alcohol

Alcohol [ethanol (EtOH)] alters immune function in part by its effects on neurotransmitter [*e.g.*, glutamate, gamma-aminobutyric acid (GABA)], neuroendocrine, and autonomic pathways and on behaviors [*e.g.*, induction of poor sleep (Redwine et al., 2003), nutritional deprivation (Blank et al., 1991; Watzl & Watson, 1993), and depressive disorders (Herbert & Cohen, 1993; Pettinati et al., 2012; Schleifer et al., 2006; Zorrilla et al., 2001)]. Alcohol abuse and dependence are among the more intensively studied SUDs. This research shows that in addition to its effects on neurotransmission and neuroendocrine signaling, alcohol exposure has effects on adaptive and innate immunity, including increased circulating immunoglobulins, alterations in cytokine expression, and impaired phagocytic functions (previously reviewed in Schleifer et al. 2007). It is important to emphasize that alcohol-induced effects on immune function vary depending on whether or not alcohol exposure is acute or chronic. Because the acute effects of alcohol are generally short-lived compared with the course of chronic AUDs, these effects may be less relevant for the treatment of AUDs. However, chronic stressors, like AUDs, can result in more enduring adaptations that compromise immune function and lead to an increased risk of developing physical or mental health disorders.

Alterations in circulating immunoglobulin (Ig) levels were among the first described immune abnormalities linked with AUDs (Bogdal et al., 1976). In humans, alcoholic liver disease is associated with hypergammaglobulinemia, particularly with high serum concentrations of IgA. However, increased IgE levels independent of liver dysfunction have also been reported (Dominguez-Santalla et al., 2001). Recently these clinical findings were corroborated in mice (Alonso et al., 2012). Male and female mice (both Swiss and C57BL/6 strains) administered ethanol evidenced increases in serum IgE concentrations, as compared to control animals. In contrast, ethanol administration was not associated with significant changes in serum IgA and IgM concentration, and appeared to decrease IgG concentrations (Alonso et al., 2012). In AUDs, the clinical impact of altered circulating immunoglobulins is still unclear, and more research is needed to determine the significance of increased IgE levels, for example, in relation to disease course and recovery outcomes.

Studies of cytokine levels in relation to alcohol exposure and AUDs suggest that patients with liver disease have significantly altered circulating levels of cytokines (Szabo et al., 2012), with more modest effects in patients without liver disease (Khoruts et al., 1991; Nicolaou et al., 2004). In a recent study of moderate alcohol drinkers (1–3 drinks/day) without alcoholic liver disease (but at risk of cardiovascular disease), consumption of alcohol (30 grams per day) increased interleukin-10 (IL-10) and decreased macrophage-derived chemokine concentrations, as compared to controls (Chiva-Blanch et al., 2012).

Similarly, studies show that there are slight increases in Type 1 helper T cell (Th1) activation in AUDs even in the absence of liver disease (Cook, 2000). However, human monocytes acutely exposed to alcohol show suppression of nuclear factor kappaB (NF- κ B) mediated production of pro-inflammatory cytokines (Mandrekar et al., 2002), and acute alcohol treatment dose-dependently reduces IL-6, IL-12p40, IL-23, and IL-10 levels in bone marrow-derived dendritic cells obtained from mice (Rendon et al., 2012).

In the context of AUDs (*i.e.*, chronic exposure), activated immune cells release inflammatory cytokines and chemokines that can have significant consequences on behavior, including the development of “sickness behaviors” (*e.g.*, decreased motility, increased fatigue and sleep, reduced appetite, increased sensitivity to pain, decreased motivation or interest, decreased sexual activity) and cognitive impairments—consequences that can have a significant impact on recovery efforts and outcomes (*see section 3.3*). Pre-clinical studies argue that brain neuroinflammatory signals may even promote excessive alcohol consumption (Blednov et al., 2011; Blednov et al., 2012) as well as contribute to depressive symptoms and cognitive dysfunction.

In addition to reports of altered circulating immunoglobins and cytokine signaling, studies show that alcohol exposure affects phagocytic functions, including in human cells (Jareo et al., 1996; MacGregor, 1986; MacGregor et al., 1978; Patel et al., 1996). As with other consequences of alcohol exposure (Hoek et al., 2005; Bravo et al., 2012), there appear to be gender differences in alcohol’s effects on phagocytic function. For example, Schleifer et al., (1999) found decreased phagocytosis in alcohol-dependent males, but not in females. There is some evidence that alcohol’s effects also differ among the phagocytic cells (Schleifer et al., 1999). In a study of predominately male participants, phagocytosis was evaluated and investigators found that the presence of an AUD affected polymorphonuclear neutrophils (PMNs) preferentially (Parlesak et al., 2003). Specifically, PMNs, but not monocyte, phagocytosis was decreased in AUD patients with and without liver disease. A more recent clinical study supports and extends these findings by showing impairment in the function of PMNs in patients with AUDs, such that the respiratory burst activity of PMNs was decreased in patients with AUDs, relative to controls (Breitmeier et al., 2008). Taken together, these findings elucidate, in part, processes contributing to impaired defense against infection in patients with AUDs and mechanisms that may play a role in the altered expression of cytokines and other immune factors. Tables 1 & 2 provide a summary of these and other immunologic effects of acute and chronic alcohol exposure.

When evaluating the psychoneuroimmunologic factors involved in AUDs there is the need to differentiate between active alcohol use and periods of withdrawal or remission. Withdrawal from alcohol induces a state of significant physiologic activation and endocrine imbalance. In addition to periodic episodes of acute withdrawal, the day-to-day experience of someone with an AUD may involve shifts in and out of varying states of withdrawal. Further, in patients trying to abstain from alcohol use, relapse is common. These intermittent patterns of alcohol exposure and abstinence can induce stress and result in substantial immune consequences. Over twenty years ago Jerrells et al. (1989) suggested that the most prominent immune effects relate to the induction of stress hormones (*e.g.*, corticosteroids) following alcohol withdrawal (Jerrells et al., 1989). These initial observations have been confirmed by a number of investigators showing that not only does alcohol withdrawal increase hypothalamic-pituitary-adrenal (HPA) axis reactivity, but it also leads to an acute inflammatory response in the CNS (Buck et al., 2012; Freeman et al., 2012). This is important because increased stress and inflammation can lead to depression, cognitive impairments, and anxiety and can contribute to increased relapse rates, lower treatment retention rates, and reduced daily functioning. Table 2 highlights selected studies that

investigate alcohol withdrawal and remission from AUDs, as these exposure patterns are important experimental and clinical considerations.

2.2 Stimulants

Substances of abuse with stimulant properties, such as cocaine, amphetamine, and methamphetamine, are among the more commonly abused drugs. These drugs are associated with well-characterized changes in the levels of catecholamines (*e.g.*, dopamine, epinephrine, norepinephrine) that have both central and peripheral effects on neurotransmission and neuroendocrine signaling. Given their activating effects on the sympathetic nervous system, abused stimulants are potential mediators of the immune system effects of stress. In particular, stimulant exposure is associated with disruption of the blood brain barrier (Kousik et al.) and activation of the HPA axis (Torres & Rivier, 1992), which have consequences on immune function, including increased leukocyte transmigration across the endothelium (Yao et al., 2012). Thus, as with AUDs, acute and chronic stimulant use is associated with effects on adaptive and innate immunity, such as alterations in lymphocyte numbers (Pellegrino & Bayer, 1998; Wrona et al., 2005), changes in cytokine expression [reviewed in (Clark et al., 2012)], and impairments in phagocytic functions [*e.g.*, alveolar macrophages (Baldwin et al., 1997), neutrophils (Mukunda et al., 2000), and resident peritoneal macrophages (Talloczy et al., 2008)]. Table 3 provides a review of selected studies that describe acute and chronic effects of stimulant exposure.

Given that both stress and substance abuse have robust, reciprocal, and potentially synergistic effects on immune system cytokines, Fox et al., (2012) examined changes in peripheral cytokine levels in cocaine dependent individuals at baseline and following exposure to stressful imagery. Cocaine abusers demonstrated decreased basal IL-10 compared with social drinkers. They also showed significant elevations in the pro-inflammatory cytokine tumor necrosis factor- α (TNF- α) when exposed to stress, compared with when they were exposed to relaxing imagery. This pro-inflammatory response was not observed in the comparison group of social drinkers (Fox et al., 2012). Consistent with the premise that cytokines can be potent modulators of mood and cognitive function, we and others have shown that repeated methamphetamine exposure induces alterations in peripheral and central immune factor expression, and that peripheral alterations are associated with cognitive impairments and mood disturbances in methamphetamine dependent humans (Letendre et al., 2005; Loftis et al., 2011). Further, the neuroinflammatory effects of methamphetamine appear to be brain-region specific and may lead to differential effects on cognitive function (Loftis et al., 2011; Chang et al., 2005; Jernigan et al., 2005).

Glial activation, a type of neuroinflammatory response, associated with stimulant use is well documented in pre-clinical studies, particularly following exposure to methamphetamine (Asanuma et al., 2004; Hebert & O'Callaghan, 2000; Thomas et al., 2004). Although microglial and astroglial responses are normal compensatory responses to brain injury, excess neuroinflammation may lead to further brain injury. Multiple lines of evidence indicate that activated microglia contribute to stimulant induced neuroinflammation and neurodegeneration through pro-inflammatory processes, including the production of TNF- α , IL-1 β and IL-6, or through oxidative mechanisms (Clark et al., 2013; Yamamoto & Raudensky, 2008). Thus, repeated stimulant exposure induces alterations in peripheral and central immune factor expression that contribute to neuroinflammatory mechanisms and neuronal damage. However, questions remain regarding how the CNS recognizes and responds to the altered immune activation taking place in the periphery as well as the neuronal damage occurring in brain. More research is needed to elucidate the specific signaling pathways (*e.g.*, NF- κ B) and cell types [*e.g.*, microglia, astrocytes, natural killer

(NK) cells, and vascular endothelial cells] that induce and perpetuate these neuroinflammatory processes.

As with alcohol exposure, when evaluating the psychoneuroimmunologic factors associated with stimulant abuse, there is the need to differentiate between acute and chronic use as well as between active stimulant use and periods of withdrawal or remission. In a classic positron emission tomography imaging study, Volkow et al (2001) evaluated striatal dopamine transporter levels and performed neuropsychological testing in methamphetamine abusers during short abstinence (<6 months) and then during protracted abstinence (12–17 months). Following the period of protracted abstinence, dopamine transporter expression was increased, as compared with levels observed during short abstinence (caudate, +19%; putamen, +16%) (Volkow et al., 2001). However, the neuropsychological test results did not improve to the same extent. This suggests that the increase of the dopamine transporters was not sufficient for complete recovery of function. Protracted abstinence may reverse some of methamphetamine-induced alterations in brain dopamine terminals, but other processes may be contributing to mood and cognitive impairments during and following stimulant exposure. In line with this theory, a global pattern of microglial activation and microgliosis persists in the brains of methamphetamine addicted adults for at least two years into abstinence (Sekine et al., 2008). Thus, although more research is needed, increasingly, studies show that the immune effects of stimulant exposure are of substantial clinical relevance.

2.3 Opiates

A large literature of more than 30 years has focused on the relationship between opioids and their effects on innate and adaptive immunity (Liu et al., 2012; Vallejo et al., 2004; Wybran et al., 1979). As with other substances of abuse, the reciprocal effects of opioids on immune activity are mediated by multiple mechanisms and consist of both direct and indirect effects in the periphery and CNS. These effects include, but are not limited to, changes in the number and/or function of lymphocytes and glial cells, alterations in cytokine levels, and impairments in phagocytosis. Exogenous opiates, such as morphine, can act like cytokines and modulate the immune response by interactions with opioid receptors on lymphocytes, glia, and neurons. Acute and chronic exposure to opiates alters T- and B-cell and NK activity as well as phagocytic functions (both macrophage and PMN) (Brown et al., 1974; Donahoe et al., 1987; Eisenstein & Hilburger, 1998; Liu et al., 2012; Novick et al., 1989; Vallejo et al., 2004) (Table 4). Consistent with these findings, chronic morphine use increases the susceptibility to opportunistic infection. Recently, mechanisms contributing to morphine induced impairments in phagocytosis were identified. Ninkovi and Roy (2012) showed that long-term morphine treatment leads to inhibition of Rac1-GTPase and p38 mitogen-activated protein kinase (MAPK), causing attenuation of FcγR-mediated phagocytosis, and decreased bacterial clearance (Ninkovic & Roy, 2012). Activation of p38 MAPK signaling in microglia is also implicated in the acquisition and maintenance of morphine-induced reward (as measured using conditioned place preference) (Zhang et al., 2012)--whereas, anti-inflammatory IL-10 microglial expression appears to be protective against morphine-induced glial reactivity and drug-induced reinstatement of morphine conditioned place preference (Schwarz et al., 2011).

As with other substances of abuse, the consequences of acute or chronic exposure on immunity should be considered in relation to variable schedules of drug exposure, withdrawal, and remission (Govitrapong et al., 1998; Rahim et al., 2002; Weber et al., 2004; Weber & Pert, 1989). Table 4 highlights selected studies that investigate the effects of acute and chronic opioid exposure as well as the effects of withdrawal and remission from opioid use. Taken together, these findings may help to explain the effects of chronic opiate exposure on altered immune reactivity and function.

3. Current treatment approaches

Addiction is a chronic disorder with behavioral components that requires long-term management and periodic professional services (NIH Publication No. 99-4180, 1999). Consistent with the concept that SUDs are chronic disorders, the percentage of people who relapse following treatment (40–60%) is similar to other chronic diseases: type I diabetes (30–50%), hypertension (50–70%), and asthma (50–70%) (McLellan et al., 2000). Consequently, effective SUD treatment often requires long-term monitoring and management aimed at reduced length, frequency, and severity of symptom re-occurrences. Long-term relapse prevention is the biggest challenge in treating patients with SUDs. Psychotherapy and pharmacotherapy are available to help patients prevent relapse. For most patients, a combination of the two is appropriate and enhances chances for longer periods of abstinence. Because SUDs impact many aspects of a person's life, a comprehensive treatment program includes core treatment services (*e.g.*, counseling/therapy, psychiatric, medical, case management, peer support groups), as well as access to support services (*e.g.*, vocational, legal, financial, housing, transportation, child care).

3.1 Non-pharmacologic interventions

Based on review of available outcome data, the American Psychiatric Association (APA) and/or Department of Veterans Affairs/Department of Defense (VA/DoD) has recommended the following evidence-based psychosocial interventions for the treatment of alcohol, stimulant, and opioid use disorders: 1) behavioral couples therapy, 2) cognitive behavioral coping skills therapy, 3) contingency management and motivational incentives, 4) community reinforcement approach, 5) motivational enhancement therapy, and 6) 12-step facilitation (APA, 2007; VA/DoD, 2009). Though not specifically recommended by the APA or VA/DoD at this time, a growing number of studies show evidence for the effectiveness of additional psychosocial treatments with addiction populations [*e.g.*, harm reduction therapy (Logan & Marlatt; Marlatt & Witkiewitz), mindfulness-based interventions (Zgierska et al., 2009), dialectical behavior therapy (Dimeff & Linehan, 2008), brief interventions (Kaner et al., 2007; Whitlock et al., 2004)]. These psychosocial interventions can successfully teach new behaviors, alter behavioral responses to stressors, and improve affective states (*e.g.*, depressed mood). The challenge is to determine whether behavior changes can be maintained over time, and whether behavioral interventions can improve health outcomes and alter disease progression. Although psychotherapeutic strategies are critical, the remainder of this review is focused on evidence-based and other pharmacotherapeutic approaches for the treatment of SUDs.

3.2 Pharmacologic treatments

Pharmacotherapy offers a promising approach for treating SUDs, and significant progress has been made in the past 20 years. Evidence-based pharmacotherapies for SUDs include: 1) medications that reduce distress during acute withdrawal [*e.g.*, benzodiazepines as a first line treatment during alcohol withdrawal, carbamazepine and valproic acid as a second line or adjunct treatment for alcohol withdrawal, gradual tapering of opioid agonist therapy (OAT) during opioid withdrawal], 2) antagonists that block drug rewards (*e.g.*, naltrexone as a first line treatment for alcohol dependence and a second line treatment for opioid dependence), 3) medications that produce adverse reactions to a substance (*e.g.*, disulfiram as a second line treatment for alcohol dependence), 4) agonists that mimic drug effects, thereby reducing withdrawal symptoms and cravings and minimizing the harms associated with uncontrolled use (*e.g.*, long-term OAT including methadone, buprenorphine, or buprenorphine-naloxone as first line treatments for opioid dependence), and 5) medications that treat psychiatric symptoms that persist during recovery (*e.g.*, acamprosate as a first line treatment for alcohol dependence). The VA and DoD have prioritized implementation of

evidence-based practices and treatment services to enhance the recognition and management of SUD in general medical and SUD specialty-care settings. Based on their evaluation of available research, the APA and VA/DoD provide guidelines for evidence based pharmacotherapies for alcohol and opioid withdrawal and dependence (APA, 2007; VA/DoD, 2009); because research is limited, recommendations are not yet available for other substances, such as methamphetamine (Table 5).

For pharmacological treatment of AUDs, the Food and Drug Administration (FDA) approved medications include: disulfiram, acamprosate, and naltrexone. Although there are only three drugs officially approved by the FDA, a number of other compounds have been and are being prescribed “off-label” for the treatment of alcohol and other SUDs. For example, baclofen, a GABA-B receptor agonist, is being investigated as a potential treatment for AUDs (and other drug use disorders). Baclofen reduces the reinforcing effects of alcohol and other drugs in pre-clinical models, and two open-label and two placebo-controlled studies in humans found that baclofen was effective for reducing alcohol craving and intake. However, one placebo-controlled study found no benefit for baclofen (Howland). Another medication, topiramate (also an anticonvulsant) is similarly used for the treatment of AUDs (and other drug use disorders). Topiramate is hypothesized to improve recovery efforts among patients with AUDs by reducing alcohol’s reinforcing effects through facilitation of GABAergic function and antagonism of glutamate activity within the corticomesolimbic system. Clinical trials show some efficacy for topiramate in the treatment of AUD (Johnson et al., 2003; Johnson et al., 2007b).

Unfortunately, these medications do not work for everyone. Reviews and meta-analyses show modest effect sizes for the FDA-approved and “off-label” approaches to SUDs probably because the drugs are often tested in large and heterogeneous samples where pre-existing genetic factors and patient subgroups are not considered. Alcoholism researcher Stephanie O’Malley of Yale University was quoted in *Science* magazine saying that; “We have effective treatments, but they don’t help everyone” (Miller, 2008). Increasingly, SUD researchers and clinicians are appreciating the need to define biological endophenotypes in order to form more homogeneous subgroups that can guide personalized treatment regimes. For example, naltrexone treatment appears to be more effective in carriers of a specific functional polymorphism of the μ -opioid receptor gene (*i.e.*, OPRM1 Asp40 allele). In a placebo-controlled clinical trial, patients with AUDs and the genetic variant who received naltrexone were able to go for more days without a drink, had fewer days where they drank heavily, and were better able to abstain from alcohol or drink only moderately for the last eight weeks of the sixteen-week trial. However, among patients without the genetic variant, those given naltrexone showed no more improvement than did the placebo group. Thus, these findings and others suggest that patients who respond to naltrexone share certain traits (*e.g.*, intense alcohol cravings, family history of alcoholism). In addition to genetic testing, biological differences between patient groups are also being detected in functional imaging studies. Naltrexone is thought to work better in a subgroup of patients with higher cue reactivity when shown appetitive alcohol pictures, and magnetic resonance spectroscopy of brain glutamate levels may detect potential acamprosate responders (reviewed in Mann & Hermann, 2012). Questions remain regarding how these patient subgroups should be defined and research is ongoing (Kranzler & McKay, 2012).

There is significant overlap among the medications currently used to treat SUDs, such as naltrexone, buprenorphine, and topiramate (Johnson et al., 2007a; Mooney et al., 2013; Tiitonen et al., 2012; Wee et al., 2012). In patients with opioid use disorders different naltrexone treatment regimes and routes of administration are being evaluated (*e.g.*, long-acting sustained-release implants *versus* oral naltrexone) (Krupitsky et al., 2012), and in patients with cocaine dependence and opioid use disorders buprenorphine is hypothesized to

reduce cocaine use (Mooney et al., 2013). Recently, the United States federal government regulations for dispensing buprenorphine were modified to allow opioid treatment programs more flexibility in dispensing take-home supplies (SAMHSA, 2012). Thus, through efforts to define biological endophenotypes and optimize treatment availability, treatment outcomes are improving.

The National Institute on Alcohol Abuse and Alcoholism's (NIAAA's) Medications Development Team has identified three long-range goals focused on the development and delivery of more efficacious medications to treat AUDs. These goals include: "1) making the drug development process more efficient; 2) identifying more efficacious medications, personalize treatment approaches, or both; and 3) facilitating the implementation and adaptation of medications in real-world treatment settings" (Litten et al., 2012). The National Institute on Drug Abuse (NIDA) is focused on similar long range objectives for the treatment of drug use disorders (NIDA). Yet, more work is needed to address the psychological and cognitive impairments that can develop and persist with SUDs.

3.3 Neuropsychiatric sequelae as barriers to recovery

Substance abuse and dependence leads to the loss of attention, poor decision making, increased impulsivity, anxiety and depression—neuropsychiatric symptoms that promote a loss of behavioral control over drug use and make the addiction extremely challenging to treat. For example, approximately one-third of patients with AUDs have major depressive disorder (Kessler et al., 1997; Penick et al., 1994), a disorder that is also associated with immune system changes [*e.g.*, increased circulating leukocytes, monocytes, and neutrophils; increased markers of immune activation and inflammation; and decreased NK cell activity and mitogen response (Herbert & Cohen, 1993; Loftis et al., 2008; Savitz et al., 2012; Zorrilla et al., 2001)].

Although for some substances the neuropsychiatric deficits tend to resolve after a few months of abstinence, for other substances longer-term impairments are more common. Moreover, problems may persist for any given patient, particularly when other risk factors, such as co-morbid HIV and/or HCV, are present. Using animal models, our laboratory and others have found that withdrawal from alcohol and other drugs of abuse results in persistent learning deficits and anxiety that are accompanied by altered expression of cytokines and chemokines (Leclercq et al., 2012; Loftis et al., 2011). Further, it has been shown that the effects of ethanol on anxiety-like behavior can be reproduced by brain injections of chemokine (C-C motif) ligand 2 (CCL2) [a.k.a. monocyte chemoattractant protein-1 (MCP-1)] and the cytokine TNF- α (Breese et al., 2008). In another study, mice self-administering ethanol in a chronic drinking model show depression-like behavior during abstinence (Stevenson et al., 2009). More recently, Goeldner et al., (2011) demonstrated impaired emotional-like behavior (*i.e.*, low sociability and despair-like behavior) in mice after four weeks of abstinence from chronic morphine. These findings are important because depression as well as cognitive impairments and anxiety can contribute to increased relapse rates, lower treatment retention rates, and reduced daily functioning. Neuropsychological assessments are typically not included in patient evaluations for SUD treatment programs, as they are time and resource consuming. However, at least one group of investigators is evaluating the validity, classification accuracy, and clinical utility of a brief screening measure, the Montreal Cognitive Assessment (MoCA) (Copersino et al., 2012), which may help to identify (and thus better treat) cognitive impairments among patients with SUDs. Other groups are evaluating whether available cognitive enhancers, such as anticholinesterase inhibitors, noradrenergics, or *N*-Methyl-D-aspartic acid (NMDA) receptor antagonists, could effectively treat substance induced cognitive impairments (Sofuoglu, 2010; Chen et al., 2012). Still others are evaluating behavioral approaches, specifically cognitive rehabilitation therapies, as a means of promoting cognitive recovery in individuals with substance use

disorders and augmenting the efficacy of available substance use treatments (Bates et al., 2013).

4. Future treatment strategies – Immunotherapies for addictions

Of note, pharmacotherapeutic approaches to SUDs have primarily centered on neurotransmitter and related receptor systems. Although a number of these medications are showing significant clinical benefit and promise [*e.g.*, (Newman et al., 2012; Walsh et al., 2013)], investigation of alternatives is warranted, particularly for substances for which there remain no FDA-approved medications and no related guidelines (*e.g.*, cocaine and methamphetamine). Given current knowledge of the psychoneuroimmunological effects of SUDs (*reviewed in Section 2*), immunotherapies to treat SUDs and the neuropsychiatric effects of SUDs pose a promising new direction for addiction treatment. Indeed, in a thorough and up-to-date review, Litten et al., (2012) provides a list of molecular targets and representative compounds that are currently being tested (pre-clinically and/or clinically) in AUDs (and other drug use disorders), and included in this list of targets is neuroimmune modulation. Although not yet FDA approved or available to the public, anti-addiction vaccines are currently the most developed immunotherapeutic approach to addiction. Anti-addiction vaccines are designed to attract antibodies to a substance so that it is too large to pass through the blood brain barrier, effectively blocking its CNS action and rewarding effect (Cerny & Cerny, 2009; Gentry et al., 2009; Kinsey et al., 2009; Kinsey et al., 2010). To date, vaccines have been developed against nicotine, morphine/heroin, cocaine, and methamphetamine, and an array of compounds are undergoing clinical trials or are in preclinical development (Goniewicz & Delijewski, 2013; Kosten et al., 2013; Shen et al., 2012). While this approach has clear potential benefit in terms of relapse prevention, a major limitation is likely to be that polysubstance use is highly prevalent (and perhaps the norm) within addiction populations, it will be infeasible to vaccinate against all addictive substances (and perhaps contraindicated since many abused substances, such as morphine, also have approved medical indications), and many individuals will seek out and use alternative substances when their preferred substance is no longer effective.

In addition to vaccine strategies, pharmacotherapies that regulate and reduce inflammation and oxidative stress are also under investigation. For example, a pre-clinical study found that supplementation with naringenin (a type of flavonoid found in grapefruit) to ethanol-fed rats, significantly decreased the levels of aspartate and alanine transaminases, iron, ferritin, TNF- α , IL-6, NF- κ B, cyclooxygenase-2 (COX-2), macrophage inflammatory protein 2 (MIP-2), CD14, and inducible nitric oxide (iNOS) in the liver as compared to the untreated ethanol fed rats (Jayaraman et al., 2012). Similarly, treatment of ibudilast (a.k.a. AV411; 3-isobutyl-2-isopropylpyrazolo-[1,5-a]pyridine; an anti-inflammatory drug, which acts as a phosphodiesterase inhibitor and suppresses glial cell activation) to mice following exposure to methamphetamine reduced the acute, chronic, and sensitization effects of the drug's locomotor activity, suggesting that glial cell activity can modulate methamphetamine's behavioral effects (Snider et al., 2012). Minocycline (a broad-spectrum tetracycline antibiotic) is another pharmacotherapeutic with anti-inflammatory and anti-oxidant properties that has demonstrated some efficacy in the treatment of psychiatric disorders and neuropsychiatric symptoms. Pre-clinically minocycline has been shown to improve deficits in novel object recognition induced by phencyclidine and methamphetamine treatment in mice (Fujita et al., 2008; Mizoguchi et al., 2008), to reduce the behavioral sensitization induced by methamphetamine and cocaine (Chen et al., 2009; Zhang et al., 2006), and to increase the motor impairment induced by ethanol in mice (Wu et al., 2010). In clinical studies, the results also vary, with findings supporting use of minocycline in schizophrenia, but showing less benefit for nicotine dependence (reviewed in Dean et al., 2012). Non-steroidal anti-inflammatory drugs [NSAIDs, traditional and selective inhibitors of

cyclooxygenase (COX)-2] have also been evaluated for the treatment of psychiatric illness (Berk et al., 2013). NSAIDs provide significant benefits in the treatment of pain and inflammation; however, they are also associated with an increased risk of gastrointestinal and cardiovascular adverse events (Patrignani et al., 2011), which may complicate their use in the treatment of SUDs. To date, the use of NSAIDs for SUD treatment has not been empirically evaluated.

An additional approach that may prove effective for addictions are immunotherapies designed to heal substance-induced neuronal damage and neuropsychiatric impairments through regulation of inflammatory responses within the CNS (Loftis & Huckans, 2011). Because it was previously shown that a partial major histocompatibility complex (MHC)/neuroantigen peptide construct (RTL551; pI-A^b/mMOG-35-55) effectively reduces the inflammatory and behavioral effects of experimental models of multiple sclerosis and stroke (Sinha et al., 2007; Subramanian et al., 2009; Vandenbark et al., 2003; Wang et al., 2006), we hypothesized that partial MHCs could also effectively address the neuropsychiatric effects of chronic methamphetamine addiction. We found that RTL containing mouse MHC coupled to myelin peptide (RTL551) improves the learning and memory impairments and CNS inflammation induced by repeated methamphetamine exposure in mouse models of chronic methamphetamine addiction (Loftis et al., 2013). Traditional immunotherapies are non-selective and therefore have side effects that impair responses to infections and diseases. In contrast, RTLs and other peptide-specific immunotherapies currently under investigation can avoid the non-specific immunosuppressive effects of traditional immunotherapies by targeting reactivity to specific peptides. Collectively, these initial results indicate that neuroimmune therapies, such as RTL551, may have potential as treatments for methamphetamine dependence and other substances of abuse.

5. Conclusion

The present review provides an updated analysis of the psychoneuroimmunological mechanisms involved in the pathophysiology of SUDs, a topic previously reviewed by Schleifer et al. (2007). Current and future pharmacological approaches that have been used or are being considered for the treatment of SUDs were also discussed. Research shows that some alcohol and drug induced immune changes are directly related to immune cell exposure, while other immune effects relate to indirect CNS effects. A number of these alcohol and drug effects on the immune system (*e.g.*, including changes in circulating immunoglobins and lymphocytes, alterations in cytokine expression, and impaired phagocytic functions) are similar to the effects of stress. Impaired phagocytic functions may be one of the processes in particular that is shared across substances of abuse, contributing to the persistent altered immune reactivity and functions observed in SUDs as well as the cognitive and neuropsychiatric impairments that accompany these alterations in immunity.

The substances of abuse considered in this review should be evaluated in relation to the pattern and type of substance exposure (*e.g.*, the majority of patients with SUDs are polysubstance dependent), characteristics of the persons who use the substances (*e.g.*, co-morbid mental health disorders, exposure to infectious diseases, and genetic factors), and the role of peripheral immune dysregulation on CNS immune signaling (Coller & Hutchinson, 2012). Collectively, the studies reviewed highlight the complex contributions of psychoneuroimmunology to the characteristics of SUD-induced behavioral dysregulation and provide a foundation for the development of pharmacotherapeutic strategies to treat aspects of SUDs, such as acute withdrawal symptoms, cravings, anxiety, depression, and cognitive impairments. In particular, immunotherapies are a promising new direction for addictions research because of their potential to prevent relapse, facilitate neuronal repair,

and treat substance induced neuropsychiatric impairments that persist during remission from addiction.

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Abbreviations

APA	American Psychiatric Association
AUD	Alcohol use disorder
CNS	Central nervous system
DoD	Department of Defense
EtOH	Ethanol
GABA	Gamma-aminobutyric acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPA	Hypothalamus-pituitary-adrenal
Ig	Immunoglobulin
IL	Interleukin
MAPK	Mitogen-activated protein kinase
MHC	Major histocompatibility complex
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer
NMDA	<i>N</i> -Methyl-D-aspartic acid
NSAID	Nonsteroidal anti-inflammatory drug
PMN	Polymorphonuclear neutrophils
PTSD	Post traumatic stress disorder
SUD	Substance use disorder
TNF	Tumor necrosis factor
VA	Veterans Affairs

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Figure 1.

Factors that can influence the psychoneuroimmunologic effects of substance use disorders on brain, behavior, and health outcomes. The pathophysiological mechanisms of SUDs differ among individuals as a function of their clinical and demographic factors (*e.g.*, pre-existing genetic vulnerabilities), substance use exposure histories, and social/economic environment. Further, the effects of a substance may be additive or synergistic with those of other drugs of abuse (*e.g.*, in cases of polysubstance abuse) or be additive or interact with immune effects of co-morbid clinical disorders [*e.g.*, chronic infectious diseases (HIV, HCV) or anxiety or depressive disorders].

Table 1
Effects of acute alcohol (EtOH) exposure on psychoneuroimmunologic outcomes in humans and animal models

Immune Effects Measured	Results	References
Acute behavioral effects of EtOH, whether EtOH induced sedation and motor impairment were influenced by microglial dependent central immune signaling	Murine subjects were administered alcohol and minocycline to block pro-inflammatory microglial activation or an IL-1 receptor antagonist (IL-1ra). The IL-1ra treated animals showed reduced alcohol- induced sedation and recovered faster from acute alcohol-induced motor impairment than control animals. Minocycline led to a greater motor impairment induced by EtOH.	(Wu et al., 2011)
Allergen Ig-E, IL-13, mast cell degranulation, eotaxin-2, and bronchoalveolar eosinophils in cockroach allergen-sensitized mice following acute EtOH exposure	30 minutes after exposure to EtOH, 74% of mast cells degranulated and asthma-like symptoms were triggered. The EtOH treatment group experienced a 5-fold increase of eotaxin-2 and a 7-fold increase in bronchoalveolar eosinophils, a 10-fold increase in IL-13, and a 5-fold increase in airway mucin production.	(Bouchard et al., 2012)
Bone marrow derived dendritic cells (BM-DC), IL-4, IL-6, IL-12p40, IL-23, and IL-19 in male mice administered increasing doses of EtOH with or before lipopolysaccharide (LPS)	Concurrent acute EtOH exposure and LPS treatment resulted in a dose-dependent suppression of IL-6, IL-12p40, IL-23, and IL-10. EtOH exposure before LPS dysregulated the IL-12p40/IL-23 balance and more profoundly suppressed IL-6 and IL-10 secretion of BM-DCs, as compared with cells concurrently treated with EtOH and LPS.	(Rendon et al., 2012)
Dendritic cell (DC), macrophage and B cells	Short-term, high dose EtOH administration had differential impact on APC populations, downregulating splenic macrophages and DC activity but up-regulating B lymphocyte function as APC, leading to a micro-environment that leads to increased activation of CD4(+) T cells.	(Andrade et al., 2009)

Table 2

Effects of chronic alcohol (EtOH) exposure, withdrawal, or remission on psychoneuroimmunologic outcomes in humans and animal models

Immune Effects Measured	Results	References
Microglial activation following EtOH dosing for 4 days followed by a 3-day withdrawal, then repeated in a cycle four more times to simulate binge drinking in humans	Microglial activation and cytokine expression in parietal association cortex, entorhinal cortex and hippocampus was evident; neurodegeneration, learning and memory declined following EtOH treatments.	(Zhao et al., 2013)
Expression of high mobility group box 1 (HMGB1), Toll-like receptor (TLR) 2, TLR3, and TLR4 in chronic EtOH-treated mouse brain, postmortem brain from patients with AUDs, and rat brain slice culture	EtOH-induced HMGB1/TLR signaling contributed to induction of the pro-inflammatory cytokine, IL-1 β . Increased expression of HMGB1, TLR2, TLR3, and TLR4 in brain from patients with AUDs and in mice treated with EtOH were also observed.	(Crews et al., 2012)
Neuroinflammatory markers: proteolipid protein (PLP), myelin basic protein (MBP), myelin-oligodendrocyte glycoprotein, 2,3-cyclic-nucleotide-3-phosphodiesterase, and myelin-associated glycoprotein in wild-type and in TLR-4 knockout mice	EtOH treatment downregulated the myelin-building proteins, while increasing chondroitin sulfate proteoglycan NG2 in several brain regions. Immunohistochemistry revealed that EtOH treatment altered myelin morphology, reduced the number of MBP-positive fibers, and led to oligodendrocyte death. Of note, most myelin alterations were not observed in TLR-4 knockout mice treated with EtOH.	(Alfonso-Loeches et al., 2012)
Cytokine levels during and following a 16-week <i>in vivo</i> rat model of binge drinking	TNF- α , IL-1 β , IL-6 increased over 16 weeks. IL-10 levels in rat serum increased at the end of weeks 4 and 8, then decreased thereafter and were significantly decreased by weeks 12 and 16.	(Zhou et al., 2013)
Tissue injury and inflammation in a rat model of chronic EtOH feeding	Chronic EtOH feeding was associated with features of steatohepatitis and increased peripheral pro-inflammatory cytokine levels.	(Ramirez et al., 2013)
Inflammatory responses in the central nucleus of the amygdala (CeA) and dorsal vagal complex (DVC) in a rat model of withdrawal following chronic EtOH exposure	Following chronic EtOH exposure, withdrawal resulted in significant increases in the expression of mRNAs for Ccl2, TNF- α , NOS-2, Tnfrsf1a, and CD74. This response was present in both the CeA and DVC and most prominent at 48 hours.	(Freeman et al., 2012)
Effects of alcohol withdrawal on neurodegeneration if TLR4 receptors are eliminated in mice	Mice lacking TLR4 receptors are protected against ethanol-induced inflammatory damage and associated behavioral effects.	(Pascual et al., 2011)
Alterations in HPA axis reactivity and cytokine response to stress challenge during withdrawal from acute EtOH in a rat model	EtOH withdrawal enhanced HPA axis reactivity to stress challenges; however, no alterations in cytokine changes evoked by stress were observed.	(Buck et al., 2011)

Table 3

Effects of stimulant exposure, withdrawal, or remission on psychoneuroimmunologic outcomes in human and animal models

Immune Effects Measured	Results	References
28 treatment seeking cocaine dependent subjects and 27 social drinkers were exposed to three 5-minute guided imagery conditions (stress, drug cue, relaxing). Salivary cortisol, TNF- α , IL-10, and IL-1ra were measured at baseline and throughout.	Cocaine abusers demonstrated decreased basal IL-10 compared with social drinkers. They also showed significant elevations in pro-inflammatory TNF- α when exposed to stress compared with when they were exposed to relaxing imagery, compared to controls. Social drinkers showed increases in the anti-inflammatory markers IL-10 and IL-1ra, following a cue to relaxing imagery.	(Fox et al., 2012)
IFN- γ , IL-10 and PBMCs including CD4+ and CD8+ were measured before and after 40 mg cocaine infusion in 15 subjects with cocaine dependence	Cocaine infusion increased IFN- γ secretion and decreased IL-10 secretion, while PBMCs collected in controls remained unaltered. Baseline IFN- γ levels were lower and IL-10 levels higher in dependent subjects compared to controls. Lymphocyte number and CD4+ and CD8+ cells all showed an increase following cocaine infusion.	(Gan et al., 1998)
TNF- α and IL-6 expression, monocyte capacity to respond at rest and in response to the bacterial ligand polyliposaccharide over a 24-hour period in humans following an active and acute 40 mg dose of cocaine	Cocaine-dependent volunteers showed a decrease in the capacity of monocytes to express TNF- α and IL-6 compared with control subjects. Acute infusion of cocaine induced a further decline in the responsiveness of monocytes to LPS, which persisted after cocaine had cleared from the blood. Cocaine alters autonomic activity and induces protracted decreases in innate immune mechanisms.	(Irwin et al., 2007)
Peripheral and central immune factor levels, following <i>in vivo</i> methamphetamine exposure in humans and mice during different periods of withdrawal/remission	A number of significant methamphetamine-induced changes in cytokines, chemokines, and adhesion factors were observed. Of particular interest were monocyte chemoattractant protein 1 (MCP-1; a.k.a., CCL2) and intercellular adhesion molecule (ICAM-1; a.k.a. CD54), which were similarly increased in the plasma of methamphetamine exposed mice as well as humans. In human participants, methamphetamine-induced changes in the cytokine and chemokine milieu were accompanied by increased cognitive impairments.	(Loftis et al., 2011)
Neuroinflammatory responses to a subsequent peripheral immune stimulus in mice administered a neurotoxic methamphetamine treatment regimen	Methamphetamine exacerbated the LPS-induced increase in central cytokine mRNA. Methamphetamine alone increased microglial Iba1 expression (a marker for microglial activation) and expression was further increased when mice were exposed to both Methamphetamine and LPS.	(Buchanan et al., 2010a, b)
Withdrawal from cocaine and immune alterations, HPA axis involvement; peripheral blood lymphocytes, T cells, B cells and monocyte levels at intervals post cessation from drug	Sprague-Dawley rats showed plasma corticosterone levels significantly elevated 2 and 24 hours after cessation of cocaine but returned to basal values by 2 days withdrawal. When treated with mifepristone within two days of withdrawal, the suppressive effects of cocaine were not observed.	(Avila et al., 2003)
Astrocyte immune factor production, following <i>in vitro</i> methamphetamine exposure	In human fetal astrocytes, methamphetamine increased IL-6 and IL-8 production (blocked by a metabotropic glutamate receptor-5 inhibitor).	(Shah et al., 2012)
Leukocyte counts, following chronic amphetamine exposure to male rats	Amphetamine decreased circulating lymphocytes and increased neutrophils. The reduction in lymphocytes was caused by the loss of B-cells, which reduced both in percentage and in absolute number by 50%. There was no difference in either CD4+ or CD8+ T lymphocyte subsets between amphetamine-treated and control groups.	(Llorente-Garcia et al., 2009)

Effects of opioid exposure, withdrawal, or remission on psychoneuroimmunologic outcomes in human and animal models

Table 4

Immune Effects Measured	Results	References
Effects of one morphine dose on the systemic immune activity of splenic NK cells	A single dose of morphine suppressed the reduction of the splenic NK cell activity/systemic immune activity caused by acute inflammatory pain.	(Sakaue et al., 2011)
TLR, NF- κ B, Keratinocyte-derived chemokine, TNF- α	An acute dose of morphine impaired TLR expression, rendering peritoneal leukocytes less effective in recognizing zymosan antigens. NF- κ B was inhibited.	(Wypasek et al., 2012)
IL-23, IL-17 mediated pulmonary host defense against <i>Streptococcus pneumoniae</i> infection	Morphine treatment caused a dysfunction in IL-23 producing dendritic cells and macrophages and IL-17 producing γ T lymphocytes in response to <i>S. pneumoniae</i> lung infection. This lead to diminished release of antimicrobial S100A8/A9 proteins, compromised neutrophil recruitment, and more-severe infection.	(Ma et al., 2010)
IL-1 β , IL-2, IL-6 in patients following abdominal surgery given one of 3 pain-relief options: Opiates on demand (IOR), patient-controlled analgesia (PCA), and patient-controlled epidural analgesia (PCEA)	IOR Group: IL-1 β and IL-6 increased; PCA Group: mitogenic responses remained suppressed, IL-1 β and IL-6 increased; PCEA Group: lower pain levels first 24 hours than other groups, mitogenic responses returned to pre-operative levels by 72 hr. IL-1 β and IL-6 almost unchanged. Exhibited reduced suppression of lymphocyte proliferation and attenuated pro-inflammatory cytokine response in the postoperative period.	(Beilin et al., 2003)
CD4+ T cells, CD4+ CD25 high regulatory cells (Tregs) in chronic heroin users compared to patients in opioid maintenance therapy (OMT)	CD4+CD25 high Tregs in the peripheral blood of patients with opioid use disorders were significantly increased compared to OMT group. The proliferative response of CD4+ T cells upon stimulation with anti-CD3 and anti-CD28 antibodies was significantly decreased in heroin users but could be restored by depletion of CD25 high regulatory T cells from CD4+ T cells to similar values as observed from healthy controls and patients in OMT.	(Riss et al., 2012)
Apoptosis of human microglia, astrocytes, and neurons following <i>in vitro</i> exposure of cell cultures to a single dose of morphine	Exposure to morphine resulted in a 4-fold increase in apoptosis to both neuron and microglia cell cultures compared to untreated controls. In addition, neurons exhibited a greater sensitivity to morphine's effect on apoptosis than microglia. Astrocytes were completely resistant to morphine-induced apoptosis.	(Hu et al., 2002)

Pharmacological treatments recommended by the American Psychiatric Association (APA) and/or the Department of Veterans Affairs/Department of Defense (VA/DoD) for the treatment of SUDs

Table 5

	For Medically Supervised Discontinuation/Withdrawal	To Treat Dependence
Alcohol	1 st : Benzodiazepines such as lorazepam or oxazepam (A, I). Fluids and thiamine (I). 2 nd : Carbamazepine and valproic acid for mild to moderate symptoms as an adjunct or alternative to benzodiazepines (B). Adj: Other medications such as beta-blockers (C), clonidine (C, II), or antipsychotics (II) as adjuncts to benzodiazepines.	1 st : Naltrexone and/or acamprosate (A, I). Naltrexone blocks opioid receptors and the rewarding effects of alcohol. Acamprosate reduces long-term withdrawal effects such as dysphoria and anxiety through its effects on the gamma-aminobutyric (GABA) system. 2 nd : Disulfiram (B, II). Disrupts alcohol degradation resulting in unpleasant side effects when drinking. Appropriate for highly motivated patients.
Cocaine	Typically only supportive care is required (II), but severe symptoms such as seizures or delusions may require intervention (II). Benzodiazepines may be appropriate for acute agitation (III).	No specific recommendations because research is limited. If psychosocial treatments fail, consider topiramate, disulfiram, or modafinil (-).
Opioids	For overdose, naloxone can reverse respiratory depression (I). 1 st : Gradual tapering of opioid agonist treatment (OAT) such as buprenorphine-naloxone or methadone (A, I). 2 nd : Abrupt discontinuation of the opioid along with clonidine or clonidine-naltrexone (II). Adj: Clonidine as an adjunct to OAT tapering. Note: Medically supervised rapid discontinuation of opioids is rarely effective long-term; long-term maintenance with an opioid agonist treatment (OAT) is preferable (B).	1 st : OAT. Methadone (A) or sublingual buprenorphine or buprenorphine-naloxone (?). Buprenorphine is a partial agonist with low overdose risk. Naloxone is an opioid antagonist and produces severe withdrawal effects in addicted individuals, reducing risk of diversion. 2 nd : Naltrexone post-opioid withdrawal (C), or in motivated opioid dependent individuals (?). Naltrexone is an opioid antagonist that blocks opioid effects.

VA/DoD Recommendations: The degree to which the VA/DoD has recommended a particular intervention is noted as follows for medications as first-line treatments (1st), second line treatments (2nd), or adjunctive treatments (Adj): A = The VA/DoD strongly recommends that clinicians provide this intervention to eligible patients based on good evidence for its efficacy and benefits. B = The VA/DoD recommends that clinicians provide this intervention to eligible patients based on fair evidence for its efficacy and benefits. C = The VA/DoD has no recommendation for or against provision of this intervention because although there is fair evidence of its efficacy, it is not clear that benefits outweigh risks. ? = The VA/DoD concludes that there is insufficient evidence to recommend for or against this intervention. APA Recommendations: The degree to which the APA has recommended a particular intervention is noted as follows: I = The APA recommends this intervention with substantial clinical confidence. II = The APA recommends this intervention with moderate clinical confidence. III = The APA indicates that this intervention may be recommended on the basis of individual circumstances. - = The APA has not indicated a degree of confidence for this recommendation.