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The Potential of Glial Cell Modulators in the Management of Substance Use Disorders

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Abstract

The pervasive and devastating nature of substance use disorders underlies the need for the continued development of novel pharmacotherapies. We now know that glia play a much greater role in neuronal processes than once believed. The various types of glial cells (e.g., astrocytes, microglial, oligodendrocytes) participate in various functions that are crucial to healthy central nervous system function. Drugs of abuse have been shown to interact with glia in ways that directly contribute to the pharmacodynamic effects responsible for their abuse potential. Through their effect upon glia, drugs of abuse also alter brain function resulting in behavioral changes associated with substance use disorders. Therefore, drug-induced changes in glia and neuroinflammatory processes have been investigated to treat various aspects of drug abuse and dependence. This manuscript presents a brief overview of the effects of each of the major classes of addictive drugs on glia. Next, the paper reviews the pre-clinical and clinical studies assessing the effects that glial modulators have on abuse-related behavioral effects, such as pleasure, withdrawal, and motivation. There is a strong body of pre-clinical literature demonstrating the general effectiveness of several glia-modulating drugs in models of reward and relapse. Clinical studies have also yielded promising results, though not as robust. There is still much to disentangle regarding the integration between addictive drugs and glial cells. Improved understanding of the relationship between glia and the pathophysiology of drug abuse should allow for more precise exploration in the development and testing of glial-directed treatments for substance use disorders.

1. The Need for Continued Discovery of Medications to Treat Substance Use Disorders

Drug abuse is a chronic, relapsing disease characterized by dysfunction in brain reward-, motivation-, and memory-related circuitry [1]. Compulsive drug seeking and use, despite harmful consequences, results in progressive disability and can lead to premature mortality

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[2]. Substance use disorders (SUDs) contribute to the deaths of millions of people each year directly through overdose or indirectly by worsening comorbid psychiatric and medical conditions. Drug abuse also aids the spread of infectious diseases, such as HIV and Hepatitis C, and is associated with crime and violence [3]. According to the most recent World Drug Report, globally, an estimated ~164 million people suffer from an alcohol or drug use disorder, meaning that their drug use is sufficiently harmful to necessitate treatment [3].

Worldwide, an estimated 27 million people suffered from opioid use disorder (OUD) in 2017 [3]. Medications to treat OUD have a well-established efficacy, improving quality of life and reducing premature mortality [4; 5]. Though long-term maintenance on μ -opioid receptor agonist (methadone), partial agonist (buprenorphine) or antagonist (naltrexone) medications have significant clinical utility, retention rates at six months are typically below 50% [6].

Like opioids, there are medication options available to the estimated 1.4% of the global population that suffer from alcohol use disorder [7]. First-line pharmacotherapies include the opioid receptor antagonist, naltrexone, and glutamatergic modulator, acamprosate [8]. Naltrexone has been shown to reduce heavy drinking but there is little evidence that it has significant effects on alcohol abstinence [9]. Meanwhile, acamprosate only increases the rate of alcohol abstinence by about 10% [10]. Second-line agents, such as disulfiram - and those not approved by the U.S. Food and Drug Administration (FDA), like topiramate and baclofen - have been shown to reduce alcohol consumption in clinical trials, but without significant effects on overall abstinence [8].

There are more treatment modalities for nicotine dependence (i.e., smoking cessation, tobacco use) than opioids and alcohol combined. There are two pharmacotherapies approved by the FDA for nicotine dependence - bupropion (norepinephrine and dopamine reuptake inhibitor) and varenicline (partial agonist of the nicotinic acetylcholine receptor) - and five forms of nicotine-replacement therapy (i.e., patch, gum, lozenge, inhaler and nasal spray) [11]. However, with all these treatments, the likelihood of long-term abstinence remains low [12; 13]. With an estimated 1.1 billion active tobacco users, the morbidity associated with tobacco use remains one of the largest global public health epidemics [14; 7]

There are no FDA-approved pharmacotherapies to assist the estimated 18.2 million cocaine users, or the 34.2 million non-medical users of amphetamine-type stimulants (e.g., methamphetamine, amphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) or 'Ecstasy')[3]. These potent psychostimulants are among the most addictive drugs classes. Similarly, there are no pharmacotherapies available to treat cannabis use disorder, which may develop in as much as 10% of the estimated 192 million users [15,16, 3].

In sum, many efficacious and effective pharmacological interventions for alcohol and drug dependence exist. However, there remains significant room to improve rates of long-term abstinence. Additionally, there are several drugs with significant potential for abuse for which there are no pharmacotherapies with reliable and robust evidence of treatment efficacy in clinical trials. Therefore, there is a clear need for additional therapeutic strategies to help those who suffer from SUDs.

2. Glia: Much More Important Than Once Believed

Glia were once considered to be passive neuronal support, simply ensuring that neurons could function properly [17]. However, we now know that glia are actively involved in the development and protection of, and are critical to, healthy CNS function [18–20]. Glia constitute over 90% of the cells in the CNS and between 33 to 66% of the total brain mass - depending upon the mammalian species being examined [21,22]. It is now widely-recognized that glia play a significant role in many neuronal processes, such as neurotransmitter modulation, along with synaptic development and plasticity [23,24]. There are a variety of subtypes of glial cells in the CNS, with microglia, and the various macroglia (i.e. astrocytes, ependymal cells, oligodendrocytes, and radial cells) each having a specialized function [25].

Microglia are the brain's immune cells, functioning to cleanse the extracellular fluid in order to maintain central homeostasis [26]. As the resident macrophage cells, microglia act as the first and main form of active immune defense in the CNS [27]. Microglial processes directly interact with neurons, other glia types and blood vessels [28]. Microglia have been observed to have receptors for neurotransmitters, allowing them to respond to neuronal activation [29,30].

Astrocytes are a type of macroglia that control the level of neurotransmitter around synapses by regulating the concentrations of important ions and providing metabolic support [31,32]. Astrocytes also connect the vasculature and neurons by regulating local blood flow in response to neuronal activity and providing energy substrates (e.g., glucose) to neurons [33,17]. Astrocytes also release numerous gliotransmitters [e.g., glutamate and adenosine triphosphate (ATP)] known to regulate many CNS functions including synaptic plasticity, neural network activity and sleep [34].

Oligodendrocytes produce and maintain the myelin sheath that surrounds axons, allowing for rapid saltatory propagation of action potentials [35, 17]. Oligodendrocytes also release several neurotrophins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 [36]. Relative to the other types of glia, little is known of the function of ependymal cells. We do know that ependymal cells line the spinal cord and ventricles of the brain and are involved in creating cerebrospinal fluid [37]. Finally, radial glia are progenitor cells that can generate neurons, astrocytes, and oligodendrocytes [38, 39].

Current SUD medication strategies focus on neuronal mechanisms underlying addiction. Common medication targets include the neurobiological substrates responsible for the rewarding and reinforcing properties of drugs of abuse, such as dopamine [40–43]. All drugs of abuse are believed to exert their reinforcing effects by increasing the transmission of dopamine within the nucleus accumbens (NAcc), achieved through various molecular pathways for each drug class [44]. Recently, however, drug and neuroimmune interactions have emerged as potential targets for treating SUDs. There is an extensive body of literature to suggest that glial cells are influenced by drugs of abuse and these interactions contribute to their acute and chronic behavioral effects [45, 46]. Therefore, the involvement of glia in the development and maintenance of SUDs has important implications for the development

of novel pharmacotherapies. The majority of this research has focused on interactions between addictive drugs and microglia, astrocytes or their gliotransmitters [47].

The purpose of the current narrative review is to summarize the pre-clinical and clinical findings from studies that have sought to evaluate the potential of glial-modulating drugs to treat features of SUDs. Several experimental paradigms have been developed to screen medications for clinical utility in treating SUD. A primary focus of these paradigms is the ability of the medication to alter the abuse potential of drugs as quantified by attenuation of the drug's rewarding and/or reinforcing effects [48]. "Reward" is conceptualized as the experienced enjoyment or arousal in response to the drug. "Reinforcement" is drug-seeking and drug-taking behaviors thought to reflect the physiological, behavioral, and cognitive drug effects. Other important experimental measures focus on other aspects of the addictive process, such as craving (subjective desire for the drug) and relapse (reinstatement of drug-seeking or drug-taking following a period of abstinence).

The review is organized by drug class (i.e., alcohol, cannabis, opioids, nicotine, and psychostimulants). First, the manuscript will briefly detail how each drug class interacts with glia and how these effects contribute to their behavioral pathology. Next, we review pre-clinical studies that have evaluated the effects of medications with glial-modulating properties on the pharmacodynamic effects of drugs of abuse (e.g., rewarding and reinforcing effects). Finally, the author reviews clinical trials that have evaluated the effects of glia modulators on addiction-related outcomes.

Using PubMed and PsychINFO, the author searched for English-language articles published between 1970 and 2019. The search included various combinations of the following terms: glia, astrocytes, microglia, addiction, substance use disorder, cocaine, alcohol, amphetamine, methamphetamine, heroin, opioids, nicotine, and marijuana. Over 500 publications were identified. After removing duplicates, titles and/or abstracts were reviewed to ensure relevance. The search criteria included original reports assessing the interaction between glia, glial products and drugs of abuse, or assessment of medications that act on glia as potential treatments for SUDs. Data from approximately 200 articles are included in the current review.

3. Drugs of Abuse and Neuroimmune Interactions as Targets for Medication Development

3.1 Opioid Effects on Glia

Glia have been shown to express all three opioid receptors subtypes (μ , κ , δ) and the mRNA that encodes them [49–51]. Glia μ -opioid receptor expression can account for 2–9% of the total observed in the CNS, with δ -opioid receptor glial expression estimated at 5% [52–55]. Though we know that glial κ -opioid receptor expression has been observed, its degree has yet to be quantified [56–57]. The endogenous μ , κ , and δ opioid receptors ligands (β -endorphin, enkephalins, and dynorphins, respectively) are synthesized in glia. However, little is known regarding the storage and release of endogenous opioid neuropeptides from glial cells [58].

Concerning exogenous opioids, both natural opiates (e.g., morphine and codeine) as well as synthetic and semi-synthetic opioids (e.g., oxycodone and heroin) have been shown to have effects on glia activity [59–60]. Pharmacologically and pharmacodynamically, morphine is commonly considered to be the archetypal μ -opioid receptor agonist (Mello and Bayer, 1998; Pathan and Williams 2012). As such, morphine is commonly used in pre-clinical investigations of opioids effects. Morphine administration increases the expression of cellular markers associated with glial cell activation, such as microglial CD11b (the β -integrin marker of microglia) and glial fibrillary acidic protein (GFAP), a hallmark intermediate filament protein in astrocytes [63–67].

The effect of morphine on GFAP is not observed when it is co-administered with the non-selective opioid receptor antagonist, naltrexone [63]. Morphine administration can also lead to increased expression of immune-modulating factors released from glial, such as cytokines: interleukin-1 beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α), and chemokines: C-C motif chemokine ligand-5 (CCL5), and monocyte chemoattractant protein-1 (MCP-1) [68–72]. Morphine also enhances microglial migration and apoptosis [73–75].

Opioids are believed to interact with glia through the pattern recognition receptor, toll-like receptor-4 (TLR-4), a key mediator of innate immunity and inflammation [76–77]. TLR-4 is widely expressed in all glia types [78, 79]. Morphine binds to the myeloid differentiation factor 2 (MD-2), which induces TLR-4 oligomerization and results in glial activation [66, 80]. TLR-4 has been found to be required for many opioid-induced effects on glia [75,76]. Genetic knockout of TLR-4/MD-2 suppressed morphine-induced glial activation [81].

Concerning addictive processes, opioid actions upon glial cells also contribute to opioid actions within the brain's reward center [82]. The mesolimbic dopamine pathway transmits dopamine from the ventral tegmental area (VTA) to the NAcc, and to components of the limbic system associated with emotion and memory formation [44, 83, 84]. Narita and Colleagues (2006) published one of the most robust studies to observe the direct actions of glia on the rewarding effects of drugs of abuse. The investigators found that intra-NAcc and intra-cingulate cortex administration of astrocyte-related soluble factors enhanced morphine conditioned place preference (CPP). Conditioned Place Preference is a pre-clinical, Pavlovian conditioning model commonly used to quantify the rewarding effects of drugs by spatially and temporally pairing distinct environments with distinct drug or non-drug states. The development of a preference for the drug-paired environment is considered to be an index of the rewarding value of the drug [85]. Conversely, microglia-related soluble factors failed to alter the rewarding effects of morphine. However, other studies suggest that opioid interactions with microglia contribute to opioid actions within the brain's reward system. Inhibition of microglial activity has been shown to attenuate morphine-induced dopamine release in the NAcc and hinder the development of morphine CPP [86, 87]. Genetic manipulation of the TLR-4 receptor has provided further evidence of the relationship between opioid effects on glia and its behavioral outcomes. For example, TLR-4 knockout mice showed impaired development of CPP to morphine and oxycodone [66,88].

3.2 Glial Modulators as Potential Treatments of Opioid Use Disorder

As reviewed above, opioid-induced activation of glia appears to contribute significantly to the behavioral effects attributed to their misuse. As such, there has been interest in evaluating the potential of glial modulators as treatments for OUD.

Pre-clinical Studies: Building upon research demonstrating the importance of TLR-4 modulation of the rewarding effects of opioids, researchers found that the low-affinity pharmacological TLR-4 inhibitor, (+)-naloxone, impairs the development of morphine CPP and the self-administration of remifentanyl - a potent synthetic opioid. (+)-Naloxone also significantly attenuates morphine-induced dopamine release in the NAcc [88]. Furthermore, chronic antagonism of TLR-4 with (+)-naltrexone blocks cue-induced reinstatement of heroin self-administration [89]. Though compelling, recent work has failed to replicate the finding with (+)-naloxone and (+)-naltrexone [90]. This lack of replication could question the hypothesized role of TLR-4, procedural differences between the two investigations may be to responsible.

Other glial-modulating drugs have shown more consistent results across preclinical studies. Bland and Colleagues [86] investigated the ability of ibudilast, a non-selective phosphodiesterase (PDE) and TNF- α inhibitor [91], to reduce morphine-induced dopamine release. The co-administration of ibudilast (AKA, AV-411) with morphine significantly attenuated morphine-induced dopamine transmission within the reward pathway. In another study, ibudilast also reduced the somatic signs of opioid withdrawal [92], a contributor to the maintenance of OUD [93].

The ability of glia-modulating drugs to reduce the abuse potential of opioids, has also been observed in behavioral models. Propentofylline is a PDE inhibitor that hinders induced TNF- α released and increased the expression of the astroglial glutamate transporter (GLT-1) [94–96]. Propentofylline has been shown to suppress the development of morphine CPP [97]. Fluorocitrate is a metabolic inhibitor of glia that has also been shown to reduce morphine CPP [98,99]. In this study, fluorocitrate also reduced the signs of opioid withdrawal. Another glia modulator that has been investigated in this capacity is the microglia inhibitor, minocycline [100]. Direct administration of minocycline into the rat NAcc blocked the maintenance of morphine CPP and the reinstatement of morphine-seeking behavior – a pre-clinical model of relapse [101]. Finally, pioglitazone, which inhibits the expression of cytokines by microglia [102], attenuates opioid withdrawal, heroin self-administration, and heroin-induced dopamine release [103–106].

There is a robust body of pre-clinical literature to suggest that opioid effects on glia contribute to other important pharmacodynamic effects of opioids [107]. Cumulating evidence has demonstrated that the pro-inflammatory effects of exogenous opioids contribute to opioid-induced hyperalgesia and the development of opioid tolerance and dependence [108–109]. Ibudilast, minocycline, propentofylline, and fluorocitrate have all shown promise to increase the clinical utility of opioid drugs by improving their analgesic efficacy or antagonizing the development of morphine tolerance and/or hyperalgesia [65,92,110–115]. Procyanidins are a structurally diverse set of compounds that can suppress morphine-induced activation of microglia and other glial markers [116]. Procyanidins have

also been found to attenuate morphine-induced antinociceptive tolerance [117]. Finally, statins are potent inhibitors of various glial pathways and products [118–120]. Simvastatin, rosuvastatin, and atorvastatin have all been shown to have significant protective effects against the development of tolerance to the antinociceptive effects of morphine, and physiological dependence [121–126]

In addition to direct actions, the downstream effects of opioid-induced changes in glial function may provide another means to pharmacologically alter the behavioral effects of opioids. Opioid effects on astrocytic glutamate transporters can lead to deficits in glutamate transmission [127]. Pharmacologically restoring these deficits in glutamate function has been shown to attenuate morphine CPP [128], reinstatement of hydromorphone CPP [129], as well as heroin-seeking behavior [130, 131]. N-acetylcysteine (NAC) is a drug that increases the expression and function of the cysteine-glutamate exchanger (xCT) and the glutamate transporter-1 (GLT-1) [132]. In rats, NAC treatment has been reported to disrupt cue-induced heroin seeking [133]. Table 1 summarizes the pre-clinical and clinical findings of the effects of glial modulators on the abuse potential of opioids.

Human Studies: Clinical research is only beginning to replicate the promising pre-clinical findings concerning the treatment potential of glia-modulating drugs (see [134] and [135] for previous reviews) Cooper and Colleagues (2016) assessed the ability of ibudilast to alter opioid withdrawal symptoms among participants with OUD. Opioid-dependent volunteers (N=31) were maintained on morphine and then abruptly transitioned to placebo (0 mg). Participants were randomized to active (20 or 40 mg twice daily [BID]) or placebo ibudilast, while being maintained on morphine (120 mg/day) for 14 days, and subsequently placebo for the last seven days of the study. Opioid withdrawal was assessed daily using the Subjective and Clinical Opioid Withdrawal Scales (SOWS and COWS, respectively). All groups exhibited withdrawal during the third week. Analyses combining the two active ibudilast conditions found that this group had lower ratings of: “anxious,” “perspiring,” “restless,” and “stomach cramps” during the week in which they were withdrawing from morphine [136].

In a later publication, Cooper and Colleagues reported no “consistent” effects of ibudilast on the subjective effects of oxycodone [137]. Metz et al., (2017) extended these findings by testing the effects of ibudilast on the positive subjective and reinforcing effects of oxycodone. Opioid-dependent participants with OUD (N=11) first underwent in-patient detoxification followed by maintenance on ibudilast (0 and 50 mg BID, double-blind, randomized). The subjective and reinforcing effects of oral oxycodone (0, 15, and 30 mg/70 kg) were assessed under each ibudilast maintenance condition. While under active ibudilast maintenance, subjects’ ratings of drug “liking” were significantly decreased for the median oxycodone dose (15 mg). Oxycodone self-administration (15 mg) was also significantly reduced in the active ibudilast condition. Similar effects of ibudilast maintenance were found on the 30 mg dose of oxycodone, though they only approached statistical significance. Self-reported “craving” for opioids was also significantly reduced by ibudilast [138].

In a pilot study, Mogali et al. (2014) also tested the ability of a glial modulator to alter the positive subjective effects of oral oxycodone, along with opioid craving. Non-dependent

recreational opioid users (N=7) participated in this randomized, double-blind outpatient study. Subjects completed five sessions in which they received acute minocycline (0, 100, or 200 mg) in combination with oral oxycodone (0, 40 mg). Compared to placebo, minocycline reduced participants' ratings of "high," drug "liking," "good effect," as well as how much participants reported that they "would pay" for the oxycodone dose they received [139]. In a later study among an opioid-dependent sample, minocycline (200 mg/day for 15 days) failed to alter outcomes, such as opioid craving and withdrawal [140]. However, the minocycline maintenance period did not significantly alter serum cytokine levels, therefore, the negative findings may be the result of an insufficient effect on glial activity.

In another investigation of dependent non-medical opioid users, Jones et al. (2018) assessed the ability of pioglitazone to alter the abuse potential of heroin. Heroin-dependent participants were recruited for a 3-week study. Upon admission, participants were randomized to either active (45 mg, n=14) or placebo (0 mg, N=16) pioglitazone maintenance for the duration of the study. After 5–7 days of stabilization on sublingual buprenorphine (8 mg, BID), participants began testing. Pioglitazone maintenance failed to alter the reinforcing or positive subjective effects of heroin, but did reduce heroin craving and overall anxiety [141].

The interaction between pioglitazone and oxycodone was also tested within a sample of non-dependent recreational prescription opioid users (N=17 completers). In this study participants were maintained for ~2 weeks on each of three doses of pioglitazone (0mg, 15mg, 45mg). Under each pioglitazone maintenance condition, participants completed a laboratory session assessing the subjective, analgesic, physiological and cognitive effects of oxycodone (0, 10, and 30 mg). Oxycodone produced typical μ agonist effects, such as miosis, decreased pain perception, and positive subjective effects. Yet, oxycodone effects did not vary as a function of the pioglitazone maintenance [142].

3.3 Psychostimulant Effects on Glia

Cocaine and amphetamine-type stimulants (e.g., d-amphetamine, methamphetamine, and MDMA) are potent psychostimulants whose abuse potential primarily results from their potent agonist effects upon monoamine transmission - particularly dopamine [143,144]. Among the cocaine-mediated secretory cytokines, upregulation of inflammatory factors, such as IL-1B, IL-6, and TNF- α has been demonstrated in both in vitro and in vivo studies [145–148]. There are numerous proposed mechanisms for cocaine-induced astrogliosis and microglial, though our understanding of them is incomplete [149–156].

Methamphetamine is also thought to have similar actions upon glia. Both cocaine and methamphetamine stimulate intracellular sigma-1 receptors, a means by which both drugs activate astrocytes and microglia [157–164]. Methamphetamine is thought to induce microglial apoptosis through this pathway [165]. Methamphetamine also differentially modulates the production of IL-6 and TNF- α in microglia [166,167].

Like opioids, TLR-4-induced microglial reactivity has been found to be critical to psychostimulant-induced dopamine release, reward, and reinforcement [156]. Of particular relevance may be the fact that many of the neuroinflammatory effects of cocaine,

amphetamine, and methamphetamine are found within the brain's reward center. The self-administration of several drugs of abuse has been found to alter gliogenesis in the medial prefrontal cortex [168], an area of the brain involved in reward processing, attention, and drug reinstatement [169]. In the NAcc, cocaine and methamphetamine increase the expression of glial fibrillary acidic protein (GFAP), an indicator of astrocyte activation GFAP [97,170–174]. Methamphetamine also increases the expression of the 27-kD heat shock protein (HSP27: a robust product of astrocytes and microglia) in the cortex, striatum, and hippocampus - all critical components of addiction neurobiology [175–177].

Region-specific, psychostimulant-induced activation of glia, has been associated with behavioral sensitization, whereby the behavioral response to a specified dose of drug increases with repeated administration [178]. Behavioral sensitization is commonly assessed in pre-clinical studies to model the impact of repeated drug exposure on behavior and neuroplasticity [179]. Studies have shown significant correlations between the degree of amphetamine-induced behavioral sensitization and the magnitude of their effects on astrocytes [170, 180, 181]. More specifically, increased GFAP immunoreactivity in the striatum and increased astrocyte proliferation/migration [indicated by increased expression of basic fibroblast growth factor (bFGF)] in the NAcc, have been shown to be direct contributors to the persistent behavioral sensitization seen with repeated exposure to psychostimulants [182–183].

Methamphetamine-induced increase in microglial activation in the reward center has been identified by increased immunoreactivity of the activated microglia marker, macrophage-1 antigen-CD11b (Mac1-CD11b). Methamphetamine effects on Mac1-CD11b have also been linked to drug-induced behavioral sensitization [175,184,185].

Dopamine depletion occurs following repeated exposure to psychostimulant drugs [186,187]. A direct association has been observed between the neurotoxic effect of methamphetamine on dopamine and its actions upon on glia [184]. Imaging studies in humans have confirmed that methamphetamine's effects on glia are conserved across rodents and humans [188]. However, differences in the expression of activated microglia seen between human methamphetamine users relative to matched-controls, were not replicated with cocaine users [189].

In both pre-clinical and clinical studies, psychostimulants are neurotoxic to striatal dopamine [190]. This neurotoxicity is at least partly mediated through glia. Furthermore, neuroadaptations in midbrain VTA neurons, induced by psychostimulant effects on glial-derived neurotrophic factor (GDNF), play an important role in craving and drug-seeking behavior [191–194]. In a human imaging study, glial activation also enhanced the striatal dopamine elevation resulting from the administration of the amphetamine-type stimulant, methylphenidate [195]. There is also a growing body of literature linking psychostimulant-induced disrupted communication between glia and neurons with the pathological learning involved in SUDs [196, 197]. Therefore, psychostimulant effects on glia may contribute directly to all of the key factors to psychostimulant addiction: drug liking, escalating use, craving, and relapse [198].

Psychostimulants also produce profound alterations in the ability of glia to regulate glutamate homeostasis. Psychostimulants produce increases in extracellular glutamate in the CNS [171; 181, 199- 201]. This effect can occur via psychostimulant actions on both microglia and astrocytes [147, 202, 203]. However, much of the research has focused on psychostimulant effects on the glutamate transporter (GLT-1) that is expressed on astrocytes, critical for clearing synaptic glutamate [204]. There is evidence that both psychostimulant exposure and extinction/abstinence contribute to alterations in astrocytic glutamate clearance [202, 205–207]. Glutamate is a neurotransmitter highly involved in the learning behaviors associated with SUDs [208]. Disruptions in glutamate homeostasis have been linked to the neural mechanisms underlying relapse. Glutamatergic hyper-excitability has also been observed in the cocaine- and stimulant-addicted brain [209].

3.4 Glial Modulators as Potential Treatments of Psychostimulant Use Disorder

Pre-clinical Studies: Medications that can restore the ability of astrocytes to regulate glutamate homeostasis have been found to alter psychostimulant-induced behavioral and neuroadaptive effects. The glutamate transport activator, MS-153, attenuates cocaine- and methamphetamine-induced CPP [128]. Ceftriaxone is an antibiotic that also modulates the uptake activity of glial GLT-1. Chronic ceftriaxone treatment blocks cocaine- and methamphetamine-seeking behavior in rodents [210–215]. NAC is a drug that increases the expression and function of the cysteine-glutamate exchanger and the GLT-1 and restore psychostimulant-induced glutamate dysregulation [216–218]. In rodent models, NAC reduces cocaine-maintained responding, escalation of cocaine self-administration, and cocaine-seeking [131, 212, 219-224, though see [225]].

Surprisingly, N-acetylcysteine has not been shown to be as efficacious in rodent studies of methamphetamine, as it has been with cocaine. [226]. However, other glial modulators that have shown promise include the microglia inhibitor, minocycline. In mice, pretreatment with minocycline significantly reduced methamphetamine-induced dopamine release across species [185, 227]. Additionally, minocycline has been shown to have protective effects against methamphetamine-induced behavioral sensitization and deficits in long-term memory associated with repeated methamphetamine exposure, [185,228]. Minocycline has also been shown to attenuate the reinforcing effects of methamphetamine, and reinstatement of methamphetamine-seeking behavior [229, 230].

Minocycline also attenuates cocaine-induced dopamine release [155] and prevented the development of cocaine-induced sensitization [231]. However, with both cocaine and methamphetamine, minocycline could not reverse drug-induced sensitization, once established. The anti-inflammatory glial attenuator and non-selective PDE inhibitor, ibudilast, is able to attenuate cocaine sensitization [232]. Ibudilast also suppresses stress- and drug-induced reinstatement of methamphetamine seeking [233], locomotor sensitization [234] and self-administration [229]. Similarly, propentofylline (a PDE inhibitor/ GLT-1 upregulator) decreases preference for methamphetamine-associated cues [97] and inhibited cue-primed cocaine seeking [235]. There is also evidence that pharmacological inhibition of TLR-4 and PPAR γ agonism (using GW9662) may alter psychostimulant effects responsible for initial use and relapse [155, 236, 237].

Human Studies: The PDE and TNF- α inhibitor, pentoxifylline, was one of the first glial-modulator drugs tested for cocaine use disorder in a pilot clinical trial by Ciraulo and Colleagues [238]. Sixteen cocaine-dependent participants were maintained for 8 weeks on pentoxifylline (1200 mg/day). The investigators found a trend towards decreased cocaine use; the only positive medication effect observed among five medications tested.

Another group of investigators examined the effects of celecoxib maintenance (200 mg/day for 8 weeks) on cocaine use outcomes [239]. Celecoxib is a cyclooxygenase 2 (COX-2) inhibitor that counteracts glia-driven neuroinflammation [240]. No significant effect of celecoxib was found on cocaine abstinence rates, craving, or related psychosocial measures. Among 30 treatment-seeking adults with cocaine use disorder, pioglitazone (45 mg/day) resulted in a significantly greater decrease in craving (vs placebo [241]). Pioglitazone treatment also improved brain white matter integrity that may be associated with impulsivity, decision making, and time to relapse [242, 243].

NAC is one of the most studied glial modulators for treating cocaine use disorder. First, in an open-label pilot study, 23 treatment-seeking cocaine-dependent patients received NAC at doses of 1200 mg/day, 2400 mg/day or 3600 mg/day for 4 weeks [244]. Higher doses of NAC (2400 and 3600 mg) increased retention in treatment and aided in reducing cocaine use. Concurrently, La Rowe and Colleagues (2007) reported that 3-day NAC treatment (600 mg) decreased cocaine desire during a cocaine cue-reactivity procedure (N=15) [245]. In another pilot study among cocaine-dependent males (N=4), NAC treatment (1200–2400 mg/day, 4 days) reduced cocaine craving following an intravenous cocaine injection [246].

Following up on their clinical laboratory data, La Rowe and Colleagues (2013) conducted a clinical trial among treatment-seeking adults with cocaine use disorder (N=111). All participants received cognitive-behavioral therapy over an 8-week treatment period and were randomized to receive either 600 or 1200 mg (twice per day) NAC or placebo during the treatment phase. Eight-week treatment with NAC failed to reduce cocaine use or craving. However, a positive signal was found for the effects of 1200 mg, showing lessened time to relapse and lower rating of drug craving [247].

Back and Colleagues (2016) tested NAC for post-traumatic stress disorder symptomology and substance abuse, among dual-diagnosed veterans (N=35). The investigators found that active NAC maintenance (2400 mg/day, for 8 weeks) significantly reduced drug craving and depression but had no effect on drug-taking behavior [248]. Most recently, Levi-Bolin et al., (2017) found that NAC maintenance (2400 mg) reduced the incentive salience of cocaine-related stimuli and has promising effects on cocaine self-administration [249]. Though clinical trials with NAC have an inconsistent pattern of results, a review and meta-analysis of the efficacy of NAC in treating SUDs found that in comparison to placebo, NAC was significantly superior in treating drug craving [250]. See also a review by Nocito-Echevarria and Colleagues (2017) [251].

In comparison to cocaine, there are fewer clinical studies examining glial modulators as a potential pharmacotherapy for the abuse of amphetamine-type stimulants. However, like cocaine, NAC has shown promise in reducing craving for methamphetamine. Significant

reductions in craving were observed among methamphetamine-dependent volunteers (N=32) following 4 weeks of maintenance on NAC (1200 mg/day) [252].

In other clinical trials, ibudilast attenuated subjective effects of methamphetamine among methamphetamine-dependent volunteers (N=11) [253]. Participants received oral placebo, or ibudilast (40 mg, 100 mg BID) for 7 days. Following intravenous methamphetamine (15 and 30 mg), active ibudilast reduced subjective effects including: “high,” “good,” and “like.” In another clinical study (N=11), ibudilast (50 mg, BID) improved attention during early abstinence from methamphetamine among methamphetamine-dependent participants [254].

The promising pre-clinical findings with minocycline have also been replicated in clinical samples. Among volunteers (N=10) with no history of drug abuse, minocycline treatment (200 mg/day for 5 days) was found to attenuate the positive subjective effects of oral dextroamphetamine (20 mg/70 kg). Minocycline treatment did not have a significant effect on dextroamphetamine self-administration [255].

3.5 Alcohol Effects on Glia

The pharmacological effects of alcohol (or ethanol) are diverse and include alterations in Gamma-Aminobutyric Acid (GABA) and glutamate receptor function, endogenous opioids, and VTA dopamine activity [256]. Alcohol is believed to activate transcription factors that increase the expression of pro-inflammatory molecules [257–259]. Alcohol effects in the CNS are also associated with elevations in various innate immune signaling molecules, including IL-1 β , IL-6, CCL3, CXCL2, GFAP, TLR-3,–4, and TNF- α [260–263]. Microglia and pro-inflammatory cytokines also alter synaptic signaling in a way that modulates alcohol effects on GABA receptors [45,264]

The effects of alcohol on glia have been shown to be dependent upon the dose and pattern of alcohol administration. For example, rats provided free access to alcohol for shorter periods (4–12 weeks) show increased activation of astrocytes (measured by GFAP), but decreased astrocyte activation was observed under conditions of extended alcohol access (36 weeks) [265, 266]. Glial response to alcohol also appears to be dependent upon the brain region assessed. Studies in rodent models of alcohol consumption have shown significant regional variability in the expression of pro-inflammatory molecules in the brain [266–271].

In humans with alcohol dependence, analysis of post-mortem tissue reveals reduced GFAP immunoreactivity in the dorsolateral prefrontal cortex, and a dramatic loss of astrocytes in the hippocampus [272,273]. Meanwhile, increased immunoreactivity for microglial-specific proteins is observed in the cingulate cortex of alcohol-dependent participants [274]. There is also evidence of increased expression of neuroinflammatory genes and protein markers in the frontal cortex [275–276].

Like all drugs of abuse covered so far, TLR-4 has been found to be a key receptor involved in alcohol-induced neuroimmune signaling [277]. Astrocytes lacking TLR-4, or its critical adaptor molecules, fail to show activation by alcohol [278]. Similar effects can be produced in vivo. For example, alcohol-induced expression of pro-inflammatory molecules was blocked by TLR-4 neutralizing antibodies [257]. Additionally, TLR-4 knockout mice

fail to demonstrate evidence of alcohol-induced glial cell activation [257, 260, 279–284]. Mice lacking TLR-4 are also protected against alcohol anxiety-like behavior associated with alcohol withdrawal, suggestive of involvement of alcohol-neuroimmune interactions in the greater pathophysiology of alcoholism [278]. Direct manipulation of TLR-4 can also influence drinking behavior. Alcohol-preferring rat strains have been found to have increased expression of TLR-4 [285]. Viral-mediated knockdown of TLR-4 expression reduces alcohol consumption in rats [285–286]. Genetic perturbation of chemokine networks can also reduce drinking behavior (Blednov et al., 2005).

One of the more intriguing and novel effects of alcohol is its effects upon high-mobility group box 1 (HMGB1), an endogenous TLR-4 agonist [288]. Alcohol administration to mice and rats can lead to persistent increases in the expression of HMGB1 (along with various TLR receptors) and triggers innate immune responses through binding to TLR-4 [268, 270, 289]. Increases in HMGB1 and TLR signaling have been correlated with the level of alcohol consumption among moderate and heavy drinkers [290]. Repeated exposure to alcohol has been shown to sensitize microglia toward hyperactivity in an HMGB1-dependent manner [291]. Sensitized or “primed” microglia produce a greater inflammatory response to immune stimuli than non-primed microglia [292]. Alcohol-induced neuroimmune sensitization is thought to be a significant contributor to the neurodegeneration seen with chronic alcohol use [266,293]. This sensitization is also thought to contribute to loss of control, increased impulsivity and negative affect, hallmarks of the pathology of alcohol use disorder [294, 295]. In humans with alcohol use disorder, plasma levels of pro-inflammatory cytokines have been shown to correlate with addiction severity and alcohol craving [296,297]. There is also a growing body of literature implicating neuroimmune systems in alcohol withdrawal [298–300].

3.6 Glial Modulators as Potential Treatments of Alcohol Use Disorder

Pre-clinical Studies: Given the proposed molecular, cellular and behavioral contribution of neuroinflammation to alcohol use disorder, immune therapies may provide benefits for prevention and recovery. As previously reported with opioids and psychostimulants, the microglial inhibitor, minocycline, has demonstrated promise in pre-clinical studies. Minocycline has been shown to reduce alcohol self-administration and reinstatement of alcohol CPP [301–304]. Minocycline has also been shown to protect the developing brain against alcohol-induced damage [166]. Other antibiotics with glial-modulating effects, such as rapamycin, indomethacin, tigecycline and glycyrrhizin, have also show promise in pre-clinical studies [305–314]. Ceftriaxone, the glial GLT-1 modulator, has shown particular effectiveness in relapse models of drinking behavior [315–318].

PDE-4 inhibitors, including ibudilast, mesopram, rolipram, and CDP-840 have also been shown to decrease alcohol intake in rodents [319–322]. Meanwhile, microglial-inhibiting effects of pioglitazone have been found to reduce the toxicity of alcohol in pre-clinical models of fetal alcohol syndrome [323, 324]. Pioglitazone has also been shown to have protective effects against alcohol-induced neuronal and cognitive damage [325], suppressing alcohol drinking and relapse to alcohol seeking [326–329].

NAC offers promising therapeutic value to inhibit alcohol-induced adverse effects in rodents [330]. In Zebrafish, withdrawal effects following repeated alcohol exposure are blocked by NAC [331]. NAC is also able to reduce extinction responding and reacquisition of alcohol self-administration in rodents [332].

Human Studies: Table 3 details candidate medications that have been found to be beneficial for alcohol use disorders in both pre-clinical and human studies. Unfortunately, there is a lack of clinical exploration of the medications that have shown promise in animal models. However, in a recent trial, ibudilast has shown potential utility in treating individuals with alcohol use disorder. Ray and Colleagues (2017) examined the effects of ibudilast (50 mg, BID) on subjective response to alcohol, drug cue and stress among participants with current alcohol use disorder (N=24). After 7 days of medication maintenance, participants completed an intravenous alcohol administration session, an alcohol cue session, and a stress-exposure session. Active ibudilast maintenance was associated with greater resilience in response to stress- and alcohol-cue exposure, reduced drug craving, and attenuation of some subjective effects of alcohol [333]. Minocycline has also been tested in clinical samples. Petrakis et Colleagues (2019) conducted a clinical trial in which heavy drinkers (N=48) were randomized to receive placebo, 100 mg, or 200 mg of minocycline for 10 days. The trial found no effect of either active dose of minocycline on subjective response to alcohol, alcohol-induced craving, or serum cytokine levels. The investigators therefore concluded that short-term minocycline maintenance may not alter alcohol-related inflammation or subjective response in humans [334].

3.7 Nicotine Effects on Glia

Due to the hundreds of chemical constituents of tobacco, it has been difficult to specify the effects of nicotine on glia [335]. We do know that smoking promotes the release of pro-inflammatory signals in a dose-dependent manner [336]. However, nicotine itself is thought to be immunosuppressive [337]. In culture, nicotine inhibits microglial proliferation through direct effects on nicotinic acetylcholine receptors (nAChRs) that are expressed on microglia [338–341]. nAChRs are widely distributed throughout the CNS and are expressed on several types of non-neuronal cells [338]. nAChR activation has been shown to have immunosuppressive properties [339] and in vitro models have also shown that long-term nicotine treatment suppresses the reactivity of astrocytes [342]. In humans, direct comparison of smokers to non-smokers using positron emission tomography (PET) found indicators of less microglia activation, the magnitude of which was inversely correlated with the number of cigarettes smoked per day [343]. There is also evidence that long-term exposure to nicotine and/or other chemicals found in tobacco smoke impairs the functions of oligodendrocytes [344–345].

Non-neuronal effects of nicotine are thought to enhance hippocampal synaptic transmission and long-term memory [346]. Nicotine effects on glia have also been shown to have neuroprotective effects on dopamine, and modulate molecular measures in the NAcc, substantia nigra and frontoparietal cerebral cortex [347–350]. Therefore, there is a substantial body of evidence to implicate the interaction between nicotine and glia in the development and progression of nicotine abuse.

Pre-clinical Studies: Concerning the utility of using glia modulators for the treatment of nicotine use, there have been relatively few studies. The glial GLT-1 modulator, ceftriaxone, has been the most extensively studied in pre-clinical models. Ceftriaxone has been shown to reduce acquisition and reinstatement of nicotine CPP, nicotine intake and withdrawal [351–353]. NAC has shown similar effects. In mice, NAC decreased nicotine's rewarding effects [354]. In rats, NAC also reduced nicotine self-administration and cue-induced reinstatement of nicotine seeking [355, 356], reduced nicotine withdrawal [357], and enhanced extinction of nicotine-associated cues [358]. Like some studies above, Powell and Colleagues (2019) found that NAC decreased extinction responding and reduced reinstatement of nicotine seeking. However, this effect was only observed with chronic NAC treatment [359].

Human Studies: Clinical research has yet to follow up on the promising pre-clinical findings with ceftriaxone. However, there has been clinical exploration into NAC as a smoking cessation pharmacotherapy. In an open-label pilot trial of NAC in adult cigarette smokers (N=19), 4 weeks of NAC treatment (1200 mg, twice daily), in combination with varenicline (1 mg, twice daily), reduced cigarettes smoked per day [360]. A more recent randomized controlled trial has also been conducted among non-treatment seeking smokers (N=16). In this study, NAC treatment (1200 mg, twice daily) significantly decreased nicotine craving and positive affect during smoking abstinence [361]. In another trial, NAC treatment (1200 mg-3000 mg/day for 24 weeks) also helped reduce smoking among nicotine-dependent pathological gamblers (N=28) [362]. In contrast to these positive findings, Knackstedt and Colleagues (2009, N=33) reported that NAC (2400 mg/day, 4-weeks) treatment had no effect on daily cigarette use, CO levels, cigarette craving, or nicotine withdrawal [363].

The microglial inhibiting effects of pioglitazone have also been found to reduce nicotine craving [364]. In this trial, cigarette smokers, not interested in smoking cessation, were randomized to either active (45 mg, N=14) or placebo (0 mg, N=13) pioglitazone maintenance. During cue-exposure sessions, pioglitazone reduced nicotine craving but did not significantly alter cigarette self-administration or positive subjective response to smoking. Similarly, minocycline (200 mg/day, 4 days) has been shown to reduce craving for cigarettes but without altering responses to nicotine in non-treatment seeking smokers (N=12) [365].

3.8 Cannabis Effects on Glia

There are robust data to suggest that the endocannabinoid system is sensitive to changes in glial activity. Acute exposure to cannabinoids [e.g., delta-9-tetrahydrocannabinol (THC), cannabidiol, and cannabinol] inhibits the production of inflammatory cytokines and chemokines [366–369]. However, chronic exposure may have different immunomodulatory effects. Individuals with cannabis use disorder show increases in plasma pro-inflammatory cytokines (IL-1 β , IL-6, IL-8, and TNF- α) compared to individuals with no history of cannabis use [370].

The data suggest that exogenous cannabinoids interact with glia through the cannabinoid CB2 receptors. Upon activation of microglia, there is a significant increase in the expression

of CB2 receptors [371–373]. In vitro, microglia produce endocannabinoids at higher levels than neurons [373], suggesting that endocannabinoid production by activated microglial cells could play a role in the pathophysiology of cannabis use disorder. Of particular interest has been the involvement of cannabinoid-glia interactions in THC-induced cognitive impairment. Studies have implicated the involvement of microglia in learning and motor coordination deficits induced by THC administration [374, 375]. However, in rodent models of THC-induced cognitive impairment, the CB1 receptor has been shown to be of particular importance. THC-induced deficits in learning and motor coordination were not observed in homozygous CB1 knockout mice [374].

Few studies have examined the effects of exogenous cannabinoids on other types of glia. Nonetheless, THC treatment was shown to increase the levels of the astrocyte marker GFAP in rats. Region-specific alternations in astrocyte reactivity have also been observed [376–377].

Pre-clinical Studies: The author could find no studies examining the interaction between glial modulators and the rewarding effects of cannabis. Reliable, robust rewarding effects of cannabinoids are difficult to observe in pre-clinical models [378]. Impairment in cognitive, executive and emotional processes are some of the more severe outcomes related to heavy cannabis use [379]. In this treatment capacity, glial modulators have shown potential clinical utility. Minocycline prevented the development of THC-induced cognitive deficits [374]. Similarly, ibudilast blocked the cognitive effects of THC [375], which contribute to the adverse effects of chronic cannabis use [335, 380].

Human Studies: It appears as though only NAC has been tested in human subjects. First, an open-label pilot trial found that NAC (1200 mg, twice daily) significantly decreased self-reported marijuana use and craving among young marijuana users (N=24) [381]. The investigators followed this study with a randomized controlled trial using the same dosing regimen among treatment-seeking cannabis-dependent adolescents (N=116). Active NAC treatment more than doubled the odds of having a negative cannabinoid urine toxicology result during the 8-week study [382]. The most recent trial of NAC was a 12-week double-blind randomized placebo-controlled investigation among treatment-seeking adults with cannabis use disorder (N=302), treated with 1200 mg of NAC, twice per day. However, this study found that NAC treatment did not alter abstinence rates [383]. Table 4 summarizes the pre-clinical and clinical findings of the effects of glial modulators on the abuse potential of nicotine and cannabis.

4.0 Conclusions

Neuroimmune signaling is emerging as a significant contributor to the development and maintenance of drug and alcohol abuse. Though we are just beginning to understand how, studies suggest that activation and long-term modulation of glial function contributes to the rewarding properties of addictive drugs, sensitization to drug effects, withdrawal, and the loss of behavioral control that is characteristic of these disorders. There remains much to learn concerning how glia and neuroinflammatory responses contribute to the pathological features of SUDs. The acute vs chronic effects of drugs of abuse have yet to be conclusively

determined. As such, it will be important to distinguish the immediate impact of drug-glia interaction on acute drug pharmacodynamics from the long-term effects that may have a persistent impact on brain function. Additionally, most of the studies for the role of glial in drug abuse focus on astrocytes and microglia, leaving the role of other glia types undefined. Furthermore, pre-clinical research suggests that there may be significant sexual dimorphism in how psychoactive drugs interact with glia. Because of the exploratory nature of most human studies, the influence of sex is rarely considered.

Pre-clinical studies employing anti-inflammatory drugs, or medications that modulate glia in other ways, have shown effectiveness in models of drug reward, reinforcement, and relapse. Findings of the therapeutic utility of medications that alter glutamate function (via glial mechanisms) have been some of the most consistently observed across drugs of abuse. Many of these medication findings have even been replicated in independent samples. Greater standardization of methodology across pre-clinical studies, and faster pace of research, make it easier to draw conclusions of treatment efficacy. The body of literature on clinical studies of glial modulators are more fragmented, with the same medication rarely being tested under the same experimental conditions.

Like, preclinical studies, clinical studies have yielded promising results, though not as robust. The most common finding among clinical trials has been medication effects on craving. Significant attenuation of the direct pharmacological effects of drugs of abuse is rare in clinical trials and may be a high bar for this class of medications. However, this should not lessen enthusiasm for continued clinical study, as craving is a significant contributor to the chronic relapsing nature of drug abuse. However, before we place limitations on the potential of glial modulators, we should note that clinical trials are often limited by dosing and maintenance conditions with established safety and efficacy for current FDA-approved indications. These parameters may not be applicable to the drug's effects on glia, making it difficult to determine if a robust effect on glial was achieved. In fact, most clinical trials do not assess for changes in target glial activity, making proof-of-concept of the treatment mechanism difficult to determine.

In sum, each class of addictive drug appears to interact with glia in unique and multiple ways. We have just begun to understand the role of the complex interplay between the two systems in the development and maintenance of SUDs. This interaction is further complicated by variability in the neuronal mechanisms across the drugs classes and the resulting differences in patterns of use. A better understanding of the relationship between glia and the pathophysiology of addiction should allow for more precise clinical exploration of glial-directed treatments for SUDs.

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Key Points

- Pre-clinical findings show that drugs of abuse have significant modulatory actions upon neuroinflammatory signaling, the most investigated of which are their interaction with microglia and astrocytes.
- There is evidence that the interaction between drugs of abuse and glia contributes to the development, maintenance and course of substance use disorders.
- Though clinical studies of glial modulators as treatments of substance abuse have not yielded the same robust findings as pre-clinical models, there are sufficient positive results to justify continued investigation.

Table 1.

Effects of Glial Modulators on the Abuse Potential of Opioids

Preclinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
Propentofylline	Phosphodiesterase (PDE) inhibitor & Glutamate Transporter-1 (GLT-1) Upregulator	3 μ M	Rewarding Effects	↓	Narita et al., 2006
Pioglitazone	Peroxisome Proliferator-Activated Receptor-Gamma (PPAR γ) Activator & Cytokine Inhibitor	60 mg/kg	Reinforcing Effects	↓	de Guglielmo et al., 2015
		30 mg/kg	Reinstatement of Drug-Seeking	↓	de Guglielmo et al., 2017
		30 mg/kg	Withdrawal or Physiological Dependence	↓	
Ceftriaxone	Cephalosporin Antibiotic & Upregulator of GLT-1 and Cystine/Glutamate Antiporter (xCT)	200 mg/kg	Reinstatement of Drug-Seeking	↓	Shen et al., 2014
		200 mg/kg	Rewarding Effects	↓	Alshehri et al., 2018
Fluorocitrate	Glial Metabolic Inhibitor	1 nmol/1 μ l	Rewarding Effects	↓	Seyedaghamiri et al., 2018
Minocycline	Tetracycline Antibiotic & Microglial Inhibitor	50 mg/kg	Rewarding Effects	↓	Hutchinson et al., 2008
		50 mg/kg	Withdrawal or Physiological Dependence	↓	Hutchinson et al., 2009
		10 & 20 μ g	Rewarding Effects	↓	Zhang et al., 2012
		1, 5, & 10 μ g/0.5 μ L	Reinstatement of Drug-Seeking	↓	Arezoomandan and Haghparast, 2016
(+)–Naloxone	Non-Opioid Isomer of the Opioid Receptor Antagonist & Toll-Like Receptor-4 (TLR-4) Antagonist	1 mg/kg	Rewarding Effects	↓	Hutchinson et al., 2012
		1 mg/kg	Reinforcing Effects	↓	
(+)–Naltrexone	Non-Opioid Isomer of the Opioid Receptor Antagonist & TLR-4 Antagonist	15 & 30 mg/kg	Reinforcing Effects	--	Theberge et al., 2013
		15 & 30 mg/kg	Reinstatement of Drug-Seeking	↓	
(+)–Naloxone (+)–Naltrexone	Non-Opioid Isomer of the Opioid Receptor Antagonist & TLR-4 antagonist	32 & 56 mg/kg	Reinforcing Effects	--	Tanda et al., 2016
Ibudilast	Phosphodiesterase and Tumor Necrosis Factor-Alpha (TNF- α) Inhibitor	15 mg/kg	Withdrawal or Physiological Dependence	↓	Hutchinson et al., 2009
N-Acetylcysteine	Upregulator of GLT-1 & Glial Cystine-glutamate Exchange Activator	90 mg/kg	Reinforcing Effects	↓	Hodebourg et al., 2019
		100 mg/kg	Reinstatement of Drug-Seeking	↓	Zhou and Kalivas 2008
MS-153	Glial Glutamate Transport Activator	10 mg/kg	Rewarding Effects	↓	Nakagawa et al., 2005
Clinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
Minocycline	Tetracycline Antibiotic & Microglial Inhibitor	100 & 200 mg	Positive Subjective Effects	↓	Mogali et al., 2014
		200 mg	Craving	--	Arout et al., 2018
Ibudilast	PDE and TNF- α Inhibitor	20 & 40 mg B.I.D	Withdrawal	↓	Cooper et al., 2016

Preclinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
		20 & 40 mg B.I.D	Positive Subjective Effects	--	Cooper et al., 2017
		50 mg B.I.D	Positive Subjective Effects	↓	Metz et al., 2017
		50 mg B.I.D	Reinforcing Effects	↓	
		50 mg B.I.D	Craving, Reinstatement, or Relapse	↓	
Pioglitazone	PPAR γ Activator & Cytokine Inhibitor	15 & 45mg	Positive Subjective Effects	—	Jones et al., 2016
		45 mg	Craving	↓	Jones et al., 2018
		45 mg	Positive Subjective Effects & Reinforcing Effects	--	

Table 2.

Effects of Glial Modulators on the Abuse Potential of Psychostimulants

Preclinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
N-Acetylcysteine	Glutamate Transporter-1 (GLT-1) Upregulator & Glial Cystine-glutamate Exchange Activator	60 mg/kg	Reinstatement of Drug Seeking	↓	Baker et al., 2003
		60 mg/kg	Reinstatement of Drug Seeking	↓	Madayag et al., 2007
		100 mg/kg	Reinstatement of Drug Seeking	↓	Moussawi et al., 2011
		100 mg/kg	Reinstatement of Drug Seeking	↓	Reichel et al., 2011
		90 mg/kg	Reinstatement of Drug Seeking	↓	Murray et al., 2012
		90 mg/kg	Reinforcing Effects	--	
		100 mg/kg	Reinstatement of Drug Seeking	↓	Reissner et al., 2015
Propentofylline	Phosphodiesterase (PDE) inhibitor & GLT-1 Upregulator	30, 60, & 120 mg/kg	Reinforcing Effects & Reinstatement of Drug Seeking	--	Charnitkov et al., 2018
		3 µM	Reinstatement of Drug Seeking	↓	Narita et al., 2006
		10 mg/kg	Reinstatement of Drug Seeking	↓	Reissner et al., 2014
		100 & 200 mg/kg	Reinstatement of Drug Seeking	↓	Sari et al., 2009
		200 mg/kg	Reinstatement of Drug Seeking	↓	Knackstedt et al., 2010
		200 mg/kg	Reinforcing Effects	↓	Ward et al., 2011
		200 mg/kg	Rewarding Effects	--	Abulseoud et al., 2012
Ibutilast	Phosphodiesterase & Tumor Necrosis Factor-Alpha (TNF-α) Inhibitor	200 mg/kg	Reinforcing Effects	↓	
		7.5 mg/kg	Reinstatement of Drug Seeking	↓	Beardsley et al., 2010
		7.5 & 10 mg/kg	Reinforcing Effects	↓	Snider et al., 2013
Minocycline	Tetracycline Antibiotic & Microglial Inhibitor	7.5 & 10 mg/kg	Rewarding Effects	↓	Poland et al., 2016
		60mg/kg	Reinforcing Effects	↓	Snider et al., 2013
		50 mg/kg	Reinforcing Effects	↓	Northcutt et al., 2015
		40 mg/kg	Reinforcing Effects	↓	Attarzadeh-Yazdi et al., 2014
Pioglitazone	Peroxisome Proliferator-Activated Receptor-Gamma (PPARγ) & Cytokine Inhibitor	40 mg/kg	Reinstatement of Drug Seeking	↓	
		50 mg/kg	Reinstatement of Drug Seeking	↓	Miller et al., 2016
(+)-Naltrexone	Non-Opioid Isomer of the Opioid Receptor Antagonist & Toll-Like Receptor-4 (TLR-4) Antagonist	30 mg/kg	Reinstatement of Drug Seeking	--	Theberge et al., 2013

Preclinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
(+) -Naloxone	Non-Opioid Isomer of the Opioid Receptor Antagonist & TLR-4 Antagonist	5 mg/kg	Rewarding Effects	↓	Northcutt et al., 2015
		5 mg/kg	Reinforcing Effects	↓	
(+) -Naloxone (+) -Naltrexone	Non-Opioid Isomer of the Opioid Receptor Antagonist & TLR-4 Antagonist	10, 17, 32 & 50 mg/kg	Reinforcing Effects	--	Tanda et al., 2016
MS-153	Glial Glutamate Transport Activator	10mg/kg	Rewarding Effects	↓	Nakagawa et al., 2005
Clinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
Pentoxifylline	Cytokine inhibitor	1200 mg	Abstinence	--	Ciraulo et al., 2005
Minocycline	Tetracycline Antibiotic & Microglial Inhibitor	200 mg	Positive Subjective Effects	↓	Sofuogo et al., 2011
		200 mg	Reinforcing Effects	--	
Celecoxib	Nonsteroidal Anti-Inflammatory (Cyclooxygenase-2 Inhibitor)	200 mg	Abstinence & Craving	--	Reid et al., 2005
N-Acetylcysteine	Upregulator of GLT-1 & Glial Cystine-glutamate Exchange Activator	600 mg	Craving	↓	LaRowe et al., 2007
		2400 & 3600 mg	Abstinence	↓	Mardikian et al., 2007
		1200-2400 mg	Positive Subjective Effects	--	Amen et al., 2011
		1200-2400 mg	Craving	↓	
		1200 mg	Craving	↓	Mousavi et al., 2015
		2400 mg	Craving	↓	Back et al., 2016
		2400 mg	Craving & Cue-Reactivity	↓	Levi-Bolin et al., 2017
		2400 mg	Reinforcing Effects	--	
Pioglitazone	PPAR γ Activator & Cytokine Inhibitor	45 mg	Reinforcing Effects	↓	Schmitz et al., 2017
		45 mg	Craving	↓	

Table 3.

Effects of Glial Modulators on the Abuse Potential of Alcohol

Preclinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
Indomethacin	Cyclooxygenase-1&2 Inhibitor	1.9, 2.5 & 5 mg/kg	Reinforcing Effects	↓	George, 1989
Rolipram	Selective Phosphodiesterase-4 (PDE-4) Inhibitor	0.25 & 0.5 mg/kg	Reinforcing Effects	↓	Hu et al., 2011
		0.1 & 0.2 mg/kg	Reinforcing Effects	↓	Wen et al., 2012
		1 mg/kg	Reinforcing Effects	↓	Blednov et al., 2014
CDP840	Selective PDE-4 Inhibitor	10 & 25 mg/kg	Reinforcing Effects	↓	
Mesopram	Selective PDE-4 Inhibitor	5 mg/kg	Reinforcing Effects	↓	
Piclamilast	Selective PDE-4 Inhibitor	1 mg/kg	Reinforcing Effects	↓	
Propentofylline	PDE Inhibitor & Glutamate Transporter-1 (GLT-1) Upregulator	5 mg/kg	Reinforcing Effects	--	
Various	PDE-1,3,5 and Non-specific Inhibitors	--	Reinforcing Effects	--	
Ibudilast	PDE & Tumor Necrosis Factor-Alpha (TNF-α)	3,6 & 9 mg/kg	Reinforcing Effects	↓	Bell et al., 2015
Minocycline	Tetracycline Antibiotic & Microglial Inhibitor	50 mg/kg	Reinforcing Effects	↓	Agrawal et al., 2011
		60 & 80 mg/kg	Reinforcing Effects	↓	Syapin et al., 2016
Rapamycin	T-Lymphocyte & Astrocyte Inhibitor	50 & 100 ng/side	Reinforcing Effects	↓	Cozzoli et al., 2016
Tigecycline	Glycylcycline Antibiotic & Microglial Inhibitor	40, 60, 80 & 100 mg/kg	Reinforcing Effects	↓	Bergeson et al., 2016
		60 & 80 mg/kg	Reinforcing Effects	↓	Syapin et al., 2016
		80 mg/kg	Withdrawal	↓	Martinez et al., 2016
Ceftriaxone	Cephalosporin Antibiotic & Upregulator of GLT-1 and Cystine/Glutamate Antipporter (xCT)	100 mg/kg	Reinforcing Effects	↓	Alhaddad et al., 2014
		100 mg/kg	Reinforcing Effects	↓	Das et al., 2015
		100 mg/kg	Reinforcing Effects	↓	Sari et al., 2014
		200 mg/kg	Reinforcing Effects	↓	Sari et al., 2016
		50 & 100 mg/kg	Reinforcing Effects & Reinstatement of Drug Seeking	↓	Qrunfleh et al., 2013
		200 mg/kg	Reinstatement of Drug Seeking	↓	Rao and Sari, 2014
		100 mg/kg	Reinstatement of Drug Seeking	↓	Weiland et al., 2015
		200 mg/kg	Reinforcing Effects	↓	Lee et al., 2013
(+)-Naloxone	Non-Opioid Isomer of the Opioid Receptor Antagonist & Toll-Like Receptor-4 (TLR-4) Antagonist	30 & 60 mg/kg	Reinforcing Effects	--	Harris et al., 2017
Pioglitazone	Peroxisome Proliferator-Activated Receptor-Gamma (PPARγ) Activator & Cytokine Inhibitor	30 mg/kg	Reinstatement of Drug Seeking	↓	Blednov et al., 2015
		10 & 30 mg/kg	Reinstatement of Drug Seeking	↓	Stopponi et al., 2013

Preclinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
Clinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
Ibutilast	PDE & TNF- α Inhibitor	50 mg	Positive Subjective Effects	--	Ray et al., 2017
		50 mg	Craving	↓	
Minocycline	Tetracycline Antibiotic & Microglial Inhibitor	100 & 200 mg	Positive Subjective Effects	--	Petrakis et al., 2019

Table 4.

Effects of Glial Modulators on the Abuse Potential of Nicotine and Cannabis

Preclinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
Nicotine					
Ceftriaxone	Cephalosporin Antibiotic & Upregulator of Glutamate Transporter-1 (GLT-1) and Cystine/Glutamate Antiporter (xCT)	200 mg/kg	Rewarding Effects	--	Alajaji et al., 2013
			Withdrawal	↓	
			Reinstatement of Drug Seeking	↓	
		200 mg/kg	Reinforcing Effects	↓	Sari et al., 2016
		200 mg/kg	Rewarding Effects	↓	Philogene-Khalid et al., 2017
N-Acetylcysteine	Upregulator of GLT-1 & Glial Cystine-glutamate Exchange Activator	15, 30 & 120 mg/kg,	Rewarding Effects	↓	Bowers et al., 2016
		15, 30 & 120 mg/kg	Withdrawal	↓	
		100 mg/kg	Reinstatement of Drug Seeking	↓	Gipson et al., 2013
		60 mg/kg	Reinstatement of Drug Seeking	↓	Ramirez-Niño & D’Souza 2013
		60 mg/kg	Reinforcing Effects	↓	
		100 mg/kg	Reinstatement of Drug Seeking	↓	Goenaga et al., 2019
		100 mg/kg	Withdrawal	↓	
		100 mg/kg	Reinstatement of Drug Seeking	↓	Moro et al., 2019
		100 mg/kg	Reinstatement of Drug Seeking	↓	Namba et al., 2019
		100 mg/kg	Reinstatement of Drug Seeking	↓	Powel et al., 2019
Cannabis					
Minocycline	Tetracycline Antibiotic & Microglial Inhibitor	40 mg/kg	Cognitive Deficits	↓	Cutando et al., 2013
Ibudilast	Phosphodiesterase (PDE) & Tumor Necrosis Factor-Alpha (TNF-α) Inhibitor	3.5 mg/kg	Cognitive Deficits	↓	Zamberletti et al., 2015
Clinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
Nicotine					
Minocycline	Tetracycline Antibiotic & Microglial Inhibitor	200 mg	Craving	↓	Sofuoglu et al., 2009
Pioglitazone	Peroxisome Proliferator-Activated Receptor-Gamma Activator & Cytokine Inhibitor	45 mg	Craving	↓	Jones et al., 2017
N-Acetylcysteine	Upregulator of GLT-1 & Glial Cystine-glutamate Exchange Activator	2400 mg	Reinforcing Effects, Craving, Abstinence, Withdrawal	--	Knackstedt 2009

Preclinical Studies					
Glial Modulator	Mechanism of Action	Dose	Behavioral Outcome	Result	Citation
		3600 mg	Craving	↓	Schmaal et al., 2011
		1200 – 3000 mg	Abstinence	↑	Grant et al., 2014
		2400 mg	Abstinence	↑	McClure et al., 2015
		2400 mg	Craving	↓	Froeliger et al., 2015
Cannabis					
N-Acetylcysteine	Upregulator of GLT-1 & Glial Cystine-glutamate Exchange Activator	1200 mg	Craving	↓	Gray et al., 2010
		1200 mg	Abstinence	↑	Gray et al., 2012
		1200 mg	Abstinence	--	Gray et al., 2017