Pharmacology & Therapeutics 125 (2010) 138–168

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: G. Dusting

New horizons for therapeutics in drug and alcohol abuse

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ARTICLE INFO

Keywords:
Addiction
Amphetamine
Cannabis
Cocaine
Inhalants
Nicotine

ABSTRACT

Alcohol, tobacco and illicit drug dependence represents a serious health and social issue within the community. As drug dependence has become more widely recognized as a clinical disorder and the severity of the problem been fully realized, options available for treatment have grown along with our understanding of the neurobiological mechanisms underlying the development and persistence of addiction. Treatment has progressed from purely social and behavioral approaches to now encompass pharmacotherapy to attempt to disrupt the mechanisms underlying these disorders. Despite these advances, many forms of addiction lack effective therapeutics and the prevalence of this disorder remains unacceptably high. As a result, a significant effort within the research community has been dedicated to the identification of novel targets for the development of therapeutics based upon our understanding of the pathological processes underlying addiction. The current review aims to provide an overview of existing and clinically trialed pharmacotherapies for alcohol, opiate, psychostimulant, nicotine, cannabis and inhalant addictions. Further, we discuss some of the potential targets that have been recently indentified from basic studies that may hold promise for the development of novel treatments.

Contents

Abbreviations: 18-MC, 18-methoxycoronaridine; 5-HT, serotonin; ACTH, adrenocorticotropic hormone; AMPA, alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; CPP, conditioned place preference; CPu, caudate putamen; CRF, corticotrophin releasing factor; CRF1, corticotrophin releasing factor receptor 1; DA, dopamine; DAergic, dopaminergic; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyric acid; HPA, hypothalamic pituitary adrenal; LAAM, levo-α-acetylmethadol; MAO, monoamine oxidase; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]-pyridine; nAChR, nicotinic acetylcholine receptor; N/OFQ, nociceptin/orphanin FQ; NAC, N-acetylcysteine; NAc, nucleus accumbens; NE, norepinephrine; NK, neurokinin; NMDA, N-methyl-D-aspartic acid; NPY, neuropeptide Y; NRT, nicotine replacement therapy; PFC, prefrontal cortex; SP, substance P; SSRI, selective serotonin reuptake inhibitor; THC, δ-9-tetrahydrocannabinol; USFDA, United States Food and Drug Administration; VTA, ventral tegmental area.

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doi:10.1016/j.pharmthera.2009.11.002

1. Introduction

Drug addiction is typically characterized as a chronically relapsing disorder involving repeated bouts of compulsive drug seeking and use despite potential adverse consequences associated with this behavior (Koob & Le Moal, 1997). Addiction is increasingly clinically recognized as a neurobiological disease and it is believed that its manifestation and enduring nature is influenced by a combination of genetic, behavioral and psychosocial factors. Drug addiction is an insidious disorder, with the extent of worldwide drug use estimated to include 2 billion alcohol users, 1.3 billion smokers and 185 million illicit drug users (WHO, 2002). This use accounts for approximately 12.4% of all deaths worldwide each year (WHO, 2002). According to estimates, alcohol, tobacco and illicit drug addiction costs the United States over $500 billion each year in healthcare, criminal justice and lost productivity costs (Harwood, 2000), while in Europe each addict has been suggested to cost its nation between €4000–12000 each year (Andlin-Sobocki, 2004). In a social context, 63% of Americans say that addiction has had an impact on their lives (Hart & Tetter, 2004).

The use of pharmacological agents has become a standard approach to attempt to ameliorate aspects of drug addiction in combination with social and behavioral treatment. While pharmacotherapy may be an effective approach to the treatment of drug addiction for individuals, the prevalence of this disorder remains unacceptably high. Further, there are addictions that at present have no therapeutics registered for treatment thereof. Given this, a significant amount of research has been dedicated to advancing the knowledge of the pathological process(es) of addiction to aid in the development of new therapeutics. The current review aims to discuss existing pharmacotherapies and those currently in clinical trials. In addition, we provide some foresight into potential targets for the development of novel treatments based upon recent basic findings. Whether the latter ultimately translate into useful therapeutic options will unfold over the coming years.

2. Neurobiology of addiction

Studies utilizing advances in technologies such as neuroimaging, molecular biological and neurochemical techniques and the development of animal models of drug-taking (use) and drug seeking (relapse) have contributed significantly to advances in recent years in the understanding of the biological basis of addiction. The complex series of molecular and cellular events that are responsible for the reinforcing effects of drugs of abuse and the adaptations that result from repeated use of these drugs may provide rational targets for the development of pharmacotherapies for drug addiction. It is not the intention of this review to discuss the neurobiological processes that underpin the transition from casual drug use to addiction. Indeed, there are already a number of excellent reviews providing a range of theories in this regard (for example Everitt et al., 2008; Koob & Le Moal, 2008; Nestler, 2008; Kalivas, 2009). Nevertheless, it is widely accepted that addiction involves significant neuroadaptation to brain structure and function.

2.1. Substrates of withdrawal, craving and relapse

Addiction involves more than the exploitation of the reward pathways of the brain by drugs of abuse. Chronic neuroadaptations contributing to the development of dependence, impairment of behavioral inhibition and enduring propensity to relapse are critical components of the disease. Studies have implicated changes in levels of neurotransmission and receptor expression/signaling within the mesocorticolimbic pathway and long-term dysregulation of brain stress systems (Koob & Le Moal, 2008) following chronic drug administration. These changes are believed to reflect homeostatic adaptations in response to chronic exposure and likely represent neurological substrates for the persistent features of addiction.

Withdrawal occurs following cessation of drug taking and is associated with the onset of negative emotional states such as dysphoria, anxiety and irritability. The emergence of such states is thought to provide a form of negative reinforcement, whereby drug taking is motivated by the desire to reduce the negative aspects of withdrawal. Functional changes that likely contribute to these behavioral changes include alteration of neurotransmitter release and changes in receptor expression. For example studies have found during periods of withdrawal following chronic psychostimulant, opioid or alcohol administration, rats demonstrate a significant decrease in dopamine (DA) and serotonin (5-HT) levels in the nucleus accumbens (NAc) (Weiss et al., 1992; Diana et al., 1993; Parsons et al., 1995; Weiss et al., 1996), features which are commonly associated with dysphoria, depression and anxiety disorders (Charney et al., 1990; Fibeger, 1991). In keeping with this idea, pharmacological stimulation of the DA system attenuates some of the somatic symptoms of opioid withdrawal (Harris & Aston-Jones, 1994). Human imaging studies of addicts during withdrawal confirm these findings (Volkow et al., 2003). Withdrawal has also been associated with other non-DAergic alterations, specifically anatomically discrete decreased levels of γ-aminobutyric acid (GABA) and neuropeptide Y (NPY) and increased dynorphin, corticotrophin releasing factor (CRF) and norepinephrine (NE), all of which can induce dysphoria, anxiety and stress (Koob & Le Moal, 2008). Changes in receptor expression levels have also been observed in withdrawal. For instance, animals in nicotine withdrawal show down regulation of nicotinic acetylcholine receptors (nAChRs) (Mugnaini et al., 2006) and up regulation of L-type calcium channels (Katsura & Ohkuma, 2005).

Significant alterations are also observed in the brain's stress system and hypothalamic pituitary adrenal (HPA) axis during withdrawal. Thus, withdrawal following chronic drug use has been demonstrated to induce elevated levels of adrenocorticotropic hormone (ACTH), corticosterone and CRF in the HPA axis, central nucleus of the amygdala (CeA) (Koob & Le Moal, 2005) and in the bed nucleus of the stria terminalis (BNST) (Olive et al., 2002). This enhanced activity is suggested to contribute to anxiety associated with withdrawal and the desire to re-administer drug. Supporting this are data demonstrating the reduction of self-administration of alcohol and alleviation of anxiety like behavior in dependent animals following pharmacological inhibition of CRF signaling (Baldwin et al., 1991; Valdez et al., 2002), particularly when targeting CRF receptor 1 (CRF1) within the CeA (Rassnick et al., 1993; Funk et al., 2006). It has been hypothesized that changes such as these may contribute to relapse during both the acute and chronic stages of withdrawal.

One of the features of addiction is persistent drug craving and susceptibility to relapse of reformed addicts well after the cessation of a withdrawal syndrome. Conditioned learning and stress appear to be critical factors associated with these features of addiction. Conditioned learning involves the association of certain environmental stimuli with drug use so that these stimuli acquire incentive motivational value; as a result exposure to these stimuli induces the expectation of drug availability (Everitt et al., 2001). Contact with such stimuli has been implicated in eliciting craving and precipitating relapse. Human functional brain imaging and animal models of conditioned cue precipitated relapse to drug seeking have revealed that major structures mediating this aspect of addiction include the orbitofrontal and prefrontal cortices, the basolateral amygdala (BLA) and NAc core (See, 2002; Lingford-Hughes, 2005; Feltenstein & See, 2008). DAergic and glutamatergic signaling between these structures is believed to underlie the acquisition, reinforcement and conditioned learning of drug associated stimuli (See et al., 2001; Backstrom & Hyytia, 2007), although there is also evidence for cholinergic involvement (See et al., 2003; Zhou et al., 2007). Reinstatement following a non-contingent drug exposure (inducing relapse by priming with low dose of the same or different drug) has been demonstrated to involve the prefrontal cortex (PFC), NAc core and VTA (Shalev et al., 2002). This effect is also mediated primarily by glutamatergic and DAergic mechanisms within these

structures (Cornish et al., 1999; Norman et al., 1999). Stress also has an established role in inducing relapse. Exposure to stress (Sinha, 2001) or stress related imagery (Sinha et al., 2000) is a potent stimulus for relapse in humans. Similarly, exposure to various stressors such as foot shock (McFarland et al., 2004) or pretreatment with drugs that induce anxiety (e.g. yohimbine) reliably induce reinstatement in animals (Feltenstein & See, 2006). Exposure to drug associated cues results in increased HPA axis dependent measures of stress (Sinha et al., 2003) and inhibition of stress responses have been demonstrated to inhibit cue-induced reinstatement (Goeders & Clampitt, 2002). Not surprisingly the neurological substrates underlying stress-induced reinstatement overlap considerably with those involved in cue and drug primed induced reinstatement, namely the PFC, NAc and VTA (Stewart, 2000), however stressors also critically involve the extended amygdala, in particular the CeA and BNST (McFarland et al., 2004). Also, unlike cue- and drug-induced reinstatement, stress-induced reinstatement appears to predominantly involve noradrenergic signaling (specifically via NE) to activate CRF projections in the CeA (Brown et al., 2009b), although there is some evidence to suggest a modulatory DAergic involvement in the prefrontal and orbitofrontal cortices (Capriles et al., 2003).

Given the neurobiological mechanisms of addiction there are at least three points along the addiction pathway at which medications may be effective to treat this disease; (i) during sporadic, intermittent use before the onset of compulsive use to inhibit the rewarding and reinforcing effects of the drug to prevent the initial spiral into drug addiction; (ii) during withdrawal to avoid/disrupt induction of neurobiological mechanisms responsible for negative affect and associated reinforcement and aid in abstinence initiation and (iii) during abstinence to inhibit mechanisms responsible for cue reactivity, stress and drug craving as well as that those that precipitate and contribute to the propensity to relapse. Currently there are a number of medications in use (Table 1) or at the clinical trial stage for the treatment of drug addictions. In addition to this, the field of addiction research continues to generate potential targets for the development of new therapeutics. Here we review those medications and targets in light of the current understanding of the neurobiological basis of addiction and previous successes and failures in the development of these pharmacotherapies. So as not to complicate the discussion of the mechanisms through which these therapeutics may be acting, studies utilizing multiple therapeutics, behavioral therapies and those investigating psychiatric co-morbidities and dual dependencies are not discussed in this review.

Table 1
Pharmacotherapies in common use for the treatment of addiction.[a]

Drug	Pharmacotherapy	Mechanism of action
Alcohol	Disulfiram	Enzymatic inhibitor of aldehyde dehydrogenase, dopamine β hydroxylase inhibitor
	Naltrexone	Non-selective opioid antagonist
	Acamprosate	Functional NMDA receptor antagonist at high concentrations but may act as an agonist at low concentrations when receptor activity is also low
Opiate	Methadone	Non-specific opioid receptor agonist
	LAAM	μ opioid receptor agonist
	Buprenorphine	Partial μ opioid receptor agonist, κ opioid receptor antagonist
	Naltrexone	Non-selective opioid antagonist
Nicotine	Nicotine replacement	Nicotinic acetylcholine agonist
	Bupropion	DA/NE reuptake inhibitor
	Varenicline	α4β2 nAChR partial agonist
Psychostimulants	None	
Cannabinoids	None	
Inhalants	None	

[a] Not all therapeutics listed here are licensed in all countries.

3. Pharmacotherapeutic approaches to the treatment of alcoholism

3.1. Current pharmacotherapies

Historically, disulfiram was the first medication used to prevent relapse to alcohol consumption through aversion therapy. Its action was thought to be via inhibition of the metabolism of acetaldehyde, a byproduct of alcohol metabolism, resulting in accumulation of this metabolite which stimulates unpleasant symptoms such as flushing, palpitations, tachycardia, hypotension, headache, nausea and vomiting (Kitson, 1977). More recently however, it has been reported that disulfiram inhibits catecholamine metabolism in the PFC, which may affect information processing (Bourdélat-Parks et al., 2005), an action which may contribute to the ability of disulfiram to inhibit alcohol consumption. Clinical trials utilizing disulfiram have produced mixed results, with reported high rates of non-compliance and risk of toxicity (Ehrenreich & Krampe, 2004), however it still remains in use, usually as an adjunct to other therapeutic approaches and is most effective when used under supervision to ensure compliance (Laaksonen et al., 2008). Other currently United States Food and Drug Administration (USFDA) approved therapeutics shown to be somewhat effective for the treatment of alcoholism include the non-selective opioid receptor antagonists, naltrexone and nalmefene. These antagonists act to block the effects of endogenous opioids, which are released after alcohol consumption or in the presence of alcohol related cues and can enhance DAergic tone in the mesocorticolimbic pathway through the inhibition of GABAergic interneurons within the VTA (Cowen & Lawrence, 1999). By inhibiting the action of these endogenous opioids the reinforcing effects of alcohol are presumably reduced, leading to the gradual extinction of alcohol seeking behaviors (Sinclair, 2001). The majority of clinical trials utilizing these drugs have reported reduced craving and alcohol consumption (Graham et al., 2002) and while nalmefene is still currently under consideration for therapeutic use, naltrexone is one of the most commonly prescribed pharmacotherapies for promotion of abstinence in alcoholics. Acamprosate is a synthetic GABA analogue and is thought to reduce alcohol consumption via several mechanisms, however one possible action is through its ability to attenuate glutamatergic activity via actions at N-methyl-D-aspartic acid (NMDA) and metabotropic glutamate subtype 5 (mGlu5) receptors (De Witte et al., 2005; Mann et al., 2008). Reduction of glutamatergic activity by acamprosate is suggested to reduce the compensatory glutamatergic hyperactivity that develops following chronic use of alcohol that is believed to be involved in the induction of withdrawal associated negative affect, aiding in relapse prevention and negative reinforcement associated with withdrawal (De Witte et al., 2005). Further, the inhibitory action of acamprosate at NMDA receptors is thought to potentially extinguish or inhibit the development of conditioned cues driven by NMDA receptor mediated synaptic plasticity to reduce craving and cue induced relapse during abstinence (De Witte et al., 2005). Despite reported positive clinical outcomes associated with the use of this drug in some trials (Mason & Ownby, 2000), animal data have demonstrated the development of tolerance to the effect of acamprosate (Cowen et al., 2005b). This finding may explain the modest effect of this drug on craving when compared to the effect of naltrexone (Morley et al., 2006; Richardson et al., 2008). It should be noted that to date US based clinical trials of acamprosate have failed to recapitulate the findings of European based trials demonstrating the efficacy of this drug for the treatment of alcoholism (Anton et al., 2006; Mason et al., 2006). There are a number of different possibilities to explain this result including discrepancies in the study population, selection criteria and methodological differences or sampling error due to the small effect size.

Pharmacological intervention is often also provided during alcohol withdrawal to relieve symptoms, prevent complications and help initiate long term abstinence from alcohol. Benzodiazepines (e.g. diazepam, lorazepam) are the primary drugs of choice for treatment of withdrawal and their successful use is well indicated within the literature (Mayo-Smith, 1997; Ntais et al., 2005). Their sedative,

anxiolytic, anticonvulsant and muscle relaxant properties are mediated via $GABA_A$ receptors to potentiate the effect of GABA. The use of benzodiazepines for long term promotion of abstinence however is generally poorly indicated due to the risk of developing benzodiazepine addiction, a potentially dangerous interaction with alcohol and the lack of animal and clinical data demonstrating an ability to reliably decrease alcohol consumption (Lejoyeux et al., 1998).

3.2. Therapeutics for alcoholism — clinical studies

There are several excellent recent reviews on the various medications that have been examined for their effectiveness in the treatment of alcohol addiction (Boothby & Doering, 2005; Srisurapanont & Jarusuraisin, 2005; Heilig & Egli, 2006; Tambour & Quertemont, 2007; Johnson, 2008). To avoid unnecessary repetition with these reviews, some key studies that have assisted in the identification and pursuit of new potential therapeutics for the treatment of alcoholism will be discussed.

3.2.1. Dopaminergic agents

Preclinical studies of DA receptor agonists and antagonists have found promising effects on alcohol self-administration and relapse rates in rats (Cohen et al., 1999; Czachowski et al., 2002; Liu & Weiss, 2002a), however this success has failed to translate to clinical studies. Trials of selective and non-selective DA receptor antagonists have revealed inconsistent results, with only the mixed DAergic/serotonergic antagonists olanzapine and quetiapine (Hutchison et al., 2001; Kampman et al., 2007), providing indications for their potential use in some forms of alcoholism, although it should be noted the side effect profile of olanzapine likely limits its use for this indication. The D2 receptor partial agonist aripiprazole has also shown some promise, while failing to demonstrate a significant effect on rates of abstinence one study found that aripiprazole was able to induce more positive subjective treatment effects and less overall severity of alcohol dependence in treated subjects, providing support for further studies of this drug (Anton et al., 2008). DA partial agonists such as aripiprazole and terguride may circumvent the paradoxical effect of agonists and antagonists through their ability to be able to act as antagonists under hypodopaminergic states (Weiss, 2005).

3.2.2. GABAergic agents

Preclinical animal studies have revealed positive effects of pharmacological modulation of GABAergic transmission on alcohol consumption and craving (Colombo et al., 2003; Besheer et al., 2004). The $GABA_B$ agonist baclofen has demonstrated promising effects on the reduction of craving and promoting abstinence in alcohol dependent patients (Addolorato et al., 2007) and is proposed to work through the enhanced GABAergic inhibition of DA release from the VTA (Cousins et al., 2002). While baclofen has proven to have a sedative effect which may prove dangerous when taken with alcohol, it has been demonstrated that alcoholics have an increased tolerance to these effects (Besheer et al., 2004; Addolorato et al., 2005). The anticonvulsant and GABA mimetic gabapentin has also demonstrated some efficacy for the treatment of alcoholism through reported reduction of craving and consumption (Furieri & Nakamura-Palacios, 2007; Mason et al., 2009). The GABA mimetic γ-hydroxybutyric acid (GHB) has also demonstrated promising effects on craving and abstinence in alcohol dependent individuals (Addolorato et al., 1996) as a substitution therapy. It should be noted however that GHB is associated with significant abuse and dependence potential as well as potentially serious interactions with alcohol in the case of relapse.

3.2.3. Glutamatergic agents

In light of the approval and use of acamprosate for the treatment of alcoholism, other drugs with glutamatergic effects have also been investigated for potential anti abuse therapeutics. Preclinical studies of the NMDA receptor antagonist memantine have revealed an effect of this drug to inhibit alcohol induced NMDA receptor up-regulation in mice to reduce alcohol sensitization and as a result may reduce the propensity for subsequent use (Kotlinska et al., 2006). Clinical trials have revealed that memantine has an effect to reduce the number of heavy drinking days and increase the number of days abstinent, and is also useful in relieving alcohol withdrawal syndrome (Krupitsky et al., 2007), however use is associated with significant side effects resulting in discontinuation of treatment, potentially limiting the efficacy of this medication (Evans et al., 2007). Acamprosate has also been investigated for potential use in relief of alcohol withdrawal with little success (Kampman et al., 2009) however there is evidence to suggest it may protect against the neurotoxicity associated with withdrawal (De Witte et al., 2005).

Recent findings have indicated the positive effects of anticonvulsants on alcohol consumption. The anticonvulsant topiramate has several effects including antagonist activity at alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors and kainate glutamate receptors, enhancement of inhibitory $GABA_A$ mediated currents, inhibits L-type calcium channels and calcium dependent second messenger systems (Johnson et al., 2007). The action through which topiramate has been hypothesized to work is twofold; during acute drinking the action of topiramate to enhance GABAergic tone inhibits DA release from the VTA to inhibit the rewarding effects of alcohol; during chronic drinking and withdrawal topiramate acts to reduce the glutamatergic component to DA hypoactivity and associated negative affect (Johnson, 2004). Preclinical animal studies of topiramate have revealed a significant effect to reduce alcohol consumption (Nguyen et al., 2007) and alcohol induced withdrawal symptoms (Farook et al., 2007; Krupitsky et al., 2007). Clinical trials of this medication have to date been promising with treatment resulting in significant reductions in reported craving and percentage heavy drinking days (Johnson et al., 2003; Johnson et al., 2007). Other anticonvulsants exerting effects on voltage gated ion channels such as carbamazepine have also had positive effects on reducing alcohol craving and consumption (Mueller et al., 1997) as well as withdrawal (Malcolm et al., 2002). Despite their potential promise for the treatment of alcoholism, the side effect profile of anticonvulsants may limit their therapeutic potential, although clinical trials of these drugs to date have provided evidence for their tolerability (Mason et al., 2009; Paparrigopoulos et al., 2009).

3.2.4. Serotonergic agents

Alcohol abuse has been suggested to be a mechanism by which some individuals may compensate for reduced serotonergic function (McBride et al., 1995). A role for 5-HT in alcohol addiction also comes from animal studies demonstrating the ability of selective 5-HT reuptake inhibitors (SSRIs) to reduce alcohol consumption (Haraguchi et al., 1990; Boyce-Rustay et al., 2006). The clinical evidence to support this finding however is controversial with a recent meta-analysis of clinical studies investigating the use of antidepressants (including SSRIs) concluding they were ineffective in reducing alcohol consumption in alcohol dependent individuals without co-morbid depression (Torrens et al., 2005), although there is some indication that certain subtypes of patients (e.g. early onset dependence — dependent adolescents; higher risk/severity) may benefit from such therapeutics (Pettinati, 2001; Dawes et al., 2005). One exception to this finding is the $5\text{-}HT_3$ receptor antagonist ondansetron which has demonstrated reduced alcohol preference in human experimental studies in non-dependent subjects (Swift et al., 1996). This effect is believed to be mediated by the inhibition of alcohol potentiated $5\text{-}HT_3$ receptor mediated ion currents on DAergic neurons in the VTA (Lovinger & White, 1991).

3.3. Potential targets

In light of the successes and failures of different classes of medications for alcoholism, and from this a better understanding of the neural substrates responsible for addiction, many new targets have been identified for their potential in the treatment of this disease. In this

context, a recent review has provided an excellent discussion of how robust animal models are contributing to the identification of new treatment candidates for alcohol and drug abuse (Koob et al., 2009).

3.3.1. Dopaminergic agents

There is recent pre-clinical evidence to suggest the potential role of the DA D3 receptor in mediating alcohol craving and relapse. Gene expression studies have identified an upregulation in DA D3 receptors in the striatum of rats following chronic alcohol self administration (Vengeliene et al., 2006). In keeping with this, studies using D3 receptor antagonists have demonstrated reduced self administration, drug- and cue-induced reinstatement (Thanos et al., 2005; Jeanblanc et al., 2006; Vengeliene et al., 2006; Heidbreder et al., 2007).

3.3.2. Glutamatergic agents

The positive indications of glutamatergic mechanisms for alcoholism have inspired much research into other drugs which might act through this system. Of particular interest have been drugs which act on metabotropic glutamate receptors, specifically the mGlu2/3 and mGlu5 receptors, which are highly expressed in the mesocorticolimbic regions of the brain (Abe et al., 1992; Bell et al., 2002). Evidence for the potential role of mGlu5 receptors in the treatment of alcoholism comes from animal studies demonstrating reduced alcohol deprivation effect (Backstrom et al., 2004) and rates of self-administration of alcohol and cue-induced reinstatement following antagonism of this receptor using 2-methyl-6-(phenylethynyl)-pyridine (MPEP) or 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) (Cowen et al., 2005a; Schroeder et al., 2005). It has been suggested these drugs may exert their effect by disrupting mGlu5 potentiation of glutamatergic signaling through NMDA receptors (Hermans & Challiss, 2001) although both MPEP and MTEP possess activity other than antagonism at the mGlu5 receptor (Heilig & Egli, 2006). A recent study has also implicated a potential interaction between the mGlu5 receptor and the adenosine A_{2A} receptor that may regulate alcohol self-administration and relapse (Adams et al., 2008). Indeed, adenosine A_{2A} receptor antagonists themselves also appear to be potential therapeutic options based on preclinical studies (Arolfo et al., 2004; Thorsell et al., 2007).

Studies of the mGlu2/3 receptor have also identified this receptor as a potential target for therapeutics for alcoholism. Microdialysis studies have demonstrated increased extracellular levels of glutamate in the NAc following treatment with mGlu2/3 antagonists, similarly agonists induced a reduction in the level of this neurotransmitter in this region (Xi et al., 2002) suggesting application of agonists may influence the effects of alcohol through inhibition of glutamatergic stimulated DA release. In keeping with this idea, administration of the mGlu2/3 agonist has been found to reduce measures of craving and alcohol deprivation effects in alcohol preferring rats (Backstrom & Hyytia, 2005; Rodd et al., 2006; Zhao et al., 2006). Further, mGlu2/3 agonists have been demonstrated to have anxiolytic and anti-stress properties (Marek, 2004) which may also aid to the reduce craving/relapse in alcohol dependent subjects.

3.3.3. GABAergic agents

As discussed previously the role of GABA in mediating the rewarding effects of alcohol and the development of withdrawal effects has been well established. Given this, much work has been dedicated to identifying compounds utilizing this mechanism of action, particularly those targeting $GABA_B$ receptor complexes. $GABA_B$ receptors are located on DAergic and glutamatergic neurons within the VTA and mediate inhibitory input from the NAc and ventral pallidum and a number of GABAergic interneurons are located within the VTA. For this reason GABA, particularly through the action of $GABA_B$ receptors is believed to play an important role in mediating DA and glutamate release within the reward pathway. As discussed previously, the clinical efficacy of $GABA_B$ agonist baclofen has been recently demonstrated, providing support for the use of other agonists for the treatment of alcoholism. There are however potential negative side effects and reported tolerance effects associated with chronic modulation of this receptor (Colombo et al., 2000). One potential approach to circumvent this limitation is through the use of allosteric modulators of this receptor, either alone or in combination with low dose agonists enhancing their effect. Recent studies investigating the potential use of such a modulator have demonstrated their ability to reduce alcohol consumption, enhance the potency of baclofen and reduce the development of tolerance to baclofen when used in combination (Orru et al., 2005; Liang et al., 2006; Adams & Lawrence, 2007). A number of studies have also demonstrated a potential for $GABA_A$ receptor ligands to be pursued as therapeutics (Wallner & Olsen, 2008). Chronic alcohol consumption has been demonstrated to produce significant effects on $GABA_A$ receptor expression and function including change in subunit composition and expression, subcellular localization and pharmacological profile in non-human primates and rats (Floyd et al., 2004; Olsen et al., 2005). Studies utilizing $GABA_A$ receptor antagonists/inverse agonists (both benzodiazepine and non benzodiazepine type) have demonstrated reduction in alcohol preference and self administration in both rats and mice (Hyytia & Koob, 1995; Stephens et al., 2005).

3.3.4. Neuropeptides

As discussed previously, the effect of drug-induced dysregulation of stress regulating mechanisms plays an important role in the development of drug addiction and propensity to relapse during abstinence. With this in mind, many studies have begun to investigate the potential use of pharmacological modulators of the brain's stress systems as potential therapeutics for drug addiction, including alcoholism. Studies of the CRF1 receptor antagonist antalarmin have demonstrated significant reduction in alcohol consumption (Lodge & Lawrence, 2003) and attenuation of stress induced reinstatement in rats (Liu & Weiss, 2002b). This effect does not appear to occur purely due to the effect of this drug to reduce anxiety with studies demonstrating the failure of the anxiolytic drug diazepam (a benzodiazepine) to reduce alcohol administration while reducing anxiety levels similar to those induced by antalarmin (Lodge & Lawrence, 2003). Importantly, in a rat model of alcoholism that combines dependence and a post-dependence syndrome, a role of the extrahypothalamic CRF system in relapse to alcohol-seeking has been clearly demonstrated (Heilig & Koob, 2007). Notably, antagonism of CRF1 receptors systemically or locally within the CeA of post-dependent (but not non-dependent) rats prevents exaggerated responding for alcohol upon representation (a model of relapse) (Funk et al., 2006). This pioneering research has resulted in the development of a number promising small molecules (e.g. MTIP; Gehlert et al., 2007). Early phase trials are currently in progress for this potential approach. The CRF receptor 2 agonist urocortin III has also demonstrated the ability to inhibit alcohol consumption (Valdez et al., 2004) further highlighting the potential for drugs targeting the CRF system for the treatment of alcoholism.

The anxiolytic effects of NPY through its action in the CeA (Heilig et al., 1993) have also implied a potential role for this neuropeptide in addiction through reduction of withdrawal induced negative affect and inhibition of stress induced relapse during abstinence. A number of studies have revealed a strong relationship between NPY and alcohol consumption and preference (for review see Thorsell, 2007) and support a role for this neuropeptide in reducing alcohol consumption in animals (e.g. Badia-Elder et al., 2001), possibly through an interaction with CRF (Thorsell et al., 2005) and offer a potential novel target for the development of therapeutics for the treatment of alcoholism. Studies investigating effects of specific NPY receptors have demonstrated that potentiation of NPY signaling via stimulation of the Y_1 receptor or antagonism of the Y_2 receptor can reduce ethanol responding in animals (Thorsell, 2007) and encourage the development of clinical therapeutics utilizing this mechanism of action for treatment of alcoholics.

Substance P (SP) is another neuropeptide with a reported involvement in stress regulation. Psychological stressors stimulate SP release in the amygdala of rodents, while antagonism or genetic deletion of the SP

receptor, neurokinin1 (NK1) induces anxiolytic effects (Holmes et al., 2003). In keeping with findings of other neuropeptides, mice null for NK1 demonstrate reduced ethanol consumption and a preliminary human experimental study utilizing the NK1 receptor antagonist LY686017, previously developed as a potential antidepressant, was conducted and found this drug reduced measures of craving (George et al., 2008). These findings support the further development of this novel therapeutic for the treatment of alcoholism.

Orexin (hypocretin) A and B are neuropeptides expressed in the lateral hypothalamus. Despite their restricted expression, orexin containing neurons project widely to numerous regions of the brain including the VTA and NAc (Fadel & Deutch, 2002) and have been demonstrated to modulate activity of DAergic neurons within the VTA (Korotkova et al., 2003). There is significant evidence to support a role for orexin in regulating alcohol seeking with studies demonstrating the ability of the orexin1 receptor antagonist SB334867 to block cue and stress-induced reinstatement (Lawrence et al., 2006; Richards et al., 2008) and activation of orexinergic neurons following cue-induced and context-induced reinstatement (Hamlin et al., 2007; Dayas et al., 2008).

The neuropeptide nociceptin/orphanin FQ (N/OFQ) has also been implicated in mediating the rewarding effects of alcohol. Studies have found agonists of the N/OFQ receptor inhibit self administration and cue- and stress-induced reinstatement (Martin-Fardon et al., 2000; Ciccocioppo et al., 2004; Kuzmin et al., 2007). Further, alcohol preferring rats have been found to have decreased expression of N/OFQ receptors in the CeA (Economidou et al., 2008). N/OFQ may potentially inhibit alcohol reward through its action to reduce ethanol augmentation of GABAergic activity in the CeA (Roberto & Siggins, 2006).

Kappa and delta opioid receptors have also been implicated in alcohol reward and therapeutics targeting these receptors such as nalmefene (partial agonist at kappa opioid receptors with mu opioid receptor antagonism) have demonstrated efficacy in treating alcohol dependent patients (Karhuvaara et al., 2007). Indeed, the partial agonist nature of nalmefene at kappa opioid receptors may be useful to modulate DA release (Bart et al., 2005). Preclinical studies of the kappa opioid receptor antagonist NorBNI have found this receptor regulates alcohol self-administration in post-dependent rats and is more effective at reducing drinking than naltrexone (Walker & Koob, 2008). Similarly, delta opioid receptor antagonists can reduce heavy drinking in rats (Franck et al., 1998; June et al., 1999; Nielsen et al., 2008) and cue-induced reinstatement (Ciccocioppo et al., 2002).

Studies' demonstrating that alcohol consumption is associated with increases in renin and angiotensin II (Puddey et al., 1985; Wright et al., 1986) have suggested a potential role of renin–angiotensin signaling in modulating alcohol consumption. Recent studies in transgenic mice have demonstrated a direct positive correlation between expression of this peptide and alcohol consumption and preference (Maul et al., 2001; Maul et al., 2005) via its action at angiotensin AT1 receptors (Maul et al., 2005). The effect of angiotensin on alcohol consumption may lie in its ability to stimulate DA release within the mesocorticolimbic region (Mendelsohn et al., 1993). In keeping with this idea the D2 antagonist raclopride was unable to reduce alcohol consumption in mice over-expressing AT1 receptors while producing a significant effect on wild type littermates (Moore et al., 2007).

Therefore, it is clear that there are a number of neuropeptides implicated in various aspects of alcohol related behaviours. The availability of small molecule antagonists to many peptide receptors means that the preclinical studies described above have the capacity for translation into future medication development programs if appropriate. Clearly, future endeavours may also uncover a role in alcohol consumption for additional peptides that interact with those discussed.

3.3.5. Endocannabinoid agents

The role for endocannabinoids in modulating alcohol consumption was first demonstrated in studies of CB1 receptor knockout mice. Mice lacking CB1 receptors were found to consume less alcohol than wild type littermates and further, administration of CB1 receptor antagonist reduced consumption of wild type animals to the same level as receptor null mice (Wang et al., 2003). A similar reduction in alcohol consumption was observed in rats treated with a CB1 receptor antagonist (Freedland et al., 2001). Further, alcohol induced DA increases in the NAc is reduced in CB1 knockout mice (Hungund et al., 2003), suggesting that endocannabinoids may play a role in mediating the rewarding effects of alcohol. The CB1 receptor antagonist rimonabant was, until recently, in development for the management of obesity (Van Gaal et al., 2005) and may have provided an attractive candidate for clinical trials in alcohol dependent patients along with other CB1 receptor antagonists that were in development (e.g. CP945-598, taranabant); however clinical trials were recently discontinued due to significantly increased rates of serious psychiatric disorders associated with use (Jones, 2008).

3.3.6. Cholinergic agents

Previous studies have demonstrated the effectiveness of the nicotinic acetylcholine receptor antagonist mecamylamine on reducing alcohol consumption in rats (Blomqvist et al., 1996) most likely through its effect on reducing alcohol induced DA release from the NAc (Ericson et al., 1998) however has shown limited efficacy in reducing alcohol preference in human experimental trials (Young et al., 2005). Further, alcohol induced DA release in the NAc is mediated by activation of acetylcholine receptors in the VTA in rodents (Ericson et al., 2003). These findings suggest a potential role for cholinergic transmission in the rewarding effects of alcohol. The specific AChRs through which alcohol mediates this effect however is unknown. The $\alpha4\beta2$ nAChR partial agonist varenicline has been demonstrated to have a significant effect to reduce alcohol seeking behavior and consumption (Steensland et al., 2007). Varenicline was recently approved for use as an aid for smoking cessation and clinical trials examining its effects on alcohol dependent patients are currently underway (NCT00580645; NCT00695500; NCT00705523, http://clinicaltrials.org). Ibogaine is an indole alkaloid derived from a native shrub in Africa. Acting primarily as an $\alpha4\beta3$ nAChR antagonist, there are some data to suggest its potential use in the treatment of alcoholism. Preclinical studies of ibogaine and its analogue 18-methoxycoronaridine (18-MC) have demonstrated their ability to reduce alcohol self administration (Maisonneuve & Glick, 2003; He et al., 2005).

3.4. Summary — therapeutics for alcoholism

Despite the availability of a number of different therapeutics for the treatment of alcoholism and their demonstrated utility, their treatment effect size typically remains small. Naltrexone, nalmefene and disulfiram are limited by rates of non compliance, while the actual efficacy of acamprosate remains controversial with US based clinical trials failing to confirm findings from European based studies. Given this, significant effort has been dedicated to determining how to increase the efficacy of these treatments and the development and investigation of new therapeutics with different mechanisms of action for the treatment of alcoholism. Baclofen and topiramate have demonstrated promising clinical results however both may encounter issues with tolerance (baclofen) and side effect profile (topiramate) that may limit their utility. Preclinically, small neuropeptides, particularly those involved in mediating the stress response and appetite, are providing new treatment targets. Clinical application of therapeutics manipulating these systems however is still to be confirmed.

4. Pharmacotherapeutic approaches to the treatment of opiate addiction

4.1. Current pharmacotherapies

There are currently two general approaches to the treatment of opiate addiction, assisted detoxification followed by relapse prevention

treatment and opiate maintenance therapy. Given the generally disappointing long term results of abstinence oriented approaches and increased risk of fatal intoxication upon relapse (Petrakis et al., 2000), opiate maintenance approaches have become the primary approach to treatment of opiate dependence in many countries (Kerr et al., 2005). Rather than improving patient outcomes by treating the addiction, opiate maintenance aims to improve the health and well being of the patient by reducing withdrawal, craving, illegal drug use and drug related harm (e.g. infectious diseases and drug related crime). Because of the extended action and steadier effect on opioid receptors, replacement therapeutics (such as methadone) minimize the 'high–low' associated with the fast onset and short action of abused opiates, alleviate craving and compulsive drug use and the development of tolerance. Methadone, a mu opioid receptor agonist, is the most commonly prescribed medication for opiate maintenance therapy. Aside from its effects on stabilizing opiate use, studies have suggested methadone also normalizes HPA axis dysfunction associated with chronic opiate abuse (Kling et al., 2000; Kreek, 2000). Importantly, where it is available, daily appearance at the methadone providing outlet also incorporates a degree of structure into the life of the addict. Levo-α-acetylmethadol (LAAM), a derivative of methadone, is also a mu opioid receptor agonist with a longer effective action than methadone and has similar effects on normalization of stress responses (Kreek, 2000). LAAM is suggested to be more effective at reducing opiate abuse than methadone (Clark et al., 2002). Buprenorphine is a mixed opioid receptor agonist–antagonist with partial mu opioid receptor agonist activity (Cowan et al., 1977) and partial kappa opioid receptor antagonist activity (Leander, 1987). It has the advantage over methadone and LAAM in that as a partial mu agonist its maximal efficacy is less than that required for suppression of consciousness and respiration, reducing rates of death from overdose and reducing its abuse liability (Nutt & Lingford-Hughes, 2008). Further, its action as a partial agonist may produce less receptor adaptation when compared to methadone, so it may be easier for patients to wean off. Its effects as a kappa opioid receptor antagonist may overcome the hyperactivity observed in this system following continued mu opioid receptor agonist use that can lead to a dysphoric state (Dole, 1988; Rothman et al., 1991), its use as a maintenance therapeutic, however is not as successful when compared to methadone (Mattick et al., 2008).

Another approach to the treatment of opiate addiction involves managed detoxification to aid in abstinence initiation. The α2 adrenoceptor agonist clonidine, (Strang et al., 1999) and naltrexone (Gowing et al., 2002) have been used with relative success for the management of withdrawal and promotion of abstinence from opiates. Clonidine is used primarily due to its ability to relieve sympathetic nervous system effects associated with withdrawal, while naltrexone is used to precipitate rapid withdrawal by blocking opiates mechanism of action, this approach is usually conducted under sedation or anesthesia to reduce the acute effects of this treatment (Streel & Verbanck, 2003). In some countries clonidine has been superseded by its structural analogue lofexidine, due to its ability for use in an out-patient setting due to its relatively limited side effect profile when compared to clonidine (Akhurst, 2000).

4.2. Therapeutics for opiate addiction — clinical studies

4.2.1. Maintenance therapies

The use of diamorphine (heroin) for the maintenance of opiate addicts has been associated with considerable controversy. There is evidence however to support the use of both oral and injectable forms of this drug for opiate maintenance therapy (Uchtenhagen et al., 1999; van den Brink et al., 2002; Frick et al., 2006). The political issues surrounding the use of this therapy however are considerable, potentially limiting the use of this approach (Fischer et al., 2007). Studies of maintenance treatments utilizing other opioid agonists with enhanced mechanisms of action including codeine (Krausz et al., 1998) and sustained release oral morphine (Eder et al., 2005), have provided further positive evidence for use of this approach for the treatment of opiate addiction.

4.2.2. Withdrawal and abstinence therapies

Despite the focus on maintenance therapeutics for the treatment of opiate dependence there is also interest in developing therapeutics for the initiation and maintenance of abstinence. A number of clinical trials investigating therapeutics with such potential have been conducted.

Previous clinical evidence of the ability of clonidine to reduce the effects of opiate withdrawal through its action on the sympathetic nervous system has inspired trials of other therapeutics with a similar mechanism of action. Lofexidine and guanfacine, selective α_{2A} adrenoceptor agonists have also recently demonstrated positive outcomes for the treatment of opiate withdrawal (Soler Insa et al., 1987; Yu et al., 2008) in clinical trials. These drugs however are unable to suppress all features of opiate withdrawal and are less effective against symptoms of anxiety, insomnia and craving. It has been suggested that altered function of neurotransmission associated with chronic use of opiates contributes to the withdrawal syndrome. Serotonin levels in particular have been demonstrated to be reduced upon withdrawal from opiates (Ahtee, 1980). Preclinical studies of pharmacotherapies able to enhance serotonergic transmission within the brain have demonstrated efficacy for reducing somatic symptoms of withdrawal in rats (Cervo et al., 1981). In keeping with this, the 5-HT, NE reuptake inhibitor venlafaxine has also recently been found to demonstrate some efficacy for the treatment of heroin withdrawal (Lin et al., 2008). A recent preclinical study of the atypical antidepressant mirtazapine, which has antagonistic actions at presynaptic α_2 adrenoceptors to disinhibit NE release and also potentiates the serotonergic system, has been found to inhibit the somatic signs of withdrawal and conditioned place preference (CPP) in rats (Kang et al., 2008).

Preclinical studies of drugs enhancing GABAergic transmission have demonstrated their promising effect on reduction of withdrawal related symptoms, opiate self-administration and relapse in dependent animals (Xi & Stein, 2000; Spano et al., 2007; Yoon et al., 2007). The $GABA_B$ agonist baclofen and the GABA mimetic GHB have both demonstrated clinical efficacy for the treatment of opioid withdrawal syndrome (Gallimberti et al., 1994; Assadi et al., 2003). These drugs have been suggested to exert their effect through normalization of the binding properties of mu opioid receptors, which are enhanced following opiate withdrawal (Diaz et al., 2006). These drugs may also act to reduce self-administration through their action to inhibit the rewarding effects of opiates through enhanced GABAergic inhibition of DA release from the VTA. This mechanism of action, as discussed previously, is proposed to mediate the effects of these drugs on alcohol consumption (Cousins et al., 2002). The use of these drugs in promoting clinical opiate abstinence however to date has not been investigated.

Preclinical investigations have revealed the role of glutamate neurotransmission in the expression and maintenance of opiate dependence (Bossert et al., 2004). Based on this the NMDA receptor antagonist memantine has been trialed clinically for its potential effects on opiate withdrawal and abstinence. Studies have found this drug is able to relieve subjective effects of withdrawal (Bisaga et al., 2001) and produce modest reductions in craving (Comer & Sullivan, 2007) suggesting this may represent a potential therapy for opiate withdrawal and dependence.

As discussed previously, ibogaine acts primarily as a α4β3 nAChR antagonist and has been used informally for many years to treat opiate addiction (Alper et al., 2008). Its use however is highly restricted in some countries due to its hallucinogenic properties. Preclinical studies have indicated its positive effects to reduce morphine self-administration in rats (Dworkin et al., 1995). A number of case studies investigating of the use of ibogaine for opiate dependence have found evidence that it reduces withdrawal and craving (Alper et al., 1999; Mash et al., 2000). Investigations as to its anti-abuse properties revealed that beyond effects at nAChRs, ibogaine also binds to the cocaine site of 5-HT

transporters and therefore may cause irreversible cerebral damage (Maisonneuve & Glick, 2003). As a result, clinical trials of this compound have been abandoned. A synthetic derivative of ibogaine, 18-MC, has been developed and has demonstrated similar effects to reduce self-administration (Glick et al., 2006) and withdrawal (Panchal et al., 2005). Clinical trials of this compound to date are still to occur.

As discussed previously, naltrexone is an effective treatment for the promotion of abstinence from opiates however is associated with significant rates of non-compliance. To potentially overcome this issue sustained release formulations have been developed and have renewed interest in this drug for opiate abuse. Clinical trials of this approach have demonstrated its effectiveness in promoting abstinence (Comer et al., 2006) however it is unknown if this is more effective when compared to standard formulation (Lobmaier et al., 2008).

4.3. Potential targets

Maintenance therapy has proven an effective approach for the treatment of opiate dependence, enabling patients to regain control over their drug use and eventually become abstinent. Despite the success of maintenance therapy, considerable interest still exists regarding the identification and development of anti-craving, abstinence promoting compounds with non-opioidergic mechanisms of action. A number of potential therapeutics have been identified and have been preclinically tested for their potential use for this approach to treatment.

4.3.1. Dopaminergic agents

As discussed previously, the role of DA in mediating the rewarding effects of drugs of abuse has been well established. However DA has also been demonstrated to play a significant role in the development of craving and withdrawal when chronic drug use results in hypofunction of this system. Drugs which enhance DAergic function have been shown to reduce the effects of withdrawal from various drugs of abuse. Mirtazepine is an antidepressant with agonist activity at 5-HT1 receptors, potent 5-HT2, 5-HT3 and pre-synaptic α_2 adrenoceptor receptor antagonistic activity (de Boer, 1996), all actions which increase DA within the brain (Devoto et al., 2004). A recent preclinical study of this drug found it was able to reduce the effects of opiate withdrawal in morphine dependent rats and block the expression of CPP (Kang et al., 2008). The D1 receptor agonist SKF 82958 was also found to reduce withdrawal symptoms in morphine dependent rats (Chartoff et al., 2006), further supporting the use of DA enhancing drugs for opiate withdrawal. However, as discussed previously, preclinical studies of DAergic ligands often fail to translate into clinical practice for addictions.

4.3.2. Glutamatergic agents

The role of glutamate in mediating the rewarding effects of, and relapse to opiates has recently been established (LaLumiere & Kalivas, 2008; Shabat-Simon et al., 2008). Glutamatergic signaling between the PFC and NAc has been demonstrated to be essential for cue-induced drug seeking (LaLumiere & Kalivas, 2008), while glutamatergic signaling in the VTA is essential for the development of self-administration and CPP (Shabat-Simon et al., 2008). Pharmacological agents capable of reducing glutamatergic signaling within these regions may potentially provide a mechanism through which to promote abstinence. Preclinical studies of an agonist for the mGluR2/3 receptor (LY379268), which when activated inhibits presynaptic release of glutamate, has been demonstrated to reduce cue-induced reinstatement (Bossert et al., 2004; Bossert et al., 2005). Similarly, N-Acetylcysteine (NAC), which also increases signaling at mGluR2/3 receptors, has also been found to inhibit both cue- and heroin-primed relapse (Zhou & Kalivas, 2008).

4.3.3. Adrenergic agents

A recent preclinical study of the α1 adrenoceptor antagonist prazosin found that administration of this compound reduced heroin self-administration in rats (Greenwell et al., 2009), blocked the acquisition of CPP and also reduced withdrawal symptoms in mice (Zarrindast et al., 2002; Ozdogan et al., 2003).

4.3.4. Neuropeptides

As discussed previously the role of the brain's stress system in the development and persistence of dependence has lead to the investigation of pharmacological modulators of this system for the treatment of withdrawal and promotion of abstinence. This is also the case for opiate dependence. Antagonists of CRF1 receptors and studies of CRF1 knockout mice have demonstrated a role for this receptor and its endogenous ligands in mediating somatic effects of opiate withdrawal (Contarino & Papaleo, 2005) and stress-induced reinstatement of drug seeking (Shaham et al., 1998). Antagonism or knockout of the NK1 receptor also reduced rates of self-administration (Ripley et al., 2002; Placenza et al., 2006). In contrast, NPY administration has been demonstrated to precipitate relapse and increase self-administration, implicating a role for this neuropeptide in opiate reward and craving (Maric et al., 2008). Further investigations with NPY receptor subtype-specific ligands are still required. A growing body of evidence has implicated vasopressinergic neuronal activity in mediating the stress response (Griebel et al., 2002; Wigger et al., 2004) and because of this may have a role in opiate dependence. A recent study of the arginine vasopressin receptor1B antagonist, SSR149415, found inhibition of signaling through this receptor was able to block both stress- and drug-induced reinstatement (Narita et al., 2006; Zhou et al., 2008) of opiate-seeking. The orexin family of neuropeptides has also been implicated in mediating opiate reward, dependence and withdrawal. For example, opiate-conditioned rats demonstrate robust activation of orexin-containing neurons (Harris et al., 2005). Studies of mice lacking orexin and use of orexin receptor antagonists demonstrate reduced CPP, sensitization and withdrawal symptoms (Narita et al., 2006; Sharf et al., 2008). These studies strongly implicate a role for this peptide in mediating opiate reward and craving and may provide suitable targets for modulation to relieve withdrawal symptoms and promote abstinence.

4.3.5. Purinergic agents

Adenosine signaling through A_{2A} receptors has also been implicated in mediating opiate withdrawal, craving and relapse. A number of studies have found genetic deletion or antagonism of the A_{2A} receptor is able to reduce the effects of morphine withdrawal (Salem & Hope, 1997; Bilbao et al., 2006; Castane et al., 2008), self-administration (Brown et al., 2009a) and drug-primed relapse to drug seeking (Yao et al., 2006). A_{2A} receptors are primarily found on the spines of GABAergic neurons and glutamatergic terminals in the striatum (Rosin et al., 2003) and may play an important role in glutamatergic transmission (Ferre et al., 2005) however it is at present unknown if A_{2A} antagonists are able to disrupt cortico-accumbens glutamatergic transmission involved in opiate reward and craving (Ferre et al., 2007).

4.3.6. Other

A number of other pharmacological agents have also been implicated in opiate dependence. Chronic opiate use induces glial activation and pro-inflammatory cytokine expression which is thought to be involved in the development of tolerance (Song & Zhao, 2001; Watkins et al., 2005) and recent evidence has suggested that activation of glial cells may also be involved in opiate withdrawal. Studies of the glial activation inhibitors AV-411 (ibudilast) and minocycline have found attenuation of morphine withdrawal symptoms in dependent rats (Ledeboer et al., 2007; Hutchinson et al., 2009). The action through which the inhibition of pro-inflammatory responses may be acting to affect opiate withdrawal may involve the ability of pro-inflammatory mediators to interact with neurons (Zhang et al., 2008) or induce downstream changes that alter the expression of neurotransmitter receptors (Nakagawa & Satoh, 2004). The safety and tolerability of AV-441 have recently been tested in

healthy volunteers and was found to be well tolerated (Rolan et al., 2008) leading to the acceptance of a Phase II clinical trial of this drug for the treatment of heroin withdrawal (NCT00723177, http://clinicaltrials.org).

4.4. Summary — therapeutics for opiate addiction

Treatment of opiate dependence largely focuses on opiate based therapeutics for maintenance which attempt to improve the health and wellbeing of the patient and to enable them to regain some structure and control of their lives. Despite the relative success of this approach, relapse still presents a major issue and considerable interest exists in the development of therapeutics for the promotion of abstinence. Interestingly, preclinical studies suggest that there appears to be a degree of overlap between therapeutics potentially effective for alcohol abstinence and those that may prove useful for opiate dependence, including those that manipulate GABAergic and stress related neuropeptide systems. Clinical trials of the potential of such therapeutics for abstinence promotion however are still lacking.

5. Pharmacotherapeutic approaches for the treatment of psychostimulant addiction

Despite the prevalence of psychostimulant addiction (i.e. cocaine or amphetamine dependence) within society there are currently no medically approved treatments for this type of addiction. While recent advances have been made in psychotherapeutic approaches for the treatment of this addiction, many patients are ineffectively managed and the rate of discontinuance is exceptionally high (Alterman et al., 1996). To help combat the relative lack of pharmacotherapeutic options for cocaine and amphetamine dependence the National Institutes on Drug Abuse have established a number of programs (e.g. Cocaine Rapid Efficacy Screening Trial – (Leiderman et al., 2005); Methamphetamine Clinical Trials Group – (Elkashef et al., 2007)) to aid in the development and clinical testing of a number of potential pharmacotherapeutics for the treatment of psychostimulant addiction. As a result, a number of recent clinical trials have been conducted on a large number of potential therapeutics. There are a number of excellent recent reviews of these medications (Sofuoglu & Kosten, 2005; Kampman, 2008; Karila et al., 2008). Thus, we will only review recent key studies and some of the newer trials that have assisted in the identification and pursuit of new potential therapeutics.

5.1. Pharmacological approaches for psychostimulant addiction — clinical trials

5.1.1. Dopaminergic agents

Therapeutics which increase the level of DA within the brain have been investigated for their potential use as a maintenance therapy, they may also have effects on altered DAergic functioning associated with chronic psychostimulant abuse. A number of non-selective DA enhancers have been investigated for their efficacy in the treatment of psychostimulant dependence. Levodopa/carbidopa, a drug combination commonly prescribed for Parkinson's disease, failed to show any effect on cocaine use, craving or mood (Mooney et al., 2007). The initial double-blind pilot trial of the DA enhancing agent amantadine demonstrated a reduction in staff reported ratings of cocaine dependence however levels of metabolite free urine tests, while reduced, did not obtain significance (Shoptaw et al., 2002). A follow-up trial with a larger cohort of patients failed to demonstrate any significant effect of amantadine on cocaine abuse related outcomes (Kampman et al., 2006). Selegiline increases DA levels in the brain by inhibiting monoamine oxidase (MAO) (Felner & Waldmeier, 1979); despite promising preclinical studies reducing cocaine discrimination in rats (Gatch et al., 2006), a double-blind placebo-controlled trial failed to find any effect of this drug on cocaine use (Elkashef et al., 2006). Trials of selegiline efficacy in amphetamine-dependent patients are currently underway (NCT00033072, http://clinicaltrials.org). The cocaine homologue cocaethylene has also been investigated for use as potential maintenance therapy. Previous studies suggest cocaethylene can mimic the subjective and cardiovascular effects of cocaine, however it has a reduced potency and longer elimination half life (McCance et al., 1995; Hart et al., 2000). A recent double-blind placebo-controlled trial found cocaethylene was also able to reduce some of the behavioral effects of cocaine (Baker et al., 2007), providing support for further clinical trials. The abuse potential of this drug may however limit its use for treatment.

Other drugs which enhance DA within the brain such as DA reuptake inhibitors have been investigated for their potential use as maintenance therapeutics, or as anti-craving therapeutics, correcting for the DAergic hypofunction observed during withdrawal and following chronic use. Bupropion, an atypical antidepressant, acts as a DA and NE reuptake inhibitor and an $\alpha 7$ containing nAChR antagonist (Arias, 2009). Randomized controlled trials investigating the efficacy of this drug to augment psychostimulant addiction have failed to demonstrate any significant effect on cocaine-dependent individuals (Margolin et al., 1995; Shoptaw et al., 2008a); however, a statistically significant reduction in use has been demonstrated in light methamphetamine users (Shoptaw et al., 2008b), warranting further evaluation of this drug in methamphetamine addicts. These trials are currently underway (NCT00572234; NCT00687713, http://clinicaltrials.org). Other DA reuptake inhibitors including vanoxerine and dextroamphetamine have also been examined for psychostimulant addiction with varying results. Preclinical studies of vanoxerine provided promising results to reduce cocaine self-administration in non-human primates (Glowa et al., 1995) and based upon these findings proceeded to Phase I trials. Unfortunately, due to an adverse heart side effect in cocaine experienced subjects, the trial was discontinued (Vocci & Ling, 2005). Analogues of this drug however are currently in development to potentially identify a therapeutic which overcomes this limitation (Rothman et al., 2008b). Methylphenidate, a DA and NE reuptake inhibitor, has been demonstrated to significantly reduce methamphetamine use in dependent patients (Tiihonen et al., 2007), additional clinical trials are underway to further evaluate its potential for treatment (NCT00603434, http://clinicaltrials.org). Dextroamphetamine, which also exerts its action at DA and NE transporters, has also been trialed for its potential for psychostimulant dependency. Despite its high abuse potential, pilot studies have found positive effects on craving and use in cocaine and methamphetamine-dependent patients (Grabowski et al., 2001; Shearer et al., 2001; Shearer et al., 2003). A double-blind clinical trial of oral methamphetamine has also demonstrated a significant reduction in cocaine craving and use (Mooney et al., 2009).

Non-amphetamine based monoamine releasers are currently under development to attempt to circumvent the abuse potential associated with amphetamines (Rothman et al., 2005). The DA beta-hydroxylase inhibitor disulfiram, as discussed previously, is clinically indicated for the treatment of alcoholism. The clinical efficacy of disulfiram has to date only been evaluated in patients co-dependent for cocaine and alcohol with some positive effects, however it is unknown whether this finding is due to a reduction in alcohol intake alone (Pennings et al., 2002). In amphetamine-dependent patients however, disulfiram enhances the subjective effects of amphetamine (Sofuoglu et al., 2008) and clinical studies of this drug are currently underway to further investigate its utility and that of another DA beta-hydroxylase inhibitor, nepicastat, for amphetamine dependence (NCT00731133; NCT00656357, http://clinicaltrials.org). Citicoline is an essential intermediate in the biosynthetic pathway of membrane biosynthesis. Besides its role in increasing phospholipid synthesis and incorporation into neuronal membranes, this compound has been found to increase levels of DA and NE while decreasing 5-HT levels (Martinet et al., 1979; Secades & Frontera, 1995). A preliminary short term double-blind trial

of citicoline in cocaine-dependent patients found this drug was able to reduce some subjective ratings of craving and use (Renshaw et al., 1999). It is unclear however if these results translate to long term increases in abstinence rates. Further studies are required.

The selective D2 receptor agonists ropinirole and cabergoline have also revealed positive results for the treatment of cocaine dependence. A recent small open label trial of ropinirole revealed a significant reduction in metabolite positive urine tests over the course of the 12 week trial (Meini et al., 2008), while a small double-blind placebo-controlled trial of cabergoline revealed a significant reduction in subjective rating of cocaine use and metabolite positive urine tests (Shoptaw et al., 2005), providing support for larger trials of both these agonists. The efficacy of the partial D2 agonist aripiprazole has been preliminarily trialed in an open label study and demonstrated a decrease in crack cocaine craving and use (Vorspan et al., 2008) however, a double-blind placebo-controlled study of this drug in amphetamine or methamphetamine-dependent patients revealed an increase in use (Tiihonen et al., 2007). Further clinical trials for this indication are currently ongoing (NCT00728312; NCT00497055, http://clinicaltrials.org). Double-blind randomized controlled trials of the mixed D1/D2 receptor agonists amantadine (Kampman et al., 2006) and pergolide (Malcolm et al., 2000) failed to demonstrate any significant effect when compared to placebo in cocaine-dependent patients. Similar findings were observed in a blinded controlled study of the D3 receptor agonist pramipexole (Ciraulo et al., 2005).

Reserpine is a rauwolfia alkaloid which acts to destabilize monoamine containing vesicles, depleting these neurotransmitters, including DA, within the brain (Henry et al., 1994). In this way reserpine may inhibit the action of psychostimulants, aiding in abstinence maintenance. An initial small pilot study of reserpine demonstrated a decrease in cocaine use (Berger et al., 2005) however a follow-up recent double-blind placebo-controlled trial of this drug failed to confirm a significant effect on use (Winhusen et al., 2007a). A trial investigating the interaction between reserpine and methamphetamine is currently underway (NCT00267657, http://clinicaltrials.org).

The dihydropyridine type Ca^{2+} channel antagonists amlodipine and isradipine not only have effects on neuronal excitability through inhibition of Ca^{2+} channel function but also have reported modulatory effects on DA function (Middlemiss & Spedding, 1985; Bourson et al., 1989). These drugs also act as vasodilators, and in this way may reverse the cerebral blood flow deficits observed in cocaine users (Gottschalk et al., 2001; Kosten et al., 2003). Promising preclinical studies of these drugs revealed effects on cocaine CPP and self-administration (Calcagnetti et al., 1995) lead to clinical trials of these drugs for the treatment of psychostimulant dependence. Isradipine, was found to enhance subjective effects of cocaine in a double-blind cross over study, limiting the anti-abuse potential of this drug (Roache et al., 2005). Further, amlodipine failed to attenuate cocaine (Malcolm et al., 2005) or methamphetamine craving or use (Hill & Sofuoglu, 2007).

5.1.2. GABAergic agents

As discussed previously, enhancement of GABAergic transmission within the mesocorticolimbic structures in the brain may attenuate DA release involved in the reinforcing effects of drugs of abuse. Cocaine acts primarily to increase DA in the VTA, a structure highly innervated by GABAergic interneurons. Studies have suggested a potential interaction between these two neurotransmitter systems. Chronic cocaine use and withdrawal have also demonstrated effects on GABAergic transmission in the NAc, disinhibiting DA neurons in this area (Cameron & Williams, 1994) as well as GABAergic receptor expression and binding characteristics (Frankowska et al., 2008). Preclinical studies of a number of pharmacological agents with mechanisms promoting GABAergic transmission demonstrating reduction in cocaine self-administration (Filip et al., 2007), CPP (Ashby et al., 2002) and reinstatement (Peng et al., 2008) also support the potential use of such an approach for the treatment of psychostimulant addiction. On the basis of these findings a number of clinical trials testing pharmacological agents stimulating GABAergic transmission have been conducted.

As discussed previously, the $GABA_B$ agonist baclofen has demonstrated its potential efficacy for the treatment of alcoholism (Cousins et al., 2002) and opioid dependence (Assadi et al., 2003) through its action to inhibit release of- and excitation by- neurotransmitters (Misgeld et al., 1995). Preclinical studies of other $GABA_B$ agonists have demonstrated similar results (Roberts, 2005). Recent clinical trials of baclofen in cocaine and methamphetamine-dependent patients have demonstrated promising results for reducing use (Shoptaw et al., 2003; Haney et al., 2006; Heinzerling et al., 2006) however, as discussed previously, its use may be limited by the development of tolerance to baclofen. The results of these studies however are still preliminary, but provide an avenue for future trials.

The GABAergic anticonvulsants tiagabine, vigabatrin, topiramate, gabapentin, and valproic acid all have profound effects on GABAergic transmission as well as other documented effects on ion channels and glutamatergic transmission. As anticonvulsants, their predominant mechanism of action is via inhibition of excitatory neurotransmission. For treatment of psychostimulant addiction, anticonvulsants may utilize this enhancement of inhibitory neurotransmission to inhibit the reinforcing effects of these drugs and normalize the chronic effects on GABAergic transmission. It has also been suggested that seizure 'kindling'-like mechanisms contribute to the development of addiction (Crosby et al., 1991); anticonvulsants may act to inhibit these mechanisms. Both preclinical studies and a limited number of small clinical studies in cocaine-dependent patients have revealed promising results for this approach to treatment. Tiagabine raises GABA levels by selectively blocking the presynaptic GABA reuptake transporter type 1 (Borden et al., 1994). Clinical studies have revealed that tiagabine is able to reduce self-reported subjective effects of cocaine (Sofuoglu et al., 2005a), however a double-blind placebo-controlled pilot study found this drug did not affect reported levels of cocaine administration and cocaine metabolite positive urine samples (Winhusen et al., 2007b). Vigabatrin inhibits GABA transaminase, increasing GABA levels in the brain (Abdul-Ghani et al., 1980). Two open label clinical trials have demonstrated promising effects on rates of abstinence in cocaine (Brodie et al., 2003; Brodie et al., 2005) and amphetamine-dependent patients (Brodie et al., 2005). Further clinical trials are currently underway to further investigate the use of this drug in cocaine and methamphetamine dependence (NCT00373581; NCT00626834; NCT00730522, http://clinicaltrials.org). Topiramate enhances GABAergic transmission at $GABA_A$ receptors and levels of GABA in the brain (Kuzniecky et al., 1998) and inhibits glutamatergic transmission through effects on AMPA/kainate receptors (Perucca, 1997) and as previously discussed has demonstrated potential for the treatment of alcohol and opiate dependence. A recent pilot double-blind clinical trial demonstrated promising effects of topiramate on rates of abstinence in cocaine-dependent patients when compared to placebo (Kampman et al., 2004). More trials are currently underway to further investigate the potential use of topiramate for the treatment of psychostimulant addiction (NCT00223626; NCT00685178; NCT00249691, http://clinicaltrials.org). Gabapentin, like topiramate, also increases GABA levels in the brain (Taylor et al., 1998). An open label study found gabapentin reduced subjective rates of craving and positive urine tests (Myrick et al., 2001). Double-blind placebo-controlled trials however have failed to demonstrate a role for this drug in promoting abstinence from cocaine (Berger et al., 2005; Bisaga et al., 2006) or methamphetamine (Heinzerling et al., 2006). Valproic acid enhances the action of glutamic acid decarboxylase and inhibits glutamate transaminase to increase GABA levels in the brain (Phillips & Fowler, 1982; Loscher, 1993). An open label study of valproate found that cocaine-dependent patients reported reduced levels of cocaine craving and metabolite positive urine tests (Myrick & Brady, 1998). The one placebo-controlled double-blind study of this drug however failed to support these findings (Reid et al.,

2005a). Despite the promising results for the use of anti-convulsants for the treatment of psychostimulant addiction a recent meta-analysis has suggested a distinct lack of evidence to support their use for the treatment of cocaine addiction (Minozzi et al., 2008). It must be noted however the limited numbers and small sample size of studies included in this analysis restrict the ability to demonstrate significant effects and indicate the need for larger clinical studies of these drugs.

5.1.3. Glutamatergic agents

Acute and chronic administrations of psychostimulants produce a number of effects on glutamatergic mechanisms. Acute cocaine and amphetamine administration increases extracellular glutamate levels in the VTA (Kalivas & Duffy, 1998), NAc and PFC (Reid et al., 1997), while chronic administration has been demonstrated to reduce extracellular glutamate levels (Keys et al., 1998) and down-regulation of NMDA receptors in the striatum (Yamamoto et al., 1999), mGlu2/3 signaling (Xi et al., 2002) and AMPA receptor expression (Lu et al., 1997) in the NAc. Given the role for glutamatergic signaling in psychostimulant addiction, a number of drugs with glutamatergic mechanisms of action have been trialed for their treatment efficacy.

Modafinil is a central nervous system stimulant used for the treatment of narcolepsy and excessive daytime sleepiness. Although its mechanism of action is not fully understood, there are certain characteristics which suggest that modafinil may be useful for abstinence initiation and promotion. It is thought to exert its stimulant properties through the inhibition of GABAergic transmission, through its action on α1 and α2 adrenoceptors to stimulate NE release, by weakly inhibiting DA transport or by stimulating orexinergic neurons in the hypothalamus (Chemelli et al., 1999; Minzenberg & Carter, 2008). It also increases levels of glutamate in a number of brain regions including the striatum, hippocampus, thalamus and hypothalamus (Ferraro et al., 1997; Ferraro et al., 1998). It is the increase in extracellular glutamate that may be responsible for its effectiveness in the treatment of psychostimulant abuse by 'normalizing' reduced glutamate levels observed during withdrawal and following chronic administration. Further, modafinil's action to enhance DAergic transmission; directly, through inhibition of DA transport; and indirectly, through the inhibition of GABAergic transmission (to disinhibit midbrain reward related DA neurons), may reverse DA depletion during withdrawal from and following chronic administration of cocaine, although studies are required to support these potential mechanisms of action. A small number of clinical trials of this drug have provided support for modafinil as a treatment for cocaine addiction. Modafinil has been found to blunt the euphoric effects of cocaine (Dackis et al., 2003; Malcolm et al., 2006) and further reduce cocaine use (Dackis et al., 2005). A number of similar studies are also currently in progress to confirm the results of these studies as well as investigating modafinil's potential in methamphetamine-dependent patients (NCT00218023; NCT00469508; NCT00218023; NCT00538655, http://clinicaltrials.org).

N-Acetylcysteine (NAC) is a mucolytic and primarily used for the treatment of paracetamol overdose. It has numerous mechanisms of action however it is believed to potentially be effective for the treatment of psychostimulant dependence by enhancing the exchange of intracellular glial stores of glutamate for extracellular cystine, increasing extracellular glutamate which then activates type I metabotropic glutamate receptors which then reduce the probability of further glutamate release, resulting in a reduced propensity to relapse (Baker et al., 2003). A recent study however has also suggested NAC may restore the ability for long term potentiation and depression, which is impaired by cocaine withdrawal, making it possible for addicts to regain their ability to produce adaptive behavior to overcome cocaine-seeking behavior (Moussawi et al., 2009). Preliminary clinical trials of NAC in cocaine-dependent patients have found this drug is able to reduce self-reported craving and withdrawal symptoms (LaRowe et al., 2006) and significantly reduce administration (Mardikian et al., 2007). A larger double-blind placebo-controlled study is currently underway to test the indication for NAC as a treatment for cocaine dependence (NCT00218491, http://clinicaltrials.org).

Unlike the other glutamatergic agents discussed within this section, riluzole may have an effect on psychostimulant dependence through inhibition of glutamatergic activity. Riluzole inhibits presynaptic glutamate release and decreases GABA uptake resulting in a decrease in excitation (Doble, 1996). Similar to the action of other drugs inhibiting excitatory activity, riluzole may have a potential role in the treatment of psychostimulant addiction by restoring the balance between excitatory and inhibitory transmission that develops following chronic use of psychostimulants that are believed to be involved in the induction of withdrawal associated negative affect. Despite preclinical findings demonstrating the effectiveness of riluzole to inhibit amphetamine CPP (Tzschentke & Schmidt, 1998), the one double-blind placebo-controlled trial conducted using this drug failed to find any effect on cocaine craving or use (Ciraulo et al., 2005).

As discussed previously, anticonvulsants with predominantly GABAergic mechanisms of action have demonstrated some potential for the treatment of psychostimulant addiction. Carbamazepine and lamotrigine, which exert their action via their effect on ion channels, have also been investigated for their potential use in treatment of this addiction. Carbamazepine acts within the brain to inactivate voltage gated Na^+ channels, reducing excitability. This action has the effect to inhibit the phenomenon of kindling in animals (Weiss & Post, 1987) and based upon this has been suggested for the treatment of psychostimulant addiction to potentially inhibit cocaine induced abnormal limbic electrical activity (Halikas et al., 1989). Further, inhibition of presynaptic Na^+ channels may inhibit the release of neurotransmitters, particularly glutamate (Rogawski & Loscher, 2004). Early open label studies suggested this drug may potentially be beneficial for the reduction of craving and use of cocaine (Halikas et al., 1989; Halikas et al., 1992). Two subsequent randomized double-blind placebo-controlled trials supported these findings, reporting a reduction in cocaine metabolite positive urine tests and reported rates of craving (Halikas et al., 1991; Halikas et al., 1997). Subsequent trials however have failed to confirm these results (Campbell et al., 1994; Cornish et al., 1995; Kranzler et al., 1995; Montoya et al., 1995). Further, a recent meta-analysis concluded there was a distinct lack of evidence to support the use of carbamazepine for the treatment of cocaine dependence (Lima et al., 2002).

Lamotrigine inhibits voltage gated Ca^{2+} and Na^+ channels (Rogawski & Loscher, 2004) resulting in the inhibition of release of various neurotransmitters, including glutamate (Leach et al., 1986). As discussed previously, inhibition of glutamate release may act to reduce the effects of withdrawal and normalize alterations in the balance between excitation and inhibition associated with chronic psychostimulant abuse and has been demonstrated to reduce the somatic signs of withdrawal from drugs such as alcohol (Krupitsky et al., 2007). Preliminary studies of lamotrigine suggested it may have potential efficacy in the reduction of cocaine related craving (Margolin et al., 1998; Brown et al., 2003) however a pilot double-blind randomized controlled trial failed to find an effect on rates of abstinence (Berger et al., 2005).

5.1.4. Serotonergic agents

Serotonin has been strongly implicated in mediating subjective effects of psychostimulants and significant changes in the serotonergic system, particularly hypofunction, are associated with withdrawal and chronic use of these drugs. Further, the serotonergic system is a known modulator of DAergic and glutamatergic transmission in the mesocorticolimbic reward pathway (Alex & Pehek, 2007). A number of SSRIs have been trialed for use in psychostimulant addiction with varying results. It was hypothesized that by increasing 5-HT levels by inhibiting reuptake, the hypofunction of this neurotransmitter system associated with withdrawal and chronic psychostimulant use may be restored. Paroxetine, sertraline, venlafaxine, fluoxetine and imipramine have all

demonstrated little to no effect on cocaine and/or methamphetamine use or craving when compared to placebo (Grabowski et al., 1995; Galloway et al., 1996; Ciraulo et al., 2005) and in some cases increased use (Shoptaw et al., 2006).

Trials of citalopram combined with the behavioral adjunct of contingency management (when patients receive reward for receiving treatment), have demonstrated significant reductions in cocaine use and craving in dependent patients (Moeller et al., 2007). Whether this effect is due to the behavioral effects of contingency management alone as has been previously demonstrated (Prendergast et al., 2006) or in combination with citalopram or the more selective activity of citalopram when compared to other compounds is unknown. Other agents which act to increase 5-HT levels have been tested for potential therapeutic use. Tryptophan is the amino acid precursor to 5-HT and ingestion increases the central production of 5-HT (Fernstrom & Wurtman, 1971). Preclinical and clinical laboratory studies demonstrated promising effects of tryptophan to reduce cocaine self-administration and cue-induced craving (Carroll et al., 1990; Satel et al., 1995). Double-blind placebo-controlled trials of L-tryptophan however have failed to demonstrate an effect on cocaine use (Chadwick et al., 1990; Jones et al., 2004).

As mentioned previously, the serotonergic system is known to modulate DAergic neurotransmission within the mesocorticolimbic system. Two key modulators are the 5-HT_{2A} and 5-HT_{2C} receptors. Ligands of these receptors have been demonstrated to affect the activity of DAergic neurons and DA release within the VTA and PFC (Bubar & Cunningham, 2008). The action of these receptors on DAergic signaling makes them potential targets for therapeutic manipulation for the treatment of psychostimulant addiction. In keeping with this idea, preclinical studies of 5-HT_{2A} antagonists suggest they reduce relapse to cocaine-seeking and CPP (Nomikos & Spyraki, 1988; Fletcher et al., 2002), while antagonists of 5-HT_{2C} receptors regulate cocaine-seeking, CPP and self-administration (Bubar & Cunningham, 2008). A number of non-selective 5-HT_2 receptor ligands have been trialed for their clinical efficacy for psychostimulant abuse. Trials of the 5-$HT_{2A/2C}$ antagonist ritanserin and the 5-HT_{2A}/D_2 like antagonists risperidone and olanzapine have proven ineffective for reducing cocaine use and craving (Ehrman et al., 1996; Johnson et al., 1997; Cornish et al., 2001; Sattar & Bhatia, 2003; Smelson et al., 2004; Reid et al., 2005a; Johnson et al., 2006; Loebl et al., 2008). One open label trial of risperidone in methamphetamine-dependent patients however revealed some efficacy in reducing craving (Meredith et al., 2007). The 5-$HT_{2A/2C}$ antagonist mirtazapine however has demonstrated some promising effects on methamphetamine withdrawal as observed in a small placebo-controlled trial (Kongsakon et al., 2005). A recent follow-up double-blind placebo-controlled study failed to reproduce these results (Cruickshank et al., 2008). Further clinical trials of mirtazapine and another 5-$HT_{2A/2C}$ antagonist escitalopram in cocaine and amphetamine-dependent patients are currently underway (NCT00732901; NCT00497081; NCT00600145, http://clinicaltrials.org).

The 5-$HT_{1A/2A/2C}$ antagonist quetiapine was also found to reduce cocaine cravings in a small open label trial (Kennedy et al., 2008), suggesting further clinical trials of this agent be conducted for the treatment of cocaine and methamphetamine dependence (NCT00631748; NCT00567866, http://clinicaltrials.org), however its use may be limited by its abuse potential (Hanley & Kenna, 2008). Other 5-HT receptor ligands have also been clinically examined for their use in cocaine addiction. Pilot trials of the 5-HT_{1A} agonists gepirone and buspirone have revealed mixed results; gepirone was found to have no effect on cocaine use and craving when compared to placebo (Jenkins et al., 1992) while buspirone was found to relieve the effects of cocaine withdrawal in a small open label trial (Giannini et al., 1993). No further studies have been completed to confirm this finding. Recently, a small double-blind placebo-controlled trial of the 5-HT_3 receptor antagonist ondansetron, which has been shown to increase DA in the NAc (Dremencov et al., 2006), has demonstrated potential utility for reducing cocaine use (Johnson et al., 2006) however was not as successful for reducing amphetamine use (Johnson et al., 2008). On the back of these results, further clinical trials investigating the use of this drug in cocaine-dependent patients are currently underway (NCT00689572; NCT00599573, http://clinicaltrials.org).

5.1.5. Opioidergic agents

There is significant evidence to implicate the endogenous opioid system in mediating the effects of psychostimulants. The DAergic and opioidergic systems both interact functionally where by opioids increase DAergic transmission in the mesocorticolimbic system and vice versa (Spanagel et al., 1992). Further, chronic cocaine administration has been demonstrated to affect the expression of opioid receptors (Azaryan et al., 1996). Preclinical studies of a number of opioid receptor ligands have revealed a role for the opioidergic system in mediating the reinforcing and behavioral effects of psychostimulants (Corrigall & Coen, 1991; Hummel et al., 2004). Given this, use of agents manipulating the opioid system could aid in promoting abstinence by inhibiting the rewarding effects of psychostimulants or restoring the DAergic or opioidergic dysfunction associated with withdrawal, craving and relapse.

Clinical trials of the kappa opioid receptor-preferring agonists enadoline and cyclazocine have demonstrated effects on reducing the subjective ratings of cocaine in dependent patients (Walsh et al., 2001; Preston et al., 2004), however the mixed opioid agonist butorphanol, which also exerts an action through the kappa opioid receptor, failed to exert a similar effect (Walsh et al., 2001). The use of enadoline and cyclazocine warrant further exploration. A number of studies suggest naltrexone can reduce the subjective effects of both cocaine and amphetamine in trials of dependent and healthy volunteers (Kosten et al., 1992; Sofuoglu et al., 2003; Jayaram-Lindstrom et al., 2004; Jayaram-Lindstrom et al., 2008b). Further, some trials have suggested naltrexone therapy is able to reduce craving and use of psychostimulants (Schmitz et al., 2001; Jayaram-Lindstrom et al., 2005; Grassi et al., 2007; Jayaram-Lindstrom et al., 2008a). A number of clinical trials continue to investigate the potential use of this agent for both cocaine and amphetamine abuse (NCT00218023; NCT00439049, http://clinicaltrials.org).

5.1.6. Cholinergic agents

The role of cholinergic neurotransmission in mediating the reward related behavioral effects of psychostimulants, particularly cocaine, are well established (for review see Williams & Adinoff, 2008). Psychostimulants are known to act on muscarinic and nicotinic cholinergic receptors (Swanson & Albuquerque, 1987; Flynn et al., 1992), and lasting alterations in cholinergic function are associated with chronic psychostimulant use and withdrawal (Macedo et al., 2004). Further, the DAergic and cholinergic systems functionally interact within the mesocorticolimbic system to modulate the activity of each other (Williams & Adinoff, 2008). Preclinical studies of cholinergic agents have revealed their ability to modulate psychostimulant induced reward and craving (See et al., 2003; You et al., 2008) and have provided evidence for the potential utility of such therapeutics for psychostimulant abuse. To date only a few cholinergic agents have been clinically tested for their efficacy for this treatment approach, however none of these agents have provided any evidence for their use. Donepezil and rivastigmine are acetyl cholinesterase inhibitors which act to increase ACh in the brain. These were found to have no effect however on cocaine/amphetamine use in dependent patients (Winhusen et al., 2005b; De La Garza et al., 2008).

Mecamylamine, a nAChR antagonist, was found to decrease cue-induced craving in nicotine co-dependent patients (Reid et al., 1999) but upon further study was found to be ineffective at reducing cocaine use, although this has only been tested in methadone maintained patients (Reid et al., 2005b). The cholinergic nootropics piracetam and hydergine, which act to increase the action of ACh, have both been tested for their treatment efficacy in cocaine-dependent patients.

Neither of these treatments however were found to have a significant effect on reducing cocaine craving or use (Kampman et al., 2003; Shoptaw et al., 2005). The partial α4β2 nicotinic agonist varenicline is currently in clinical trial for the treatment of cocaine dependence (NCT00567008, http://clinicaltrials.org).

5.1.7. Adrenergic agents

Psychostimulants also exert their action through inhibition of NE uptake in the brain and chronic use is associated with alterations in the function of this neurotransmitter system (Horne et al., 2008). There is also a degree of functional modulation of the DAergic system by the adrenergic system. Many regions of the mesocorticolimbic system, including the VTA, NAc and amygdala receive noradrenergic input so that adrenergic stimulation increases DAergic activity (Blanc et al., 1994). Further, many of the symptoms associated with psychostimulant withdrawal (anxiety, heart palpitations etc.) are mediated by the sympathetic nervous system. Preclinical studies of adrenergic agents and adrenergic lesion models have also provided evidence for the role of this neurotransmitter in mediating the subjective rewarding effects of psychostimulants and cue- and drug-induced relapse (Sofuoglu & Sewell, 2009). Given the implicit role of this neurotransmitter system in the behavioral effects of psychostimulants, some potential therapeutic agents exploiting this mechanism of action have been assessed for psychostimulant addiction.

The beta adrenoceptor blocker propranolol has been tested for clinical efficacy in cocaine-dependent patients on the basis that its use may block the unpleasant sympathetic effects of psychostimulant withdrawal, aiding in abstinence. Trials of these drugs however have failed to demonstrate any effect on levels of cocaine abstinence (Sofuoglu et al., 2000; Kampman et al., 2001; Kampman et al., 2006). In preliminary laboratory studies, two other beta blockers, which also have alpha antagonist activity, labetalol and carvidilol, have demonstrated effects on reducing the physiological effects of cocaine as well as reducing self-administration (Sofuoglu et al., 2005a,b).

As discussed previously chronic use of psychostimulants induces profound changes in the activity of the adrenergic system, NE reuptake inhibitors may act to overcome this hypofunction to reduce craving and promote abstinence. The antidepressant desipramine is a non-selective NE reuptake inhibitor and has been tested for its clinical efficacy for cocaine and amphetamine dependence. Despite a number of promising studies suggesting the potential for desipramine to reduce craving (Gawin & Kleber, 1984; Gawin et al., 1989b), clinical trials of this drug have failed to support its ability to promote abstinence and prevent relapse (McElroy et al., 1989; Campbell et al., 2003). Recently, preliminary trials of the more selective NE reuptake inhibitors reboxetine and atomoxetine have been conducted and have revealed mixed results. Reboxetine was found to significantly reduce rates of abstinence in cocaine-dependent patients (Szerman et al., 2005) while atomoxetine was able to reduce the physiological effects of cocaine and amphetamine (Stoops et al., 2008; Sofuoglu & Sewell, 2009) but only attenuated the subject effects of amphetamine (Sofuoglu & Sewell, 2009). In keeping with these findings a number of clinical trials are currently underway to further evaluate the effectiveness of this drug for reducing psychostimulant dependence (NCT00617201; NCT00697138, http://clinicaltrials.org).

5.1.8. Cocaine vaccine

The cocaine vaccine TA-CD acts to stimulate the production of cocaine specific antibodies so that upon administration the antibodies sequester cocaine molecules in the peripheral circulation, preventing them from crossing the blood–brain barrier. By inhibiting the central action of cocaine the rewarding effects of this drug are blocked, potentially promoting abstinence by preventing drug-induced relapse. Preclinical studies of this vaccine have provided promising effects for reducing cocaine induced behavioral sensitization, self-administration and relapse to drug seeking (Carrera et al., 1995; Carrera et al., 2000; Kantak et al., 2000). Early clinical trials of this vaccine have supported the positive results of these preclinical studies in terms of tolerance, persistence of antibodies following immunization and reduction in cocaine use in patients with high antibody titers (Kosten et al., 2002; Martell et al., 2005). Despite its promising effects on reducing cocaine use, this approach to treatment is potentially limited by the ability of users to possibly override the action of the vaccine by increasing their cocaine use, limiting the use of this therapeutic to dependent patients motivated to quit. Moreover, this approach will not prevent individuals switching to use other drugs not impacted by the vaccine. The bioavailability of the vaccine also presents an issue as multiple vaccinations may be required to maintain an adequate antibody titre for effectiveness. The ethical issues surrounding vaccination, particularly how and by who it should be used, for example as a prevention for addiction or purely as a treatment option, are also important to consider (Ashcroft & Franey, 2004).

5.2. Potential targets

Despite the large number of pharmacological agents that have been tested for their efficacy for the treatment of psychostimulant dependence, only a few have shown potential utility for this approach. Based upon these findings a number of pharmacological agents with similar mechanisms of actions are in preclinical development. Further, as our understanding of the neurochemical basis of psychostimulant induced addictive behaviors, compounds with novel mechanisms of action have identified new targets for the development of therapeutics.

5.2.1. Dopaminergic agents

Partial and selective ligands for dopamine D1 and D2 receptors such as aripiprazole and cabergoline have demonstrated their potential efficacy in clinical trials for treatment of psychostimulant dependence through their use as maintenance treatments, inhibiting the DAergic action of psychostimulants or reversing the DAergic hypofunction associated with withdrawal and chronic use. Until recently however investigations of ligands for the DA D3 receptor have been lacking. It has been hypothesized that activation of the D3 receptor may enhance the rewarding effects of cocaine (Parsons et al., 1996), so blockade of these receptors may inhibit drug reward and relapse (Caine & Koob, 1993). A number of promising preclinical studies of the effect of D3 selective ligands on the behavioral aspects of psychostimulant addiction have revealed the potential utility of these drugs for treatment. The partial D3 agonist BP-897, has been demonstrated to inhibit cocaine and amphetamine self-administration (Beardsley et al., 2001), cocaine CPP (Duarte et al., 2003) and drug- and cue-induced reinstatement (Cervo et al., 2003; Gilbert et al., 2005) in studies of rat and primate. Two other partial agonists have demonstrated effects in behavioral models. CJB-090 was found to reduce cocaine self-administration in non-human primates (Martelle et al., 2007) while RGH-237 was able to inhibit cocaine induced CPP in rats (Gyertyan et al., 2007). D3 antagonists such as NGB-2904, SB-277011A and S-33138 have been demonstrated to reduce the rewarding effects of cocaine and amphetamine as assessed by electrical brain stimulation reward (Spiller et al., 2008; Peng et al., 2009), CPP (Vorel et al., 2002; Cervo et al., 2005), self-administration (Xi & Gardner, 2007; Peng et al., 2009), and cue-, stress- and drug-primed reinstatement (Vorel et al., 2002; Di Ciano et al., 2003; Xi et al., 2004; Gilbert et al., 2005; Xi et al., 2006; Cervo et al., 2007; Peng et al., 2009). These data provide evidence for the potential utility of ligands acting at D3 receptors for the treatment of psychostimulant abuse and warrant further investigation of such compounds in this regard.

DA reuptake inhibitors methylphenidate, vanoxerine and dextroamphetamine have clinical implications for their potential use in psychostimulant addiction. In keeping with this a number of other DA reuptake inhibitors which lack the adverse side effects and abuse potential associated with some of these agents may provide therapeutic options. These compounds should ideally exert high affinity for the DA

transporter, possess a slow onset and long duration of action, thereby reducing the potential for abuse and maximizing the time between each dose for effective treatment. The compounds 30, 640, RTI-336, RTI-113, (−)2beta-propanoyl-3beta-(4-tolyl)-tropane (PTT), and GBR 12909 have all demonstrated the ability to reduce cocaine self-administration (Tella, 1995; Schenk, 2002; Lile et al., 2004; Carroll et al., 2006; Gardner et al., 2006; Negus et al., 2009) however, both GBR-12909 and PTT were found to also induce reinstatement at the same doses that were effective for reducing self-administration (Schenk, 2002; Lile et al., 2004). While these data fail to support the use of these particular DA reuptake inhibitors, analogues of GBR 12909 are currently in development (Rothman et al., 2008b).

Another approach to potentially overcome the side effects and abuse potential associated with therapeutics which enhance monoamine levels is the development of compounds which enhance release of both DA and 5-HT. The ability of 5-HT to inhibit the stimulant and reinforcing effects mediated by increases in DA has been well documented (Czoty et al., 2002; Daw et al., 2002; Burmeister et al., 2004). Given this, an agent that is able to enhance both DA and 5-HT levels would be able to correct the DA and 5-HT hypofunction associated with psychostimulant withdrawal and chronic use while inhibiting the rewarding effect of DA increase thereby limiting the abuse potential of the compound. The novel non-amphetamine dual 5-HT/DA releaser PAL-287 has demonstrated efficacy for reducing cocaine administration without stimulating locomotion or reinforcement (Rothman et al., 2005). Other compounds with similar mechanisms of action are currently under development for their potential use in the treatment of psychostimulant dependence (Jin et al., 2008; Rothman et al., 2008a).

5.2.2. GABAergic agents

A number of drugs with GABA enhancing mechanisms of action have proven successful in reducing psychostimulant craving and use. Of particular interest is the $GABA_B$ agonist baclofen, which has demonstrated promising clinical evidence for its efficacy in both cocaine and amphetamine dependence. Based upon these findings, other $GABA_B$ receptor agonists are under development and preclinical testing for their potential therapeutic use. Studies of CGP44532 have demonstrated a profound effect to dose dependently reduce cocaine self-administration in rats and non human primates (Brebner et al., 1999; Weerts et al., 2005). Despite these promising trials, clinical use of $GABA_B$ agonists can be associated with adverse side effects, such as sedation and motor impairment, and as such may limit their potential utility in a clinical setting. Given this, considerable interest has been devoted to allosteric modulators of GABA receptors, which are able to enhance the action of GABA, limiting the dose of the ligand required to exert therapeutic effect and as a result potentially reduce associated side effects. The $GABA_B$ allosteric modulators CGP7930 and GS39783 have demonstrated the ability to reduce cocaine self-administration in animals, albeit less potently than baclofen (Smith et al., 2004). There is also potential that co-administration of these modulators in combination with an agonist may provide an enhanced therapeutic profile than the agonist alone.

5.2.3. Glutamatergic agents

Preclinical studies of a number of compounds that have NMDA antagonist properties have provided evidence for their potential use in psychostimulant abuse. These agents may act to inhibit the rewarding effects of psychostimulants through inhibition of glutamatergic transmission. Dextromethorphan, ifenprodil, LY235959 and acamprosate have all provided positive effects on reducing the rewarding effects of cocaine as assessed by discriminative stimulus (Witkin & Acri, 1995; Fujiwara et al., 2007), CPP (Jhoo et al., 2000; McGeehan & Olive, 2003a; McGeehan & Olive, 2006) and self-administration (Kim et al., 1997; Pulvirenti et al., 1997; Allen et al., 2005; Allen et al., 2007). The abuse potential and off target effects of dextromethorphan potentially limits its therapeutic use in psychostimulant dependence, however analogues of this compound with improved abuse profile are currently in development (Shin et al., 2008). On the basis of these preclinical findings and studies of acamprosate in alcohol and opiate dependent patients, this drug is currently in Phase II trials for the treatment of cocaine dependence (NCT00385268, http://clinicaltrials.org).

The mGlu5 antagonist MPEP was found to reduce psychostimulant-mediated motor effects (McGeehan et al., 2004) and reward as measured by CPP (McGeehan & Olive, 2003b; Herzig & Schmidt, 2004), self-administration (Kenny et al., 2003; Lee et al., 2005; Osborne & Olive, 2008; Platt et al., 2008), cocaine enhanced brain reward thresholds (Kenny et al., 2005), as well as effects on incentive motivational properties (Paterson & Markou, 2005), and cue- and drug-induced reinstatement (Lee et al., 2005; Backstrom & Hyytia, 2006). The mGlu5 antagonist MTEP has not been as extensively studied but has been demonstrated to attenuate self-administration of amphetamine (Osborne & Olive, 2008), cue- and drug-induced reinstatement of methamphetamine-seeking (Gass et al., 2009) cue induced reinstatement to cocaine seeking (Iso et al., 2006). Analogues of these agents are currently in development for further investigation and potential use (Iso et al., 2006; Carroll, 2008).

5.2.4. Serotonergic agents

As discussed previously, drugs acting as ligands at a number of serotonergic receptors have demonstrated significant clinical effects to reduce psychostimulant craving and use. For a review of compounds currently in development (see Bubar & Cunningham, 2008).

5.2.5. Endocannabinoids

There are a number of studies investigating the role of the endocannabinoid system in mediating the rewarding effects of psychostimulants (Arnold, 2005; Wiskerke et al., 2008). Of the studies that have been conducted there is mixed evidence suggesting a role for this neurotransmitter system in mediating the rewarding effects of psychostimulants. Studies of CB1 receptor antagonists and CB1 receptor knockout mice have failed to demonstrate a role for endocannabinoids in reducing self-administration (Cossu et al., 2001; De Vries et al., 2001). This receptor however does appear to be involved in relapse to cocaine-seeking, with CB1 receptor agonist HU210 dose dependently precipitating relapse to drug seeking while CB1 receptor antagonist SR141716 inhibiting both drug- and cue-induced relapse (De Vries et al., 2001). Despite the potential role for endocannabinoids in mediating relapse to drug seeking, the CB1 receptor antagonist rimonabant and other related compounds have been withdrawn due to adverse psychiatric side effects observed in clinical trials for the treatment of obesity and alcohol dependence (Jones, 2008), limiting the further evaluation of drugs with this mechanism of action for the treatment of psychostimulant addiction.

5.2.6. Neuropeptides

The involvement of drug-induced dysregulation of the stress system in the development and persistence of drug dependency has been discussed previously. Preclinical studies have also implicated this system in psychostimulant dependence. Studies of CRF1 receptor antagonists have revealed the ability of these agents to inhibit drug primed-, stress- and cue-induced reinstatement of cocaine and amphetamine seeking (Erb et al., 1998; Shaham et al., 1998; Przegalinski et al., 2005; Moffett & Goeders, 2007) without any apparent effect on self-administration (Mello et al., 2006). In keeping with this approach to treatment, the cortisol synthesis inhibitor metyrapone has passed Phase I clinical trials for its safe use in cocaine-dependent patients (Winhusen et al., 2005a) providing evidence for further investigation of its efficacy as a therapeutic. A recent review has suggested the oxytocin system may also represent a possible target in relation to psychostimulant abuse (McGregor et al., 2008).

5.2.7. Vaccine pharmacotherapy

The relative success of clinical trials of the cocaine vaccine TA-CD has stimulated the development of a vaccine for amphetamine dependence.

Early preclinical trials in animals have demonstrated the ability of monoclonal antibodies for amphetamine to reduce amphetamine enhanced locomotion and self-administration (McMillan et al., 2002; Byrnes-Blake et al., 2005; Gentry et al., 2006). These studies support the further development of amphetamine targeted vaccines as a potentially effective clinical tool for the treatment of amphetamine dependence, but note the caveat regarding lack of protection against other drugs.

5.3. Summary — therapeutics for psychostimulant addiction

Despite its prevalence within the community there are currently no therapeutics approved for the treatment of psychostimulant abuse. An overwhelmingly large number of clinical studies have so far failed to demonstrate an effect of any therapeutic on abstinence from psychostimulants despite a number of promising preclinical and pilot clinical studies. There also appears to be a number of conflicting results between different clinical trials of promising therapeutics. This failure in translation is particularly interesting given the relative success of the "bottom up" translational approach in other forms of addiction. Whether this failure demonstrates a lack of appropriate preclinical models, clinical trial design or an as yet unestablished stratification of psychostimulant addicts, for example by genetics or comorbidities, that confounds this research is unknown. As discussed later, this represents a significant limitation to the discovery of drugs for the treatment of not only psychostimulants but other addictions. As our understanding of the mechanisms underlying addiction and the influence that genetics and patient subpopulations have on treatment efficacy improve, we may begin to discover an effective approach for the treatment of psychostimulant addiction.

6. Pharmacotherapeutic approaches to the treatment of nicotine addiction

6.1. Current pharmacotherapies

Tobacco use is the main preventable cause of morbidity and premature death worldwide. Given this, effective treatment of this form of addiction is important to reduce the significant burden tobacco use places on the health system. A number of pharmacotherapies have been approved by the United States Food and Drug Administration (USFDA) for the treatment of nicotine addiction. Currently, the primary approach to the treatment of nicotine addiction is nicotine replacement therapy (NRT). Similar to maintenance treatment for opiate dependence, NRT aims to reduce craving and promote abstinence through the therapeutic administration of nicotine. A variety of products are available which vary based upon their route of nicotine administration; transdermal patch, gum, inhaler, nasal spray, lozenge and microtab. A number of trials have revealed the efficacy of the different forms of NRT for the treatment of nicotine addiction, with the use of this therapy associated with an increased probability of successful cessation for 6–12 months in heavy smokers, motivated to quit of approximately 50–70% depending on the product used (Stead et al., 2008), this equates to 4–5% of people who attempt to quit smoking. Much debate surrounds whether NRT can indeed be considered a successful approach for smoking cessation given the relatively low long-term success rates observed in clinical trials to date (Aveyard et al., 2009; Siegel, 2009). Further, this raises the question whether nicotine is the only reinforcing component associated with tobacco smoking. In this context it should be noted that nicotine can potentiate the response to stimuli associated with the use of tobacco to the point that these stimuli themselves can become reinforcing (Palmatier et al., 2006). In other words, nicotine can act as both a primary reinforcer and also a reinforcement enhancer, increasing the salience of accompanying stimuli (Caggiula et al., 2009). NRT seemingly fails to address this latter aspect of tobacco addiction, so while it may provide therapeutic relief from nicotine withdrawal, it does little to abate craving induced from smoking related stimuli.

Non-nicotinic based therapies have also been developed for treatment of nicotine addiction. The atypical anti-depressant bupropion has proven an effective alternative for the treatment of this dependence (Hurt et al., 1997; Jorenby, 2002) with a slightly greater efficacy than NRT for heavy smokers (Stead et al., 2008). As discussed previously, it primarily acts to inhibit DA and NE reuptake as well as block nAChRs. Enhanced DA and NE may act to reduce nicotine craving and withdrawal symptoms, while antagonism at nAChRs inhibits the ability of nicotine to induce its rewarding effects. Varenicline is the newest anti-smoking drug to become available on the market. It is a nicotinic $\alpha4\beta2$ receptor partial agonist and to date has proven the most efficacious therapy for smoking cessation (Stead et al., 2008). As a partial nicotinic agonist, varenicline is able to stimulate DA release in the NAc to counteract the reduction in DAergic activity associated with craving and withdrawal while inhibiting the rewarding effects of nicotine administration (Coe et al., 2005). Use of this drug however is associated with side effects, (e.g. nausea) although their appearance has not been associated with an increased rate of trial drop-out when compared to placebo (Cahill et al., 2007). In conjunction with this, a recent statement was released by the USFDA regarding the potential for serious psychiatric side effects including suicidal tendencies in patients treated with varenicline; their investigation is ongoing (Kuehn, 2008).

Two drugs have been used as second line approaches for the treatment of nicotine addiction where other therapies have failed and have been endorsed by the US Clinical Practice Guideline (Fiore et al., 2008), however have as yet not been approved for use by the USFDA. The α_2 adrenoceptor agonist clonidine is hypothesized to reduce nicotine craving through its action to reduce the sympathetic nervous system effects of withdrawal. A recent meta-analysis revealed that clonidine approximately doubles abstinence rates when compared to placebo (Gourlay et al., 2004). The tricyclic antidepressant nortriptyline is also indicated for use in smoking cessation. It inhibits reuptake of 5-HT and DA and potentially has effects as a nicotinic antagonist (Hughes et al., 2005). As for bupropion, nortriptyline likely reduces the effects of withdrawal and craving through its action to enhance DA levels and inhibit the rewarding effects of nicotine but also through its ability to increase 5-HT levels. A recent meta-analysis of a number of clinical trials of nortriptyline has revealed the efficacy of this therapeutic for nicotine dependence (Wagena et al., 2005).

Despite the described efficacy of these pharmacotherapies between 6 and 12 months following cessation, long term follow-up studies (12 months and greater) have found the rate of sustained abstinence to be low (Eisenberg et al., 2008). Previous data also suggest that from smokers who are abstinent at six months following cessation of use, with or without pharmacological or behavioral intervention, approximately only half of them will remain abstinent for life (Moore et al., 2009). As discussed previously, while nicotine is a strong primary reinforcer it also is extremely effective in potentiating the response to cues associated with tobacco use. Tobacco therapeutics fail to address this side of addiction, highlighting the requirement for research and development of more effective treatment approaches that incorporate this issue.

6.2. Clinical trials

6.2.1. Dopaminergic agents

The decreased levels of DA observed following withdrawal and chronic use of nicotine have lead researchers to investigate a number of agents with DA enhancing mechanisms for the treatment of tobacco dependence. The antidepressants selegiline and moclobemide both have actions to inhibit the metabolism of DA through inhibition of MAO. Preliminary placebo-controlled trials of these compounds have found reduced levels of craving and increased rates of abstinence (Houtsmuller et al., 2002; George et al., 2003). The DA reuptake inhibitor methylphenidate has also been investigated for its potential use in smoking cessation. An open label trial of this drug found decreased subjective

ratings of withdrawal symptoms and supported pursuit of a larger, placebo-controlled trial (Robinson et al., 1995). Following these results, a further clinical investigation of methylphenidate is currently in progress (NCT00549640, http://clinicaltrials.org). Based upon the success of DAergic enhancing agents, a compound which enhances presynaptic synthesis of DA and NE (Fava et al., 1990), S-adenosyl-L-methionine, is currently being investigated for its potential use to ameliorate the symptoms of nicotine withdrawal (NCT00722124, http://clinicaltrials.org).

6.2.2. Glutamatergic agents

There is much evidence regarding the effects of nicotine on glutamatergic signaling within the mesocorticolimbic system. It has been suggested that nicotine may exert some of its effects on α_7 nAChR located on glutamatergic afferents projecting to the VTA (Jones & Wonnacott, 2004) and that administration of nicotine results in elevated glutamate levels in many regions of the brain including the striatum and NAc (Toth et al., 1992; Reid et al., 2000). Further, chronic administration of nicotine results in alterations in the expression of metabotropic glutamate receptors in the amygdala, NAc and VTA (Kane et al., 2005). Two drugs with glutamatergic mechanisms of action have been preliminarily trialed for their ability to aid in smoking cessation, memantine and modafinil. A double-blind placebo-controlled study however found that rather than assist in cessation, modafinil increased subjective ratings of withdrawal and negative affect, arguing against the use of this drug in nicotine dependence (Schnoll et al., 2008). Preclinical studies of the NMDA antagonist memantine have demonstrated positive effects to reduce the rewarding effects of nicotine. A preliminary clinical double-blind study however found this drug was ineffective for reducing consumption and had no effect on subjective ratings of craving or withdrawal symptoms (Thuerauf et al., 2007). A study of the partial NMDA agonist D-cycloserine has also been completed (NCT00633256, http://clinicaltrials.org) however the results have to date not been reported.

6.2.3. GABAergic agents

The GABA enhancing antiepileptic medications gabapentin, tiagabine and topiramate have revealed mixed results in early pilot clinical trials for nicotine addiction. Tiagabine and gabapentin were both found to reduce the subjective effects of nicotine and craving in dependent patients (Sofuoglu et al., 2005b; White et al., 2005) while topiramate enhanced subjective effects and withdrawal (Sofuoglu et al., 2006; Reid et al., 2007). Clinical trials further investigating gabapentin (NCT00578552, http://clinicaltrials.org) and topiramate (NCT00755716, http://clinicaltrials.org) as well as another antiepileptic, pregabalin (NCT00644137, http://clinicaltrials.org) are currently underway. The $GABA_B$ agonist baclofen, despite its promise in psychostimulant, opiate and alcohol addiction, has demonstrated no significant effect on nicotine craving or subjective effects, although this represents the results from one small placebo-controlled laboratory test (Cousins et al., 2001). A further larger clinical trial was begun (NCT00257894, http://clinicaltrials.org) however has been terminated.

6.2.4. Serotonergic agents

The relationship between smoking, anxiety and depression, particularly during withdrawal, has suggested a potential link between reduced levels of 5-HT and nicotine dependence. Clinical trials of the SSRI fluoxetine however have generally failed to demonstrate a significant effect on long term maintenance of nicotine abstinence (Niaura et al., 2002; Hughes et al., 2007). While fluoxetine has demonstrated a decrease in negative affect associated with withdrawal (Cook et al., 2004) it is not clear that this is associated with increased abstinence. St John's Wort is also suggested to exert its mechanism of action by enhancing serotonergic transmission and preclinical studies have demonstrated its potential use in reducing nicotine withdrawal symptoms (Catania et al., 2003; Mannucci et al., 2007). A small open label trial of this medication in nicotine-dependent patients failed to demonstrate any effect on rates of abstinence (Barnes et al., 2006). A larger double-blind placebo-controlled trial of St John's Wort is currently underway to confirm these results (NCT00405912, http://clinicaltrials.org). Buspirone is a 5-HT receptor type 1 partial agonist with mixed D2 receptor agonist/antagonist properties that has been tested for its use in smoking cessation through its ability to enhance serotonergic function. Preliminary open label trials provided promising results suggesting this drug reduced withdrawal symptoms and increased quit rate (Gawin et al., 1989a; Robinson et al., 1991) however, follow up placebo-controlled trials found mixed results with some studies suggesting increased cessation rates (West et al., 1991; Hilleman et al., 1992), while others failed to support these findings (Robinson et al., 1992; Schneider et al., 1996) and found increased rates of craving (West et al., 1991; Schneider et al., 1996). The $5HT_3$ antagonist, ondansetron has also been tested based upon its ability to modulate DA release in the mesocorticolimbic structures induced by nicotine, thereby reducing its rewarding effects (Carboni et al., 1989). Clinical studies of this drug however failed to demonstrate any effect on cigarette consumption, withdrawal or rates of abstinence (Zacny et al., 1993; West & Hajek, 1996).

6.2.5. Opioidergic agents

A recent meta-analysis of naltrexone use for smoking abstinence has not supported the use of this approach, but indicates the continued study of opioid receptor antagonists to clarify the ambiguity of previously reported results (David et al., 2006). Further studies are currently underway (NCT00271024; NCT00105482, http://clinicaltrials.org).

6.2.6. Cholinergic agents

Nicotine acts primarily through stimulation of nicotinic acetylcholine receptors. Therapeutics acting to block this mechanism of action may inhibit the rewarding effects of this drug, thereby promoting abstinence and have been investigated for their clinical efficacy for promoting smoking abstinence and reducing withdrawal symptoms with variable effect. The $\alpha4\beta2$ nicotinic partial agonist cytisine has been utilized as a smoking cessation aid for the past 40 years in parts of Eastern and Central Europe however is not currently approved for use in other countries such as the USA. A recent meta-analysis of the placebo-controlled trials of cytisine have supported the use of this drug for smoking cessation (Etter, 2006) however methodological limitations have restricted their acceptability to current regulatory bodies (Etter et al., 2008). There is one ongoing trial of cytisine in the United Kingdom (TASC — ISRCTN37568749) however more are required. Preclinical studies of another partial $\alpha4\beta2$ agonist, dianicline (SSR-591,813) have supported the development of this compound for nicotine dependence, reducing withdrawal and self-administration (Cohen et al., 2003). While safety and efficacy clinical trials of this compound have been conducted, the results have as yet not been reported (NCT00356967; NCT00387946, http://clinicaltrials.org). The antagonist mecamylamine has also demonstrated some efficacy in clinical trials of smoking cessation, with reported reduction in the subjective effects of nicotine, however is associated with significant side effects (Tennant et al., 1984). Combination therapy with NRT has been proposed as a more effective approach and studies have revealed significant increases in rates of abstinence (Glover et al., 2007). Lobeline, a partial agonist, derived from the Indian tobacco plant (*Lobelia inflata*), has to date been poorly studied, with a lack of long term follow up. None of the short term studies however have revealed evidence of an effect on smoking rates (Stead & Hughes, 2000).

6.2.7. Endocannabinoids

The endogenous cannabinoid system has also been implicated in nicotine addiction. Nicotine administration has been demonstrated to alter levels of the endogenous cannabinoid arachidonoylethanolamide

in a number of different brain regions including the limbic forebrain and striatum (Gonzalez et al., 2002), although interestingly expression of cannabinoid receptors is unaffected by chronic nicotine administration (Gonzalez et al., 2002). Further, nicotine has been shown to potentiate the effects of δ-9-tetrahydrocannabinol (THC) (Valjent et al., 2002). In keeping with findings of other drugs of abuse which demonstrate an interaction with the endocannabinoid system, preclinical studies of CB1 receptor antagonists and CB1 knockout animals have demonstrated attenuated nicotine mediated measures of reward (Castane et al., 2002; Cohen et al., 2005). Clinical trials of CB1 receptor antagonist rimonabant and the inverse agonist taranabant have revealed an effect to prolong rates of abstinence when compared to placebo (Cahill & Ussher, 2007; Fremming & Boyd, 2008). Further combination of rimonabant with NRT was found to further increase rates of abstinence (Rigotti et al., 2009). Due to recent findings suggesting use is associated with increased rates of serious psychological side effects, these drugs have been withdrawn (Jones, 2008).

6.2.8. Nicotine vaccines

A number of nicotine vaccines have been developed for their potential ability to block the rewarding effects of nicotine to promote abstinence from smoking. To date three different vaccines (NicQb, NicVAX and TA-NIC) have been tested for their safety and tolerability and have demonstrated promising profiles in Phase I trials (Orson et al., 2008). Further studies investigating the efficacy of NicQb have demonstrated that patients who were able to produce high antibody titres had significantly increased rates of abstinence when compared to placebo (Cornuz et al., 2008), while patients receiving the highest dose of TA-NIC have demonstrated significant increases in rates of abstinence (LeSage et al., 2006). Further Phase II clinical trials of TA-NIC and NicVAX (NCT00633321; NCT00598325, http://clinicaltrials.org) and a Phase I study of NIC002 (NCT00736047, http://clinicaltrials.org) are currently underway. It has recently been suggested that the efficacy of nicotine vaccines might be improved by also targeting cotinine, the major metabolite of nicotine, which has also been demonstrated to exert reinforcing effects (Oliver et al., 2007). This approach is currently in preclinical development, and the combined effects of this multiple approach are still to be tested.

6.3. Potential targets

6.3.1. Dopaminergic agents

A number of preclinical studies of D3 antagonists have begun to illustrate their potential utility in nicotine dependence. The selective competitive antagonist SB-277011A and the partial agonist BP897 have reported effects on inhibiting nicotine reward as measured by CPP (Le Foll et al., 2005; Pak et al., 2006), self-administration (Ross et al., 2007), brain stimulation reward thresholds and locomotor activity (Le Foll et al., 2003; Pak et al., 2006) and drug seeking through its inhibition of drug-primed reinstatement (Andreoli et al., 2003). In keeping with these promising preclinical findings, a number of clinical trials are currently underway to test the effects of the D3 antagonists GSK598809 and GSK618334 for nicotine dependence. Initial Phase I safety and tolerability tests have been completed for GSK598809 (NCT00437840, http://clinicaltrials.org) and the compound is currently being trialed further for safety (NCT00728052, http://clinicaltrials.org), its ability to attenuate nicotine reward (NCT0060524, http://clinicaltrials.org) and enhance abstinence (NCT00793468, http://clinicaltrials.org), while GSK618334 has not progressed past safety and tolerability testing to date (NCT00513279, http://clinicaltrials.org).

6.3.2. Glutamatergic agents

The poor outcome observed in clinical trials of therapeutics acting on glutamatergic transmission suggest this approach to treatment may not provide an effective approach for promoting abstinence from nicotine. Despite these findings, a number of preclinical studies of glutamatergic modulators have provided some promising results for potential use in nicotine dependence. Preclinical studies of non competitive antagonists of mGlu5 receptors have demonstrated the ability to be able to attenuate the rewarding effects of alcohol, opiates and psychostimulants, and modulate drug seeking potentially through their action to inhibit glutamatergic signaling associated with reward. Consistent with these findings, preclinical studies of MPEP and/or MTEP have demonstrated attenuated nicotine self-administration (Kenny et al., 2003; Paterson et al., 2003; Markou et al., 2004; Tessari et al., 2004; Liechti & Markou, 2007), seeking (Palmatier et al., 2008) and drug-induced relapse (Tessari et al., 2004). Withdrawal was however exacerbated (Liechti & Markou, 2007). Other inhibitors of glutamate transmission have demonstrated potential use in attenuating nicotine reward. Previous studies have demonstrated the ability of the glycine-site directed NMDA receptor antagonist 1-aminocyclopropanecarboxylic acid to inhibit CPP to nicotine (Papp et al., 2002). GW4868816 also exhibits this activity and has demonstrated the ability to reduce cocaine- and opiate-mediated reward behaviors (Kotlinska, 2001; Backstrom & Hyytia, 2006) and is currently in clinical trials for its potential to treat nicotine dependency (NCT00218465, http://clinicaltrials.org). Glaxo-Smith Kline also have a glycine site antagonist in development for nicotine dependence which is in Phase II trials (GSK468816, http://www.gsk.com/investors/product_pipeline/docs/gsk-pipeline-feb08.pdf). Another NMDA receptor antagonist LY235959 has also demonstrated the ability to attenuate the rewarding effects of nicotine as demonstrated by reduction in nicotine enhanced brain stimulation and self-administration (Kenny et al., 2009).

6.3.3. GABAergic agents

Clinical trials of modulators of GABAergic transmission have also demonstrated positive effects on nicotine dependence. The $GABA_B$ agonist CGP44532 and the $GABA_B$ positive allosteric modulators BHF177, CGP7930 and GS39783 have demonstrated significant effects to reduce nicotine self-administration (Markou et al., 2004; Paterson et al., 2004; Paterson et al., 2005; Paterson et al., 2008), nicotine enhanced brain stimulation (Paterson et al., 2008) and drug-primed reinstatement (Paterson et al., 2005). Further, combination of the $GABA_B$ agonist CGP44532 and the allosteric modulator GS39783 was found to have a greater effect on self-administration and brain stimulation than either the agonist or modulator alone (Paterson et al., 2008). As discussed previously $GABA_B$ agonists are often associated with side effects and the development of tolerance (Colombo et al., 2000). Allosteric modulators potentially provide a means to circumvent these issues and given the positive indications for their use in the treatment of nicotine dependence warrant further investigation.

6.3.4. Serotonergic agents

A number of preclinical studies of selective 5-HT modulators have demonstrated efficacy in reducing nicotine related reward and withdrawal. 5-HT_{1A} receptor antagonists LY42695 and WAY100635, which likely act to increase serotonergic function, have demonstrated some ability to reduce aspects associated with withdrawal (Rasmussen et al., 1997; Rasmussen et al., 2000). Similarly, the 5-HT_{1A} antagonist p-MMPI, when combined with fluoxetine has also been demonstrated to reduce withdrawal related effects (Harrison et al., 2001). 5-HT_{2C} receptor agonists, WAY161503 and Ro60-0175 have demonstrated the ability to inhibit the rewarding properties of nicotine as measured by discriminative stimulus (Quarta et al., 2007), locomotion, sensitization and self-administration (Grottick et al., 2001; Hayes et al., 2009) providing a rationale for the treatment of nicotine dependence. It should be noted that 5-HT_{2C} agonist are associated with severe side effects of anxiety, hypophagia and suppression of locomotor activity (Giorgetti & Tecott, 2004), potentially limiting such an approach clinically. A drug which inhibits dephosphorylation of the 5-HT_{2C} receptor, Tat-3L4F, however has been demonstrated to induce similar effects on DAergic

transmission as the 5-HT_{2C} agonist Ro60-0175 and inhibits nicotine-induced CPP without inducing many of the adverse side effects associated with agonist activity at this receptor (Ji et al., 2006), potentially providing a better therapeutic approach.

6.3.5. Cholinergic agents

The relative success of nicotine replacement therapy as a first line smoking cessation therapy has lead to the continued development and testing of a number of agonists, partial agonists, antagonists or negative allosteric modulators to either effect the rewarding effects of nicotine or reduce withdrawal related effects and craving. While a number of compounds with either selective or mixed activity at nAChRs have been previously demonstrated to inhibit nicotine self-administration (Rowland et al., 2008), due to the success of varenicline much interest currently exists in novel nicotine analogues with activity at $\alpha4\beta2$ receptors for the treatment of nicotine addiction. Recent studies have revealed the effectiveness of two partial agonists 1′-N-ethyl-(S)-nornicotine, 1′-N-cyclopropylmethyl-(R,S)-nornicotine, and one antagonist, 5′-trans-methylnicotine, to block nicotine self-administration (Rowland et al., 2008). Given these findings it is likely that development will continue into development of analogues of these compounds. Whether these compounds progress to clinical trials however still remains to be seen.

6.4. Summary — therapeutics for nicotine addiction

Smoking remains one of the leading causes of preventable death in the world. Significant advances have been made in the treatment of nicotine addiction, progressing from the use of NRT to the development and successful use of the abstinence promoting compounds, bupropion and varenicline, although NRT remains the main first line approach to the pharmacotherapeutic treatment of nicotine addiction. Relapse however is still a significant issue even with the development of these compounds. Clinical and preclinical studies have revealed a number of promising compounds particularly those enhancing DAergic or cholinergic transmission for reducing craving and relapse. Of particular interest is the development and early promising results of trials of the nicotine vaccine, providing a unique approach and importantly proof of concept for the potential utility of vaccine therapeutics for the treatment of addiction.

7. Other drugs of abuse

7.1. Cannabis

Marijuana remains the most widely used illicit drug in the United States, Europe and Australia (AIHW, 2005; SAMHSA, 2007; EMCDDA, 2008) and is associated with dependence and withdrawal (Budney & Hughes, 2006). Despite the prevalence of its use, no medically approved pharmacotherapeutics currently exist for this form of addiction. In spite of the distinct lack of therapies there are still only a few clinical trials and laboratory studies that have been conducted for this form of addiction, predominantly with therapeutics with previous evidence of anti-abuse potential, although there are some preclinical studies of compounds with novel mechanisms of action which are also generating some interest.

7.1.1. Clinical trials

The majority of clinical studies have aimed to treat the cannabis withdrawal syndrome which can manifest itself as increased anger and aggression, anxiety, depressed mood, irritability, restlessness, sleep difficulty and strange dreams, decreased appetite, and weight loss (Budney et al., 2004). Headaches, physical tension, sweating, stomach pain, and general physical discomfort have also been observed during cannabis withdrawal, but are less common (Budney et al., 2004). The withdrawal syndrome contributes significantly to an individual's inability to maintain abstinence (Budney & Hughes, 2006), so that therapeutics able to alleviate these symptoms may provide increased rates of abstinence. Small, primarily pilot clinical trials have been conducted for bupropion, lithium, oral THC (dronabinol), atomoxetine, nefazodone, valproate, and lofexidine with variable effect on withdrawal symptoms. All drugs with the exception of bupropion and valproate, which increased withdrawal effects (Haney et al., 2001; Haney et al., 2004), atomoxetine, which had no effect and was associated with serious adverse side effects (Tirado et al., 2008), and lofexidine (Haney et al., 2008; Haney & Spealman, 2008), were able to reduce subjective ratings of withdrawal (Haney et al., 2003; Winstock et al., 2009). While the pharmacological mechanisms of action through which these drugs are presumably working vary, they may act through two different approaches, either to reverse the neurochemical effects of withdrawal (e.g. dronabinol as a maintenance drug) or to treat the withdrawal symptoms themselves (e.g. anti-anxiety effects of lithium and nefazodone). Lithium, valproate, buspirone, lofexidine were also found to either reduce use or inhibit relapse (Haney et al., 2004; McRae et al., 2006; Haney et al., 2008; Winstock et al., 2009). There are also case reports demonstrating the effectiveness of dronabinol for promoting abstinence in cannabis dependent patients (Levin & Kleber, 2008). These findings support larger clinical trials of these therapeutics. At least one clinical trial of dronabinol is currently underway to further investigate its utility for cannabis dependence (NCT00217971, http://clinicaltrials.org).

A number of other clinical trials are currently underway of therapeutics based on their efficacy for other forms of addiction. The $GABA_B$ agonist baclofen, as discussed previously, is suggested to inhibit the rewarding effects of drugs of abuse, which may translate to cannabis and is currently in clinical trials for this indication (NCT00373295, http://clinicaltrials.org). Gabapentin, which also acts to enhance GABAergic function has also recently been trialed (NCT00395044, http://clinicaltrials.org) however the results have as yet not been reported. Agents which enhance DA are also being investigated based on their potential ability to correct the hypofunction associated with chronic use and withdrawal from drugs of abuse. Citicoline and quetiapine are both under examination for use in cannabis addiction based upon this potential effect (NCT00158249; NCT00158249, http://clinicaltrials.org). The glutamate enhancing drug NAC is also being investigated for its use in cannabis dependence for its potential ability restore the glutamatergic deficit associated with withdrawal and chronic use (NCT00542750, http://clinicaltrials.org).

7.1.2. Potential targets

Preclinical studies of compounds to modify cannabis addiction related behaviors are still relatively limited when compared to other drugs of abuse. Despite this there are a few targets which may yield therapeutic potential for cannabis dependence. Of particular interest is the role of α_7 nAChRs. A recent study found that the α_7 nicotinic ACh receptor antagonist methyllycaconitine was able to inhibit DA release produced by administration of THC and further was able to block self-administration of the CB1 agonist WIN55212-2 and the discriminative effects of THC (Solinas et al., 2007), implicating this receptor in the rewarding effects of cannabis. The adenosine A_{2A} receptor has also been implicated in mediating some of the effects of cannabis withdrawal and reward. A study of A_{2A} knockout mice found that deletion of this receptor resulted in attenuation of THC induced CPP and somatic withdrawal symptoms when compared to their wild-type littermates (Soria et al., 2004).

7.2. Inhalants

Inhalant addiction, while not as prevalent as for other drugs of abuse, still represents a significant issue particularly in low-income or abusive households (Oetting et al., 1988) and in indigenous communities (Beauvais & Oetting, 1988; Chalmers, 1991), where rates of use appear

to be highest. Inhalant abuse is associated with significant toxic effects to the brain, kidney and other systems and is associated with significant neurological deficits and cognitive impairment (Lubman et al., 2008). Despite the problems associated with inhalant abuse, there are no approved pharmacotherapeutics for this form of addiction, nor have any pharmacological agents been sufficiently clinically tested for their ability to modulate dependence upon these drugs.

7.2.1. Case studies

Three case reports have been reported within the literature for the treatment of inhalant withdrawal syndrome and reduction in use. The $GABA_B$ agonist baclofen, as discussed previously, has demonstrated positive effects for reducing withdrawal from ethanol and cocaine dependence. Based upon these findings, baclofen was tested on series of three patients in Bangalor, India, and was found to reduce the effects of inhalant withdrawal in all patients and was effective in reducing craving and promotion of abstinence in two of the three patients (Muralidharan et al., 2008). Buspirone and lamotrigine have also been reported for their ability to be able to reduce the use of inhalants in single patient case studies (Niederhofer, 2007; Shen, 2007) and again were trialed due to their effective use in other forms of addiction. Despite these case reports, to date there are still no clinical trials underway to examine these therapeutics or others for inhalant abuse.

7.2.2. Potential targets

As for other drugs of abuse, the neurobiological basis underlying the rewarding effects and alterations associated with chronic use of inhalants however may provide some clues to targets for the development of potential therapeutics for this form of abuse. Studies have revealed that inhalants work on a number of receptor systems in the brain to mediate their effect. Effects are seen at NMDA, $GABA_A$, glycine, 5-HT_3, nicotinic ACh receptors as well as voltage gated ion channels (Bowen et al., 2006). Inhalants appear to act much like other drugs of abuse, and exert their reinforcing effect by enhancing DAergic transmission within the mesocorticolimbic system and animal models demonstrate behavioral effects of reward to a number of inhalants (Lubman et al., 2008). A number of neurochemical alterations are also observed following chronic administration of inhalants including changes in opiate and GABA receptor expression, as well as DA and 5-HT levels (Lubman et al., 2008). Therapeutics which act to disrupt these effects may prove useful for modulating withdrawal, craving and use of inhalants. In keeping with this idea some pharmacological agents have been demonstrated to affect the expression of behavioral effects of inhalants by disrupting these mechanisms. The GABA analogue vigabatrin has been demonstrated to block the expression of toluene induced CPP, likely through its ability to inhibit DA release (Lee et al., 2004). Inhibition of glutamatergic signaling by treatment with mGluR2/3 agonist LY379268 has also been demonstrated to inhibit the locomotor stimulant effects of toluene (Riegel et al., 2003). Further study of therapeutics for inhalant abuse is limited primarily by the lack of a model of self-administration and represents an area where development is clearly required.

7.3. Summary — treatment for cannabis and inhalant addiction

The utility of pharmacotherapeutic treatment for cannabis and inhalant addiction are still relatively under recognized considering the limited medication development for these addictions when compared to other types of addiction, despite their prevalence within the community. This is particularly true for inhalant abuse where no clinical trials have been conducted. Preclinical studies are severely limited by a lack of appropriate animal models and represent a key area for development. A number of clinical trials are currently underway for cannabis dependence; however the majority of these therapeutics are being tested based upon their indication in other forms of addiction.

8. Future directions in the identification and development of therapeutics for drugs of abuse

It is clear that a large volume of research has been dedicated to the development, preclinical and clinical testing of therapeutics for the treatment of addiction to drugs of abuse. Despite this effort, many forms of addiction still have no clinically indicated therapeutics and for those that do, many addicts are still ineffectively treated by these medications. While these limitations may arise due to limits that still exist in our understanding of the behavioral, molecular and cellular basis of addiction, it highlights the need for new approaches for the identification and development of pharmacological treatments for addiction.

8.1. From bench to bedside — lost in translation?

It is clear from this review that many of the therapeutics which have shown promise preclinically, fail to translate into the human condition. No more so is this the case than for psychostimulant dependence. Over seventy different compounds have been through clinical trials and of those only a few have shown positive outcomes for reducing craving and promoting abstinence. This then raises the question as to the relevance and validity of the rodent, non-human primate and human laboratory models in use as sufficient representations of the disorder. While anthromorphising is always fraught with theoretical danger, preclinical testing of potential pharmacotherapies is an essential part of medications development. A recent review by Haney and Spealman highlight some of the methodological and theoretical assumptions that are made in the attempt to translate preclinical and laboratory findings to positive clinical outcomes that potentially limit their successful translation (Haney & Spealman, 2008). The authors suggest that while animal models of self-administration and reward are effective for identification of the abuse liability and potential adverse side effects of pharmacological agents, studies using these models are limited for their ability to identify modulators of the addicted state due to a number of factors. Until recently many preclinical researchers have assumed drug use by animals is synonymous with drug addiction in humans (Tecott & Nestler, 2004), however only animals which satisfy other criteria such as escalation of drug taking and relapse following abstinence are more relevant models of the human condition (Ahmed & Koob, 1998). In this regard, a recent review has highlighted the importance of using validated animal models that more closely represent human addiction for the evaluation of potential new treatments (Koob et al., 2009). Beyond this fundamental aspect of modeling, many studies utilize schedules of acute rather than chronic administration of potential therapeutics, making it impossible to identify the development of tolerance or allow development of adaptations that may be required for effective treatment. Further, the majority of animal studies have failed to provide access to alternative non-drug rewards in their experimental design and therefore potentially only model those in the population that are at high risk of developing addiction. As suggested by Ahmed (Ahmed & Koob, 2005), when animals are provided with alternative non-drug rewards, the proportion that learn to self-administer drug reward is reduced and those that do, administer less (Carroll et al., 1989). This phenomenon has also been observed in humans (Higgins et al., 1994). Experimental animal studies are also typically highly controlled, utilizing an administration paradigm of single drug use at any one time and therefore fail to model the chaotic, uncontrolled and often poly-drug abuse associated with addiction. Further, the relevance of certain paradigms such as extinction-reinstatement is perhaps over-emphasized within the literature given the relatively small proportion of addicts who undergo rehabilitation (SAMHSA, 2007).

Another major limitation in translational studies lies in the interpretation of human laboratory trials. The majority of studies have only investigated the effect of therapeutics on subjective ratings of drug effects or cravings as opposed to self-administration. While it

is reasonable to assume that the subjective effects of a drug contribute to its abuse liability and that medications that disrupt this effect should predict clinical outcome, this has largely proven not to be the case. Many positive findings in laboratory studies have failed to translate to clinical trials whereas self-administration studies have proven to be more accurate predictors of medication success. Finally, it is important to realize that animal models of addiction may never be able to encompass the full complexity of the human condition in terms of the psychosocial and genetic predisposition associated with addiction. With this in mind it is important that we are able to incorporate these features of the disease into future studies so that therapeutics with potential efficacy in one population of addicts is not discarded on the basis of their failure in another.

8.2. Pharmacogenomics

The recent advances in genetic technologies have enabled the development of genetic testing to predict the response of an individual to a particular drug based upon their genetic makeup. Within psychiatry a number of polymorphisms have been identified that indicate the efficacy or development of side effects to a particular drug (Murphy et al., 2003; Gupta et al., 2006). In the case of addiction there is strong evidence to suggest a genetic predisposition to many forms of addiction (Goldman et al., 2005). The phenotypes of these addictions however are so diverse, identification of predisposing genes is a complex task and is dependent upon identification of endophenotypes, such as specific reactions to particular medications. To date, a few polymorphisms have been identified that predict an individual's response to medications for the treatment of addictions. For example alcoholics who express the A118G single nucleotide polymorphism in the mu opioid receptor gene appear to demonstrate a greater response to the abstinence promoting effects of naltrexone (Ray & Hutchison, 2007). Polymorphisms predicting response to therapeutics have been identified for alcohol, opiate, tobacco, cocaine and cannabinoid addictions (Kreek et al., 2005; David & Munafo, 2008; Haile et al., 2008; Haughey et al., 2008). While this approach to individualized treatment based upon genetics is still far from becoming mainstream, it has great potential for improving treatment for drug dependency. Further, it highlights the importance of genetics in determining response to therapeutics and is an important aspect to consider when examining the efficacy of medications in small cohorts of patients.

8.3. Psychiatric co-morbidities

While falling beyond the scope of the current review, it is important to highlight the relationship of psychiatric co-morbidity to addiction treatment outcomes. It has been well established that drug-dependent patients have an increased rate of psychiatric illness when compared to that of the general community (Compton et al., 2007). It is unclear whether this represents a cause or effect relationship. Studies have demonstrated that drug dependent individuals with psychiatric co-morbidity have a more severe clinical course than those with one or the other (Mueller et al., 1994; Hasin et al., 2002). Further, drugs which are clinically indicated for one form of addiction may not be as effective in patients with co-morbid psychiatric disorders. The converse is also true, where co-morbid patients react better to certain medications than dependent patients. For example carbamazepine treatment for cocaine dependence has been demonstrated to be more efficacious in patients with affective disorder (Brady et al., 2002). This is reflected in the multitude of studies of new therapeutics in patients with co-occurring disorder. This is an important point to consider when assessing new therapeutics, those which are deemed ineffective in dependent patients may provide positive outcomes in patients with co-occurring disorder and vice versa.

8.4. Behavioral therapies

Another key issue for the treatment of drug dependence not covered in the current review is the use of behavioral therapy. Psychotherapy is almost universally a part of treatment for drug addictions and despite its prevalence and general assumptions regarding its efficacy, surprisingly little is known about these forms of treatment and their relative usefulness (Onken & Blaine, 1990). Accurate assessment of the efficacy of behavioral therapy for the treatment of drug addiction is inherently difficult and there are many limitations associated with the clinical trials that have been conducted to assess the usefulness of these techniques (Morgenstern & McKay, 2007). Inherent variability in therapists, therapy, population and outcome measures all potentially overwhelm and obscure any significant differences between techniques (London, 1990). Further difficulty arises when assessing the contribution of behavioral therapy to the effectiveness of pharmacotherapeutics. There are many examples within the literature where combined use of behavioral techniques with therapeutics is more efficacious than the drug or behavioral therapy alone, or where the use of one behavioral technique is more effective than another when combined with pharmacotherapy. For example naltrexone with cognitive behavioral therapy maintains higher rates of abstinence from alcohol when compared to naltrexone combined with a program with limited therapeutic content (Oslin et al., 2008) and cognitive behavioral therapy alone (Anton et al., 1999). The combination of psycho- and pharmacotherapy however does not always enhance treatment outcomes (De Wildt et al., 2002; O'Malley et al., 2007) and in some cases worsens them, for example type B alcoholics treated with fluoxetine and cognitive behavioral therapy have poorer drinking related outcomes than those treated with placebo (Kranzler et al., 1996). Given these findings, it is important that well controlled trials incorporating the different behavioral therapies are conducted in order to fully assess the potential utility of a therapeutic.

9. Conclusions

Many therapeutics have been tested for their potential efficacy to treat substance use disorders and advances in our understanding of the behavioral, molecular and cellular basis of these very difficult to treat conditions has driven much of this research. The identification of novel targets through preclinical research and the continued review and evaluation of clinical and preclinical studies has proven vital for these advances. Despite this there is still a substantial lack of effective therapies for the treatment of addictions. New and improved approaches incorporating our understanding of the disorder in terms of the theory of addiction, the underlying genetics, importance of clinical diagnoses, the contribution of behavioral therapies and the most efficacious approaches to assess the value of new therapeutics are necessary for the continued development of better treatments for addiction.

Acknowledgments

This research was supported by The National Health & Medical Research Council of Australia (NHMRC) of which AJL is a Senior Fellow.

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