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Agents in Development for the Management of Cocaine Abuse

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Abstract

Cocaine abuse is a serious health problem in many areas of the world, yet there are no proven effective medications for the treatment of cocaine dependence.

Preclinical studies suggest that the reinforcing effect of cocaine that promotes its abuse is mediated by blockade of the presynaptic dopamine transporter. This results in increased dopamine activity in the mesolimbic or meso-accumbens dopamine reward system of brain. Development of new medications to treat cocaine dependence has focused on manipulation of this dopamine system, either

by direct action on dopamine binding sites (transporter or receptors) or indirectly by affecting other neurotransmitter systems that modulate the dopamine system. In principle, a medication could act via one of three mechanisms: (i) as a substitute for cocaine by producing similar dopamine effects; (ii) as a cocaine antagonist by blocking the binding of cocaine to the dopamine transporter; or (iii) as a modulator of cocaine effects by acting at other than the cocaine binding site.

The US National Institute on Drug Abuse has a Clinical Research Efficacy Screening Trial (CREST) programme to rapidly screen existing medications. CREST identified four medications warranting phase II controlled clinical trials: cabergoline, reserpine, sertraline and tiagabine. In addition, disulfiram and selegiline (deprenyl) have been effective and well tolerated in phase II trials. However, selegiline was found ineffective in a recent phase III trial.

Promising existing medications probably act via the first or third aforementioned mechanisms. Sustained-release formulations of stimulants such as methylphenidate and amfetamine (amphetamine) have shown promise in a stimulant substitution approach. Disulfiram and selegiline increase brain dopamine concentrations by inhibition of dopamine-catabolising enzymes (dopamine-β-hydroxylase and monoamine oxidase B, respectively). Cabergoline is a direct dopamine receptor agonist, while reserpine depletes presynaptic stores of dopamine (as well as norepinephrine and serotonin). Sertraline, baclofen and vigabatrin indirectly reduce dopamine activity by increasing activity of neurotransmitters (serotonin and GABA) that inhibit dopamine activity.

Promising new medications act via the second or third aforementioned mechanisms. Vanoxerine is a long-acting inhibitor of the dopamine transporter which blocks cocaine binding and reduces cocaine self-administration in animals. Two dopamine receptor ligands that reduce cocaine self-administration in animals are also undergoing phase I human safety trials. Adrogolide is a selective dopamine D_1 receptor agonist; BP 897 is a D_3 receptor partial agonist.

A pharmacokinetic approach to treatment would block the entry of cocaine into the brain or enhance its catabolism so that less cocaine reached its site of action. This is being explored in animals using the natural cocaine-metabolising enzyme butyrylcholinesterase (or recombinant versions with enhanced capabilities), catalytic antibodies, and passive or active immunisation to produce anti-cocaine binding antibodies. A recent phase I trial of a 'cocaine vaccine' found it to be well tolerated and producing detectable levels of anti-cocaine antibodies for up to 9 months after immunisation.

1. Scope of the Problem

Cocaine use and misuse represent a significant global public health problem. The United Nations Drug Control Program (UNDCP) estimates that cocaine use affects about 13.4 million people (0.3% of the global population above age 14 years), making it the second most common illegal drug of abuse in terms of treatment demand.[1] This problem is not spread evenly around the world. Two-thirds (67.9%) of cocaine users live in the Americas (47% in North America) and another fifth (20.9%) in Western Europe. In contrast, only 3% live in Asia and Oceania.

Especially detailed information about the extent of cocaine use and its consequences is available from the US. The National Household Survey on Drug Abuse[2] estimated in 2001 that 27 788 000

Americans had used cocaine at least once in their lifetime, 4 186 000 had used it in the past year, 1 676 000 had used it in the past month and 756 000 were dependent on cocaine (by US psychiatric criteria[3]). These estimates are based on interviews with a stratified random sample of 68 929 non-institutionalised individuals 12 years or older designed to be representative of the US population. That same year a survey of over 500 acute care hospitals estimated that 193 034 cocaine-using patients visited hospital emergency departments in 2001, a rate of 76 visits per 100 000 population.[4] A 1999 survey of publically funded substance abuse treatment programmes in the US found almost a quarter of a million (218 311) patients seeking treatment for cocaine abuse.[5] In addition to the direct effects of cocaine, cocaine use contributes to other health problems, such as the spread of infectious diseases (e.g. HIV, hepatitis C and tuberculosis).

These epidemiological data illustrate the continuing need for effective treatment for cocaine dependence. More than two dozen medications developed and marketed for other indications have been evaluated as treatment for cocaine dependence (for reviews, see Gorelick[6,7] and de Lima et al.[8]). Yet, after almost two decades of research, there is still no well established, effective medication for the treatment of cocaine dependence, nor is any medication approved for this indication by any national medications regulatory authority (such as the US FDA). One factor contributing to this lack is the relatively small amount of drug development activity for this indication by pharmaceutical companies, especially large multinational companies. In addition to perceived inadequacy of the science base, several market barriers have been identified as contributing to the dearth of activity by pharmaceutical companies:[9] (i) the small and uncertain market for cocaine dependence pharmacotherapy, because of uncertain market penetration and poor patient compliance; (ii) a substance abuse treatment system that limits access to the market because of limited physician involvement and anti-medication attitudes among non-physician clinicians; and (iii) limited and uncertain payment for medication because of poor insurance coverage and price resistance by government funders.

This article describes the potential leads to effective medication provided by the increasing knowledge of the neuropharmacology of cocaine, and then briefly reviews those medications currently undergoing clinical evaluation.

2. Approaches to the Problem

2.1 Pharmacological Strategies

In principle, at least four pharmacological approaches might be useful in the treatment of cocaine dependence.[6,7] First, substitution treatment with a cross-tolerant stimulant might suppress withdrawal symptoms and cocaine craving and/or make patients tolerant to acute reinforcing effects of cocaine. This is analogous to methadone maintenance treatment for heroin dependence or nicotine replacement therapy for tobacco dependence. Compounds that mimic the effects of cocaine should have a slow onset of action (and slow binding to site of action) to minimise substance abuse liability.[10] Secondly, an antagonist medication that blocks the binding of cocaine to its site of action might lead to extinction of cocaine-taking behaviour because cocaine would no longer be rewarding. This is analogous to naltrexone treatment for heroin dependence (naltrexone being a long-acting antagonist at the opioid μ receptor at which heroin acts). Thirdly, a medication might act at other sites to functionally antagonise the effects of cocaine, leading to a reduction of reinforcing effects of or craving for cocaine. Because cocaine is considered to exert its reinforcing effect primarily by increasing dopamine activity in the brain mesocorticolimbic 'reward' circuit, this approach might be implemented by influencing brain dopamine activity, either by direct action on dopamine binding sites (see section 3.1) or by affecting other neurotransmitters that modulate dopamine activity (see section 3.2).[11,12] This is analogous to naltrexone treatment for alcoholism (alcohol does not act directly on the opioid μ receptors blocked by naltrexone, but its effects are influenced by endogenous opioid activity). Fourthly, cocaine pharmacokinetics

could be altered so that less drug reached the brain or remained at its site(s) of action in the brain (see section 6).

Preclinical research has focused on several approaches to these goals: (i) development of more selective ligands for the presynaptic dopamine transporter, the presumed major site of action for cocaine in producing dependence, and for the several subtypes of dopamine receptors; (ii) manipulation of other neurotransmitter systems that influence the dopaminergic reward system; (iii) prevention or amelioration of consequences of actions of cocaine; and (iv) alteration of cocaine pharmacokinetics to reduce brain concentrations.

2.2 Animal Models

Preclinical animal models of cocaine dependence and relapse are used to screen for potential clinically effective anti-addiction medications. The true predictive validity of any animal model is unknown until an effective treatment medication is available as a 'gold standard'.

The following six behavioural models are commonly used in preclinical research to develop new medications for the treatment of cocaine (and other drug) dependence.[13]

1. Drug self-administration is the model with the most face validity for human drug taking.[14] Laboratory animals will work to self-administer addictive drugs such as cocaine by a variety of routes of administration. In a variant of this model, animals will work to receive a sensory stimulus previously associated with drug administration (so-called second-order reinforcement model). This has been considered an animal model of drug seeking.
2. The reinstatement model is considered a model of relapse to drug use after abstinence (for review, see Shaham et al.[15]). Animals are trained to stable drug self-administration behaviour, and then the drug-taking behaviour is completely extinguished. Relapse to drug-taking behaviour is then provoked by exposure to external stimuli. Three types of external stimuli reliably trigger relapse in this model – a single 'free' administration of drug, stress, or environmental stimuli previously associated with drug taking. These are triggers that can provoke relapse to drug taking in humans.
3. The conditioned place preference model uses Pavlovian conditioning to model drug craving (for review, see Tzschentke[16]). Animals are tested (when free of drug) to determine whether they prefer an environment in which they previously experienced drug as compared with another environment.
4. The drug discrimination model assesses the degree to which the subjective effects of one drug resemble the subjective effects of another drug (for review, see Colpaert[17]). The animal is trained to make one response when drugged (e.g. with cocaine) and another when given inactive vehicle. It is used in anti-addiction drug development to evaluate whether a putative therapeutic agent enhances or diminishes the overall subjective state induced by the addictive drug (e.g. cocaine).
5. The electrical brain stimulation reward model assesses the degree of drug-induced enhancement of brain reward in animals trained to respond for electrical stimulation of specific brain-reward loci, such as the ventral tegmental area, medial forebrain bundle, and nucleus accumbens.[18] This model is useful both to screen compounds for potential anti-addictive therapeutic properties and, conversely, to screen compounds for potential reward-enhancing properties, which might be predictive of addictive potential.
6. The behavioural sensitisation (sometimes termed reverse tolerance) model refers to the progressive increase of behavioural responses to psychostimulants that develops during their repeated administration, an effect that persists long after drug withdrawal.[19,20] Locomotor sensitisation in rodents has been used as an animal model of the progressive intensification of drug-induced reward and/or incentive motivation,[21] the latter perhaps relating to drug craving and relapse.

3. Drug Development Strategies

A wide variety of compounds have been evaluated for therapeutic potential, based upon current knowledge (or belief) about the brain mechanisms, loci and neurotransmitter systems underlying drug

taking, drug seeking and/or relapse. A promising compound is considered one that reduces effects of cocaine in animal models (e.g. self-administration, conditioned place preference, reinstatement of drug taking) at doses that do not disrupt other behaviours. A promising compound should preferably not itself be self-administered, suggesting that it has low abuse liability.

3.1 Direct Action on the Dopamine System

The addictive qualities of cocaine are believed to be mediated primarily by its enhancement of activity in the meso-accumbens dopamine system of the brain. This enhancement occurs by cocaine binding to presynaptic dopamine transporters and blocking the reuptake of dopamine, resulting in more dopamine remaining in the synapse (for review, see Gardner,[14] Wise and Gardner[22]). Evidence that this action mediates rewarding and reinforcing effects of cocaine includes the facts that: (i) brain-stimulation reward is elicited specifically from dopaminergic loci within the meso-accumbens dopamine system; (ii) dopamine antagonists selectively inhibit brain-stimulation reward at doses that have no effect on motor performance; (iii) cocaine potentiates the rewarding effects of brain-stimulation reward; (iv) the potencies of cocaine and cocaine-like drugs in animal self-administration studies correlate highly with their potencies to bind to the dopamine transporter but not to other presynaptic and postsynaptic binding sites; (v) cocaine is preferentially self-administered by animals into dopaminergic brain loci as opposed to other brain loci; (vi) dopamine-selective lesions of the nucleus accumbens attenuate the rewarding effects of intravenous cocaine; (vii) dopaminergically selective pharmacological blockade enhances intravenous cocaine self-administration at low doses (a compensatory effect, similar to the effect of decreasing the amount of cocaine per infusion) and completely blocks it at higher doses; (viii) addictive drugs, including cocaine, preferentially increase dopamine levels in the nucleus accumbens as opposed to other brain loci; (ix) self-administered cocaine preferentially elevates nucleus accumbens dopamine levels; and (x) animals self-administering intravenous cocaine appear to do so in order to maintain nucleus accumbens dopamine levels within a set range, with decreased nucleus accumbens dopamine triggering volitional self-administrations and increased nucleus accumbens dopamine correlating with behavioural indices of receipt of drug reward. Therefore, much preclinical research has been devoted to pharmacotherapeutic strategies targeted on this dopamine system.

3.1.1 Compounds Targeting the Dopamine Transporter

Primate, including human, studies show a positive correlation between dopamine transporter occupancy by cocaine and the positive reinforcing effects of cocaine, with at least 50% occupancy needed to produce an effect.[23,24] Reduction of cocaine self-administration in animals by dopamine transporter blockers is also associated with their degree of transporter occupancy, with at least 50% occupancy required to show an effect.[23]

These findings suggest the potential of dopamine transporter blockers[25] with slow onset and long duration of action to minimise abuse liability. Selectivity in blocking the cocaine binding site without affecting the dopamine site (thereby leaving normal dopamine reuptake) is also desirable in minimising abuse liability.[26] A wide variety of chemical structures have been used as templates in developing such a compound. These include cocaine analogues,[27] methylphenidate analogues,[26] tropanes,[28] benzatropine (benztropine) analogues,[29] substituted piperazines[30] and indanamines.[31]

Drugs that rapidly enter the brain and quickly elevate nucleus accumbens dopamine levels appear to have high addictive potential.[32] Thus, the best candidates are compounds with slow onset and/or prolonged duration of action, which appear to confer lower addictive potential. Table I lists promising compounds in this class and their effects in various animal models. One compound from this class, vanoxerine (GBR 12909), is currently undergoing clinical evaluation (see section 5).

Table I. Potential anti-cocaine addiction compounds with direct action on the dopamine system

Compound	Mechanism of action	Effects		Self-administered?	References
		on cocaine action (behavioural model)	other		
PTT RTI 113 HD-23 Vanoxerine (GBR 12909)	Dopamine transporter inhibitor	↓ (SA)	↑ ExDA, ↓ locomotion	Yes	33-39
SKF 77434 SKF 83959	Dopamine D_1 receptor partial agonist	↓ (Discr), ↓ (SA), ↓ (Sens), ↓ (RS)		No	40-42
Adrogolide (ABT 431; DAS 431)	D_1 receptor agonist	↓ (SA), ↓ (RS)		Yes	43,44
Ecopipam (SCH 39166)	D_1 receptor antagonist	↓ (SA), ↓ (RS)		No	12,45,46
Flupentixol	D_1/D_2 receptor antagonist	↓ (Discr), ↓ (SA)	EPS	No	47,48
Haloperidol Pimozide Eticlopride	D_2-like receptor antagonist	↓ (SA), ↓ (Discr), ↓ (Sens)	EPS, catalepsy	No	12,49,50
BP 897	D_3 receptor partial agonist	↓ (SA), ↓ (Sens), ↓ (Discr), ↓ (RS), ↓ (2^{nd}-Reinf)	Catalepsy, sedative, binding to α_1-adrenoceptors and serotonin 5-HT_{1a} receptors	No	51
SB 277011	Selective D_3 receptor antagonist	↓ (SA), ↓ (CPP), ↓ (EBSR), ↓ (RS), ↓ (2^{nd}-Reinf)	No EPS, no effect on feeding, no catalepsy	No	52,53

2^{nd} Reinf = second-order reinforcement model; **CPP** = conditioned place preference model; **DAT** = dopamine transporter (reuptake pump); **Discr** = drug discrimination model; **EBSR** = electrical brain stimulation reward model; **EPS** = extrapyramidal side effects; **ExDA** = extracellular dopamine concentration in nucleus accumbens; **PTT** = 2β-propanoyl-3β-(4-tolyl)tropane; **RS** = reinstatement model; **SA** = cocaine self-administration model; **Sens** = behavioural sensitisation model; ↓ indicates decrease; ↑ indicates increase.

3.1.2 Compounds Targeting Dopamine Receptor Subtypes

Another drug development strategy has been to focus on the dopamine receptor itself, of which there are five currently known subtypes.[54] Attention in anti-addiction drug development has focused chiefly on the dopamine D_1 and D_3 receptor subtypes (see table I). D_1 receptor-mediated mechanisms are implicated in the substrates of brain-stimulation reward, cocaine self-administration, cocaine-induced conditioned place preference, and cocaine-induced neurochemical and behavioural sensitisation (for review, see Platt et al.[12] and Rothman and Glowa[25]). The D_3 receptor, which is preferentially localised in the mesolimbic dopamine system,[55] plays a role in emotional, motivational and reinforcement functions, including the reinforcement produced by addictive drugs.[51] D_3 receptor inhibition may activate the meso-accumbens dopamine system,[56] which has been postulated to be pathologically under-active in drug addicts and individuals vulnerable to dependence (for reviews, see Gardner[57] and Volkow et al.[58]).

D_2 receptor ligands are no longer considered promising candidates for drug development, despite the role of D_2 receptor-mediated mechanisms in brain reward, cocaine self-administration and cocaine-induced conditioned place preference (for review see Platt et al.,[12] Rothman and Glowa[25]). D_2 receptor agonists are self-administered by animals and enhance the behavioural effects of cocaine. D_2 receptor antagonists (e.g. antipsychotics used to treat psychosis) do not stop cocaine use in humans, even when taken in high doses,[59-62] and often cause clinically significant adverse effects such as dysphoria and abnormal movements.

Table I lists dopaminergic compounds that have been studied preclinically. Three such compounds are undergoing clinical evaluation (see section 5): CEE 03310 (D_1 receptor antagonist), adrogolide

(ABT 431; DAS 431) [D_1 receptor agonist] and BP 897 (D_3 partial agonist).

3.2 Indirect Modulation of the Dopamine System

A wide variety of other neurotransmitter systems synapse with and regulate and/or modulate activity in the dopamine brain circuits subserving brain reward, associative learning related to dependence and relapse to drug-seeking behaviour.[63-65] These include serotonergic, endogenous opioid peptidergic, GABAergic, glutamatergic, endocannabinoid and neuropeptide (especially cholecystokinin [CCK], neurotensin [NT] and corticotropin-releasing factor [CRF]) systems. A promising drug development strategy is to indirectly modulate the dopamine circuits relevant to dependence by targeting these other neurotransmitter systems.

3.2.1 Compounds Targeting the Serotonin System

Cocaine inhibits the presynaptic reuptake of serotonin and has a high affinity for the serotonin 5-HT_3 receptor.[66,67] The meso-accumbens dopamine reward system is heavily innervated by serotonin afferents from the raphe nuclei both at the level of the ventral tegmental area and the nucleus accumbens. Serotonin also regulates and modulates dopaminergic function within the dopamine forebrain projection systems. Thus, the serotonin system presents a possible target for indirectly modulating dopaminergic brain substrates relating to drug-induced reward and relapse.[68]

Table II lists serotonergic compounds that have been evaluated preclinically. Two compounds from this class, ondansetron and sertraline, are being evaluated clinically (see section 4.4).

3.2.2 Compounds Targeting the Opioid System

The endogenous opioid peptides regulate and modulate dopaminergic function within the dopamine brain reward system and its forebrain projections.[81,82] Endogenous opioid neurons are found in the ventral tegmental area, nucleus accumbens and ventral pallidum, and may play a role in neural mechanisms mediating drug craving in the absence of reward.[83]

Endogenous brain opioids belong to four distinct neurotransmitter families: the endorphins, enkephalins, dynorphins and endomorphins.[84-86] These endogenous opioid peptide neurotransmitters interact with three major classes of opioid receptors, i.e. μ, δ and κ. Endomorphins display extremely high affinity and selectivity for the opioid μ receptor, enkephalins for the opioid δ receptor, and dynorphins for the opioid κ receptor. β-Endorphin binds with about equal affinity to both opioid μ- and δ receptors. Activation of opioid μ- and δ receptors enhances dopamine release in the nucleus accumbens and activates reward-related processes, whereas activation of opioid κ receptors inhibits dopamine

Table II. Potential anti-cocaine addiction compounds targeting the serotonin (5-HT) system

Compound	Mechanism of action	Effects		Self-administered?[a]	References
		on cocaine action (behavioural model)	other		
Tryptophan	Serotonin precursor	↓ (SA)			69,70
Fluoxetine Sertraline	Serotonin transporter inhibitor	↓ (SA), ↓ (EBSR), ↑↓ (Discr)		No	71,72
WAY 100635	5-HT_{1A} receptor antagonist	↓ (SA), ↓ (RS)	↓ locomotion		73-75
Chlorophenylpiperazine (MCPP) MK 212 RO 600175	5-HT_{2C} receptor agonist	↓ (SA), ↓ (Discr), ↓ (RS)	↓ locomotion		72,76,77
Tropisetron Ondansetron	5-HT_3 receptor antagonist	No effect in SA, Discr, CPP or RS models	↓ locomotion		78-80

a Empty cells indicate no data available.

CPP = conditioned place preference model; **Discr** = drug discrimination model; **EBSR** = electrical brain stimulation reward model; **RS** = reinstatement model; **SA** = cocaine self-administration model; ↓ indicates decrease; ↑ indicates increase.

Table III. Potential anti-cocaine addiction compounds targeting the opioid system

Compound	Mechanism of action	Effects		Self-administered?[a]	References
		on cocaine action (behavioural model)	other		
Naloxone Naltrexone Naloxonazine β-Funaltrexamine	Opioid μ receptor antagonist	↓ (CPP), ↓ (SA), ↓ (EBSR)	Dysphoric, ↓ feeding, ↓ social interaction	No	87-91
Naltrindole	Opioid δ receptor antagonist	↓ (CPP), ↓ (SA), ↓ (EBSR), ↓ (Discr)	Dysphoric, ↓ feeding	No	87,88,92
Dynorphin U 50488H U 69593	Opioid κ receptor agonist	↓ (CPP), ↓ (SA), ↓ (EBSR), ↓ (Sens), ↓ (RS)	Dysphoric ↓ (DA)	No	93,94
Buprenorphine	Mixed (partial opioid μ receptor agonist and opioid κ receptor antagonist)	↓ (SA), ↓ (RS), ↑ (EBSR), ↑ (CPP), ↑ (Discr)		Yes/No	95

a Empty cells indicate no data available.

CPP = conditioned place preference model; **DA** = dopamine; **Discr** = drug discrimination model; **EBSR** = electrical brain stimulation reward model; **RS** = reinstatement model; **SA** = cocaine self-administration model; **Sens** = behavioural sensitisation model; ↓ indicates decrease; ↑ indicates increase.

release and produces aversion.[82,85] Candidate compounds which differentially target opioid μ-, δ- and κ receptors have been evaluated preclinically for possible utility as anti-cocaine medications.

Table III lists preclinical findings with opioid compounds. Opioid μ receptor ligands, especially agonists or partial agonists, appear most promising. Buprenorphine (see section 4.8), a partial opioid μ receptor agonist and opioid κ receptor antagonist, and enadoline (CI 977) [see section 5], an opioid κ receptor agonist, are the only compounds evaluated in humans. Several clinical trials suggest that high-dose buprenorphine reduces cocaine use (along with opioid use) in patients abusing both cocaine and opioids.

3.2.3 Compounds Targeting the GABAergic System

GABA acts as an inhibitory neurotransmitter. GABAergic neurons modulate meso-accumbens brain reward functions via their heavy innervation within the ventral tegmental area and nucleus accumbens.[96] Activation of $GABA_B$ receptors on dopamine perikarya inhibits meso-accumbens dopaminergic reward functions.[97] These findings have spurred the development of GABA-mimetic compounds acting specifically at the $GABA_B$ receptor as possible anti-cocaine medications. Much work has focused on two approaches for increasing GABAergic activity: (i) by inhibiting GABA transaminase, the primary enzyme involved in catabolism of GABA; or (ii) by directly stimulating GABA receptors with an agonist.[98,99]

Table IV lists preclinical findings with GABAergic agents. Several GABAergic agents are undergoing clinical trials (see section 4.3).

3.2.4 Compounds Targeting the Glutamate System.

Glutamate is an amino acid neurotransmitter that mediates most excitatory synaptic transmission in the mammalian brain. Glutamatergic regulation of the meso-accumbens dopamine reward-related circuitry involves extensive inputs into the ventral tegmental area and the nucleus accumbens.[114,115] In addition, there are glutamatergic interconnections within the meso-accumbens dopamine system. This complex interconnected glutamatergic-dopaminergic network (which also has GABAergic links) has been proposed to constitute a 'motive circuit' which translates cortical information into adaptive behavioural responses.[116] Functional dysregulation of this circuit has been proposed as a neural substrate of drug dependence.[20,114,115]

Glutamate receptors are divided into two families: the ionotropic and the metabotropic. The iono-

tropic glutamate receptor family is further divided into three types: NMDA, α-amino-3-hydroxy-5-methyl-4-isoxasoleproprionate (AMPA) and kainate receptors. The metabotropic glutamate receptor family is also divided into three types, each with subtypes: metabotropic glutamate group I receptors (containing the mGluR1 and mGluR5 receptor subtypes), metabotropic glutamate group II receptors (containing the mGluR2 and mGluR3 receptor subtypes) and metabotropic glutamate group III receptors (containing the mGluR4, mGluR6, mGluR7 and mGluR8 receptor subtypes).

Glutamate is a focus of anti-cocaine medication development because neuroadaptations within the glutamate system may underlie some aspects of the development of cocaine dependence or the incubation of relapse vulnerability. In general, acute cocaine administration has little effect on glutamate neurotransmission. On the other hand, repeated cocaine administration results in neuroadaptations in glutamate neurotransmission in both the ventral tegmental area and nucleus accumbens.[114-116] Among these glutamatergic neuroadaptations is an enduring reduction in basal levels of nucleus accumbens glutamate during cocaine withdrawal and markedly enhanced glutamatergic transmission after re-exposure to cocaine.[117-121] The increased responsiveness of the cocaine-withdrawn glutamate system to cocaine re-exposure manifests itself only in the presence of environmental cues that have been previously associated with cocaine,[122] suggesting that it may constitute a neurobiological substrate of cue-triggered relapse.

Such preclinical findings suggest a number of potential pharmacotherapeutic targets. Normalisation (increase) in basal glutamate neurotransmission during cocaine withdrawal and abstinence might be helpful in relieving drug craving and relapse,[117] while a treatment that inhibits glutamate transmission after re-exposure to cocaine might attenuate rewarding effects of cocaine and abort the initiation of a cocaine binge.[118,121]

Table V lists preclinical findings with glutamatergic compounds. Two NMDA receptor antagonists are undergoing clinical evaluation (see section 4.5).

3.2.5 Compounds Targeting the Endocannabinoid System

Another brain neurotransmitter system that synaptically connects with and modulates the meso-accumbens dopaminergic reward-related system is the endocannabinoid system.[136,137] This system comprises several endogenous neurotransmitters/neuromodulators, such as anandamide, which act on cannabinoid CB1 receptors in the brain. Dronabinol (Δ-tetrahydrocannabinol), the psychoactive constituent of marijuana, activates cannabinoid CB1 receptors, which results in activation of the meso-accumbens dopamine system.[138] A high-potency synthetic cannabinoid agonist, HU 210, triggers relapse to cocaine-seeking behaviour in rats withdrawn from cocaine self-administration behaviour.[139] The cannabinoid CB1 receptor antagonist rimonabant (SR 141716A) blocks relapse to cocaine-seeking behaviour in the reinstatement model that is triggered by re-exposure to cocaine or to cocaine-associated environmental cues, but not relapse triggered

Table IV. Potential anti-cocaine addiction compounds targeting the GABAergic system

Compound	Mechanism of action	Effects		Self-administered?	References
		on cocaine action (behavioural model)	other		
Vigabatrin	GABA transaminase inhibitor	↓ (SA), ↓ (Sens), ↓ (CPP), ↓ (EBSR)	Visual field defects ↓ (DA), ↓ locomotion	No	100-103
Imidazenil Diazepam	$GABA_A$ modulator (partial agonist)	↓ (SA), ↓ (Discr)	↓ (DA), ↓ locomotion	Yes	104-108
Baclofen	$GABA_B$ agonist	↓ (SA), ↓ (DA), ↓ (CPP), ↓ (RS), ↓ (Sens)		No	109-113

CPP = conditioned place preference model; **DA** = dopamine; **EBSR** = electrical brain stimulation reward; **RS** = reinstatement model; **SA** = cocaine self-administration model; **Sens** = behavioural sensitisation model; ↓ indicates decrease; ↑ indicates increase.

Table V. Potential anti-cocaine addiction compounds targeting the glutamate (excitatory amino acid) system

Compound	Mechanism of action	Effects		Self-administered?[a]	References
		on cocaine action (behavioural model)	other		
GPI 5000 (2-PMPA) GPI 5693	Glutamate release (NAALADase)	↓ (CPP), ↓ (Sens), ↓ (RS), ↓ (SA)			123,124
NAC OTC	Cystine-glutamate exchange	↓ (SA), ↓ (RS)	Normalise basal glutamate		117
Dizocilpine Memantine	NMDA receptor antagonist	↓ (SA), ↓ (Sens), ↓ (CPP), ↓ (RS)	Block normal glutamate transmission	Yes	125-128
LY 379268	MGluR2/3 receptor agonist	↓ (SA), ↓ (Sens), ↓ (CPP), ↓ (RS)	Dopamine release, glutamate release	No	129-131
MPEP	mGluR5 receptor antagonist	↓ (SA), ↓ (CPP), ↓ (RS)	Short acting	No	132-135

a Empty cells indicate no data available.

2-PMPA = 2(phosphono-methyl)-pentanedioc acid; **CPP** = conditioned place preference model; **Discr** = drug discrimination model; **ExDA** = extracellular dopamine concentration in nucleus accumbens; **EBSR** = electrical brain stimulation reward model; **MGluR** = metabotropic glutamate; **MPEP** = 2-methyl-6-(phenylethynyl)-pyridine; **NAALADase** = N-acetylated-α-linked acidic dipeptidase; **NAC** = N-acetylcysteine; **OTC** = L-2-oxothiazolidine-4-carboxylic acid; **RS** = reinstatement model; **SA** = cocaine self-administration model; **Sens** = behavioural sensitisation model; ↓ indicates decrease; ↑ indicates increase.

by stress.[139] These findings suggest an important role for the endocannabinoid system in the neural processes mediating relapse to cocaine-seeking behaviour and suggest that cannabinoid receptor antagonists are potentially useful anti-cocaine medications in humans. However, no cannabinoid compound is currently undergoing clinical evaluation for the treatment of cocaine abuse.

3.2.6 Compounds Targeting Neuropeptides

Several non-opioid neuropeptide neurotransmitter systems are potential targets for anti-cocaine addiction pharmacotherapeutic agents, including CCK, NT, CRF and neurotrophic factors.

Cholecystokinin

CCK is the most widespread and abundant neuropeptide in the mammalian CNS.[140,141] Two CCK receptors have been identified: CCK_1 (previously known as CCK-A) and CCK_2 (previously known as CCK-B). CCK appears to be co-localised with dopamine within the meso-accumbens reward-related circuit and to modulate nucleus accumbens dopamine release. CCK_1 receptor agonists excite dopaminergic neuronal firing, enhance nucleus accumbens dopamine release and enhance dopamine-mediated behaviours. Activation of the CCK_2 receptor decreases nucleus accumbens dopamine release and generally decreases dopamine-mediated behaviours.[142,143]

The endogenous CCK system modulates both the development and expression of cocaine sensitisation.[143,144] CCK_1, but not CCK_2, receptor-mediated mechanisms in the nucleus accumbens play a key role in the acquisition, but not expression, of cocaine-conditioned behaviour.[142] Table VI lists preclinical findings with CCK agents.

Neurotensin

There are three NT receptor types in the mammalian brain: NT_1, NT_2 and NT_3.[154] Their functions remain poorly understood. The only known NT agonists are modified subfragments of the NT peptide itself.[155] Several non-peptide NT antagonists have been identified, of which reminertant (SR 48692) and SR 142948A are the best characterised.[156,157]

Substantial anatomical and functional interactions exist between the NT system and the meso-accumbens reward-related dopamine system.[158] NT cell bodies, which co-localise dopamine and CCK, are found preferentially in the ventral tegmental area. They heavily innervate the basolateral amygdala and the bed nucleus of the stria terminalis – areas implicated in cue-triggered relapse and stress-triggered relapse to cocaine-seeking behaviour, respectively. Most dopamine neurons in the

ventral tegmental area express NT receptors, primarily the NT_1 receptor. NT neurons in the nucleus accumbens co-localise GABA and express D_1, D_2 and D_3 receptors. NT appears to act as a modulator of dopaminergic function, rather than changing cell firing on its own. NT/dopamine co-release appears to serve as a limiting factor on dopaminergic transmission.

Table VI lists preclinical findings with NT receptor ligands. There has been no clinical evaluation of NT ligands.

Corticotropin-Releasing Factor

CRF, or corticotropin-releasing hormone (CRH), is another neuropeptide that functions as a neurotransmitter and/or neuromodulator in the mammalian brain.[159] There are six CRF receptors, divided into three families: CRF_1, CRF_2 and CRF binding protein (CRF-BP). The anatomical distribution of CRF-containing neurons and of CRF receptors suggests a role in the neural encoding of emotion and stress,[160] and in mediating the hormonal and behavioural manifestations of stress.[161]

In animal models, stress plays an important role in cocaine-seeking and cocaine-taking behaviour and cocaine withdrawal. Stress increases self-administration of addictive drugs, potentiates their rewarding effects in the conditioned place preference model, triggers relapse to drug-seeking behaviour in the reinstatement model and reinstates extinguished electrical brain-stimulation reward.[159,162] Administration of the stress hormone corticosterone facilitates the acquisition of psychostimulant self-administration, while inhibition of corticosterone decreases cocaine self-administration.[163] Acute cocaine withdrawal increases CRF release from the central nucleus of the amygdala,[164] and decreases CRF-like immunoreactivity in the hypothalamus, amygdala and ventral limbic forebrain.[165]

On the basis of these findings, anti-CRF compounds have been studied as potential anti-cocaine medications. Table VI lists preclinical findings with CRF antagonists. Indirect attenuation of hypothalamic-pituitary-adrenal (HPA) axis function with ketoconazole (blockade of cortisol synthesis) or dexamethasone (suppression of ACTH [adrenocorticotrophic hormone] release) has not been effective in phase I clinical trials (see section 4.8). However, development of CRF antagonists remains an active area. One caution in developing CRF_1-receptor antagonists as anti-cocaine medications is the potential for abuse liability. At least one non-peptide CRF_1-receptor antagonist, antalarmin (a close analogue of CP 154526), supports at least transient self-administration by monkeys.[166]

Brain Trophic Factors

Neurotrophins, or neurotrophic factors, are target-derived trophic factors which are crucial to the growth, differentiation, survival and maintenance of neurons in the central and peripheral nervous systems.[167] One member of this family is brain-derived neurotrophic factor (BDNF). In addition to its purely trophic functions, BDNF appears also to function as a neurotransmitter or neuromodulator in the mammalian CNS.[168] Chronic microinfusion of

Table VI. Potential anti-cocaine addiction compounds targeting neuropeptides

Compound	Mechanism of action	Effects		Self-administered?[a]	References
		on cocaine action (behavioural model)	other		
Devazepide	CCK_1 antagonist	↓ (CPP), ↓ (RS), ↓ (Sens), ↓ (Discr)			142-146
LY 262691 GV 150013 L 365260	CCK_2 antagonist	↓ (RS), ↓ (CPP)	↓ (DA)		147,148
CP 154526 CRH 9 41 (α-helical CRF) D-Phe-CRF	CRF1 antagonist	↓ (SA), ↓ (CPP), ↓ (RS)	↓ locomotion	Yes	149-153

a Empty cells indicate no data available.

CCK = cholecystokinin; **CPP** = conditioned place preference model; **CRF** = corticotropin-releasing factor; **Discr** = drug discrimination model; **RS** = reinstatement model; **SA** = cocaine self-administration model; **Sens** = behavioural sensitisation model; ↓ indicates decrease; ↑ indicates increase.

BDNF into the nucleus accumbens or ventral tegmental area enhances the initial stimulant effects of cocaine, facilitates the development of cocaine sensitisation and augments responding for a conditioned reward.[169] Conversely, cocaine sensitisation is significantly attenuated in heterozygous BDNF gene-deleted ('knock-out') mice.[169]

These findings suggest a role for meso-accumbens dopamine system-associated BDNF in long-term adaptations of the brain to cocaine. BDNF protein levels in the mesolimbic reward-related dopamine system show progressive augmentation over a 90-day period following withdrawal from cocaine self-administration[170] which precisely parallels the progressive incubation of vulnerability to cue-triggered relapse to cocaine-seeking behaviour over a similar 90-day period.[171] The implication is that time-dependent increases in BDNF levels may lead to synaptic changes that mediate progressively enhanced vulnerability to relapse following the termination of cocaine self-administration. Thus, BDNF antagonists specific to the mesolimbic dopamine system are promising candidates for anti-cocaine-relapse medication. There has been no clinical evaluation of BDNF-related compounds.

4. Marketed Medications Undergoing Clinical Evaluation

4.1 US National Institute on Drug Abuse Clinical Research Efficacy Screening Trial Programme

The US National Institute on Drug Abuse (NIDA) has an active medication development effort for treatment of cocaine abuse. One component of this effort is the Clinical Research Efficacy Screening Trial (CREST) programme. The goal of CREST is to rapidly and efficiently screen marketed medications to identify those with potential efficacy and safety that warrant further (and more expensive) evaluation. This is accomplished by single-blind testing of two to three medications and placebo at a time in parallel groups of 15–20 patients each. Each trial lasts 14 weeks (2 weeks baseline, 8 weeks medication and 4 weeks follow-up), with each subject receiving standardised weekly psychosocial therapy. Outcome measures include urine benzoylecgonine concentration (benzoylecgonine being the primary urinary metabolite of cocaine), self-reported cocaine use and structured observer ratings.

The CREST programme has tested 21 medications to date (table VII). Of these, four showed enough promise to undergo further clinical efficacy (phase II) trials: cabergoline, reserpine, sertraline and tiagabine. Several other marketed medications are being evaluated outside of the CREST programme (table VIII), supported either by NIDA and/or pharmaceutical companies.

4.2 Dopaminergic Agents

Two dopaminergic agents, disulfiram and selegiline (deprenyl), identified as promising by CREST programme are undergoing more extensive, multisite, clinical efficacy (phase III) trials.

Table VII. Marketed medications evaluated for the treatment of cocaine dependence by the medications development programme of the US National Institute on Drug Abuse

Medications evaluated by the CREST programme (phase II)	Medications found promising in the CREST programme	Medications in phase III trials
Celecoxib	Cabergoline	Disulfiram
Ubidecarenone/	Reserpine	Selegiline STS
levocarnitine	Sertraline	
Donepezil	Tiagabine	
Gabapentin		
Ginkgo biloba		
Ergoloid mesylates (hydergine)		
Hypericum		
Lamotrigine		
Levodopa/carbidopa		
Olanzapine		
Paroxetine		
Pentoxifylline		
Piracetam		
Pramipexole		
Riluzole		
Valproate semisodium		
Venlafaxine		

CREST = Clinical Research Efficacy Screening Trial; **STS** = selegiline transdermal system.

Table VIII. Marketed medications being evaluated for the treatment of cocaine dependence

Medication	US FDA-approved indication	Mechanism of action	Phase
Disulfiram	Alcoholism	Dopamine-β-hydroxylase inhibitor	III
Selegiline	Parkinson's disease	MAO-B inhibitor	III
Cabergoline	Hyperprolactinaemia	Dopamine D_2 receptor agonist	II
Reserpine	Hypertension	Biogenic amine depletion	II
Tolcapone	Parkinson's disease	COMT inhibitor	I
Baclofen	Muscle relaxant	$GABA_B$ receptor agonist	II
Gabapentin	Antiepileptic	Enhanced GABA activity	I
Valproate semisodium	Antiepileptic, mood stabiliser	Enhanced GABA activity	II
Tiagabine	Antiepileptic	GABA reuptake inhibitor	II
Topiramate	Antiepileptic	Enhanced GABA activity, glutamate receptor antagonist	II
Vigabatrin	Antiepileptic[a]	GABA transaminase inhibitor	I
Ondansetron	Antiemetic	Serotonin 5-HT_3 receptor antagonist	II
Sertraline	Antidepressant	Serotonin transporter inhibitor	II
Memantine	Dementia	NMDA receptor antagonist	II
Isradipine	Hypertension	Calcium channel antagonist	II
Citicoline	Stroke[a]	Enhanced phospholipid synthesis	I
Modafinil	Anti-sleepiness	Dopamine transporter inhibitor, enhanced glutamate activity	II

a Not approved in the US.

COMT = catechol-*O*-methyl transferase; **MAO** = monoamine oxidase.

Disulfiram has been widely used for several decades in the treatment of alcoholism. Several studies found that at the commonly used dosage of disulfiram 250 mg/day, it significantly reduced both cocaine and alcohol use in outpatients dependent on both substances.[172,173] The reduction in cocaine use might have been secondary to the reduction in alcohol use, because alcohol is known to trigger cocaine craving and use.[174] However, three recent controlled clinical trials found that disulfiram 250 mg/day significantly reduced cocaine use even among cocaine-dependent outpatients not also dependent on alcohol (but with concomitant opioid dependence in two studies).[175-177] One additional unpublished trial also found disulfiram to be better than placebo in reducing cocaine use [table IX; F. Vocci, personal communication].

A possible mechanism for beneficial effect of disulfiram is increased brain levels of dopamine (and/or decreased levels of norepinephrine). This would be caused by inhibition of the enzyme dopamine-β-hydroxylase, which catalyses the conversion of dopamine to norepinephrine. One caution to the use of disulfiram is the possibility of adverse interactions among disulfiram, cocaine and alcohol, should a patient not remain completely abstinent. A recent human laboratory study found that 3 days of pretreatment with disulfiram 250 mg/day significantly increased cocaine plasma concentrations and potentiated the tachycardic and hypertensive effects of intranasal cocaine (1 or 2 mg/kg).[178] Concern over the safety of the triple interaction among disulfiram, cocaine and alcohol has delayed initiation of a phase III clinical trial to confirm the efficacy of disulfiram. A phase I clinical trial evaluating the safety of these interactions is being conducted (A. Elkashef, personal communication).

Selegiline, marketed for the treatment of Parkinson's disease, is an irreversible inhibitor of monoamine oxidase (MAO). At the recommended dose of 10 mg/day, it is selective for MAO-B, the predominant MAO type in brain, and does not substantially inhibit MAO-A, the predominant type in the gastrointestinal tract. It is inhibition of MAO-A that leads to serious adverse interactions (e.g. hypertensive crisis) with tyramine-containing foods or catecholaminergic medications. Phase I studies show that selegiline is well tolerated by cocaine users and may blunt the positive psychological effects of acute cocaine administration.[179] Selegiline, administered

Table IX. Clinical trials of disulfiram as treatment for cocaine dependence in patients without alcoholism

Study design (n)	Cocaine-free urine samples (%)		Reference
	disulfiram	placebo	
All subjects on buprenorphine (20)	41	24	175
All subjects on methadone (67)	35	25	176
CBT vs 12-step vs clinical management (115)	55	40	Unpublished
CBT vs interpersonal therapy (121)	57	45	177
Weighted average of four studies (323)	51	38	

CBT = cognitive-behavioural therapy; **n** = number of subjects.

as a transdermal patch to decrease the risk of interaction with foods or medication, was recently evaluated in a phase III, multicentre, controlled clinical trial involving 300 cocaine-dependent outpatients.[180] Patients received either selegiline 20mg applied every 24 hours or a matching placebo for 8 weeks. Preliminary analysis of the data suggested no significant benefit of selegiline over placebo.

The mechanism by which selegiline might exert a beneficial effect is not known. MAO-B catalyses the breakdown of catecholamines, such as dopamine and norepinephrine, so that its inhibition by selegiline would increase brain catecholamine levels. Selegiline has a neurotrophic effect by stimulating synthesis of nerve growth factors, and may be neuroprotective as a scavenger of free radicals and inhibitor of NMDA-mediated excitotoxicity. Finally, selegiline metabolites include amfetamine and metamfetamine, which may act as substitutes for cocaine.

Three other marketed dopaminergic agents are undergoing phase II clinical trials. Cabergoline is a long-acting D_2 receptor agonist marketed for the treatment of hyperprolactinaemia. It is currently being evaluated in a multicentre, controlled clinical trial at a dosage of 0.5mg twice weekly for 12 weeks.[181] Reserpine is a Rauwolfia alkaloid marketed as an antihypertensive. It acts by depleting biogenic amines (including dopamine, norepinephrine and serotonin) in presynaptic and other tissue storage vesicles. A recent controlled clinical trial was halted early because of failure to show efficacy.[181] Tolcapone is a reversible inhibitor of the enzyme catechol-*O*-methyl-transferase (COMT) which readily crosses the blood-brain barrier.[182] It is marketed for Parkinson's disease[182] and under study as an antidepressant.[183] COMT is a major extraneuronal inactivator of catecholamine neurotransmitters such as dopamine and norepinephrine. Thus, tolcapone would be expected to increase dopamine levels and activity in the brain. Clinical use of tolcapone has been suspended in Europe because of cases of acute liver failure. A clinical trial of tolcapone-cocaine interactions in the US has been suspended because of concern over liver toxicity (J. Mojsiak, personal communication).

4.3 GABAergic Agents

Medications that increase brain GABA activity are attracting interest because GABA is an inhibitory neurotransmitter the activity of which inhibits dopamine release and reduces the reinforcing effects of cocaine in animals[98,184] (see section 3.2.3). Baclofen is a $GABA_B$ receptor agonist marketed as a muscle relaxant. Baclofen 20mg twice daily reduced cocaine craving and use in a small open-label trial.[185] In a human laboratory study with experienced cocaine users, baclofen 10–20mg twice daily for 7–10 days reduced video cocaine cue-induced cocaine craving and cue-induced activation of anterior cingulate and amygdala brain regions (assessed by positron emission tomography scanning).[98] A recent phase II controlled clinical trial found that baclofen 20mg twice daily significantly reduced cocaine craving and increased the proportion of cocaine-abstinent subjects, although other outcome measures (e.g. proportion of cocaine-negative urine samples) showed no significant difference from placebo.[186]

Tiagabine is marketed as an adjunctive antiepileptic drug. It acts as an inhibitor of presynaptic reuptake of GABA to increase functional GABA

activity in synapses. Two recent 10-week, placebo-controlled clinical trials in methadone-stabilised cocaine users found that high-dose tiagabine (24 mg/day), but not low dose (12 mg/day), significantly increased the proportion of cocaine-free urine samples compared with placebo.[187,188]

Valproate semisodium enhances brain GABA activity by one of several mechanisms, including increased synthesis, decreased metabolism and/or potentiation of postsynaptic effects of GABA. It is marketed as an antiepileptic drug and mood stabiliser in mania. While earlier clinical trials were not promising,[189,190] two more recent studies using higher doses (20 mg/kg/day) or achieved plasma concentrations (>50 mg/L) have reported better success.[191,192]

Topiramate has a dual mechanism, both enhancing GABA activity (by potentiating its effect on chloride ion channels) and acting as a glutamate receptor antagonist. It is marketed as an antiepileptic drug. A recent controlled clinical trial found that outpatients taking topiramate 200 mg/day had significantly more cocaine-free urine samples than those taking placebo, although both groups had fewer such samples than at baseline.[193]

Vigabatrin is a selective, irreversible inhibitor of GABA transaminase, a main enzyme metabolising GABA. It is marketed outside the US as an antiepileptic drug, but is not approved in the US because of concern over visual field defects. A recent open-label outpatient study in Mexico found that 8 of 20 subjects achieved sustained cocaine abstinence of at least 4 weeks at a dosage of 2g twice daily.[194] Three other subjects reduced their cocaine use by at least 50%, while eight subjects dropped out within the first 10 days. Phase I and IIa controlled clinical trials in cocaine users are being planned.

Gabapentin enhances GABA activity. It is marketed as an antiepileptic drug, and also widely used as a mood stabiliser. An open-label outpatient trial found that gabapentin 800–2400 mg/day reduced the number of cocaine-positive urine samples and increased the number of weeks of cocaine abstinence.[195] However, two recent controlled clinical trials did not find gabapentin 1600 or 2400 mg/day significantly better than placebo in reducing cocaine use.[188,196]

4.4 Serotonergic Agents

Ondansetron is a selective 5-HT_3 receptor antagonist marketed as an antiemetic. It is also being evaluated in a phase II controlled clinical trial. Sertraline is a selective serotonin reuptake inhibitor marketed as an antidepressant and anxiolytic agent. A recent controlled clinical trial in depressed, cocaine-dependent outpatients found sertraline 200 mg/day no better than placebo in relieving depressive symptoms or reducing cocaine use.[197]

4.5 NMDA Antagonists

Activation of the NMDA type of glutamate (excitatory amino acid) receptor enhances activity in the brain dopamine reward system, while their blockade reduces such activity (see section 3.2.4) and reduces cocaine-self-administration.[198] Clinical research on this treatment approach has been limited by the unavailability, until recently, of NMDA antagonists that could be used in humans. Memantine is a non-competitive, low-to-moderate affinity NMDA antagonist approved in the US for the treatment of Alzheimer's disease and in the EU for the treatment of various neurological disorders.[199] It is currently undergoing a placebo-controlled outpatient clinical trial (phase IIb), although an earlier phase IIa study found that memantine 20 mg/day enhanced, rather than reduced, the psychological effects of cocaine.[200]

4.6 Calcium Channel Antagonists

Calcium channel antagonists have been studied as treatment for cocaine dependence because of their action in reducing cocaine-induced neurotransmitter release and reinforced behaviours in animal studies, and in preventing or reversing cocaine-induced deficits in cerebral blood flow in humans.[201,202] Previous open-label outpatient case series found that several calcium channel antagonists (amlodipine, diltiazem, nifedipine) did not reduce cocaine use.[189,203]

Much current research attention has focused on isradipine, a dihydropyridine-type (L-type) calcium channel antagonist marketed for hypertension. A recent interaction study found that subacute pretreatment with isradipine (30 mg/day sustained release for 4 days, followed by 15 mg/day immediate release for 3 days) reduced the acute psychological and blood pressure effects of a cocaine challenge.[204,205] A placebo-controlled clinical trial of isradipine 2.5–5mg twice daily for 7 weeks found no significant reduction in cocaine use,[206] suggesting that higher daily doses are needed for efficacy.

4.7 Stimulants

Several research groups are working on a stimulant substitution approach. Earlier studies using standard formulations of marketed stimulants such as amfetamine, methylphenidate and phenmetrazine gave disappointing results, with patients sometimes reporting increased cocaine craving.[7] Recent controlled clinical trials with amfetamine have been more encouraging, especially those using sustained-release formulations.[207-209] Cocaine itself has been used in phase IIa clinical trials. Chronic exposure to either oral cocaine (100mg four times daily for 10 days) or continuous 24-hour intravenous infusion (0.25–0.5 mg/kg/h, total dose 6 mg/kg) has been well tolerated and reported to reduce the acute effects of an intravenous cocaine challenge.[210,211]

Modafinil is a stimulant-like medication marketed for the treatment of excessive sleepiness. Although its mechanism of action is not clearly understood, it does inhibit the dopamine transporter and enhance glutamate function.[212] Modafinil is self-administered by animals and partially discriminated as stimulant-like. In humans, it produces some stimulant-like psychological effects which are distinguishable from those of cocaine[213] and appears to have less abuse liability.[214] Two recent double-blind interaction studies found that pretreatment with modafinil 200, 400 or 800 mg/day for 4 or 7 days blunted some of the acute psychological effects of a cocaine challenge without causing any adverse cardiovascular effects.[215,216] Several case reports suggest that modafinil reduces craving and drug use in non-cocaine stimulant abusers.[217,218] A recent open-label trial in 13 cocaine-dependent outpatients found that modafinil 200 or 400 mg/day for 8 weeks was well tolerated and significantly improved treatment retention and reduced cocaine use when compared with 23 placebo-treated subjects in another study.[212,219] A phase II controlled clinical trial found that modafinil 400 mg/day significantly increased the cocaine abstinence rate compared with placebo.[220]

4.8 Other Medications

Buprenorphine is a partial opioid μ receptor agonist and opioid κ receptor antagonist (see section 3.2.2) that is marketed worldwide as an analgesic and for treatment of opioid dependence (both uses relying chiefly on its action at the opioid μ receptor). Because of its addiction potential as an opioid μ receptor agonist, buprenorphine has been studied clinically only in cocaine-abusing patients with opioid dependence. Clinical studies suggest that sublingual buprenorphine, at high doses of 8–16 mg/day, reduces cocaine use, as well as opioid use, in patients abusing or dependent on both.[221,222]

Citicoline is marketed in Europe and Japan as a treatment for ischaemic stroke and head trauma.[223] Development of citicoline for the treatment of stroke has been halted in North America after disappointing results in a recent 12-week phase III clinical trial.[224] Citicoline is a naturally occurring mononucleotide that serves as an intermediary in the biosynthesis of membrane phospholipids such as phosphatidylcholine. Administration enhances the incorporation of phospholipids into membranes and activates biosynthesis of structural phospholipids in nerve cell membranes, potentially stimulating repair of cocaine-damaged nerve cell membranes. Acute treatment increases brain levels of dopamine and norepinephrine. Citicoline is transformed in the CNS into uridine, a ligand at GABA receptors. It is not known which of these effects might mediate a therapeutic response in cocaine dependence.[225] A phase I clinical trial found no harmful interactions between citicoline 1 g/day for 4 days and intranasal cocaine 0.9 mg/kg, and no significant influence of

citicoline pretreatment on the acute psychological or physiological effects of the cocaine challenge.[226] A recent double-blind, placebo-controlled pilot study involving 14 cocaine-dependent outpatients found that citicoline 500mg twice daily for 8 weeks was well tolerated, improved mood and sleep, and reduced cocaine craving and use.[225]

Metyrapone is marketed as a diagnostic agent for hypothalamic-pituitary function. It blocks synthesis of cortisol in the adrenal cortex by inhibiting the 11-β-hydroxylation reaction. Interest in metyrapone as a treatment for cocaine dependence stems from preclinical studies suggesting that blockade of HPA axis function, for example, with CRF antagonists, reduces the rewarding effects of cocaine (see section 3.2.6), and clinical observations on the associations among stress, HPA hormones and cocaine dependence.[227] A recent human study found a significant association between intravenous cocaine-induced increases in plasma ACTH concentrations and cocaine-induced euphoria,[228] suggesting a role for HPA hormones in the psychological effects of cocaine. Two earlier phase I trials found no effect of attenuation of HPA axis function on the acute subjective effects of smoked cocaine, either through blockade of corticol synthesis by ketoconazole[229] or suppression of pituitary function by dexamethasone.[230] Despite these negative findings, a phase I study evaluating the interaction of metyrapone and intravenous cocaine is currently underway.

Prasterone (dehydroepiandrosterone) is an endogenous adrenal androgen available over-the-counter in the US. It directly stimulates dopamine release in animals and circulating levels of prasterone are lower than normal in chronic cocaine users.[227] These findings led to a recent controlled clinical trial, which found that prasterone 100 mg/day worsened treatment retention and increased cocaine use compared with placebo.[231]

The negative findings with ketoconazole, dexamethasone and prasterone suggest that manipulation of the HPA axis may not be a promising treatment approach in humans. This seems contrary to the promising results in animal studies (see section 3.2.6), but there are important differences between the animal and human studies. The most promising results with HPA axis inhibition in rodent studies have been found during initial acquisition of cocaine self-administration or when low unit doses of self-administered cocaine are used,[232] that is, when the incentive and reward values of cocaine are low. This is not the case in human cocaine dependence. Also, the most promising animal findings with CRF antagonists were targeted at the central brain CRF neural circuit originating in the central nucleus of the amygdala and terminating in the bed nucleus of the stria terminalis, not the HPA axis (see section 3.2.6). Further research with CRF antagonists in human will be needed to clarify this situation.

5. Unmarketed Medications Undergoing Clinical Evaluation

Animal studies have identified several compounds not yet marketed for any other clinical indication that show promise for the treatment of cocaine dependence, based on the neuropharmacological mechanisms described in section 3. Several of these have undergone phase I safety evaluation (table X).

Vanoxerine is a long-acting, noncompetitive inhibitor of the presynaptic dopamine transporter which was originally developed as an antidepressant.[233] In animal studies, self-administered vanoxerine increases extracellular dopamine levels in the striatum and exerts other stimulant-like effects, for example increased alertness and motor activity, not distinguished from cocaine.[25,233] On the other hand, pretreatment with vanoxerine reduces cocaine self-administration and cocaine-induced increases in brain extracellular dopamine levels.[25,233] These findings suggest that vanoxerine might act either as a true cocaine antagonist (i.e. blocking cocaine's access to the dopamine transporter) or as a stimulant that substitutes for the effects of cocaine. In human phase I studies, vanoxerine was well tolerated, and produced sedation, rather than excitation.[234] A phase I cocaine-interaction study is currently underway; phase II clinical trials are under consideration (F. Vocci, personal communication).

Table X. New compounds undergoing evaluation in humans as possible treatments for cocaine dependence

Compound	Sponsor	Mechanism of action	Phase
Adrogolide (ABT 431, DAS 431)	Drug Abuse Sciences, CA, USA	Dopamine D_1 receptor agonist	IIa[a]
BP 897	Bioproject, Paris, France	D_3 receptor partial agonist	I[b]
Vanoxerine (GBR 12909)	NIDA, MD, USA	Dopamine transporter inhibitor	IIa[a]
NS 2359	NeuroSearch, Ballerup, Denmark	Dopamine transporter inhibitor	I[b]
Enadoline (CI 977)	Parke-Davis, MI, USA	Opioid κ receptor agonist	IIa[a]
GV 196771	GlaxoSmithKline, Uxbridge, UK	Glycine antagonist	I[b]
Anti-cocaine vaccine (cocaine abuse vaccine TA-CD)	Xenova, Slough, UK	Blocking antibody	IIa[a]

a Administration with cocaine to cocaine-using subjects to evaluate safety, influence on acute cocaine effects.

b Administration to healthy subjects to evaluate safety.

NIDA = US National Institute on Drug Abuse.

NS 2359 is another inhibitor of the dopamine transporter that is undergoing a phase I human laboratory study evaluating the safety of single doses and their interaction with cocaine (A. Elkashef, personal communication communication). Additional dopamine transporter inhibitors that produce slow-onset, long-lasting blockade or that may block cocaine binding without influencing dopamine reuptake[235] are in preclinical development. For example, (+)-CPCA is a piperidine-based cocaine analogue that is similar in binding to the dopamine and norepinephrine transporters, but weaker in binding to the serotonin transporter.[236] As might be expected, it is self-administered by animals, but is a weaker reinforcer than cocaine.[236] Thus, it might be useful in the stimulant substitution approach. It is scheduled for human phase I safety trials. Methylphenidate analogues are also in preclinical development as substitution treatment.[26]

Two selective dopamine receptor agonists are undergoing phase I and IIa trials.[87] Adrogolide is a prodrug which is rapidly converted in plasma to A 86929, a D_1 receptor agonist.[43] In animal studies, it reduces cocaine self-administration and the ability of a priming dose of cocaine to reinstate self-administration, without itself being self-administered (see section 3.1.2). In a human laboratory study, adrogolide (2 or 4mg intravenously) was well tolerated by cocaine abusers and reduced some of the acute psychological effects of smoked cocaine (12 or 50mg), while not reducing cocaine self-administration.[237] A practical drawback of adrogolide is its high hepatic first-pass metabolism, resulting in very low bioavailability (about 4%) after oral administration. This obstacle may be circumvented by the development of a formulation suitable for inhalation (intrapulmonary delivery). BP 897 is a partial agonist of D_3 receptors.[51] It reduces cocaine self-administration in rats (although not in monkeys), without itself being self-administered (see section 3.1.2). Human phase II trials are currently underway.[51]

CEE 03310 is a selective D_1 receptor antagonist being developed for sleep disorders and substance abuse. Phase I studies show that it is well tolerated.[238] Phase II studies in substance abuse are scheduled to begin shortly in the US. Another D_1 receptor antagonist, ecopipam (SCH 39166), was found to increase cocaine self-administration and positive subjective ratings of cocaine in a human experimental study,[239] while not altering cocaine craving.[240] It is no longer considered a promising candidate for development.

Animal studies suggest that stimulation of opioid κ receptors inhibits the firing of and release of dopamine from neurons of the dopamine reward system (see section 3.2.2), and reduces the rewarding effects of cocaine in several animal behavioural models, for example self-administration, conditioned place preference and reinstatement.[241,242] Given these findings, opioid κ receptor agonists are promising candidates for medication development for the management of cocaine abuse. Existing agonists, such as cyclazocine, are not useful because of dysphoric and psychotomimetic effects. A newer

opioid κ agonist, enadoline, was well tolerated in phase I and IIa clinical trials, but did not significantly reduce the acute psychological effects of cocaine or cocaine self-administration in a laboratory study of cocaine users.[242]

GV 196771 is an NMDA antagonist at the glycine binding site that is undergoing phase I evaluation.[243] A controlled clinical trial (phase IIb) in cocaine-dependent outpatients is planned.

6. Pharmacokinetic Treatment Approach

There is growing interest in pharmacokinetic approaches to the treatment of cocaine dependence, that is, to preventing cocaine from reaching its site(s) of action in the brain. This could be accomplished by preventing ingested cocaine from entering the brain (crossing the blood-brain barrier) or by enhancing the elimination of cocaine from the body so that less reached the site of action.[244] The success of a pharmacokinetic treatment would depend on its having sufficient activity to preclude ability of a patient to overcome the treatment by taking larger amounts of cocaine.

Three pharmacokinetic techniques are being studied: (i) binding with anti-cocaine antibodies that form complexes too large to cross the blood-brain barrier (blocking approach); (ii) increasing cocaine catabolism with enzymes; or (iii) increasing cocaine catabolism with catalytic antibodies (catalytic approach). All three techniques, when used as pretreatment before cocaine administration, have been successful in animal studies in reducing brain cocaine concentrations and the behavioural effects of cocaine.[245-247] The enzyme technique has been implemented preclinically with both the naturally occurring enzyme butyrylcholinesterase, a major cocaine metabolising enzyme in primates, or with recombinant versions of the human enzyme which have enhanced catalytic properties.[248] Other naturally occurring enzymes that catabolise cocaine, such as bacterial cocaine esterase, are also being considered.[249] There have not yet been any human studies with either enzyme or catalytic antibody.

The blocking approach (so-called 'cocaine vaccine') has been implemented in two ways.[250] The cocaine molecule, itself too small to be antigenic, has been coupled to a large carrier protein. Alternatively, an antibody molecule configured to mimic the cocaine molecule can serve as the antigen (anti-idiotypic antibody).[251] Both types of antibodies can significantly alter cocaine pharmacokinetics. The only human studies to date have used succinylnorcocaine covalently linked to recombinant cholera toxin B subunit to make cocaine antigenic (cocaine abuse vaccine TA-CD).[252] In a randomised, double-blind, placebo-controlled, phase I study, 34 healthy, abstinent cocaine abusers received up to three doses (13, 82 or 709μg) of this vaccine (with aluminium hydroxide adjuvant) over 8 weeks and were followed up for 1 year.[252] Two phase IIa trials have been conducted. In the first trial, 19 cocaine abusers received up to five doses (82 or 360μg) of this vaccine over 12 weeks.[253] In the second trial, 21 cocaine abusers received up to five doses (100 or 400μg) of this vaccine over 12 weeks, with some subjects receiving a booster dose at 15–18 months.[254] Findings in all three studies were consistent. The active immunisation was well tolerated locally and systemically. Serum levels of anti-cocaine antibody correlated with both vaccine dose and number of vaccinations. Detectable antibody levels appeared after the second vaccination, peaked 8–12 weeks later and remained for up to 9 months. Subjects who used cocaine during the phase IIa studies anecdotally reported attenuation of the expected euphoric effects of cocaine.[253,254] There was a rough negative association between vaccine dose or peak antibody level and degree of cocaine use, that is, the higher the dose or antibody level, the less cocaine use (assessed by urine toxicology). A phase II efficacy study in cocaine-abusing patients on methadone maintenance treatment should begin in the near future (F. Vocci, personal communication).

At least two other companies have anti-cocaine antibodies in preclinical development:[255] one a blocking antibody (ITAC-cocaine; Drug Abuse Sciences, CA, USA) induced by active immunisation (analogous to cocaine abuse vaccine TA-CD); and

another a monoclonal catalytic antibody (15A10; MedImmune, MD, USA) that would metabolise cocaine.

7. Conclusion

Cocaine dependence is a significant public health problem in many countries of the world, yet there is no effective medication approved for its treatment. Screening of several dozen marketed medications developed for other indications identified two agents, disulfiram and selegiline, that warranted further evaluation. Both probably act by increasing brain dopamine activity by inhibiting enzymes in the dopamine metabolic pathway, i.e. dopamine-β-hydroxylase (disulfiram) and MAO-B (selegiline). Selegiline was recently found no better than placebo in a phase III, controlled clinical trial.

Increasing knowledge of the neuropharmacology of cocaine dependence, gained from preclinical research, suggests that modulation of the dopamine mesocorticolimbic brain reward system is a fruitful approach for drug development. This could be accomplished either directly, by targeting dopamine receptors or the presynaptic dopamine transporter, or indirectly by influencing other neurotransmitter systems which modulate the dopamine system, or by altering neuronal function (e.g. calcium channel function, phospholipid synthesis). Targeted neurotransmitters include GABA, serotonin and excitatory amino acids (NMDA). Preclinical screening for promising compounds is hampered by the absence of an animal model with confirmed predictive validity in identifying effective medications.

A variety of marketed (table VIII) and newly developed medications (table X) that act by one of the aforementioned mechanisms are undergoing clinical evaluation. Two other approaches being clinically evaluated are substitution with another stimulant-type medication and reduction of cocaine concentration in the brain (pharmacokinetic approach). The latter is being implemented using anti-cocaine antibodies evoked by active immunisation (cocaine vaccine).

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