A method of treating substance addiction

The present invention relates generally to methods of therapy and the combinations and compositions suitable therefor. In particular, the invention relates to methods for the treatment of substance abuse, including alcohol and opiate addiction.

Substance addiction involves an overwhelming and uncontrollable physical or psychological craving for a particular substance such as alcohol, heroin, morphine, methadone, nicotine, amphetamines, cocaine or marijuana and can impose significant social and financial costs to both the addict and the community. In many cases, withdrawal from the substance without adjunctive treatment, either pharmacological or psychotherapeutic, can cause acute physical and mental illness. Attempts to treat substance addiction by methods such as psychotherapy, behaviour modification or certain other drugs has had only limited success, with many addicts relapsing to chronic use.

It is well known that the powerful and long-acting competitive and specific CNS μ, δ, κ-opioid receptor antagonist naltrexone is used for rapid opiate detoxification, but the method is not without hazard. Since the chronic addicting action of ethanol also appears to be mediated substantially, either directly at CNS opioid receptors or indirectly by liberation of endogenous opiates, long-term daily naltrexone treatment has also been used successfully to prevent craving and relapse in both detoxified opiate and ethanol addicts. However when given alone, naltrexone does not provide an effective long-term cure for these conditions, relapse to chronic opiate or ethanol craving and dependence frequently recurring within 3-12 months.

It has now been found that a combined treatment using a μ-opioid receptor antagonist (μORA) and a calcium channel blocker (CCB) which is either long acting or formulated in a sustained release form may be effective in the treatment of substance abuse and may provide a longer term remission or cure of, or reduction in, craving for, or relapse to chronic dependence on substances such as opiates, ethanol (alcohol) and other addicting drugs.

Accordingly in a first aspect, the present invention provides a method of treating substance addiction in a subject, which method comprises administering to said subject a combination of:

(i) a μ-opioid receptor antagonist; and

(ii) a calcium channel blocker which is long-acting or in sustained release form, said calcium channel blocker selected from the group consisting of verapamil, nifedipine, amlodipine and felodipine.

Without intending to limit the invention by theory, it is believed that the advantage of the combination of a μORA, such as naltrexone, with a CCB selected from verapamil, nifedipine, amlodipine or felodipine is as follows:

The mesolimbic system appears to be the reward area of the brain that is primarily involved in the addictive potential of each of the following types of major drugs of dependence that are commonly abused by humans. For example:

1. the opiates such as heroin, codeine and morphine and derivatives such as pethidine and methadone. Methadone, because of its very long half-life, is also frequently prescribed legally as a helpful controlled alternative to decrease or prevent the use of an illicit opiate such as heroin.
2. the sedative-hypnotics ethanol, the barbiturates pentobarbitone and quinalbarbitone, and the benzodiazepines temazepam, diazepam and flunitrazepam.
3. the psychostimulants amphetamine and cocaine, and
4. the chemically distinct drugs nicotine, marijuana and phenyclidene.

Each of these drugs appears to produce its addictive rewarding euphoria in humans by promoting the release of the excitatory CNS neurotransmitter dopamine (DA) from the midbrain ventral tegmental area (VTA) for action in the mesolimbic nucleus accumbens (NAC). The mesolimbic excitatory dopaminergic neurotransmitter system originates in VTA which projects its efferent dopamine-secreting nerve terminals to the functionally-related NAC.

It is considered that the addicting action of the above-listed drugs of abuse stems primarily from the following events that occur in the VTA and NAC.

Using morphine as an example, these events involve the functionally-integrated actions of four primary CNS neurotransmitter systems (presynaptic inhibitory $GABA_A$ergic, presynaptice inhibitory opoidergic, calcium-dependent excitatory dopaminergic and calcium-dependent glutamatergic), each resident in the VTA, as follows:

(i) under normal conditions, the opioidergic and dopaminergic systems show only physiological activity, the former under the control of the endogenous opioid neurotransmitter β-endorphin acting on μ opioid receptors, and the latter under the tonic inhibitory control of the system. Injection of the $GABA_A$ergic antagonista picrotoxin and bicucculine into the VTA increases the activity of the dopaminergic neurones.

(ii) VTA dopaminergic neurones do not contain opioid receptors and do not respond directly to opiates.

(iii) morphine activates the inhibitory opioidergic system which suppresses the action of (disinhibits) the tonic inhibitory $GABA_A$ergic control. The resulting morphine-evoked $GABA_A$ergic disinhibition leads to activation of the excitatory dopaminergic system which results in increased release and action of DA in the NAC, manifesting in humans as a feeling of rewarding euphoria. Such increased DA release and action are blocked by perfusion of the opioid receptor antagonist naloxone into the VTA/NAC indicating the primary importance of the opioidergic system.

(iv) The other aforementioned major addicting drugs appear to produce their rewarding effects in a similar manner by primary action on these and possibly, in some cases, on associated neurotransmitter systems (eg, glutamatergic, cholinergic, serotonergic, neuropeptidergic) also relayed to the VTA from other parts of the brain.

The long acting non-specific μ, δ, κ -opioid receptor antagonist, naltrexone, on the one

hand, and the CCBs, verapamil, nifedipine, amlodipine and felodipine on the other hand, act by different mechanisms on different neurotransmitter components of this primary functionally-integrated VTA neurotransmitter system. Naltrexone powerfully blocks VTA μ opioid receptors thereby preventing morphine activation of the inhibitory opioidergic system. Thus naltrexone restores $GABA_A$ergic inhibition of DA release and action in the NAC, and thereby terminates the maintenance of morphine-evoked rewarding europhoria. In addition, naltrexone rapidly precipitates the opiate withdrawal syndrome which also leads to significant depression of DA release and action in the NAC, accompanied in humans by dysphoria and anxiety similar to the acute aversive effects produced by κ opioid ligands which also depress DA release and action in the NAC in rodents. Since naltrexone is also a powerful blocker of related CNS δ and κ opioid receptors it will similarly block δ and κ opioid receptor-regulated events which may also contribute to the opiate, ethanol and related addicting processes.

On the other hand, verapamil, nifedipine amlodipine and felodipine appear to prevent the rewarding actions of opiates, ethanol and other addicting drugs by blocking VTA- and NAC-responsive voltage-operated presynaptic and postsynaptic L-type calcium channels. Such blockade would inhibit the morphine-evoked calcium-dependent presynaptic release of DA from the VTA and the postsynaptic rewarding action of DA released in the NAC.

Craving for drug-induced reward or reinforcement is evoked by detoxification from chronic dependence on opiates, ethanol or related addicting drugs. Craving may occur during or following such drug withdrawal and may signify, at least in part, the temporary sub-optimal release and action of DA in the NAC until their return to physiological levels.

Thus, craving may involve:

1. addicting drug withdrawal-evoked depression of DA release and action in the NAC induced by opiates, ethanol and related addicting drugs,
2. addicting drug withdrawal-induced activation of local dynorphin-regulated inhibitory κ opioid receptors in the NAC which would also decrease DA release

and action in the NAC, and produce associated dysphoria and aversion. This would also tend to promote craving.

3. the associated addicting drug involvement of glutamatergic, $GABA_A$ergic, serotonergic, dopaminergic auto-inhibitory, and opioidergic and non-opioidergic neuropeptide neurotransmitter systems considered to be functionally integrated with the controlling excitatory dopaminergic transmitter system in the VTA/NAC.

4. addicting drug-responsive calcium-dependent mechanisms in the VTA, NAC and functionally-related components of the brain's reward system such as amygdala, hippocampus and medial pre-frontal cortex. This seems likely from the results of a recent clinical in-patient pilot study involving selected CCB-evoked detoxification of chronic addicts dependent on opiates, ethanol, amphetamine, temazepan or marijuana.

It would appear that naltrexone as well as verapamil, nifedipine, amlodipine and felodipine act on the same key functionally-integrated VTA/NAC multi-neurotransmitter system concerned primarily in mediating the rewarding and adverse effects of commonly abused major addicting drugs, although naltrexone on the one hand and the CCBs verapamil, nifedipine, amlodipine and felodipine on the other do so by different mechanisms involving different components of this same system.

It is now proposed that the combinations of the invention may display beneficial additive or synergistic effects in the prophylactic management of craving and/or regression in detoxified addicts chronically dependent on opiates or ethanol, or on other addicting drugs discussed herein, each of which appears to involve similar calcium-related CNS processes.

Any compound which is capable of long term blockade of μ-opioid receptors in the brain may be useful in the present invention. Suitable μORAs include naltrexone and nalmefine It will be understood that although the μORA must be capable of binding to and blocking the μ-opioid receptors in the brain, it may also be capable of binding to and blocking the other opioid receptors such as δ- and κ-opioid receptors. A preferred μORA for use in the present invention is naltrexone which non-specifically blocks μ,δ, and κ-opioid receptors

in the CNS .

The CCB, selected from verapamil, nifedipine, amlodipine or felodipine, is long-acting (amlodipine) or administered in a dosage form which is formulated as a sustained release preparation. "Long acting" refers to amlodipine which has a half life of 30-50 hours and takes some 5-10 days to reach a plateau plasma concentration. A "sustained release" preparation is one in which the active ingredient is slowly released within the body once administered and maintains the desired drug concentration over a minimum period of time. A sustained release preparation of verapamil, nifedipine or felodipine preferably releases the active ingredient over a period of some 24 hours and maintains a plateau concentration that avoids or minimizes acute reflex cardio-acceleration manifesting as palpitations, dizziness and flushing. Such plateau concentrations may depend on the general health, age and weight of the patient and can be readily determined by those skilled in the art or the attending physician. Preferably a sustained release preparation of verapamil, nifedipine or felodipine is active over a period of at least 18 and preferably 24 hours in maintaining the desired plateau concentration for at least this period of time, thereby requiring only once daily administration to the patient.

The active ingredients may be administered as a combined dose or as discrete doses. While it may be possible for an active ingredient to be administered alone, it is preferable to present it to a subject as a pharmaceutical composition. Where the CCB is not inherently long acting, (eg verapamil, nifedipine and felodipine) it is administered in a sustained release formulation. The preparation of sustained release formulations is well know to the person skilled in the art and is described in references such as *Remington's Pharmaceutical Sciences*, Chapter 91, pages 1976-93, 18$^{th}$ Edition, MACK Publishing Company. Dosage forms may include oral, parenteral, transdermal forms or implants. It will be understood that a sustained release dosage form while releasing the active ingredient at a rate such that adverse effects are avoided or minimized, will nevertheless release the active ingredient at a rate which provides the useful clinical effects of the invention.

Oral sustained release dosage forms may include suitable coatings around particles, tablets, capsules etc or the suspension or distribution of the active agent within a polymeric matrix which slowly releases the active agent.

Parenteral sustained release dosage forms may include emulsions, solutions and suspensions.

Transdermal sustained release forms may include ointments, lotions, gels etc in which the active ingredients are suspended as slow release particles or liposomes. Alternatively, patches may be used which may comprise a microporous membrane made from suitable materials such as cellulose nitrate/acetate, propylene and polycarbonates. The patches may also contain a suitable skin adhesive and backing materials.

Implants, eg subcutaneous implants, may comprise a drug bearing polymeric device wherein the polymer is biocompatible and non-toxic. Suitable polymers may include hydrogels, silcones, polyeythylenes and biodegradable polymers.

The composition containing the active ingredient may contain any suitable carriers, diluents or excipients. These include all conventional solvents, dispersion media, fillers, solid carriers, coatings, antifungal and antibacterial agents, surfactants, isotonic and absorption agents and the like. It will be understood that the compositions of the invention may also include other physiologically active agents where appropriate.

The carrier, diluent or excipient must be pharmaceutically "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurous to the subject. Preferably the compositions are suitable for oral administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely

divided solid carriers or both, and then if necessary shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as, capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus or paste.

A tablet may be made by compression or moulding optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (eg, inert diluent, preservative disintegrant (eg, sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Where appropriate, the active ingredients may be administered as a salt or pro-drug thereof.

The term "salt", or "pro-drug" includes any pharmaceutically acceptable salt, ester, solvate, hydrate or any other compound which, upon administration to the recipient is capable of providing (directly or indirectly) the μORA or CCB. The term "pro-drug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to the active ingredients used in the invention. Such derivatives would readily occur to those skilled in the art.

Suitable pharmaceutically acceptable salts include, but are not limited to salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, hydroxymaleic, fumaric, maleic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluensulphonic, benezenesulphonic, salicyclic sulphanilic, aspartic, glutamic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic, and valeric acids.

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylmmonium.

Basic nitrogen-containing groups may be quarternised with such agents as lower alkyl halide, such as methyl, ethyl, propyl and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

In a preferred form of the invention the combination of μORA and CCB is administered to the subject for some 12 to 24 weeks. In a further preferred form, following the administration of the combination for about 12 to 24 weeks, should the beneficial effects of naltrexone no longer be maintained, the treatment may be followed by administration of the CCB alone for as long as it is safe and beneficial activity persists. This can be determined by the attending physician.

The subject, depending on the nature of the addiction, may be a suitably detoxified subject, preferably detoxified for at least 5-7 days. The long term alcohol or opiate dependent subject is generally symptomatically detoxified prior to receiving the new combination treatments of the invention. Processes of detoxification are well known by the skilled person.

Opiate dependent subjects treated by the combinations of the present invention are detoxified. Detoxification methods are known in the art. For opiate addicts, detoxification

may involve an acute dose of naltrexone and subsequent symptomatic treatment. About 6-7 days after detoxification, the extent of withdrawal may be determined by the Narcan test, wherein naloxone is administered. Symptoms of morphine intoxication are then observed for.

Alcoholics may optionally be detoxified. Again, detoxification methods are known within the art. For alcohol addicts, acamprosate may be administered and the subject then treated symptomatically for 5-6 days. If the prior symptoms of alcoholism (eg impaired cognition and motor skills) are no longer present, or only minimally present, the subject is considered to be detoxified.

It will be recognised that the μORA and CCB can be administered simultaneously, or sequentially, either one immediately after the other or separated by a suitable interval. Where the μORA and CCB are administered simultaneously, they can be administered either as discrete dosage forms or as a combined form, ie, a composition containing both the μORA and CCB.

Thus, in a further aspect, the invention also provides compositions containing a μORA and a CCB which is long lasting or in a sustained release form, said CCB selected from the group consisting of verapamil, nifedipine, amlodipine and felodipine.

In another aspect, the invention provides a kit comprising a μORA and a CCB which is long acting or in sustained release from, said CCB selected from verapamil, nifedipine, amlodipine and felodipine, wherein said kit is in compartmentalized form adapted for the simultaneous or sequential administration of the μORA and the CCB.

In still another aspect, the invention provides for the use of a μORA in the preparation of a medicament for the treatment of substance addiction, wherein said medicament is adapted for administration to a subject in combination with a CCB, which is long acting or in sustained release form, said CCB selected from the group of verapamil, nifedipine, amlodipine and felodipine.

The invention also provides for the use of a CCB selected from the group consisting of verapamil, nifedipine, amlodipine and felodipine in the preparation of a medicament for the treatment of substance abuse, which is long-acting or in sustained release form, wherein said medicament is adapted for administration in combination with a μORA.

The invention further provides for the use of a μORA and a CCB selected from verapamil, nifedipine, amlodipine and felodipine, in the preparation of a medicament for the treatment of substance addiction, wherein the CCB is long acting or formulated in the medicament such that it is in sustained release form.

The μORA and CCB are administered in a treatment-effective amount. A treatment effective amount is the amount of each active ingredient which when administered according to the desired dosing regimen provides the desired therapeutic effect such as remission, cure or reduction in craving for (eg at least 30%, more preferably at least 50% even more preferably at least 70%, 80% or 90%), or prevention or delay in relapse to chronic dependence on the substance of addiction. The active ingredients may be administered in additive or synergistically effective amounts, Preferably the active ingredients are administered in combination, each in an amount which is less than the amount of an ingredient which gives a therapeutic effect when administered alone, ie the active ingredients are administered in synergistically effective amounts. In a preferred form each of the active ingredients is administered at about half conventionally recommended therapeutic dosage rates. Thus, approximately half therapeutic doses of each component of the combination Dosage forms may be formulated such that they contain the required amount or alternatively, may contain a larger amount but the dosage form eg a tablet, is formed such that it can easily be divided without affecting the sustained release mechanism, eg scoring of a tablet.

Suitable dosage amounts and regimens can be determined by the attending physician and may depend on the particular substance addiction being treated, as well as the general health, age and weight of the subject.

For example, the ratio of naltrexone to verapamil or nifedipine can vary over a range, such as, 1 part by weight of naltrexone to 1 to 20 parts by weight, and preferably 3 to 5 parts by weight of verapamil; and 1 part by weight of naltrexone to 0.1 to 10 parts by weight (eg 1 to 10 parts), and preferably 0.5 to 4 parts by weight, of nifedipine. In a preferred embodiment, the composition or combination in dosage form comprises 12.5 to 100 mg (eg 25 or 50 mg) of naltrexone to 120 to 480 mg of sustained release verapamil or 30 to 120 mg (eg 60 mg) of sustained release nifedipine. Thus for example, the treatment may be based on a once daily dose of 50 mg naltrexone and a once daily dose of 120, 180 or 240 mg of sustained release verapamil or 30 or 60 mg of sustained release nifedipine.

It is preferred to administer orally adapted long-acting or sustained-release preparations on a once daily basis, and most preferably once daily to ensure patient compliance. Examples of combinations are: naltrexone as a conventional 50 mg tablet; verapamil as a 180 or 240 mg sustained release tablet; nifedipine as a 30 or 60 mg sustained release tablet.

In another example the ratio of naltrexone to amlodipine or felodipine can vary such as, 1 part of naltrexone by weight to 0.1 to 20 parts by weight (eg 0.1-10 or 1-10), and preferably 3 to 5 parts by weight of amlodipine; and 1 part by weight of naltrexone to 0.1 to 20 parts by weight (eg 0.1-10), and preferably 0.5 to 4 parts by weight of felodipine. In a preferred embodiment, the composition or combination in dosage form comprises 12.5 to 100 mg eg 25 or 50 mg of naltrexone to 2.5 to 10 mg eg 2.5, 5 or 10 mg of long-acting amlodipine or 2.5 to 20 mg eg 2.5, 5, 10 or 20 mg of sustained release felodipine. Thus for example, the treatment may be based on a once daily dose of 50 mg naltrexone and a once daily dose of 2.5 mg or 5 mg of long-acting amlodipine or 2.5- 5 mg or 10 mg of sustained release felodipine or 120 or 180 mg of sustained release verapamil.

It is preferred to administer oral long-acting or sustained-release preparations on a once daily basis to ensure patient compliance Examples of combinations are: naltrexone as a conventional 50 mg tablet; amlodipine as a half a 5 mg (2.5 mg), or as a 5 or 10 mg long-acting tablet; felodipine as a 2.5 mg or 5 mg or 10 mg sustained release tablet.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise" and variations such as "comprises" and "comprising" will be understood to imply the inclusion of a stated integer or step or group of integers but not the exclusion of any other integer or step or group of integers.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications which fall within the spirit and scope. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

The invention will now be described with reference to the following Examples which are intended for the purpose of illustration only and should not be construed as limiting the scope of the generality hereinbefore described.

## EXAMPLES

### Example 1

Particularly suitable examples of combinations and compositions in accordance with the present invention may include:

a) 12.5 mg naltrexone together with 120, 180, 240, 360 or 480 mg of sustained release verapamil as a daily dose.

b) 25 mg naltrexone together with 120, 180, 240, 360 or 480 mg of sustained release verapamil as a daily dose.

c) 50 mg naltrexone together with 120, 180, 240, 360 or 480 mg of sustained release verapamil as a daily dose.

d) 100 mg natrexone together with 120, 180, 240, 360 or 480 mg of sustained release verapamil as a daily or, for naltrexone, second daily dose.

e) 12.5 mg naltrexone together with 30, 60, 90 or 120 mg of sustained release nifedipine as a daily dose.

f) 25 mg naltrexone together with 30, 60, 90 or 120 mg of sustained release nifedipine as a daily dose.

g) 50 mg naltrexone together with 30, 60, 90 or 120 mg of sustained release nifedipine as a daily dose.

h) 100 mg naltrexone together with 30, 60, 90 or 120 mg of sustained release nifedipine as a daily or, for naltrexone, second daily dose.

i) 12.5 mg naltrexone together with 2.5 mg, 5 mg or 10 mg of long-acting amlodipine as a daily dose.

j) 25 mg naltrexone together with 2.5 mg, 5 mg or 10 mg of long-acting amlodipine as a daily dose.

k) 50 mg naltrexone together with 2.5 mg, 5 mg or 10 mg of long-acting amlodipine as a daily dose.

l) 100 mg naltrexone together with 2.5 mg, 5 mg or 10 mg of long-acting amlodipine as a daily or, for naltrexone, second daily dose.

m) 12.5 mg naltrexone together with 2.5 mg, 5 mg, 10 mg or 20 mg of sustained release felodipine as a daily dose.

n) 25 mg naltrexone together with 2.5 mg, 5 mg, 10 mg or 20 mg of sustained release felodipine as a daily dose.

o) 50 mg naltrexone together with 2.5 mg, 5 mg, 10 mg or 20 mg of sustained release felodipine as a daily dose.

p) 100 mg naltrexone together with 2.5 mg, 5 mg, 10 mg or 20 mg of sustained release felodipine as a daily or, for naltrexone, second daily dose.

**Example 2**

**Double blind placebo-controlled trial involving 3 patients**

Three detoxified opiate-dependent patients (aged 18, 19 and 32 years) were treated for two weeks under double-blind placebo controlled conditions. Each opiate-dependent patent

received a once daily oral dose of naltrexone (25 mg) and one of the CCBs. All trial subjects were detoxified, and treatment commenced at least one week following detoxification.

Some patients exhibited only initial mild typical transient CCB-evoked symptoms (e.g., palpitations, flushing) which did not necessitate symptomatic treatment nor termination of the specific trial treatments. In addition, most patients reported a self-rated decrease (on a 0-10 scale) of 30-50% in their frequency and intensity of craving for their drug of abuse, over the two week trial period. Further, one patient, an 18 year old opiate addict, reported almost complete loss of craving over this period.

The opiate addicts self-rated (on a 0-10 scale), in four following questions, their frequency and intensity of craving, relapse potential and consumption or abstinence from their specific drug of abuse. They also provided answers concerning any treatment-evoked or other side-effects they had experienced and the progress of these events.

**Example 3**

**Open therapeutic clinical trial in seven naltrexone rapid detoxified long-term opiate-dependent subjects**

A contemporaneous open clinical trial was conducted in fully recovered naltrexone rapid detoxified chronic opiate addicts receiving subsequently 50 mg oral prophylactic naltrexone on a once daily basis.

Seven such detoxified subjects participated in this trial and received daily adjunctive oral CCB identical in type and dosage to those administered in the double-blind clinical trial discussed above. These subjects (4 male and 3 female aged 21-44 years) have been self-administering heroin (approx. 0.5-1.5gm daily) intermittently, and in three cases receiving intermittent methadone maintenance treatment, for some 2-15 years; most had also been

taking modest doses of other common major addicting drugs such as alcohol, benzodiazepines, psychostimulants or marijuana. They underwent rapid naltrexone detoxification some 2-8 weeks before they entered this open trial to determine if the concomitant once daily oral administration of 50 mg naltrexone and long-acting amlodipine (2.5 mg), nifedipine$_{SR}$ (30 mg), felodipine$_{SR}$ (2.5 mg) or verapamil$_{SR}$ (180 mg) would improve the length and quality of their abstinence and remission from craving and relapse to predominant opiate abuse. They also self-rated these parameters (on a 0-10 scale, where 0 denotes nil and 10 maximal craving) when questioned (although less intensively) as described above. Three subjects received amlodipine, three were given nifedipine$_{SR}$ and one received verapamil$_{SR}$ in the stated doses. The results are as follows:

1. Two patients (previously detoxified for 6 or 8 weeks and receiving daily oral 50 mg naltrexone) reported moderate craving and severe nausea and abdominal cramps. They stopped their naltrexone which rapidly terminated their nausea and cramps. However their craving increased substantially, and they agreed to receive concomitantly oral daily nifedipine$_{SR}$ (30 mg) or amlodipine (2.5 mg) together with naltrexone (50 mg) on a trial basis. These daily treatment were administered for two weeks and resulted in both cases in a self-assessed 50-70% reduction in craving and complete elimination of nausea and abdominal cramps.

2. Two subjects (previously detoxified for 2 or 8 weeks and receiving daily oral 50 mg naltrexone) were treated concomitantly with once daily oral naltrexone (50 mg) and verapamil$_{SR}$ (180 mg) or amlodipine (2.5 mg). Both experienced mild transient typical CCB side-effects which required no change in treatment. These subjects have remained abstinent and have reported a self-assessed 50-70% reduction in craving following two weeks of such combined treatment which is continuing.

3. Two subject (previously detoxified for 2 or 3 weeks and receiving daily oral 50 mg naltrexone) both received once daily oral naltrexone (50 mg) together with nifedipine$_{SR}$ (30 mg) for two weeks. CCB treatment was withdrawn in the first patient after four days owing to the presence of distressing peripheral oedema in both legs. This cleared in 2-3 days without treatment. She continued with daily oral naltrexone 50 mg and still manifested her former moderate level of craving which was tempered by other agents. The second subject accomodated rapidly to the mild, typical and transient CCB side-effects, and reported a self-assessed reduction of some 30% in the intensity of his craving following the two week combination of naltrexone/nifedipine$_{SR}$ treatment which is still continuing.

4. The final patient (previously detoxified for 3 weeks and receiving daily oral 50 mg naltrexone) received combined daily oral treatment with naltrexone (50 mg) and amlodipine (2.5 mg). She reported that this treatment began to decrease her craving noticeably in some 5 days without disturbing side-effects. Following some two weeks of this combination treatment she also reported that, when she was not stressed by her husband, her craving had almost completely gone and her confidence had returned to the stage where she felt she had lost her dependence on drugs and had made plans to re-organise her life to escape the problems created by her aggressive alcoholic husband.

**Sources of drugs used in the treatments**

Naltrexone (Revia$^{R}$, Orphan Australia Pty Ltd) – this drug is manufactured for Orphan by Du Pont Pharmaceuticals Company USA).

Amlodipine (Norvasc$^{R}$, Pfizer Australia Ltd).

Nifedipine$_{SR}$ (Adalat Oros$^{R}$, Bayer Australia Ltd).

Felodipine$_{ER}$ (Plendyl$^{R}$, AstraZeneca Pty Ltd).

Varapamil$_{SR}$ (Isoptin$^{R}$, Knoll Australia Pty Ltd).




THE CLAIMS

1. A method of treating substance addiction in a subject, which method comprises administering to said subject a combination of: (i) a μ-opioid receptor antagonist; and (ii) a calcium channel blocker which is long-acting or in sustained release form, said calcium channel blocker selected from the group consisting of verapamil, nifedipine, amlodipine and felodipine.

2. A method according to claim 1 wherein the μ-opioid receptor antagonist is naltrexone.

3. A method according to claim 1 or 2 wherein the calcium channel blocker is verapamil in sustained release form.

4. A method according to claim 1 or 2 wherein the calcium channel blocker is nifedipine in sustained release form.

5. A method according to claim 1 or 2 wherein the calcium channel blocker is felodipine in sustained release form.

6. A method according to claim 1 or 2 wherein the calcium channel blocker is amlodipine .

7. A method according to claim 1 or 2 wherein the calcium channel blocker and/or μ-opioid receptor antagonist is adapted for oral adminisration.

8. A method according to claim 7 wherein naltrexone is administered in a once daily oral dose of 25 or 50 mg.

9. A method according to claim 3 wherein verapamil is administered in a once daily oral dose of 180 mg.

10. A method according to claim 4 wherein nifedipine is administered in a once daily oral dose of 30 mg.

11. A method according to claim 5 wherein felodipine is administered in a once daily oral dose of 2.5 mg.

12. A method according to claim 6 wherein amlodipine is administered in a once daily oral dose of 2.5 or 5 mg.

13. A method according to claim 1 or 2 wherein the μ-opioid receptor antagonist and calcium channel blocker are administered in the ratio of 1 part μ-opioid receptor antagonist to 1-20 parts verapamil, or 0.1-10 parts nifedipine or 1-20 parts amlodipine or 0.1-10 parts felodipine.

14. A method according to claim 1 wherein the substance of addiction is an opiate or alcohol.

15. A composition comprising a μ-opioid receptor antagonist and a calcium channel blocker, which is long lasting or in a sustained release form, said calcium channel blocker selected from the group consisting of verapamil, nifedipine, amlodipine and felodipine.

16. A kit comprising a μ-opioid receptor antagonist and a calcium channel blocker which is long lasting or in a sustained release form, said calcium channel blocker selected from verapamil, nifedipine, amlodipine and felodipine, wherein said kit is in compartmentalized form adapted for the simultaneous or sequential administration of the μ-opioid receptor antagonist and calcium channel blocker .

17. Use of a μ-opioid receptor antagonist in the manufacture of a medicament for the treatment of substance addiction, wherein said medicament is adapted for

administration in combination with a calcium channel blocker, which is long acting or in sustained release form, said calcium channel blocker selected from the group of verapamil, nifedipine, amlodipine and felodipine.

18. Use of a calcium channel blocker selected from the group consisting of verapamil, nifedipine, amlodipine and felodipine in the manufacture of a medicament which is long-acting or in sustained release form, wherein said medicament is adapted for administration in combination with a μ-opiod receptor antagonist.

19. A combination comprising a μ-opioid receptor antagonist and a calcium channel blocker which is long lasting or in a sustained release form, said calcium channel blocker selected from verapamil, nifedipine, amlodipine and felodipine.

20. An agent for treating substance addiction said agent comprising a μ-opioid receptor antagonist and a calcium channel blocker which is long lasting or in a sustained release form, said calcium channel blocker selected from verapamil, nifedipine, amlodipine and felodipine, wherein said μ-opioid receptor antagonist and said calcium channel blocker are adapted for administration in separate or combined form.

21. Use of a μ-opioid receptor antagonist and a calcium channel blocker selected from verapamil, nifedipine, amlodipine and felodipine, in the manufacture of a medicament for the treatment of substance addiction wherein the calcium channel blocker is long acting or formulated in the medicament such that it is in sustained release form.

* C L M S *