Title: SUBSTANCE

Abstract: The present invention relates to the use of a nitric oxide donor compound in the manufacture of a medicament for treating a drug addiction disorder.
The present invention relates to the use of a dopamine receptor agonist or antagonist, in particular a nitric oxide donor compound, in the treatment of a drug addiction disorder such as nicotine or cocaine addiction.

Drug addiction and/or abuse and/or dependency (collectively referred to herein as "drug addiction disorders") is extremely common. Individuals suffering from such addictions are generally subject to significant symptoms of withdrawal upon attempting to cease use of the addictive substance (whether drugs such as cocaine, heroine, nicotine etc.).

Psychostimulant drugs of abuse such as nicotine, cocaine and heroin appear to produce their addictive rewarding euphoria in humans by promoting the release of the excitatory CNS neurotransmitter dopamine from the midbrain ventral tegmental area (VTA) for action in the mesolimbic nucleus accumbens (NAC). The mesolimbic excitatory dopaminergic neurotransmitter system originates in the VTA which projects its efferent dopamine-secreting nerve terminals to the functionally-related NAC.

Dopamine (DA) exerts its effecting the brain by acting on a family of receptors. These receptors can be divided into two broad categories, D-1 type and D-2 type (Bonci et al. Trends in Pharmaceutical Science 24 (4): 172-177 (2003); Kapsimali, et al. Neurological Disease 56: 1-44 (2003). Two D-1 type receptors have been identified, D-1 and D-5. They are excitatory and stimulate the formation of cAMP. The D-2 Type receptor family has three main subtypes, D-2, D-3 and D-4. These receptors are inhibitory and have a number of transduction mechanisms including cAMP formation. D-1 and D-2 type receptors are expressed in areas of the brain innervated by DA-secreting neurones and comprise approximately 80% of all DA receptors. Both subtypes are found in the principal subdivisions of the accumbens.
Neurotransmitter interaction at the mesolimbic brain region induces "reward" when DA is released from the neuron at the nucleus accumbens and interacts with the dopamine receptor, particularly the D2 receptor. The reward cascade involves the release of serotonin, which in turn inhibits GABA at the substantia nigra, which in turn fine tunes the amount of DA released at the nucleus accumbens (Blum et al., J. Psychoactive drugs 32: 1-4 (2000)). DA receptors are activated when DA is released into the synapse. This ultimately leads to feelings of well being.

Cocaine and amphetamine exert their effects on DA overflow in the nucleus accumbens by binding to the DA transporters located along the exons. In contrast, nicotine appears to exert its effect on DA release by acting on nicotinic receptors located on or close to the cell bodies in the midbrain (Balfour et al., Pharmacol. Biochem. Behav., 59: 1021-1030 (1998)). Thus, the effects of nicotine depend upon its ability to influence impulse flow to the terminal field. The effects of all three drugs, nevertheless, is to elicit a marked increase in extracellular DA in the accumbens.

The repeated administration of psychostimulant drugs of abuse characteristically leads to sensitisation of their effects on DA overflow in the nucleus accumbens.

Cocaine acts on monoamine transporters blocking reuptake of dopamine, norepinephrine and serotonin from synapses following their release. This acutely increase activity at dopamine, adrenergic and serotonin receptors. Amphetamines also increase dopamine concentration in the nucleus accumbens. Nicotine acts on nicotinic acetylcholine receptors. Little tolerance to nicotine develops however extreme dependence and withdrawal are common.

It is thought that increased extracellular levels of dopamine in nucleus accumbens are responsible for addictive and motivational effects (Cami and Farre, New England Journal of Medicine 349(10): 975-986 (2003)).
A number of medical therapies for treating drug addiction disorders have been tried with differing levels of success. The majority of treatment methods are based on slowly reducing doses of the addictive drug, making the addictive drug aversive or less reinforcing, or providing a replacement drug. For example, for treating nicotine addiction, nicotine reduction therapy is employed using nicotine chewing gum, transdermal patches, nasal sprays, or inhalers. Alternative nicotine delivery devices such as toothpicks, lip balms, and lollipops also have been proposed. Replacement therapies, including bupropion hydrochloride, have also been employed for nicotine addiction.

"Nicotine replacement therapies" (NRT), replace the amount of nicotine which the user previously received from smoking and act to wean the user off nicotine. However, certain drawbacks are seen with this type of therapy. Particularly, there is low penetration of nicotine into the bloodstream and therefore an increased desire to smoke. Problems such as mouth irritation, jaw soreness, nausea, have been associated with use of nicotine chewing gum. Problems such as skin irritations, sleep disturbance, and nervousness have been associated with use of nicotine transdermal patches.

There is required an improved means for treating drug addiction disorders which overcomes the problems associated with known treatments.

According to a first aspect, the present invention provides the use of a dopamine receptor agonist or antagonist in the manufacture of a medicament for treating a drug addiction disorder.

In a further aspect, the invention provides a method of treatment of a drug addiction disorder in a human patient which method comprises administering to the patient a therapeutically effective amount of a dopamine receptor agonist or antagonist.
Dopamine receptor agonists are substances which, while structurally different from dopamine, bind to different subtypes of dopamine receptors and trigger an effect which is comparable to that of dopamine.

Dopamine receptor antagonists are substances which may exert an inhibitory effect on dopamine re-uptake. In this way the amount of bioavailable dopamine is increased.

In a preferred aspect the dopamine receptor is a D-1 type or D-2 type receptor.

Preferably, the D-1 type receptor is a D-1 or D-5 subtype receptor. Preferably, the D-2 type receptor is a D-2, D-3 or D-4 subtype receptor.

The expression “treatment of a drug addiction disorder” includes treatment of disorders associated with addiction. The treatment may promote withdrawal from the addictive drug or removal of the dependency on the addictive drug.

In a preferred aspect, the drug is selected from the group consisting of opioids, cannabinoids, barbiturates, benzodiazepines, amphetamines, hallucinogens, sedatives, hypnotics, inhalants and anxiolytics including ketamine, PCP (phencyclidine), dextromethorphan, LSD, Ecstasy, caffeine, alcohol, nicotine, tobacco, cocaine, cannabis.

Opioids work on family of neurotransmitter receptors, the mu, delta and kappa opioid receptors (MOR, DOR and KOR). Endogenous ligands for these receptors are a family of neuropeptides, the endorphins, the enkephalins, B-endorphin, and the dynorphins. Receptors are found on peripheral and central nervous system, but also on immune cells (Cami and Farre, New England Journal of Medicine 349(10): 975-986 (2003)).

Cocaine acts on monoamine transporters to block reuptake of dopamine, norepinephrine and serotonin from synapses following their release. This will
increase activity of dopamine, adrenergic and serotonin receptors. Cannabinoids act on cannabinoid receptors. CB1 in CNS, CB2 in PNS. Plant derived cannabinoids mimic action of endogenous CB receptor ligands. Barbiturates act on the GABA A receptor, an inhibitory neurotransmitter receptor that is activated by the amino acid GABA to open a chloride channel.

Benzodiazepines act as modulators of the GABA A receptor to increase chloride ion conductance. Amphetamines are thought to reverse dopamine and norepinephrine transporters, dumping dopamine and NE into dopaminergic and adrenergic synapses.

Caffeine produces its effect by antagonising adenosine receptors

In a preferred embodiment of the invention, the use is in the treatment of a drug addiction disorder wherein the drug is nicotine.

In an alternative embodiment, the use is in the treatment of a drug addiction disorder where the drug is an opioid such heroin, codeine and morphine or a derivative thereof such as pethidine and methadone.

In a preferred aspect of the invention the dopamine receptor agonist or antagonist is a nitric oxide donor compound.

By "nitric oxide donor" compound it is meant a compound which is able to donate, transfer or release nitric oxide, or a related redox species, or more generally provides nitric oxide bioactivity that is activity which is identified with nitric oxide, e.g., vasorelaxation or stimulation or inhibition of a receptor protein. The nitric oxide donor may promote an increase in nitric oxide, for example as a NO synthase substrate, through endogenous stimulation of NO synthesis.

The nitric oxide (NO) donor may be selected from the group consisting of O-nitroso, S-nitroso, C-nitroso and N-nitroso compounds and nitro derivatives thereof and
metal NO complexes. The O-nitroso compounds may include nitrates (e.g. organic) and organic nitrites. S-nitroso compounds may include thionitrates and thionitriles, for example, S-nitrosothiols. N-nitroso compounds may include N-nitrosamines, N-hydroxy-N-nitrosamines, N-nitrosamides, N-nitrosoguanidines, N-nitrosohydrazines, nitramines and N-nitrosoimines.

The NO donor may be an inorganic NO donor such as a nitrite, nitrosonium salt or nitrosyl halide, peroxynitrite (HOONO) or sodium azide.

The NO donor may be a metal nitrosyl such as nitroprusside, dinitrosyl-iron (II) complex, iron nitrosyl compounds, nitrosyl complex of iron-sulphur cluster or of other transition metals.

The NO donor may be a heterocyclic NO donor such as a sydnonimine, an oxadiazole (furoxan), oxatriazole or diazetidine-di-N-oxide.

The NO donor may be a nitroxyl-generating compound such as Angeli’s salt, Piloy’s acid, cyanamide.

The NO donor may be an oxime (FK-409 analog), hydroxylamine, N-hydroguanidine, diazeniumdiolate (NONOate) sodium trioxidinitrate (Na₂N₂O₃), benzenesulfohydroxamic acids (R-SO₂NHO⁻), sodium nitroprusside, nitrosoester compounds.

The nitrate may include a nitrate ester, or an organic nitrate.

In a preferred aspect the nitrate is an organic nitrate. The organic nitrate may include ethylene glycol dinitrate; isopropyl nitrate; glyceryl-1-mononitrate; glyceryl-1,2-dinitrate; glyceryl-1,3-dinitrate; nitroglycerin (GTN); butane-1,2,4-trioltrinitrate-; erythritol tetranitrate (ETN); pentaerythrityl tetranitrate (PETN); isosorbide mononitrate (ISMN), which may include isosorbide-2-mononitrate (IS2N) and/or
isosorbide-5-mononitrate (ISSN); and/or isosorbide dinitrate (ISDN). Isorsorbide or glyceryl trinitrate may be a NO synthase substrate.

The NO donor may include a nitroso polypeptide, nitrosated modified or unmodified oligonucleotides or nitrosated haemoglobin (described in US6538116 and US6207855). Also encompassed are partial pro-drugs that release NO after biotransformation of the nitrite group to NO (described in US6538033), and nucleophile or nitric oxide adducts (nucleophile being a primary, secondary or tertiary amine).

The NO donor may be a N₂O₂ containing compound that may release NO by enzymatic or non-enzymatic oxidation as described in US6511991.

The terms dopamine receptor “agonist” or “antagonist” as used herein are not intended to be functionally limiting on the nitric oxide donor compound of the invention such that any nitric oxide donor compound that is useful for treating a drug addiction disorder, but which does not provide said agonistic/antagonistic effect, is encompassed by the invention.

In a further preferred embodiment of the invention the dopamine receptor agonist or antagonist is an antibody, or an active binding fragment of an antibody. Preferably, said antibody, or binding fragment, is a monoclonal antibody.

Antibodies or immunoglobulins (Ig) are a class of structurally related proteins consisting of two pairs of polypeptide chains, one pair of light (L) (low molecular weight) chain (κ or λ), and one pair of heavy (H) chains (γ, α, μ, δ and ε), all four linked together by disulphide bonds. Both H and L chains have regions that contribute to the binding of antigen and that are highly variable from one Ig molecule to another. In addition, H and L chains contain regions that are non-variable or constant. The L chains consist of two domains. The carboxy-terminal domain is essentially identical among L chains of a given type and is referred to as the
“constant” (C) region. The amino terminal domain varies from L chain to L chain and contributes to the binding site of the antibody. Because of its variability, it is referred to as the “variable” (V) region. The variable region contains complementarity determining regions or CDR’s which form an antigen binding pocket. The binding pockets comprise H and L variable regions which contribute to antigen recognition. It is possible to create single variable regions, so called single chain antibody variable region fragments (scFv’s). If a hybridoma exists for a specific monoclonal antibody it is well within the knowledge of the skilled person to isolate scFv’s from mRNA extracted from said hybridoma via RT PCR. Alternatively, phage display screening can be undertaken to identify clones expressing scFv’s.

In a preferred embodiment of the invention the antibody fragment is a single chain antibody fragment. Preferably, the antibody fragment is a single chain antibody variable region fragment.

In a further preferred embodiment of the invention said antibody, or binding fragment thereof, is a chimeric antibody. In an alternative preferred embodiment of the invention said antibody, or binding fragment thereof, is a humanised antibody.

A chimeric antibody is produced by recombinant methods to contain the variable region of an antibody with an invariant or constant region of a human antibody. A humanised antibody is produced by recombinant methods to combine the CDR’s of an antibody with both the constant regions and the framework regions from the variable regions of a human antibody.

Antibodies from non-human animals provoke an immune response to the foreign antibody and its removal from the circulation. Both chimeric and humanised antibodies have reduced antigenicity when injected to a human subject because there is a reduced amount of rodent (i.e. foreign) antibody within the recombinant hybrid antibody, while the human antibody regions do not elicit an immune response. This results in a weaker immune response and a decrease in the clearance of the antibody.
This is clearly desirable when using therapeutic antibodies in the treatment of human diseases. Humanised antibodies are designed to have less “foreign” antibody regions and are therefore thought to be less immunogenic than chimeric antibodies.

In an alternative preferred embodiment the dopamine receptor agonist or antagonist is a peptide. Preferably said peptide is a modified peptide.

It will be apparent to one skilled in the art that peptides are susceptible to modifications such as acetylation and/or amidation. Alternatively or preferably, said modification includes the use of modified amino acids in the production of peptides according to the invention. It will be apparent that modified amino acids include, by way of example and not by way of limitation, 4-hydroxyproline, 5-hydroxylysine, $N^6$-acetyllysine, $N^6$-methyllysine, $N^6,N^{\epsilon}$-dimethyllysine, $N^6,N^\epsilon,N^{\epsilon}$-trimethyllysine, cyclohexylalanine, D-amino acids, ornithine. Other modifications include amino acids with a $C_2, C_3$ or $C_4$ alkyl R group optionally substituted by 1, 2 or 3 substituents selected from halo (e.g. F, Br, I), hydroxy or $C_1$-$C_4$ alkoxy. Alternatively, peptides could be modified by cyclisation. Cyclisation is known in the art, (see Scott et al Chem Biol (2001), 8:801-815; Gellerman et al J. Peptide Res (2001), 57: 277-291; Dutta et al J. Peptide Res (2000), 8: 398-412; Ngoka and Gross J Amer Soc Mass Spec (1999), 10:360-363).

In a still further alternative embodiment of the invention said dopamine receptor agonist or antagonist is an aptamer.

Nucleic acids have both linear sequence structure and a three dimensional structure which in part is determined by the linear sequence and also the environment in which these molecules are located. Conventional therapeutic molecules are small molecules, for example, peptides, polypeptides, or antibodies, which bind target molecules to produce an agonistic or antagonistic effect. It has become apparent that nucleic acid molecules also have potential with respect to providing agents with the requisite binding properties which may have therapeutic utility. These nucleic acid
molecules are typically referred to as aptamers. Aptamers are small, usually stabilised, nucleic acid molecules which comprise a binding domain for a target molecule. A screening method to identify aptamers is described in US 5,270,163 which is incorporated by reference. Aptamers are typically oligonucleotides which may be single stranded oligodeoxynucleotides, oligoribonucleotides, or modified oligodeoxynucleotide or oligoribonucleotides.

The term “modified” encompasses nucleotides with a covalently modified base and/or sugar. For example, modified nucleotides include nucleotides having sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position. Thus modified nucleotides may also include 2' substituted sugars such as 2'-O-methyl; 2-O-alkyl; 2-O-allyl; 2'-S-alkyl; 2'-S-allyl; 2'-fluoro; 2'-halo or 2;azido-ribose, carboxyclic sugar analogues a-anomeric sugars; epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, and sedoheptulose.

Modified nucleotides are known in the art and include by example and not by way of limitation; alkylated purines and/or pyrimidines; acylated purines and/or pyrimidines; or other heterocycles. These classes of pyrimidines and purines are known in the art and include, pseudoisocytosine; N4, N4-ethanocytosine; 8-hydroxy-N6-methyladenine; 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil; 5-fluorouracil; 5-bromouracil; 5-carboxymethylaminomethyl-2-thiouracil; 5-carboxymethylaminomethyl uracil; dihydropuracil; inosine; N6-isopentyl-adenine; 1-methyladenine; 1-methylpseudouracil; 1-methylguanine; 2,2-dimethylguanine; 2-methyladenine; 2-methylguanine; 3-methylcytosine; 5-methylcytosine; N6-methyladenine; 7-methylguanine; 5- methylaminomethyl uracil; 5-methoxy amino methyl-2-thiouracil; δ-D-mannosylqueosine; 5-methoxycarbonylmethyluracil; 5-methoxyuracil; 2-methylthio-N6-isopentenyladenine; uracil-5-oxyacetic acid methyl ester; psueouracil; 2-thiocyotosine; 5-methyl-2 thiouracil, 2-thiouracil; 4-thiouracil; 5-methyluracil; N-uracil-5-oxyacetic acid methylester; uracil 5—oxyacetic acid; queosine; 2-thiocyotosine; 5-propyluracil; 5-propylcytosine; 5-ethyluracil; 5-
ethylcytosine; 5-butyrluracil; 5-pentyluracil; 5-pentylcytosine; and 2,6-
diaminopurine; methylpsuedouracil; 1-methylguanine; 1-methylcytosine.

The aptamers of the invention are synthesized using conventional phosphodiester
linked nucleotides and synthesized using standard solid or solution phase synthesis
techniques which are known in the art. Linkages between nucleotides may use
alternative linking molecules. For example, linking groups of the formula P(O)S,
(thioate); P(S)S, (dithioate); P(O)NR’2; P(O)R’; P(O)OR6; CO; or CONR’2 wherein
R is H (or a salt) or alkyl (1-12C) and R6 is alkyl (1-9C) is joined to adjacent
nucleotides through –O- or –S-. The binding of aptamers to a target polypeptide is
readily tested by assays hereindisclosed.

It will be appreciated that for the antibody, antibody fragment, peptide, aptamer, or
other dopamine receptor agonist or antagonist, of the invention to be useful in
treating a drug addiction disorder, it must be able to permeate the blood-brain barrier.

To facilitate brain permeation, the dopamine receptor agonist or antagonist is
preferably of a molecular weight below 1000, more preferably below 500. Other
factors useful in determining whether a substance will pass the blood-brain barrier
are described in Clark, DDT: 8, 20 (2003).

Drug transporters at the blood-brain barrier may provide means for the uptake of the
dopamine receptor agonists/antagonists of the invention into the brain. Receptor-
mediated endocytosis (RME) provides a means for selective uptake of
macromolecules. Cells have receptors for the uptake of many different types of
ligands, including hormones, growth factors, enzymes, and plasma proteins. RME is
a highly specific type of energy dependent transport (Boer et al., Annu. Rev.

Absorptive-mediated transport (AME) is another means for the uptake of molecules
into the brain. AME is triggered by an electrostatic interaction between a positively
charged substance, usually a charge moiety of a peptide, the negatively charge plasma membrane surface (i.e. glycocalyx).

Carrier-mediated efflux is another significant transport mechanism at the blood brain barrier. This mechanism is involved in extruding drugs from the brain, with the ABC (ATP binding cassette) transporter P-glycoprotein being the principle efflux mechanism of these agents. Efflux transporters may be useful for transporting organic anions, via multidrug resistance associated protein (MRP), and anionic and cationic cyclic peptide. Additionally, peptide transport systems, e.g. (PTS)-1, have provided efflux transport of synthetic drugs (Boer et al., Annu. Rev. Pharmacol. Toxicol. 43: 629-656 (2003).

The present invention encompasses dopamine receptor agonists/antagonists that have affinity for one of the carrier-mediated transporters within the blood-brain barrier. Also encompassed is a molecule that is capable of permeating the blood brain barrier and which has been grafted with a "NO donor" group thus acting as a NO donor drug.

Preferably, the dopamine receptor agonist/antagonist (i.e., the active agent) is formulated as a pharmaceutical composition comprising the dopamine receptor agonist in combination with a pharmaceutically acceptable carrier or diluent. Carriers or diluents useful in the pharmaceutical composition may include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol and combinations thereof.

The pharmaceutical composition may be administered in any effective, convenient manner including, for instance, administration by oral, intravenous (injection or infusion), intramuscular, intradermal, intracavity, intracranal, sublingual, intranasal, topical routes among others.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder (e.g. as a compressed pellet) or liquid form. A tablet may comprise a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally
comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included.

For intravenous injection, the active agent may be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has a suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants, solubilising agents and/or other additives may be included, as required.

It is also envisaged that the composition may be in the form of a subcutaneous implant or transdermal formulation. For making implants, the active agent may suitably be formulated together with one or more polymers that are gradually eroded or degraded when in use, e.g. silicone polymers, ethylene vinylacetate, polyethylene or polypropylene.

Where transdermal formulations are concerned, they may be prepared in the form of matrices or membranes or as fluid or viscous formulations in oil or hydrogels. For transdermal patches, an adhesive which is compatible with the skin may be included, such as polyacrylate, a silicone adhesive or polyisobutylene.

For the preparation of transdermal solutions or gels, water or organic solvents or mixtures thereof may be used. Transdermal gels may furthermore contain one or more suitable gelling agents or thickeners such as silicone, starch or starch derivatives, cellulose or cellulose derivatives or polyacrylic acids or derivatives thereof. Transdermal formulations may also suitably contain one or more substances that enhance absorption though the skin, such as bile salts or derivatives thereof and/or phospholipids.
The active agent may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol.

The active ingredient may be inhaled using metered-dose inhalers or dry powder inhalers or nebulisers when the active ingredient may be dissolved in suitable solvent. If the active ingredient presents in the gas form, suitable pressurized canisters can be used for precise inhaled delivery (such as system described in WO0001434).

A therapeutically effective amount of the active agent is typically one which is sufficient to achieve the desired effect and may vary according to the nature and severity of the addictive disorder and the potency of the active agent. In the case of treating a drug addiction disorder, the desired response is withdrawal from the addictive drug and/or removal of the need or desire/craving for the addictive drug. It will be appreciated that different concentrations may be employed for prophylaxis than for treatment of a disorder.

The active agent used in the foregoing use or method of treatment preferably is sterile and contain an effective amount of active agent for producing the desired response in a unit of weight or volume suitable for administration to a patient.

The doses of active agent administered to a subject can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localised delivery route) may be employed to the extent that patient tolerance permits.
For administration, it is expected that the daily dosage level of the active agent may be from 0.5 to 50 mg, such as 5, 10, 15 or 30 mg over a 24 hour period. Ultimately, however, the amount of active agent administered will be at the discretion of a physician.

The pharmaceutical composition may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated. Other treatments may include drug reduction or replacement therapies such as nicotine reduction therapy (e.g. a nicotine transdermal patch), nicotine replacement therapy or methadone.

The invention further provides a kit of parts comprising the active agent, formulated as a pharmaceutical composition, for administration in combination with one or more other active agents described herein or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated. Other treatments may include drug reduction or replacement therapies such as nicotine reduction therapy (e.g. a nicotine transdermal patch), nicotine replacement therapy or methadone. The kit may be useful in the treatment of drug addiction disorders hereindescribed.

In a preferred embodiment, the kit of parts comprises a nitric oxide donor compound, formulated as a pharmaceutical composition, in combination with an active agent described herein.

The invention present invention encompasses a method of treating a drug addiction disorder in a human patient, the method comprising administering to the patient a medicament to increase the systemic concentration of nitric oxide in the patient. The medicament may comprise a substrate for the enzyme, nitric oxide synthase, or other means for increasing the production or activity of nitric oxide synthase in the patient for example, antioxidants (such as tocopherol or vitamin c) may be included to enhance NO bioactivity by scavenging toxic radicals and/or reduced thiols (such as
cysteine, glutathione) may be incorporated to protect NO bioactivity. Alternatively, the medicament may comprise means for reducing the effect of substances (e.g. superoxide radicals) that inhibit nitric oxide synthase activity, such as by removal of such substances from the systemic system.

According to a further aspect of the invention there is provided a screening method for the identification of dopamine receptor agonists/antagonists which have a therapeutic effect in treating drug addiction disorders, comprising the steps of:

i) forming a preparation comprising a dopamine receptor and an agonist/antagonist to be tested; and

ii) testing the binding of said agonist/antagonist for said receptor.

In a preferred method of the invention said agonist/antagonist is a nitric oxide donor compound as hereindescribed.

In a preferred method of the invention said agonist/antagonist is an antibody, or a binding fragment thereof, as hereindescribed.

In an alternative preferred method of the invention said agonist/antagonist is a peptide, or modified peptide as hereindescribed.

In a further alternative method of the invention said agonist/antagonist is an aptamer as hereindescribed.

Preferred features of each aspect of the invention are as for each of the other aspects mutatis mutandis.

The present invention will now be described by way of example only.
EXAMPLE

A randomised, double-blind, double dummy, four-way parallel-design trial investigated the efficacy of treatment with transdermal glyceryl trinitrate (Minitran, Bayer) to aid smoking-cessation. In a subset of patients, a study of brain activity in response to stimuli designed to provoke areas associated with dopamine reward circuits, e.g. mesolimbic regions, is carried out using Blood Oxygen-level Dependent functional magnetic resonance imaging (fMRI).

The patients are subjects who smoke at least 10 cigarettes per day. The patients attend a 6-week smoking cessation course. The patients will be treated for 12 weeks. The primary outcome is difference in quit rates. A subset of patients (n=6) will undergo functional Magnetic Resonance Imaging to detect brain activation after exposure to smoking-related images.
CLAIMS

1. The use of a nitric oxide donor compound in the manufacture of a medicament for treating a drug addiction disorder.

2. Use as claimed in claim 1 wherein the drug is selected from the group consisting of opioids, cannabinoids, barbiturates, benzodiazepines, amphetamines, hallucinogens, sedatives, hypnotics, inhalants and anxiolytics including ketamine, PCP (phencyclidine), dextromethorphan, LSD, Ecstasy, caffeine, alcohol, nicotine, tobacco, cocaine, cannabis.

3. Use as claimed in claim 2 wherein the drug is nicotine.

4. Use as claimed in any of claims 1 to 3 wherein the nitric oxide (NO) donor is selected from the group consisting of O-nitroso, S-nitroso, C-nitroso and N-nitroso compounds and nitro derivatives thereof and metal NO complexes.

5. Use as claimed in claim 4 wherein the O-nitroso compound is an organic nitrate or nitrite.

6. Use as claimed in claim 4 wherein the S-nitroso compound is a thionitrate or thionitrite.

7. Use as claimed in claim 4 wherein the N-nitroso compound is a N-nitrosamine, N-hydroxy-N-nitrosamine, N-nitrosamine, N-nitrosoguanidine, N-nitrosohydrazine, nitramine or N-nitrosoimine.

8. Use as claimed in any of claims 1 to 3 wherein the NO donor is an inorganic NO donor.
9. Use as claimed in claim 8 wherein the NO donor is a nitrite, nitrosonium salt nitrosyl halide, peroxynitrite (HOONO) or sodium azide.

10. Use as claimed in claim 4 wherein the NO donor is a metal nitrosyl.

11. Use as claimed in claim 10 wherein the NO donor is a nitroprusside, dinitrosyl-iron (II) complex, iron nitrosyl compound, nitrosyl complex of iron-sulphur cluster or of other transition metals.

12. Use as claimed in any of claims 1 to 3 wherein the NO donor is a heterocyclic NO donor.

13. Use as claimed in claim 12 wherein the NO donor is a sydnonimine, oxadiazole (furoxan), oxatriazole or diazetidine-di-N-oxide.

14. Use as claimed in any of claims 1 to 3 wherein the NO donor is a nitroxyl-generating compound.

15. Use as claimed in claim 14 wherein the NO donor is Angeli’s salt, Piloy’s acid or cyanamide.

16. Use as claimed in any of claims 1 to 3 wherein the NO donor is an oxime (FK-409 analog), hydroxylamine, N-hydroguanidine, diazeniumdiolate (NONOate) sodium trioxodinitrate (Na$_2$N$_2$O$_3$), benzenesulfohydroxamic acid, sodium nitroprusside or nitrosoester compound.

17. Use as claimed in claim 5 wherein the organic nitrate is ethylene glycol dinitrate; isopropyl nitrate; glyceryl-1-monomonitrate; glyceryl-1,2-dinitrate; glyceryl-1,3-dinitrate; nitroglycerin (GTN); butane-1,2,4-trioltrinitrate ; erythrityl tetranitrate (ETN); pentaerythrityl tetranitrate (PETN); isosorbide mononitrate (ISMN).

18. Use as claimed in claim 17 wherein the organic nitrate is nitroglycerin.

20. A method as claimed in claim 19 wherein the nitric oxide donor compound is administered by oral, intravenous (injection or infusion), intramuscular, intradermal, intracavity, intracranal, sublingual, intranasal or topical means.

21. A screening method for the identification of a nitric oxide donor compound that has a therapeutic effect in treating a drug addiction disorder, comprising the steps of

   iii) forming a preparation comprising a dopamine receptor and a nitric oxide donor compound to be tested; and

   iv) testing the binding of said compound for said receptor.