Recent Advances in the Pharmacotherapeutic Management of Drug Dependence and Addiction

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Abstract: Drug addiction is a syndrome of impaired response inhibition and salience attribution, which involves a complex neurocircuitry underlying drug reinforcement, drug craving and compulsive drug-seeking and -taking behaviours despite adverse consequences. The continued elucidation of the neurobiological underpinnings of withdrawal symptoms, drug intake, craving, relapse, and co-morbid psychiatric associations has significantly boosted the development of new pharmacotherapies for the treatment of drug addiction. The present review will focus on recent advances in the development of innovative pharmacotherapeutic agents, which should promote long-lasting drug abstinence and long-term recovery, ensure satisfactory patient compliance, and have a good safety profile.

First, the magnitude of the drug dependence problem will be presented by reviewing some of the most recent epidemiological data. Second, a short overview of the neurobiological substrates of drug craving and addiction will be presented. We will show that despite individual variation in the liability to the abuse of psychoactive substances, there is substantial commonality shared by drugs of abuse. The knowledge of these common mechanisms is critically important for the development of new therapeutic strategies. Third, pharmacological approaches and drug development strategies will be thoroughly discussed. The most promising strategies will be presented by reviewing key targets for drug discovery at both clinical and pre-clinical levels.

Keywords: Alcohol, cocaine, drug addiction, nicotine, opiates, pharmacotherapy.

1. INTRODUCTION

Drug *dependence* refers to the progressive adaptation of cells, circuits, and organ systems in response to excessive exposure to a drug. Thus, dependence represents a new equilibrium of physiological functions in response to the repeated, continuous exposure to a drug and the related organism's compensatory counter-mechanisms. Tolerance to the drug occurs if one observes either a decrease in the effect of the drug despite delivery of a constant dose or the need to increase the dose to maintain drug efficacy. Cessation of drug use is also typically associated with the occurrence of a withdrawal syndrome. In contrast, drug *addiction* refers to (1) compulsive drug use despite physical, psychological or social harm; (2) loss of control over amount and frequency of drug use; (3) irresistible cravings and urges; (4) denial of indisputable negative consequences, and (5) the emergence of a negative emotional state when the drug is absent. Thus, from a psychiatric perspective drug addiction has aspects of impulse control disorders and compulsive disorders. It is important to note that although many drugs can produce tolerance, dependence, and withdrawal they do not necessarily produce addiction or compulsive use. Conversely, drugs such as cocaine and the amphetamines do not produce physical withdrawal symptoms, yet these drugs may lead to compulsive use and relapse or reinstatement of drug-seeking and drug-taking behaviours even after relatively long periods of abstinence. It is this late relapse that makes the therapeutic management of drug addiction a major challenge for current research and drug development.

Over the last 30 years, a vast majority of work confirmed the role of the mesolimbic dopamine (DA) system and related limbic circuits including the amygdala, hippocampus, and medial prefrontal cortex, in the acute rewarding properties of drugs of abuse, but also in mechanisms of craving and relapse. Importantly, this work also revealed that most drugs of abuse are sharing common neural, molecular, and neurochemical substrates to produce acute reward and long-term neuroadaptations, which ultimately lead to addiction. The understanding of those mechanisms responsible for persistent changes in the so-called reward pathways is critical for the development of new pharmacotherapies for the treatment of drug dependence and addiction.

The present review will first describe the magnitude of the drug addiction problem by reviewing recent epidemiological data. Second, we will focus our attention on common neural substrates shared by most drugs of abuse. We will show how persistent alterations in these common pathways may explain, at least in part, drug craving and relapse. Third, we will show how our current understanding of these commonalities may contribute to the identification of new "targets" for drug discovery. Finally, we will review some of the most promising approaches for the development of new pharmacological agents for the treatment of compulsive drug use.

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2. MAGNITUDE OF THE DRUG ADDICTION PROBLEM

Despite significant efforts to eradicate drug use, there is growing evidence of the intractable nature of the drug abuse epidemic, which targets large segments of the World population. According to the World Health Organization (WHO), global trends reflect a general increase in the use of illegal addictive drugs and alcohol abuse and concerning increases among the youngest sectors of the population. There are about 200 million users of illegal drugs worldwide, which represent 3.4 percent of the world population. Alcohol dependence impacts 32 million adults in the top seven markets whereas about 1.2 billion smokers are estimated worldwide, comprising approximately one-third of the global population aged 15 or older. WHO estimates that the worldwide number of smokers will continue to increase to 1.6 billion by 2025.

The National Household Survey on Drug Abuse (NHSDA) was first conducted in 1971 and has since released national surveys of drug use up to 2003. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) also captured drug use and related problems across countries belonging to the European Union. The following paragraphs will briefly summarize the main outcome of the last surveys held in 2003.

2.1. Illicit Drugs

The most recent surveys performed by the National Survey on Drug Use and Health (NSDUH, previously named NHSDA) in 2003 [1] revealed that an estimated 19.5 million Americans aged 12 or older had used an illicit drug[1] during the month prior to the survey. This estimate represents 8.2 percent of that specific population. Marijuana remains the most commonly used illicit drug in the United States, with 14.6 million current users (6.2 percent of the population). This situation also holds true for the European Union where cannabis is the most commonly used drug, with lifetime prevalence rates in excess of 20 % of the general population, although prevalence of recent use is below 10% [2].

Cocaine is currently used by an estimated 2.3 million Americans (1.0 percent) [1]. In the European Union, data suggest an increase in cocaine use in the United Kingdom and, to a lesser extent, in Denmark, Germany, Spain and The Netherlands, a figure that correlates with treatment demand, toxicological findings in victims of overdose deaths, drug seizures and studies of populations at risk [2]. Europe remains also an important area for the use of amphetamines and ecstasy, with rates of lifetime experience among the adult population generally ranging between 0.5 % and 5 % [2]. In the United States, 0.6 and 0.47 million people are current users of Ecstasy and methamphetamine, respectively [1]. Hallucinogens are used by 1.0 million Americans (0.4%) [1]. The United States also have approximately 119, 000 current heroin users (0.1%) [1]. In the European Union, with the exception of Sweden and Finland, where amphetamine use is more prevalent, injecting drug use remains characterized by the use of heroin, often in combination with other drugs. National estimates of injecting drug use vary between 2 and 10 cases per 1,000 of the adult population (that is between 0.2 % and 1 %) [2].

Finally, of the 8.8 million current American users of illicit drugs other than marijuana in 2003, 6.3 million are current users of psychotherapeutic drugs [1]. This represents 2.7 percent of the population aged 12 or older. Of those who reported current use of any psychotherapeutic agents, 4.7 million used pain relievers, 1.8 million used tranquillisers, 1.2 million used stimulants, and 0.3 million used sedatives.

2.2. Alcohol

The same 2003 NSDUH survey [1] also showed that 50.1 percent of Americans aged 12 or older reported being current drinkers of alcohol. This translates to approximately 118.9 million people. An estimated 22.6 percent (53.8 million) participated in binge drinking[2] and 6.8 percent (16.1 million) were heavy drinkers[3].

2.3. Tobacco

An estimated 70.7 million Americans reported current use of a tobacco product[4], which represents 29.8 percent of the population aged 12 or older [1]. Of those who used tobacco products in 2003, 60.4 million (25.4 percent of the total population) smoked cigarettes, 12.8 million (5.4 percent) smoked cigars, 7.7 million (3.3 percent) used smokeless tobacco, and 1.6 million (0.7 percent) smoked tobacco in pipes. Among the 60.4 million past month cigarette smokers, 59.0 percent were nicotine-dependent.

2.4. Co-morbidities

In 2003, there were 19.6 million adults aged 18 or older suffering from severe mental illness (SMI)[5]. This represents 9.2 percent of all adults. There is also significant co-morbidity between drug use and abuse and SMI: adults who used illicit drugs in the past year were more than twice as likely to have SMI as adults who did not use an illicit drug (18.1 and 7.8 percent, respectively). SMI was also significantly correlated with substance dependence or abuse. Among adults with SMI in 2003, 21.3 percent were dependent on or abused alcohol or illicit drugs, while the rate among adults without SMI was only 7.9 percent. Adults with SMI were more likely than those without SMI to be

[1] Illicit drugs include marijuana, cocaine (and crack), heroin, hallucinogens (LSD, PCP, peyote, mescaline, mushrooms, and "Ecstasy" or MDMA), inhalants (amyl nitrite, cleaning fluids, gasoline, paint, and glue), and non-medical use of prescription-type pain relievers, tranquillisers, stimulants, and sedatives.

[2] Binge drinking is defined as having five or more drinks on the same occasion at least once in the past 30 days.

[3] Heavy drinking is defined as having five or more drinks on the same occasion on at least 5 different days in the past 30 days.

[4] Tobacco products include cigarettes, chewing tobacco, snuff, cigars, and pipe tobacco.

[5] SMI is defined as having at some time during the past year a diagnosable mental, behavioral, or emotional disorder that met the criteria specified in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association [APA], 1994) and that resulted in functional impairment substantially interfering with or limiting one or more major life activities.

dependent on or abuse illicit drugs (8.6 *vs.* 2.0 percent) and alcohol (17.0 *vs.* 6.7 percent) [1].

A significant prevalence of co-morbidity between alcohol and nicotine dependence has also been observed. Importantly, smoking cessation seems to enhance abstinence from alcohol, and combined treatment for both dependencies may achieve the best treatment outcome. Surveys of both inpatient and outpatient treatment participants for alcohol dependence typically show an 86–97% smoking rate among males and an 82–92% rate among females [3-9]. A 91.5% prevalence rate of nicotine dependence among outpatients who met DSM-III-R criteria for both disorders has also been reported [10]. Furthermore, a large epidemiological survey revealed that, in contrast with alcohol abstainers, current heavy drinkers are making the fewest cessation attempts and have the least success in quitting smoking [11].

3. NEUROBIOLOGICAL SUBSTRATES OF DRUG CRAVING AND ADDICTION

Most drugs of abuse appear to have the following characteristics: (1) they produce an effect that is sufficiently pleasant or rewarding to reinforce self-administration; (2) they produce an effect that the recipient can use to discriminate the drug from others, and (3) they elicit a sustained increase in extracellular DA in the mesolimbic system that originates in the ventral tegmental area (VTA) and projects towards limbic forebrain regions including the nucleus accumbens (NAc). This increase in mesolimbic DA activity would then facilitate incentive learning or the attribution of positive incentive salience to cues. These cues include the discriminative cue properties of the drug itself, which are associated with its administration. Thus, any responses to the drug, which occur during the period of raised extracellular DA, may have the potential to acquire positive incentive salience and contribute to the progressive enhancement of the attentional processing of drug-related cues. Such attentional bias towards drug-related cues would elicit drug craving and contribute to compulsive drug use.

3.1. Is Dopamine a Common Substrate of Addictive Drugs' Action?

Caution must be exercised before generalizing the role of DA in the meso-accumbens pathway to *all* addictive drugs. First, the DA hypothesis of addiction may hold true for psychostimulants, but the situation for drugs such as opiates [12], nicotine [13], and phencyclidine [14] may be more complex than originally thought [15]. Second, the concept that the mesolimbic DA system simply encodes hedonic tone has been called into question. Enhanced dopaminergic activity in the NAc is not only elicited by reward-related stimuli, but can also be triggered by aversive stimuli or exposure to a novel environment that has no obvious rewarding property [16]. Furthermore, analysis of response patterns of single DA neurons to reward presentation has led to the suggestion that mesolimbic DA may be more involved in prediction of reward and the use of such information to strengthen behaviours and increase their future likelihood [17-20]. Thus, the DA signal may constitute an alert message about reward prediction error, which rapidly informs postsynaptic structures about unexpected rewards or reward omissions, without detailed information about the nature of the reward *per se*. Such a reward alert signal would allow rapid behavioural reactions towards rewarding stimuli, while the exact nature of the reward would be evaluated by slower systems during the approach behaviour to the rewarding stimulus (for a recent review, see [20]). Third, rats with extensive neurotoxic lesions of the DA neurons in the NAc show normal hedonic response patterns to sucrose [21]. Finally, a drug like cocaine is still rewarding in mutant mice lacking the DA transporter (DAT) [22-23] suggesting that additional transporters and/or mechanisms contribute to the reinforcing properties of the drug.

Together these findings clearly support the idea that the meso-accumbens DA system is involved in learning the *motivational significance* of a stimulus rather than mediating the hedonic value of the stimulus *per se*. These studies also highlight the need to direct investigations towards complex neurocircuits including brain regions such as the amygdala, hippocampus, and medial prefrontal cortex, which play an important role in the core feature of drug addiction that is the compulsive seeking and taking of the drug as well as the risk of relapse.

3.2. Beyond the Meso-Accumbens DA Pathway: Neural Substrates of Relapse or Reinstatement of Drug Seeking and Drug Taking Behaviour

The circuitry that mediates reinstatement of drug seeking behaviour remains largely unknown, but involves at least core regions such as the NAc, the amygdala and medial prefrontal cortex. The presentation of a drug-associated conditioned stimulus (CS) to animals can induce large conditioned increases in DA neurotransmission in the NAc [24, 25], suggesting that DA in the NAc is involved in cue-controlled drug-seeking behaviour [26]. However, the amygdala has been shown to play an important role in drug-enhanced stimulus-reward associations [27, 28], which may underlie drug craving and compulsive drug taking in humans [29, 30]. Enhanced monoaminergic tone in the basolateral subregion of the amygdala (BLA) appears to increase the motivational properties or salience of cocaine-associatedcues during reinstatement of cocaine-seeking behaviour, whereas inactivation of the BLA produces the reverse effect [31]. The central amygdala (CeA) may mediate conditioned increases in DA measured in the NAc following the non-contingent presentation of a CS [27, 28] perhaps *via* projections to the VTA [32] and seems to also play a key role in stress-triggered relapse to cocaine-seeking behaviour [33, 34]. Finally, the anterior cingulate cortex (ACC) seems to serve as a common link in the neural circuitry underlying reinstatement of drug-seeking behaviours [35-38].

Functional magnetic resonance imaging (fMRI) and PET scan studies have shown that regions typically activated during drug craving partially overlap those activated during a working memory [39, 40] suggesting that both craving and attentional processes may involve similar neural circuits. The ACC is activated both in selective attention and response competition processes [41-43] as well as in cue-induced cocaine craving [37, 44-46]. Importantly, the ACC

has reciprocal connections with both the amygdala and NAc (for a review, see [38]). Thus, one may suggest that the ACC, in concert with the NAc and the amygdala, contributes to discriminate between multiple stimuli on the basis of their association with reward. This notion further supports the idea of DA release in key terminal projection areas of the mesolimbic system as an error prediction signal to modify synaptic weights depending on the valence (better-than-expected *vs.* worse-than-expected) of the environmental stimuli. Sustained increase of the DA signal following exposure to drugs of abuse or stress might result in an attentional narrowing towards reward-related stimuli, which would lead to craving and ultimately relapse [47-49].

3.3. Drug Addiction, Neuroadaptations and Synaptic Plasticity

We have hypothesised that changes in the ACC-NAc-amygdala pathway may only partly explain enhanced focusing towards drug-related stimuli and that alteration of the rheostatic role of DA in this circuit may lead to the inability to control the intake of the drug and the intense craving to seek for and take the drug. If this hypothesis has credence, then one must posit that neuroadaptations progressively occurred in specific brain regions. These neuroadaptations may translate to mechanisms of synapse-specific plasticity such as long-term potentiation (LTP) and long-term depression (LTD). Indeed, there is growing evidence suggesting that exposure to drugs of abuse including cocaine, morphine, nicotine, and ethanol can elicit LTP at excitatory synapses in the mesolimbic DA system, in the VTA in particular [51, 52]. Importantly, stress can also trigger LTP at VTA synapses [51]. The exact mechanisms by which most drugs of abuse and stress elicit LTP at VTA synapses are ill understood, but one may hypothesise that drug- or stress-induced increase in extracellular glutamate levels in the VTA plays an important role in this process. In fact, exposure to psychostimulants produces an increase in glutamate efflux in the VTA, probably through an impairment of the astrocytic reuptake of glutamate [52-54]. In addition, nicotinic acetylcholine receptors are localized on presynaptic glutamatergic nerve terminals in the VTA, and activation of these receptors by nicotine has been shown to increase glutamate release [55]. Thus, enhanced glutamate efflux in the VTA may promote LTP at excitatory synapses on DA neurons. This LTP mechanism may be even more effective if one considers that several drugs of abuse also block LTD at VTA synapses [56, 57].

Together, these findings support the idea that drugs of abuse produce persistent behavioural changes that are most probably mediated by long-lasting changes in synaptic weights in key brain pathways. In fact, recent studies have shown that the repeated administration of either amphetamine or cocaine produces an increase in dendritic spine density and an increase in the number of branched spines in the rat NAc and prefrontal cortex [58, 59]. The question of whether or not there is a causal relationship between altered synaptic weight in specific brain circuits and particular behavioural phenotypes remains to be demonstrated.

4. CURRENT PHARMACOTHERAPEUTIC STRATEGIES FOR THE MANAGEMENT OF DRUG ADDICTION

4.1. Current Pharmacotherapies for Nicotine Dependence

4.1.1. Nicotine Replacement Therapies

To date, nicotine replacement therapies (NRTs) have shown superior efficacy in all placebo-controlled clinical trials at both short-term (end of trial) and long-term (6-12 months) assessments. NRTs are currently available in two main formulations, including the slow-acting transdermal nicotine patch (TNP) formulation, and faster-acting formulations such as the nicotine gum, nicotine nasal spray, nicotine vapour inhaler, and the nicotine lozenge (Table **1**). The rationale behind the use of NRTs is to provide relief from tobacco withdrawal by replacing sufficient levels of nicotine from an alternative source than smoking behaviour. NRTs seem to reduce the reinforcing effects of smoking cigarettes and to disrupt the usual pairing of nicotine with environmental cues.

Elan has produced a transdermal formulation of nicotine using its Dermaflex system. The patch delivers approximately 1 mg of nicotine per hour for up to 24 hours. Novartis has developed a TNP in collaboration with Hefa-Frenon Arzneimittel and Lohmann Therapie-Systeme. It is available in 10, 20 and 30 cm^2 patches. Ortho-McNeil (Johnson and Johnson; J and J) and Pharmacia (now Pfizer) have also jointly developed a TNP, which consists of 3 patches containing 15, 10 and 5 mg nicotine, worn successively over a period of 16 weeks. TheraTech (Watson) proposes a TNP using the TheraDerm-MTX patch. Finally, Alza (Johnson and Johnson) has developed a transdermal controlled-release nicotine patch under a royalty-bearing licence for Sanofi-Aventis. Meta-analyses have confirmed the efficacy of various TNP preparations in improving the success of smoking cessation attempts [60, 61]. The efficacy of TNP treatment is further supported by a dose–response relationship between the nicotine content of the patch and smoking cessation success rates [62].

Nasal sprays are capable of faster systemic nicotine delivery than gum or TNPs, and their use is recommended for rapid relief of craving symptoms. The efficacy of nasal sprays has been demonstrated in a randomised placebo-controlled study, which showed that abstinence rates associated with spray and placebo use were 32% and 12%, respectively, at 6 months, and 26% and 10%, respectively, at 1 year [63]. Pharmacia (now Pfizer) has developed a chewing gum containing 2 or 4mg of nicotine bound to a cationic resin. Pharmacia and Upjohn (now Pfizer) has also developed a nasal spray formulation of nicotine.

Lozenges deliver nicotine through mucosal membranes, and their use is recommended for rapid relief of craving symptoms. Lozenges containing 1 mg nicotine can be administered every 1 or 2 hours up to a maximum of 25 mg per day. Sublingual NRT spray preparations are also readily absorbed across mucosal membranes and up to one spray per hour can be used for prompt relief of withdrawal symptoms. NRT can also be delivered using inhaler devices, which consist of a mouthpiece and plastic cartridge containing 4 mg nicotine. A double-blind placebo-controlled trial found

Table 1. Current Medications for the Treatment of Drug Addiction

Nicotine		
Mechanism of Action	**Product Name**	**Company**
Sublingual formulation of nicotine beta-cyclodextrin	Nicotine beta-cyclodextrin (Nicorette Microtab; nicotine, sublingual, Pharmaci)	Pfizer (US)
Nicotine inhaler	Nicotine inhaler, Ortho-McNeil (Nicorette inhaler; Nicotrol inhaler, Ortho-McNeil; Nicotrol inhaler, Kabi)	Johnson & Johnson (US)
Oral formulation of nicotine	Nicotine lozenge	Watson (US)
Nasal spray formulation of nicotine	Nicotine nasal, Pharmacia (Nicorette nasal spray; Nicotrol NS)	Pfizer (US)
Transdermal formulation of nicotine	Nicotine transdermal, Elan (Exodus; Nicodil; Nicolan; Niconil; Nicotrans; ProStep)	Elan (IE)
Transdermal formulation of nicotine	Nicotine transdermal, Novartis (Habitrol; Nicomed; Nicopatch; Nicotinell; Nicotinell Gum; Nicotinell TTS)	Novartis (CH)
Transdermal formulation of nicotine	Nicotine transdermal, Ortho (Nicorette-NTDS; Nicorette patch; Nicotrol; Nicotrol 16; Nicotrol Inhaler; nicotine transdermal, Johnson; nicotine transdermal, Kabi; nicotine transdermal, Warner)	Johnson & Johnson (US)
Transdermal formulation of nicotine	Nicotine transdermal, Thera	Watson (US)
Transdermal formulation of nicotine	Nicotine transdermal, Alza (Nicabate; Nicabate TTS; NicoDerm CQ; Nicoderm; Nicoderm HP; Niquitin CQ; nicotine transdermal, HMR; nicotine transdermal, SB; TTS-Nicotine; Niquitin Clear)	Johnson & Johnson (US)
Chewing gum containing 2 or 4mg of nicotine bound to a cationic resin	Nicotine, Pharmacia (Nicorette; nicotine polacrile-x)	Pfizer (US)
Sustained-release formulation of bupropion	Bupropion SR (Wellbutrin SR; Zyban; Zyban LP; Quomem; Zyntabac)	GlaxoSmithKline (GB)
Alcohol		
NMDA receptor antagonist; blockade of presynaptic $GABA_B$ receptors	Acamprosate (Aota-Ca; Aotal; acamprosate calcium; Campral; Campral EC; NS-11)	Merck KGaA (DE)
GABA receptor agonist	Tetrabamate (Atrium 300; Sevrium)	Hoffmann-La Roche (CH)
Opioid receptor antagonist	Naltrexone (Antaxone; Celupan; EN-1639A; Nalorex; Nemexin; ReVia; Trexan; UM-792)	Bristol-Myers Squibb (US)
Narcotics/Opiates		
Opioid mu receptor agonist/Opioid kappa receptor antagonist	Buprenorphine (Buprenex; Buprex; CL-112302; Lepetan; NIH-8805; RX-6029; Subutex; Temgesic; UM-952)	Reckitt & Colman (GB)
Opioid receptor antagonist	Naltrexone (Antaxone; Celupan; EN-1639A; Nalorex; Nemexin; ReVia; Trexan; UM-792)	Bristol-Myers Squibb (US)
Vasodilatory antihypertensive	Lofexidine (Ba-168; BritLofex; Lofetensin; Loxacor; MDL-14042; RMI-14042A)	Sanofi-Aventis (FR)

that 28% of subjects who received inhaled NRT therapy attained smoking abstinence at 1 year, compared with 18% in those who received placebo [64]. TheraTech (Watson) has developed an oral formulation of nicotine using its lozenge technology. Ortho-McNeil (Johnson and Johnson) and Pharmacia (now Pfizer) have jointly developed a nicotine inhaler using technology licensed from Advanced Therapeutic Products. The device delivers 5 mg nicotine that is absorbed *via* the lining of the mouth rather than the lungs, typically providing 30% of the nicotine derived from cigarette smoking. Finally, Pharmacia (now Pfizer) has developed a sublingual formulation of nicotine beta-cyclodextrin.

4.1.2. Sustained Release Bupropion (Bupropion SR)

The sustained-release formulation of the phenylaminoketone atypical antidepressant agent bupropion (Zyban®) was approved by the Food and Drug Administration (FDA) in the USA in 1997, and is the first non-nicotine pharmacotherapy for smoking cessation. Interest in bupropion grew by early observations of reduced craving symptoms in patients diagnosed with depression who discontinued smoking [65]. Bupropion is believed to inhibit both DA and norepinephrine uptake mechanisms, and may also block high-affinity neuronal nicotinic receptors (nAChRs) [66]. It is still unclear whether the major metabolite 6-hydroxybupropion, which is formed by cytochrome P450 2D6 metabolism [67], contributes to the anti-smoking actions of bupropion. Bupropion's efficacy is

independent of a more general antidepressant effect [67]. Randomised studies have demonstrated the efficacy and tolerability of bupropion SR [68, 69], with the most robust anti-smoking effects at a dose of 300 mg/day. Recent studies have extended its use to prevent relapse to nicotine-seeking behaviour after the initial achievement of smoking cessation [70].

A double-blind, placebo-controlled study also examined the effects of bupropion SR, TNP, or combined treatment, and combination therapy was found to be superior to either alone [69]. Cessation rates at 1 year after attempted quitting were 16% for placebo, 16% for bupropion SR, 30% for NRT, and 36% for combined therapy.

4.1.3. Other Pharmacotherapeutic Strategies

Mecamylamine is a non-competitive nicotinic receptor antagonist, which has shown promise as an adjunct to TNPs [71, 72], although further studies must confirm these trends. The use of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac®) alone [73] or in combination with NRT [74, 75] have yielded either equivocal or negative results. Similarly, the use of the 5-HT_{1A} partial agonist Buspirone (Buspar®) might be potentially interesting in anxious smokers although a placebo-controlled trial failed to support its efficacy in smoking cessation [76]. Several clinical trials demonstrated that the α2-adrenoceptor agonist clonidine has modest efficacy in smoking-cessation trials [77-80]. However, significant side-effects, including orthostatic hypotension, might limit its use. Preliminary studies have also investigated the efficacy of naltrexone alone or when given in combination with TNPs [81], but the results gathered so far have been largely inconclusive. Finally, lobeline, which is a nicotine-like alkaloid, and silver acetate, which causes an aversive taste when combined with cigarette smoke have been suggested as smoking cessation aid [82, 83].

In summary, most of these clinical trials generated equivocal results and the efficacy of the compounds mentioned above remains uncertain mainly because their potential benefits have not been reproduced in well-designed placebo-controlled studies.

4.2. Current Pharmacotherapies for Alcohol Dependence

There are currently four main pharmacological strategies used to treat alcohol dependence, which led to positive findings: aversive agents (disulfiram), acamprosate, naltrexone, and the treatment of co-morbid psychiatric disorders (Table **1**).

The great majority of studies assessing the efficacy of treatment with aversive drugs such as disulfiram have yielded some positive results compared with placebo only when distribution of the drug was supervised [84-86].

The efficacy of acamprosate and naltrexone as pharmacotherapies for alcohol dependence has been assessed in several randomized, double-blind, placebo-controlled trials across a range of countries. Seventeen studies assessing the efficacy of acamprosate have been published so far. About 80% of these acamprosate clinical trials across Europe have reported consistent results showing beneficial effects of treatment in terms of rate of abstinence, cumulative abstinence duration, and time to first drink [87-89]. Several of these studies also suggested that acamprosate is efficacious in preventing relapse to alcohol drinking for up to 12 months post-treatment [87-89]. Recent trials conducted in the United States of America confirmed these effects, although the methodology used to design the latter clinical studies differed considerably from that used in the European trials [88].

The clinical outcome of studies with naltrexone is not as homogeneous as that of acamprosate [88, 89]. The use of different methodologies makes the comparison between these studies and the interpretation of their respective results rather difficult. Despite these differences, prevention of relapse to heavy drinking has been most consistently reported. In contrast with acamprosate, the safety profile of naltrexone might be problematic and poorly tolerated side effects such as nausea, headache, and hepatotoxicity may limit its therapeutic use [88, 89]. A recent interesting finding suggests that co-administration of acamprosate and naltrexone significantly increases the rate and magnitude of absorption of acamprosate [90, 91]. The question of whether or not combination of both compounds translates to higher clinical efficacy is currently under investigation by a large clinical program (COMBINE study) in the United States of America.

4.3. Current Pharmacotherapies for Cocaine Dependence

The review of multiple clinical trials leads to one single conclusion: there are currently no efficacious pharmacological strategies for the treatment of cocaine dependence and addiction. Although some preliminary findings may have looked promising, most trials have demonstrated the lack of efficacy of compounds such as naltrexone [92, but see 93], risperidone and pergolide [94, 95], desipramine and carbamezapine [96], amantadine [97], nootropic agents such as piracetam and ginkgo biloba [98], or olanzapine [99].

An additional issue with regards to cocaine addiction is that cocaine addicts are most often poly-substance abusers who use different combinations of cocaine, opioids, alcohol and benzodiazepines. This fact has led several authors to suggest that treatment of poly-substance abusers with either methadone or buprenorphine may reduce both heroin and cocaine consumption [100-105]. This hypothesis, however, has not been confirmed by other studies [106-108], and there is a need for additional work to clarify this potential strategy.

4.4. Current Pharmacotherapies for Opiate Dependence

The short-acting opioid receptor antagonist naloxone is effective in preventing non-fatal overdose among opioid addicts [109]. However, the best strategy for detoxification still consists in substituting heroin with either the long-acting opioid receptor agonist methadone [110] or the partial opioid receptor agonist buprenorphine [111] (Table **1**). An alternative strategy is to use α2-adrenoceptor agonists such as clonidine or lofexidine [112, 113] either alone or in combination with an opioid receptor antagonist such as

naltrexone or naloxone [114] (Table **1**). Lofexidine is a potent vasodilatory antihypertensive, developed by Nattermann (Sanofi-Aventis). A multicentre, US Phase III trial for opiate withdrawal symptoms, conducted by Britannia and the National Institute on Drug Abuse (NIDA), has been stopped[6]. In a double-blind, randomized, placebo-controlled Phase II part, subjects that remained on lofexidine + opiate antagonist regimen were more likely to remain opiate-free, were more compliant, had decreased cravings and lower perceived stress compared with patients receiving placebo.[7] In the Phase I part, varying doses of lofexadine + opiate antagonist were safe and well tolerated, with 72% of subjects completing the treatment period[8].

As with other drugs of abuse, prevention of relapse remains one of the main challenges for the long-term management of opiate dependence. The long-term prescription of naltrexone might be one option, but compliance to treatment makes the efficacy of such strategy rather unlikely [115, 116], although the use of a 5-week depot formulation of naltrexone might improve treatment outcome [117]. Finally, long-term maintenance programs currently include treatments with methadone, levo-acethylmethadol (LAAM), and buprenorphine [118-120].

5. NEW PHARMACOTHERAPEUTIC ADVANCES IN THE MANAGEMENT OF DRUG ADDICTION

In the third section of the present work, we have seen that drug addiction is a syndrome of impaired response inhibition and salience attribution, which involves a complex neurocircuitry underlying drug reinforcement, drug craving and compulsive drug-seeking and -taking behaviours despite adverse consequences. The continued elucidation of the neurobiological and neurochemical underpinnings of withdrawal symptoms, drug intake, craving, relapse, and co-morbid psychiatric associations has recently boosted the development of new pharmacotherapeutic approaches for the treatment of drug addiction (for a detailed summary see Tables **2**-**5**). These new strategies target different neurotransmitter systems with the hope of developing new compounds that will promote long-lasting drug abstinence and long-term recovery, ensure satisfactory patient compliance, and have a good safety profile. In the following sub-sections we will review some of the neurotransmitter systems that are currently targeted to that aim.

5.1. Targeting Dopamine Systems

The role of the mesolimbic DA system in the attentional processing of drug-related stimuli pointed towards DA neurotransmission for the development of new receptor agonists and antagonists for the treatment of drug addiction. However, the use of non-selective DA receptor antagonists such as haloperidol, SCH 23390 and tiapride is limited by their long-term neurological side effects. One alternative approach is to develop selective DA D_1 receptor agonists and antagonists to avoid some of these adverse effects. For example, adrogolide hydrochloride (DAS-431) is a DA D_1 receptor agonist currently under development by Drug Abuse Sciences (DAS) as a treatment for cocaine dependence[9]. In Phase II clinical trials in cocaine-dependent patients, the intravenous administration of adrogolide hydrochloride decreased the subjective effects of cocaine, reduced cocaine craving and was well tolerated[10].

The rationale for the use of selective DA D_1 receptor antagonists has also been reported. For example, ecopipam (SCH 39166) attenuates cocaine-induced effects in several preclinical paradigms [121]. However, two out of three inpatient studies demonstrated that ecopipam fails to alter the subjective effects of cocaine and that the prototypic profile of cocaine remains largely unchanged [122, 123]. Addex is currently planning to initiate a US Phase II trial with ADX 10061 (CEE-03-310, formerly NNC-01-0687), a benzazepine DA D_1 receptor antagonist, for use in smoking cessation. A US Phase II trial with CEE-03-310 was previously conducted at Yale University to improve alcohol craving in problem drinkers[11]. CEE-03-310 also showed potential in cocaine dependence[12]. TSR-1938 (CEE-03-320) is another DA D_1 receptor antagonist, under development by CeNeS (TheraSci before the acquisition) for the treatment of substance abuse and sleep disorders[13]. Phase I trials for substance abuse and sleep disorders are expected by the end of 2004[14].

Contrary to DA D_1 and D_2 receptors, DA D_3 receptors are expressed preferentially in medium-sized spiny neurons of the rostral and ventromedial shell of the NAc and in granule cells of the islands of Calleja, regions in which D_2 receptors are scarcely expressed [124-127]. Thus, the specific localization of the DA D_3 receptor in key elements of the mesolimbic DA system in both the rat and human brain, suggests a major role of the DA D_3 receptor in emotion, cognition and processing of motor and sensory information [128]. Postmortem and preclinical studies also point towards the possibility that chronic abuse of cocaine, nicotine and morphine is associated with an adaptive change in the expression of D_3 receptor mRNA [129-131]. However, the precise role of the D_3 receptor in drug dependence processes has been significantly hampered by the lack of pharmacological tools showing significant selectivity for DA D_3 over D_2 receptors. In contrast with non-selective DA receptor antagonists, the selective DA D_3 receptor antagonist SB-277011-A (trans-N-[4-[2-(6-cyano-1, 2, 3, 4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-4-quinolininecarboxamide), which shows high affinity and 100-fold selectivity for D_3 over D_2 receptors [132] is efficacious in animal models of cocaine [133, 134], nicotine [135], alcohol [136, 137], and heroin [138] seeking behaviours. Altogether these findings suggest that selective DA D_3 receptor antagonists may hold highest promise for attenuating cue-, drug- or stress-evoked relapse to addictive drug use. The National Institute on Drug

[6] Press release, Britannia, 10 Jun 2002
[7] Press release, Britannia, 17 Jun 2003
[8] Press release, Britannia, 17 Jun 2003

[9] Company Web Page, DAS, 19 Feb 2001
[10] Company Web Page, DAS, 19 Feb 2001
[11] Press release, CeNeS, 4 Apr 2001
[12] Company Web Page, CeNeS, 13 Dec 2000
[13] Company presentation, CeNes, Dec 2003
[14] Company Web Page, CeNes, 8 Sep 2004

Table 2. Clinical and Preclinical Development of Molecules for the Treatment of Nicotine Dependence

Mechanism of Action	Product Name	Company
Phase III Clinical Trials		
Nicotinic alpha$_4$beta$_2$ partial agonist	Varenicline (Varenicline tartrate; CP 526555; CP 526555-18)	Pfizer (US)
Cannabinoid 1 (CB_1) receptor antagonist	Rimonabant (SR 141716; SR 141716A; SR 141616; ACOMPLIA)	Sanofi-Aventis (FR)
Drug delivery system, oral transmucosal nicotine	Drug delivery system, oral transmucosal nicotine; nicotine transmucosal	Watson (US)
Drug delivery system, transdermal nicotine + mecamylamine	Drug delivery system, transdermal nicotine + mecamylamine; nicotine + mecamylamine transdermal; mecamylamine + nicotine transdermal	Sano (US)
Phase II Clinical Trials		
Nicotinic alpha$_4$beta$_2$ partial agonist	SSR-591813	Sanofi-Aventis (FR)
Nicotine vaccine	NicVAX	Nabi Biopharmaceuticals (US)
Nicotine vaccine	Nicotine-Qbeta (CYT002-NicQb)	Cytos Biotechnology (CH)
Glycine site antagonist	GW-468816	GlaxoSmithKline (UK)
Metabotropic glutamate receptor 2/3 agonist	Eglumegad (LY-354740; LY-379268)	Eli Lilly (US)
Dopamine D_1 receptor antagonist	ADX 10061; CEE 03310; NNC 010687; NNC 687; NO 687; NNC 01-0687	Novo Nordisk (DK)
Oral delivery system for nicotine (single-use plastic straw containing small beads of nicotine)	The Straw	Recovery Pharmaceuticals (US)
Dopamine D_3 partial agonist	BP4.897	Bioprojet (FR)
Selective and irreversible inhibition of cerebral monoamine oxidase-B (MAO-B)	Selegiline	Chinoin (HU)
Phase I Clinical Trials		
Cannabinoid 1 (CB1) receptor antagonist	SR-147778	Sanofi-Aventis (FR)
Nicotine vaccine	TA-NIC	ImmuLogic (US)
Cotinine	Cotinine; NIH 10498	LecTec (US)
Preclinical		
Nicotinic receptor agonist	CMI 477	Millennium (US)
Nicotine metabolism	Nornicotine	Yaupon Therapeutics (US)
Transdermal nicotine patch	Drug delivery system, TheraDerm-MTX transdermal nicotine; nicotine TheraDerm-MTX	Watson (US)
Transdermal nicotine patch	Drug delivery system, transdermal nicotine patch second generation; nicotine transdermal patch	Pfizer (US)
Transdermal formulation of nicotine	Nicotine MDTS (nicotine, Acrux; nicotene, Acrux)	Acrux (AU)
Nicotinic alpha$_4$beta$_2$ partial agonist	nicotine analogues, Florida University	Florida University (US)
Anti-cotinine antibodies	Anti-cotinine antibodies, GlaxoSmithKline	GlaxoSmithKline (UK)
Cannabinoid 1 (CB1) receptor antagonist	CB1 antagonists, Vernalis	Vernalis (GB)
Metabotropic glutamate receptor agonists/antagonists	ADX-1 series	Addex (CH)
Metabotropic glutamate receptor agonists/antagonists	ADX-3 series	Addex (CH)
Oral inhibitors of the CYP2A6 enzyme	Nicog	Nicogen (CA)
Dual monoamine oxidase A inhibitor and centrally acting cholinesterase inhibitor	Desoxypeganine (DOP)	HF Arzneimittelforschung (DE)

Table 3. Clinical and Preclinical Development of Molecules for the Treatment of Alcohol Dependence

Mechanism of Action	Name	Company
Phase III Clinical Trials		
Naltrexone depot, a microencapsulated formulation of naltrexone, using Lactiz sustained-release technology	Naltrexone DAS (Naltrel; naltrexone, Serquest; naltrexone, Lactiz; naltrexone depot, DAS)	DrugAbuse Sciences (US)
Sustained-release naltrexone formulations, using Medisorb formulation system	Naltrexone, Alkermes (Vivitrex; Medisorb Naltrexone)	Alkermes (US)
Tablet formulation of nalmefene	Nalmefene, BioTie (CPH-101; Soberal)	BioTie Therapies (FI)
Cannabinoid 1 (CB_1) receptor antagonist	Rimonabant (Acomplia; SR-141716; SR-141716A)	Sanofi-Aventis (FR)
Phase II Clinical Trials		
Nalmefene	Nalmefene (Arthene; Cervene; Incystene; JF-1; nalmetrene; ORF-11676; Revex)	IVAX (US)
Non-competitive NMDA receptor antagonist	Neramexane (MRZ-2/571; MRZ-2/576; MRZ-2/579)	Merz (DE)
Dopamine D_1 receptor antagonist	CEE-03-310 (NNC-01-0687; NO-687; nicotine addiction ther, Addex; antismoking ther, Addex; ADX 10061)	CeNeS (GB)
Phase I Clinical Trials		
Cannabinoid 1 (CB_1) receptor antagonist	SR-147778	Sanofi-Aventis (FR)
Preclinical		
Nalmefene	Nalmefene, ProNeura (nalmefene, Titan; Promafen)	Titan Pharmaceuticals (US)
Broad-spectrum neurotransmission reuptake inhibitor	Albrex	Recovery Pharmaceuticals (US)
Dual monoamine oxidase A inhibitor and centrally acting cholinesterase inhibitor	Desoxypeganine (DOP)	HF Arzneimittelforschung (DE)
Other Opportunities		
Inhibitor of alcohol oxidation at the acetaldehyde stage/free radical scavenger and iron sequestrant	Disulfiram	NIDA (US)
Cholinesterase inhibitor	Galantamine, transdermal, HF	HF Arzneimittelforschung (DE)
Carbonate dehydratase inhibitor; sodium channel blocker; AMPA receptor antagonist; GABA receptor agonist	Topiramate	Johnson & Johnson (US)
5-HT uptake stimulant	Tianeptine	Servier (FR)
Prostaglandin synthase stimulant/Thromboxane A_2 synthesis stimulant	Evening primrose oil	Scotia Pharmaceuticals (GB)

Table 4. Clinical and Preclinical Development of Molecules for the Treatment of Cocaine and Metamphetamine Dependence

Mechanism of Action	Name	Company
Phase II Clinical Trials		
Cocaine vaccine	TA-CD (cocaine vaccine, Xenova; Pharmaprojects No. 4395)	Xenova (GB)
Irreversible inhibitor of GABA transaminase	Vigabatrin (gamma-vinyl-GABA; GVG; MDL-71754; MO-71754; RMI-71754; Sabril; Sabrilex; MD-71754; Sabrilan)	Sanofi-Aventis (FR)
GABA uptake inhibitor (GAT-1 inhibitor)	Tiagabine (tiagabine hydrochloride; NO 050328; A 70569; NO 328; NNC 050328; NNC 328; NN 301; ABT 569; GABITRIL; TIABIX; GABATRIL)	Novo Nordisk (DK)
DA D_2 receptor antagonist/5-HT_2 receptor antagonist	Quetiapine fumarate (ICI-204636; Seroquel; ZD-5077; ZM-204636; FK-949; Seroquel 50% Fine Granule)	AstraZeneca (GB)

(Table 4). contd.....

Phase II Clinical Trials		
Mechanism of Action	**Name**	**Company**
DA D_1 receptor agonist	Adrogolide hydrochloride (DAS-431; A-86929; ABT-431)	DrugAbuse Sciences (US)
Phase I Clinical Trials		
Tetrodotoxin-based compound with analgesic properties, isolated from blowfish	Tetrodin	Int Wex Technologies (CA)
Alkaloidal constituent of Lobelia inflata (Indian tobacco)	Lobeline, Yaupon	Yaupon Therapeutics (US)
Preclinical		
Optimized derivative of butyrylcholinesterase (BChE)	AME-359 (BChE, AME; butyrylcholinesterase der, AME; BChE, Lilly; butyrylcholinesterase der, Lil;)	Eli Lilly (US)
Small molecule DA reuptake inhibitor	ATI-61X (Cobrex)	Recovery Pharmaceuticals (US)
Pro-drug of amphetamine	NRP-104 (amfetamine prodrug, New River)	New River Pharmaceuticals (US)
DA D_3 receptor antagonist	NGB-2904	NIDA (US)
DA D_1 receptor antagonist	TSR-1938 (CEE-03-320; NNC-22-0215)	CeNeS (GB)
Other Opportunities		
N-acetylated alpha-linked acidic dipeptidase (NAALADase) inhibitor	GPI-16072	Guilford (US)
N-acetylated alpha-linked acidic dipeptidase (NAALADase) inhibitor	GPI 5000	Guilford (US)
N-acetylated alpha-linked acidic dipeptidase (NAALADase) inhibitor	GPI 5693	Guilford (US)
GR-II antagonists	GR-II antagonists, Argenta/Corcept	Argenta (UK)/Corcept (US)
Inhibitor of alcohol oxidation at the acetaldehyde stage/free radical scavenger and iron sequestrant	Disulfiram	NIDA (US)
Sigma receptor antagonists	Sigma receptor antagonists, Oklahoma University	The University of Oklahoma (US)
Vasodilatory antihypertensive	Lofexidine	Sanofi-Aventis (FR)

Table 5. Clinical and Preclinical Development of Molecules for the Treatment of Narcotic/Opiate Dependence

Phase II Clinical Trials		
Mechanism of Action	**Name**	**Company**
Naltrexone depot, a microencapsulated formulation of naltrexone, using Lactiz sustained-release technology	Naltrexone DAS (Naltrel; naltrexone, Serquest; naltrexone, Lactiz; naltrexone depot, DAS)	DrugAbuse Sciences (US)
Phase I Clinical Trials		
Non-competitive NMDA receptor antagonist	Memantine hydrochloride (Akatinol; D-145; DMAA; Mrz 2/145; SUN-Y7017; Ebixa; Axura; Namenda)	Merz (DE)
Tetrodotoxin-based compound with analgesic properties, isolated from blowfish	Tetrodin	Int Wex Technologies (CA)
Subcutaneous delivery formulation of buprenorphine, using ProNeura drug delivery system	Buprenorphine, ProNeura (Probuphine; buprenorphine, Titan)	Titan Pharmaceuticals (US)
Preclinical		
Sustained-release naltrexone formulations, using Medisorb formulation system	Naltrexone, Alkermes (Vivitrex; Medisorb Naltrexone)	Alkermes (US)
Immediate-release formulation of oxycodone + low-dose opioid antagonists (naloxone or naltrexone)	Oxycodone + naltrexone, Pain T (PTI-801; naltrexone + oxycodone, Pain T; Oxytrex; oxycodone + naloxone, Pain T; naloxone + oxycodone, Pain T)	Pain Therapeutics (US)
Extended release (3mth or more) implant formulation of naltrexone	Naltrexone, Valera (VP-004)	Valera (US)
Luteinising hormone releasing factor agonist/Gonadotropin releasing factor agonist	Histrelin, Valera-1 (RL-0903; SPD-424; VP-001; Vantas)	Valera (US)

Abuse (USA) is currently investigating another DA D_3 receptor antagonist, NGB 2904, for the potential treatment of cocaine addiction.

A series of studies also demonstrated the efficacy of the partial DA D_3 receptor agonist BP4.897 in animal models of cocaine [139-141, but see 142], nicotine [143], and amphetamine [144, 145]. However, recent studies also show that BP4.897 alone may produce conditioned place aversion [146] and may have anxiolytic properties [147]. BP4.897 was in Phase II trials in schizophrenia, Parkinson's disease and the prevention of relapse in cocaine, alcohol and nicotine addiction, but no development update has been released over the last couple of years.

ATI-61X (Cobrex) is a small molecule DA reuptake inhibitor, currently under development by Recovery Pharmaceuticals (formerly Addiction Therapies (ATI)) for the treatment of cocaine addiction[15]. It is designed to replace the reinforcing signal of cocaine and to act as a cognitive enhancer to overwrite the memories driving drug-seeking behaviour[16].

NRP-104 is a pro-drug of amphetamine, under development by New River Pharmaceuticals for the treatment of attention deficit hyperactivity disorder (ADHD). NRP-104 received US fast-track designation for the treatment of cocaine dependence. It is in clinical trials for the treatment of ADHD in paediatric populations. Approval for the treatment of cocaine dependence has been granted by the FDA in the United States of America. New River is collaborating with NIDA to design clinical programs for cocaine dependence[17].

5.2. Targeting Serotonin Systems

The acute administration of drugs of abuse is known to increase levels of monoamines by blocking their presynaptic reuptake, whereas chronic exposure to drugs of abuse typically leads to down-regulation of monoamine systems [148]. This down-regulation may explain, at least in part, withdrawal-induced depression and drug craving. One may hypothesize that pharmacotherapies that enhance serotonin (5-HT) levels may also reduce the reinforcing efficacy of drugs of abuse and alleviate drug withdrawal, dysphoria, and craving. In fact, the acute co-administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), and p-MPPI, a 5-HT_{1A} receptor antagonist, alleviates the diminished interest in brain stimulation reward observed during withdrawal from either nicotine or amphetamine in rats [149]. These findings suggest that co-administration of a selective antagonist at 5-HT_{1A} receptors and an SSRI may be a useful approach to prevent relapse to drug seeking behaviour.

Tianeptine is a 5-HT uptake stimulant, developed by Servier for neurological disorders. In 380 non-alcoholic depressed patients and 130 patients with depression due to alcohol withdrawal treated with tianeptine for 1 year, an improvement was seen in haematological and biochemical parameters, especially of hepatic function. There were no changes in body weight or ECG recordings, no orthostatic hypotension and no withdrawal symptoms even in high-risk alcoholic patients[18].

The 5-HT_{2C} receptor may also be a potential target for the pharmacological treatment of drug addiction. In contrast with the 5-HT_{2C} receptor antagonist SB-242084, the 5-HT_{2C} receptor agonist Ro 60-0175 reduces responding for cocaine and nicotine self-administration, oral ethanol consumption in rats, and is effective in a model of drug reinstatement [148]. These pharmacological experiments are further supported by the behavioural phenotype of 5-HT_{2C} knockout mice [148].

5.3. Targeting GABA Systems

The increase in synaptic levels of gamma-amino butyric acid (GABA) is thought to reduce psychostimulant-induced increases of DA in the NAc, thereby reducing their reinforcing properties. This hypothesis is also supported by studies showing that gabapentin, which increases the release of GABA by binding to the alpha2/3 protein subunit of voltage-gated calcium channels, significantly reduces the amount and frequency of cocaine craving, increases cocaine-free urines in cocaine-dependent patients [150], and can be used as an add-on medication to a standard detoxification regime in heroin addicts undergoing outpatient opiate withdrawal treatment [151].

Tiagabine (Gabitril), a selective blocker of the presynaptic GABA reuptake transporter type 1 (GAT-1) currently used as an add-on anticonvulsant, was reported to increase the number of cocaine-free urine samples, and to decrease self-reported cocaine use following a 6-week dosing escalation design with 24 mg tiagabine administered daily in two doses of 12 mg each [152]. However, recent studies using lower acute doses (8 mg) of tiagabine failed to alter the psychomotor stimulant effects of cocaine (0-150 mg oral dosing) [153].

In addition to selective GAT-1 inhibitors, γ-vinyl GABA (GVG, Vigabatrin), an irreversible inhibitor of GABA transaminase currently used for the treatment of epilepsy and infantile spasms, is also a potential pharmacotherapy to treat drug addiction and craving. In an open-label, dose-escalating, outpatient study in Mexico in 20 people who had used cocaine daily for 3 years, vigabatrin up to 4 mg/day eliminated cravings in 8 subjects after 2-3 weeks of treatment. Of the 8 subjects who completed the trial, all remained drug-free for 74 days, and improvement in self-esteem, family relationships and work was reported [154]. Despite the emergence of visual field defects following GVG treatment [155], preclinical and preliminary clinical findings suggest that GVG might be effective in treating addiction to cocaine, metamphetamine, amphetamine, heroin, nicotine, and alcohol. Double-blind, placebo-controlled trials are now required to further assess this possibility.

Topiramate has been shown to be significantly more effective than placebo with regard to all self-reported

[15] Press release, ATI, 25 Feb 2002
[16] Company Web Page, Recovery Pharmaceuticals, 5 Jun 2003
[17] Press release, New River, 31 Aug 2004
[18] Company communications, Jul 1993 and Feb 1996

drinking and craving outcomes (measured using the four-factor empirically derived subscales [156] of the obsessive–compulsive drinking scale [157]), and on the biochemical measure of drinking that is the level of serum γ-glutamyl transferase (GGT) [158]. These studies also revealed that patients who received topiramate, compared with placebo, were significantly less likely to have a "positive" serum cotinine level, and that drinking reductions were accompanied by smoking decreases in the topiramate group, but not the placebo group. Further studies are now warranted to assess whether or not topiramate may be useful to treat both nicotine and alcohol dependencies.

Several preclinical and clinical studies have evaluated the potential of gamma-amino butyric acid-B ($GABA_B$) receptor subtype agonists such as baclofen (beta-(4-chlorophenyl)-γ-aminobutyric acid) as a pharmacotherapy for substance abuse (for reviews see [159, 160]). Studies with rats suggest that baclofen shows efficacy in animal models of cocaine, nicotine, morphine, alcohol, and metamphetamine abuse [161-165]. In clinical populations, baclofen has also been shown to reduce cocaine and alcohol craving and to decrease cocaine and alcohol intake [166, 167]. The recent identification of positive allosteric modulators of the $GABA_B$ receptor such as CGP7930 and GS39783, which interact synergistically with GABA to enhance its effects, might also represent a potentially new development in the use of GABAergic drugs to treat drug dependence [168]. Both CGP7930 and GS39783 are effective at decreasing rat cocaine self-administration under different schedules of reinforcement [169]. These effects are similar to those reported previously for baclofen, thus supporting the potential use of $GABA_B$ positive allosteric modulators as pharmacotherapies for drug addiction.

5.4. Targeting Glutamate Systems

Withdrawal from cocaine is associated with decreased basal levels of extracellular glutamate in the NAc, which are under the control of a non-synaptic cystine–glutamate transporter that exchanges extracellular cystine for intracellular glutamate [170]. Decreased extracellular levels of glutamate in the NAc following withdrawal from cocaine are also associated with a reduced affinity of the cystine–glutamate transporter for cystine [171]. Importantly, the systemic administration of cysteine pro-drugs (N-acetylcysteine and (-)-2-oxothiazolidine-4-carboxylic acid) blocks reinstatement of cocaine seeking [171]. These findings suggest that targeting extrasynaptic glutamate transmission by using cysteine pro-drugs or compounds acting on metabotropic glutamate receptors (mGluRs) might have a selective effect on reinstatement of drug seeking behaviour. In fact, mGluRs preferentially regulate slow intracellular activity related to long-lasting neuroadaptive changes by modifying multiple second-messenger systems [172]. On the basis of the amino acid sequence identity, pharmacology and transduction mechanisms, these receptors can be classified into three groups. Group I includes mGluR1 and mGluR5, Group II, mGluR2 and mGluR3, and Group III, mGluR4, mGluR6, mGluR7 and mGluR8 [172].

Increased interest in the role of mGluR5 in drug addiction came from studies showing that mice with targeted deletion of mGluR5 fail to self-administer cocaine and do not respond to the acute locomotor activating effects of cocaine [173]. These findings were corroborated by the observation that the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks the behavioural effects of cocaine, nicotine, and alcohol [174, 175]. Furthermore, both MPEP and 3-[(2-methyl-1, 3-thiazol-4-yl) ethyl]pyridine (MTEP) reduce naloxone-precipitated somatic signs of morphine withdrawal [174]. Group II mGluRs (mGluR2 and mGluR3) have also been implicated in drug addiction processes. This is supported by the reduced capacity of mGluR2/3 stimulation to inhibit both the cystine/glutamate anti-porter and the *in vivo* release of glutamate by potassium [170]. The functional down-regulation of mGluR2/3 could be associated with the increased release of glutamate in response to a cocaine challenge injection or a cocaine-paired cue during cocaine withdrawal [176]. This hypothesis is strengthened by the finding that the mGluR2/3 receptor agonist (–)-2-oxa-4-aminobicylco hexane-4, 6-dicarboxylic acid (LY-379268) blocks the expression of amphetamine sensitization [177] and prevents conditioned reinstatement of cocaine-seeking behaviour [178]. LY-379268 is the 2-oxabicyclo-(3.1.0)-hexane analogue of Eglumegad (LY-354740) that is currently being developed by Eli Lilly for both anxiety and to aid smoking cessation.

Extensive preclinical literature and preliminary clinical observations suggest that NMDA receptor antagonists are also potential candidates to treat withdrawal syndromes from opioids, alcohol and other sedatives [179]. It is suggested that the efficacy of these compounds to reverse the neuroadaptive changes leading to physiological dependence underlies their effects on withdrawal symptoms. Recent studies showed that known (erythro-ifenprodil, CP-101, 606 [Pfizer], CI-1041 [Purdue Neuroscience Corp/Pfizer Inc], and Co-101, 244 [Pfizer Inc/Purdue Neuroscience Corp/Senju Pharmaceutical Co Ltd]) and novel indole-2-carboxamide derivative NR2B antagonists (RG-13579 and RG-1103) as well as acamprosate (calcium-acetyl homotaurinate), potently attenuated withdrawal-induced toxicity in ethanol pre-treated neuronal cultures [180].

Merz is currently developing Neramexane (MRZ 2/579: 1-amino-1, 3, 3, 5, 5-pentamethyl-cyclohexane hydrochloride), a low-affinity non-competitive NMDA receptor antagonist with rapid blocking/unblocking kinetics and strong voltage dependence, for the treatment of Alzheimer's disease, cerebral ischaemia, alcohol dependence and pain. Neramexane is currently in a placebo-controlled US Phase II trial for alcohol dependence. Preliminary results from clinical studies also suggest that memantine hydrochloride, a non-competitive NMDA receptor antagonist, may decrease morphine intake in addicts[19].

GlaxoSmithKline is developing GW468816, a selective glycine antagonist. In a phase I/II study involving 126 subjects, GW468816 showed no adverse cardiovascular effects, sedation, insomnia or significant central nervous system effects. In a placebo-controlled study involving 317 patients, 57% of patients given 150 mg GW468816 abstained from smoking after 4 weeks of treatment,

[19] Company Web Page, Merz, 10 Jul 2000

compared with 36% of patients given placebo. Phase II trials are ongoing in the UK for the treatment of smoking cessation, and the company anticipates a regulatory filing by the second half of 2007.

5.5. Targeting Cholinergic Systems

5.5.1. Development of New NRTs

A series of new NRTs is currently under development by different pharmaceutical companies. Watson (formerly TheraTech) is developing an oral transmucosal delivery system for nicotine, which has potential for treating nicotine withdrawal. The product is being developed in phase III trials in the USA for use in smoking cessation therapy. Sano, subsidiary of Elan, is also developing a transdermal delivery system combining nicotine with the nicotine antagonist mecamylamine for the treatment of nicotine withdrawal, using Sano's drug-in-adhesive technology. However, the combination patch failed to demonstrate a statistically significant advantage over a patch containing nicotine alone in three phase III studies. Recovery Pharmaceuticals (formerly Addiction Therapies (ATI)) is developing an oral delivery system for nicotine, The Straw, for the treatment of tobacco dependence. It is a single-use plastic straw containing small beads of nicotine. The entire dose of nicotine beads can be delivered in the first sip. The empty straw can then be discarded or retained to occupy the individual's hand and mouth, replacing the stimuli associated with smoking. A Phase III trial is currently planned[20]. In a double-blind, placebo-controlled Phase I/II safety and pharmacokinetic study in 24 smokers, a single initial dose of nicotine in The Straw (placebo, 4, 8 or 12 mg), followed by doses every 1.5 hour over a 10.5 hour period resulted in increased systemic levels of nicotine comparable to or higher than those of currently-marketed nicotine replacement products. Early indications of efficacy were noted by the smokers' reduced cravings for cigarettes. There were no serious or unexpected adverse events[21].

Watson's (formerly TheraTech) transdermal nicotine product for the treatment of nicotine withdrawal is in preclinical trials in the USA. The product incorporates Watson's matrix transdermal drug delivery technology. Pfizer is also developing second generation transdermal nicotine patches for smoking cessation therapy.

5.5.2. Nicotine Metabolism

The nicotine metabolite cotinine is in development by LecTec in the USA as an oral treatment for nicotine withdrawal. A pilot clinical study has been completed and approval granted to begin further clinical trials with the agent. Nornicotine is under development by Yaupon Therapeutics as a smoking cessation aid. It is in late preclinical development. Finally, Nicogen is developing oral inhibitors of the CYP2A6 enzyme. In humans, 85% of nicotine is primarily metabolized by this enzyme, and the treatment would theoretically slow the elimination of nicotine from the body, reducing the number of cigarettes smoked and smoke exposure.

[20] Company pipeline, ATI, 17 Jan 2003
[21] Press release, ATI, 25 Feb 2002

5.5.3. Neuronal Nicotinic Cholinergic Receptors

Studies on nAChRs have led to the identification of 2 major nAChR heteromeric isotypes in the mesostriatal DA system: alpha4-beta2 nAChRs and alpha4-alpha6-beta2 nAChRs. Strong evidence suggests that beta2 nAChRs play a prominent role in the effects of nicotine on DA neurons, including DA release in the NAc and nicotine self-administration [181]. Varenicline (CP 526555) is a partial agonist at alpha4-beta2 nAChRs, which is being developed by Pfizer as a potential aid to smoking cessation and is currently being evaluated in a US phase III trial.[22] In a phase II, double-blind parallel study, smokers were treated with placebo, bupropion or 0.3 mg, 1 mg or 1 mg bid varenicline. Sixty of 125 smokers stopped smoking following treatment with 1 mg bid varenicline, 47 of 126 smokers on 1 mg varenicline and 35 of 126 smokers receiving 0.3 mg varenicline, compared with 42 of 126 smokers treated with 150 mg bupropion and 20 of 123 smokers treated with placebo[23].

Sanofi-Aventis is also developing SSR 591813, another selective partial agonist at alpha4-beta2 nAChRs. No nicotinic side effects such as hypothermia, increased blood pressure and heart rate were observed in freely moving rats at oral doses of up to 100 mg/kg. In behavioural models, 20 mg/kg SSR 591813 decreased intravenous nicotine self-administration in trained rats. At intraperitoneal doses of 10 mg/kg, the compound prevented mecamylamine-precipitated withdrawal signs in nicotine-dependent rats. Phase IIa trials of SSR 591813 are under way in Europe[24].

The University of Florida (USA) is also investigating nicotine analogues that act as partial agonists at the alpha4beta2 receptor, as potential agents to aid smoking cessation. The agents are being evaluated in preclinical studies in the USA[25].

5.5.4. Neuronal Muscarinic Cholinergic Receptors

In addition to nAChRs, muscarinic cholinergic receptors have also been implicated in mechanisms of drug dependence. Among all muscarinic cholinergic receptors (M_1–M_5), the M_5 receptor is the most recent member to have been cloned. Recent studies showed that the rewarding effects of morphine and cocaine were significantly reduced in M_5 receptor-deficient mice [182, 183]. The rewarding and stimulating effects of other drugs of abuse also result from increased release of DA from terminals in the basal forebrain. Cholinergic neurons in the laterodorsal tegmental nucleus (LDT) of the pons are a main source of this excitatory cholinergic input to DA-containing neurons in the VTA and electrical stimulation of the LDT can evoke a rapid increase in DA release in the NAc. This effect is absent in M_5-receptor-deficient mice or in wildtype mice receiving either systemic scopolamine or intra-VTA scopolamine treatment [184]. Thus, selective antagonism at M_5 receptors might represent a novel target for the treatment of drug addiction.

[22] Company presentation, Pfizer, 17 Jun 2003
[23] Company presentation, Pfizer, 17 Jun 2003
[24] Company presentation, Sanofi-Synthelabo, 16 Feb 2004; Company Web Page, Sanofi-Synthelabo, 16 Mar 2004
[25] 33rd Annual Meeting of the Society for Neuroscience, 8-12 November 2003, Abstract 158.6

5.6. Targeting Opioid Systems

DrugAbuse Sciences (DAS) is developing naltrexone depot, a microencapsulated formulation of naltrexone, using its Lactiz sustained-release technology, for the treatment of alcohol and opiate addiction. It is administered by monthly intramuscular injections to overcome compliance problems with the tablet formulation of naltrexone, which must be taken daily. DAS has a licensing agreement with Serquest (SRI International) for formulation development using Serquest's patented microsphere technology[26]. A Phase III trial to assess naltrexone depot in alcohol and opiate addiction is expected in 2004[27]. Naltrexone depot has completed a 12-week US double-blind, placebo-controlled, multicentre Phase III trial in 300 DSM-IV alcohol-dependent patients[28]. At 6 month, patients treated with naltrexone depot were four times as likely not to drink heavily and eight times more likely to avoid alcohol altogether compared with those treated with placebo and psychotherapy alone.[29] The efficacy of naltrexone depot was also assessed in a double-blind, placebo-controlled, multicentre US Phase II trial in opiate-dependent patients. A single dose of naltrexone depot blocked opiate effects over a 6-week period, and was well tolerated[30].

Alkermes is developing Medisorb Naltrexone, a once-a-month sustained-release naltrexone formulation, using its Medisorb formulation system for the treatment of alcohol and opiate addiction[31]. A US filing is expected in late 2004 or 2005[32]. Medisorb Naltrexone is in a randomized, double-blind, placebo-controlled Phase III trial in 624 alcohol-dependent patients across 24 centres in the US, to study the efficacy and safety of repeated intramuscular doses over 28 days. Enrolment is complete in an extension study to obtain long-term safety data[33]. Preliminary results indicated a reduction in heavy drinking rate *vs.* placebo of 17 and 25% on 190 and 380 mg, respectively. In male patients (66% of enrolled patients), the reduction in heavy drinking rate was 25 and 48% for 190 and 380 mg, respectively, suggesting a dose-response relationship in these groups. In female patients, there was no significant difference in rate reduction at either dose. It was generally well tolerated and the most common adverse events were nausea, headache and fatigue[34].

BioTie Therapies (Contral Pharma before the merger) is developing a tablet formulation of the opioid antagonist nalmefene for the treatment of alcohol addiction. In multicentre, placebo-controlled Phase III trials in Finland in 400 patients and in the United Kingdom (UK) in 150 patients, self-administration of nalmefene before drinking alcohol over a 28-week period produced a 50% reduction in the number of heavy drinking days *vs.* 33% with placebo. In the Finnish study the difference was statistically significant; however, the same difference was not observed in the UK study due to patient drop-out rate. No serious adverse effects related to nalmefene were observed[35]. Two completed Phase II multicentre, placebo-controlled trials in alcohol abuse suggested that the best responses may be obtained in patients with a family history of alcohol problems. In a US Phase II multicentre trial in 200 patients suffering from pathological gambling, nalmefene significantly reduced gambling-related urges and behaviour *vs.* placebo after 4-month treatment[36].

ProNeura (Titan Pharmaceuticals) is developing Probuphine, a subcutaneous delivery formulation of buprenorphine, using its ProNeura drug delivery system, for the treatment of opiate addiction over a 6-month period[37]. An Australian pilot Phase I trial is underway in 18 heroin-dependent subjects, who will be switched from sublingual buprenorphine to 3 doses of Probuphine to evaluate safety, pharmacokinetics and maintained therapeutic benefit[38]. Preliminary results from the first 6 patients showed no significant signs of withdrawal or craving following switching, and therapeutic benefit was maintained for 6 month, with no adverse events. Pharmacokinetic data showed steady-state serum buprenorphine concentrations in the targeted therapeutic range. Additional patients are currently being treated with the second dose[39].

Finally, VP-004 is an extended release (3 month or more) implant formulation of naltrexone, under development by Valera for the treatment of opioid dependence. Phase II clinical trials are expected in the second half of 2004.

5.7. Targeting Cannabinoid Systems

Research on the interaction between cannabinoids and brain reward function grew significantly with the isolation of the major psychoactive component of the hemp plant, Δ^9-THC, the cloning of the central CB_1 cannabinoid receptor, and the characterization of the selective CB_1 receptor antagonist, SR141716 (Rimonabant) [185]. A growing body of evidence has shown that Δ^9-THC acts on brain reward systems in a manner similar to non-cannabinoid addictive drugs [186]. This fact may partly explain the efficacy of SR141716 in blocking the reinforcing properties of heroin [187], morphine [188], ethanol [189], cocaine [190], and nicotine [191]. These findings suggest that activation of the endogenous cannabinoid system may participate in the motivational and DA-releasing effects of several drugs of abuse. Rimonabant is under development by Sanofi-Aventis and is currently in Phase III trials in the US, Europe, Australia, and Canada for obesity, smoking cessation and alcohol addiction. In the US STRATUS phase III trial, 784 smokers were given either rimonabant (5 mg/day [n=262] or 20 mg/day [n=261]) or placebo [n=261] following a 2-week screening period. Efficacy of the drug was measured over a 4-week period, which was seven weeks after treatment and smoking cessation began. In the placebo, 5 and 20 mg/day rimonabant groups, the percentage of prolonged abstinence rate during the last 4 weeks of treatment was 20.6%, 20.2% and 36.2%, respectively. The mean body weight change from baseline in the non-obese subjects with prolonged

[26] Company Web Page, DAS, 26 Nov 1999
[27] Scrip's Target Daily Online, 1 Apr 2004, W00839130
[28] Press release, DAS, 5 Mar 2001
[29] Press release, DAS, 6 Jan 2003
[30] Press release, DAS, 7 Feb 2001
[31] Press release, Alkermes, 11 Dec 2000
[32] Scrip's Target Daily Online, 23 Apr 2004, W00841356
[33] Press releases, Alkermes, 1 Apr 2002 and 31 Mar 2003
[34] Press release, Alkermes, 8 Dec 2003
[35] Press releases, BioTie, 24 and 28 Apr 2003
[36] Press release, BioTie, 30 May 2003
[37] Company Web Page, Titan, 25 Jan 2002
[38] Press release, Titan, 19 Jun 2003
[39] Press release, Titan, 26 Sep 2003

abstinence was +3 kg, +2.4 kg, and +0.7 kg. Adverse events, including gastrointestinal disorders and anxiety, were observed in 78.5%, 80.5% and 86.2% of patients, serious adverse events were noted in 2.3%, 1.5% and 2.7% of patients, and discontinuation of treatment occurred in 3.8%, 5.7% and 6.9% of patients[40]. Sanofi-Aventis is also developing another selective CB_1 receptor antagonist, SR-147778 [192]. The compound is in Phase I trials for smoking cessation, obesity and alcohol dependence.

Vernalis is developing selective cannabinoid CB1 receptor antagonists for the treatment of obesity. They may also have potential in assisting smoking cessation. Vernalis is planning to identify a development candidate in 2004.

Finally, researchers at Pfizer have recently reported a series of pyrazolo[1, 5-a] pyrimidine derivatives that act as cannabinoid CB1 receptor antagonists. These compounds are expected to be useful for the treatment of obesity, bulimia, attention deficit disorders, dementia, alcoholism and tobacco abuse, among other disorders[41].

5.8. Targeting the Hypothalamic-Pituitary-Adrenal (HPA) Axis

Several drugs of abuse, including psychomotor stimulants (cocaine, amphetamine, and nicotine), depressants (morphine and alcohol), and hallucinogens (LSD and *N*, *N*-dimethyltryptamine) can affect the activity of the HPA axis [193]. In addition, the drug withdrawal syndrome resembles physiological and behavioural changes associated with responses to stressors linked to activation of the brain corticotropin-releasing factor (CRF) [194]. Furthermore, exposure to stressors is associated with increased drug-taking behaviour and relapse to drug seeking behaviour in both humans and laboratory animals [195]. These findings together with data on the effect of selective CRF_1 receptor antagonists on cocaine self-administration, drug withdrawal from several drug classes and stress-induced relapse to heroin, cocaine, and alcohol seeking in rats [196, 197] provide a rationale for the use of CRF_1 receptor antagonists in the treatment of compulsive drug use in humans.

Glucocorticoid hormones have also been shown to facilitate the acquisition, stable maintenance, and relapse to cocaine self-administration [198]. It has been hypothesised that the glucocorticoid receptor (GR) is implicated in these effects. For example, mice with inactivation of GR in the CNS show a flattened cocaine self-administration dose-response curve and do not seem to develop behavioural sensitization to cocaine [199]. In addition, the GR antagonist, mifepristone, reduces the reinforcing efficacy of cocaine and the behavioural sensitization to amphetamine [199]. These findings suggest that the development of selective GR antagonists may be useful for the treatment of psychostimulant addiction.

5.9. Immunopharmacotherapy

The rationale behind the use of immunopharmacological strategies for the treatment of drug addiction is to elicit the production of antibodies, which will bind drugs of abuse and alter their pharmacokinetic properties in a manner that is therapeutically helpful. In the setting of drug addiction, the aim of the vaccine is to reduce the extent or rate of drug distribution to the brain. On the basis of preclinical work, vaccines for cocaine and nicotine are now in Phase I and Phase II clinical trials because they may offer long-term protection with minimal treatment compliance [200, 201]. Xenova is developing TA-CD as an injectable therapeutic vaccine for cocaine addiction. The vaccine consists of a cocaine derivative linked to recombinant cholera toxin B and adsorbed onto aluminium hydroxide gel adjuvant in saline. It is in a randomized, placebo-controlled Phase IIb trial (supported by NIDA) in 132 methadone-dependent cocaine addicts to assess efficacy and to determine appropriate endpoints for a Phase III trial[42]. Interim results are expected in the first half of 2006. In an open-label, dose-escalation, 12-week relapse-prevention Phase II study in 9 cocaine users, TA-CD (100-300 micrograms x 3-5 doses) resulted in abstinence for the duration of the trial in 75% of subjects. In a second open-label, dose-escalation Phase II trial in 13 cocaine users, TA-CD (100-300 micrograms x 3-5 doses) resulted in 58% achieving and maintaining abstinence for 12 weeks, and 42% remaining cocaine-free after 6 month. It was well tolerated in both trials[43]. In a NIDA-sponsored Phase IIa dose-escalation study in 13 patients, TA-CD (18-360 micrograms x 4-5 doses) was safe and well tolerated, with a dose-related immune response. About 13 patients completed the 12-month evaluation period[44]. A Phase IIa 10-patient cocaine administration study funded by NIDA has also been initiated. The latter study is designed to evaluate the effect of TA-CD on behavioural changes associated with cocaine administration, and the results are due in 2005[45]. In two additional Phase IIa studies, 14-16 patients receiving TA-CD reported a drop in enjoyment from taking cocaine[46]. In a Phase IIa outpatient trial, 9 cocaine addicts received up to 4 vaccinations (at 0, 2, 4 and 8 weeks) of TA-CD (82 micrograms, intramuscular injection). Cocaine-specific antibodies persisted for the 12-week study and no cocaine metabolites were detected in the urine of 5-8 patients, indicating no further cocaine use. Attenuation of the usual euphoric effects of cocaine was reported by 5-6 patients who relapsed during the study[47]. In the second outpatient trial in 13 cocaine addicts to study abstinence initiation, 58% of patients maintained abstinence during the 12-week study and 42% were cocaine-free after 6 months. The likelihood of cocaine use decreased with more intense vaccination schedules, and higher levels of antibodies produced. In both outpatient studies the maximum mean antibody response occurred between 70-90 days post-vaccination, with specific antibodies persisting for at least 6 months[48].

The nicotine abuse vaccine began human testing in early 2002 by Nabi Biopharmaceuticals under the trade name NicVAX. NicVAX is a nicotine conjugate vaccine,

[40] Company presentation, Sanofi-Aventis, 14 Sept 2004
[41] Patent International Publication Number WO 04069838

[42] Press release, Xenova, 24 Oct 2003
[43] Scrip Daily Online, 15 Jun 2004, S00847244
[44] Press releases, Xenova, 2 Apr 2002 and 17 Jun 2003
[45] Press release, Xenova, 14 Apr 2003
[46] Press release, Reuters, 17 Jun 2003
[47] Press release, Xenova, 16 Apr 2003
[48] Press release, Xenova, 14 Jun 2004

conjugated to a carrier protein, recombinant exoprotein A (rEPA). Nabi Biopharmaceuticals recently announced positive Phase II clinical results for NicVAX[49]. The Phase II trial was a double-blinded, placebo-controlled, randomized study designed to assess safety and antibody response in smokers. In addition, standard measures of anti-smoking efficacy, such as percentage of patients who quit smoking, were included. The trial was conducted at three clinical sites across the United States, with a total of 68 smokers randomized to receive a series of up to 4 injections containing either NicVAX or placebo. Three doses (50, 100 or 200 micrograms) of NicVAX or a placebo were administered on days 0, 28, 56 and 182. The results showed that, at the 200 microgram dose, 33% of smokers in the treated group quit smoking (defined as no smoking for at least 30 consecutive days) *vs.* 9% in the placebo group. In addition, results showed a substantial reduction in average cigarette consumption in smokers who received the highest dose of NicVAX *vs.* lower doses or placebo. Smoking cessation was confirmed by determining cotinine and carbon monoxide levels. Nicotine dependence was also measured by a questionnaire and results showed a substantial reduction with the top dose of NicVAX compared with placebo or the lower dose levels. NicVAX was apparently well tolerated and side effects were similar between the active dose levels and the placebo group. The results indicated a vaccine-only effect, as patients were only given NicVAX without any supplemental treatments, behavioural support or counselling. The complete data set from this study is expected to be released sometime during 2005.

Nicotine-Qbeta (CYT002-NicQb) is another nicotine vaccine under development by Cytos Biotechnology for the treatment of smoking addiction. The vaccine uses antigens delivered in a repetitive configuration such as viruses or virus-like particles (VLPs) that can directly activate B cells and are, therefore, in contrast with soluble and monomeric antigens, highly immunogenic. Cytos has just completed full enrollment for a one-year, randomized, double-blind, placebo-controlled phase II trial in three centers in Switzerland[50]. This study will involve 300 smokers in order to evaluate the safety and efficacy of the vaccine. The primary endpoint of the study is the continuous abstinence from smoking, determined by self-reporting and confirmed by measuring cotinine levels. The first results of the study are expected in the second quarter of 2005.

TA-NIC is an intramuscular vaccine for nicotine abuse under development by Xenova. The vaccine comprises nicotine conjugated to the carrier protein, rCTB, and an adjuvant. Xenova has reported results from a dose-escalating, randomized, double-blind, placebo-controlled phase I trial of TA-NIC. The trial involved three cohorts of 20 smokers to assess the safety, tolerability, anti-nicotine antibody response, and to select a dose of the agent for phase II/III trials. No serious TA-NIC-related adverse events were reported at all doses. Subjects demonstrated dose-dependent anti-nicotine antibody responses. Minimal injection-site effects were observed with the selected dose. After six weeks of the 12-week trial, 43% of subjects given TA-NIC voluntarily quit smoking or reported decreased smoking pleasure compared with 9% of subjects receiving placebo. The final results from this trial are expected at the end of 2004, with phase II trials planned to begin shortly after.

Together, these findings suggest the viability of the drug vaccine approach. Key success criteria for the vaccine approach can be defined around issues of immunogenicity, immunospecificity, immunotolerance, as well as clinical safety and efficacy. Potential issues such as the lack of protection against a structurally dissimilar molecule that produces the same effects as the drug, the individual variability in antibody formation, and the potential lack of motivation to take booster vaccinations must still be addressed. Furthermore, vaccination is not likely to be a stand-alone monotherapy, as it is not expected to show efficacy against drug craving and withdrawal. Thus, vaccination may complement the actions of existing medications or prove useful in combination with them.

Finally, the use of filamentous phage-displayed proteins designed to sequester cocaine in the CNS has recently been described [202]. The intranasal administration of the antibody-displaying construct GNC 92H2-pVIII reduced the acute locomotor activating effects of cocaine. Additional studies to investigate the potential therapeutic use of combined phage display and immunopharmacotherapy are warranted.

5.10. Other Pharmacological Approaches

Desoxypeganine (DOP) is an alkaloid derived from Peganum harmala, under development by HF Arzneimittelforschung (HFA) for the treatment of dependence in depressed and cognitively impaired alcoholics and smoking cessation[51]. It is a dual monoamine oxidase A inhibitor and centrally acting cholinesterase inhibitor. A 3-step dose-escalation Phase I trial is under preparation and is scheduled for completion by the end of 2004. Long-term toxicity trials in rats are complete, and long-term toxicity trials in dogs and metabolism studies are ongoing[52]. In genetically alcohol-preferring rats, acute oral doses of DOP (5-40 mg/kg) and a multiple oral dosing schedule of DOP (20 mg/kg/day for 2 weeks) reduced voluntary alcohol consumption by 25 and 20%, respectively, *vs.* control animals[53].

Selegiline is a selective and irreversible monoamine oxidase B inhibitor, developed by Chinoin for the treatment of Parkinson's disease. Chinoin marketed the product in Hungary in 1981. Selegiline has been marketed in the USA under the name ELDEPRYL by Somerset. The drug was approved by the FDA in June 1989 as an adjunct to levodopa in the treatment of Parkinson's disease, for which it holds Orphan Drug status. Canada's Health Protection Board approved selegiline for use as first line treatment for patients diagnosed with Parkinson's disease in April 1992. Researchers at Yale University (USA), supported by NIDA, are evaluating the potential of the agent as a treatment for

[49] Company Web Page, 28 Sept 2004

[50] Press release, Cytos Biotechnology AG, 23 Sept 2004

[51] 23rd CINP Meeting, Montreal, 2002, Abstract P.2.W.083; Direct communication, HFA, 19 Mar 2004

[52] Direct communication, HFA, 19 Mar 2004

[53] 23rd CINP Meeting, Montreal, 2002, Abstract P.2.W.083

nicotine addiction in a placebo-controlled phase II study in 40 cigarette smokers. Subjects were administered the agent or placebo for eight weeks. During the first seven days, patients received treatment once a day and, from day eight onwards, twice a day. Day 15 was the quit date. Following eight weeks of treatment, 45% of subjects treated with selegiline had stopped smoking, compared with 15% in the placebo group. After six months, 20% of selegiline-treated patients had quit smoking, compared with 5% of those receiving placebo. Selegiline did not affect the craving for nicotine[54].

Albrex is a broad-spectrum neurotransmission reuptake inhibitor, under development by Recovery Pharmaceuticals (formerly Addiction Therapies (ATI)) for the treatment of alcohol addiction. It is designed to overwrite associative memories of addiction, and to treat the cognitive deficits and depression that are commonly seen in alcoholics. It is in late-stage preclinical development[55].

HF Arzneimittelforschung (HFA) has suspended the development of a transdermal formulation of the cholinesterase inhibitor galantamine for the treatment of alcohol and nicotine dependence[56]. In a double-blind trial in 151 recently detoxified alcoholic outpatients, transdermal galantamine significantly increased the frequency of severe relapse (86.5% *vs.* 66.7% with placebo) and shortened time to severe relapse (39 days *vs.* 63 days with placebo). In addition, 20% of patients given transdermal galantamine remained abstinent by the end of the treatment phase, *vs.* 41% of placebo. The only positive outcome was that the mean amount of alcohol consumed following relapse was 990 g in those given transdermal galantamine, *vs.* 1254 g in patients receiving placebo. The total number of drinking days in the observation period was not significantly different between groups, whereas reported side-effects were skin reactions, headaches and insomnia.

Tetrodin is a tetrodotoxin-based compound with analgesic properties, isolated from blowfish, under development by International Wex Technologies (IWT) for the treatment of opiate and cocaine addiction[57]. IWT is also developing other tetrodotoxin-based compounds for the treatment of pain (Tectin) and as a local anaesthetic (Tocudin). A Canadian 12-week double-blind, placebo-controlled Phase IIa trial in 16 heroin withdrawal patients using a fixed repeated-dose regime to evaluate safety and efficacy was expected to begin in Aug 2003, and results were expected in the first quarter of 2004. Phase II trials in Europe and the US were expected to begin in mid-2003 and mid-2004, respectively[58]. In a Phase I trial in 127 volunteers, a safety dose range was established[59]. A double-blind, randomized, placebo-controlled, fixed repeat-dose safety and efficacy trial for the treatment of cocaine withdrawal symptoms in Peru is underway[60].

AME-359 is an optimized derivative of butyrylcholinesterase (BChE), under development by Applied Molecular Evolution (AME) (Lilly) for the treatment of cocaine toxicity and addiction[61].

Lobeline is an alkaloidal constituent of Lobelia inflata (Indian tobacco), under development by Yaupon Therapeutics for the treatment of methamphetamine addiction and attention deficit disorder (ADHD). It is in Phase I trials for methamphetamine addiction.

Finally, Valera is developing histrelin, a luteinising hormone releasing factor and gonadotropin releasing factor agonist for the treatment of opioid addiction. Phase II trials are expected in the second half of 2004[62].

5.11. Towards Transcriptomics, Neuroproteomics, and Molecular Genetics

The number of genes in the human genome is significantly lower than originally thought, with current estimates ranging between 30000 and 40000 genes [203]. Although a functional understanding for many of these genes is still lacking, completion of the Human Genome Sequencing Project will undoubtedly contribute to disease understanding, diagnosis and potential therapeutic interventions. Recently, microarrays, also called DNA microarrays or gene chips have allowed the monitoring of gene expression for tens of thousands of genes simultaneously [204, 205]. A review of the most important findings from microarray studies in the drug addiction field goes well beyond the remits of the present work. We will only briefly mention here that recent investigations using brain tissues from animal models or human postmortem studies revealed main alterations in a number of myelin-related genes, energy metabolism genes, oligodendrocyte function genes, cytoskeleton-associated genes, and genes implicated in neuronal plasticity [206-209]. Importantly, several studies also showed that a series of genes are only transiently expressed and return to baseline expression levels shortly after exposure to the drug [210, 211]. Some of these genes overlap with those that might be involved in the regulation of synaptic function [212-214]. The question of whether or not genes transiently altered by drugs of abuse might trigger persistent changes in synaptic structure, which in turn would be responsible for specific changes in behaviour will be one of the main challenges of future research. Gene microarray techniques are still in their infancy and currently lack sensitivity to detect low abundance genes and splice variants. Despite these main drawbacks, the value of the microarray technology lies in its substantial high-throughput screening capabilities to quickly identify key molecular changes following drug exposure as well as molecular fingerprints or biomarkers that may help targeting specific therapeutic strategies. Emerging technologies such as single-cell polymerase chain reaction (PCR) [215-217] or laser capture microdissection [218, 219] may soon allow the capture of cDNA from single cells and the study of gene expression in a single cell or specific cell populations. In

[54] NIDA, Feb 2003
[55] Company Web Page, Recovery, 17 May 2004
[56] Direct communication, HFA, 19 Mar 2004
[57] Direct communications, IWT, 21 Mar 2000 and 30 Apr 2001
[58] Press release, IWT, 13 Feb 2002; Analysts' Reps, Golden Capital Securities, 10 Jun 2002 and 5 Mar 2003
[59] Press release, IWT, 12 Jul 2001
[60] Press release, IWT, 29 Mar 2004
[61] Company Web Page, Applied Molecular Evolution, 19 Nov 2003
[62] Company pipeline, Valera, 27 Feb 2004

addition, significant efforts are currently deployed to gain information on the downstream consequences of changes in gene expression by developing neuroproteomics technologies [220]. Future studies combining parallel transcriptomics screen with proteomics investigations should offer unprecedented opportunities to track down key genes associated with drug addiction. Similarly, recent advances in molecular genetics will contribute to the discovery of genes, chromosomal regions, haplotypes, and allelic variants that are associated with individual vulnerability to drug addiction [221].

6. CONCLUSION

As NIDA celebrates its 30th anniversary (1974-2004), drug addiction research requires sustained support to palliate the significant unmet medical needs that are associated with drug dependence and addiction. Room for improvement exists in both the efficacy (acute cessation, reduction in the number of cessation attempts, reduction in craving, prevention of relapse, long-term maintenance of abstinence, and compliance to treatment) and safety (improved side-effect profile) domains.

In the present review, we have shown that repeated exposure to drugs of abuse produces long-term molecular and neurochemical changes, which may explain the core features of addiction, that is the compulsive seeking and taking of the drug and the drug-, cue-, or stress-dependent risk of relapse. A growing number of new molecular and cellular targets of addictive drugs have been identified. Furthermore, rapid advances are being made in relating those targets to specific behavioural phenotypes in animal models of addiction. As such, one hopes that current research efforts will lead to the discovery of new pharmacotherapeutic strategies that will help managing the life of those for whom drugs of abuse provided the illusion of control with the sad reality of degradation.

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