Compositions for inhibiting the development of tolerance to and/or dependence on an additive substance
Zusammensetzungen zur Hemmung der Entwicklung von Widerstandsfähigkeit und/oder Abhängigkeit von Drogen
Compositions destinées à l’inhibition du développement de la tolérance et/ou de la dépendance à une drogue

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This invention relates to a composition containing an addictive substance and a component which inhibits the development of tolerance to and/or dependence on the addictive substance. More particularly, the invention relates to a composition containing an addictive substance such as morphine or codeine and at least one nontoxic substance that blocks the N-methyl-D-aspartate (NMDA) receptor, e.g., a morphinan such as dextromethorphan or dextrophan.

Morphine is a rapid and effective drug for the treatment of severe pain but its long term administration has been limited due to its negative side effects, principally tolerance and dependence, which develop rapidly after administration. In an effort to make morphine of greater use in the treatment of pain, it has been combined with a variety of substances intended to inhibit one or more of its undesirable side effects. U.S. Patent No. 2,770,569 describes the combination of morphine with the compound levo-d-hydroxy-N-allyl-morphinan which is said to suppress or eliminate such undesirable side reactions of morphine as depression, nausea and vomiting. U.S. Patent No. 4,126,684 discloses reducing either the addiction liability of an addictive substance such as a narcotic analgesic or a barbiturate or the withdrawal symptoms caused by deprivation of such a substance in an addicted subject by administering the addictive substance, e.g., morphine, with a 4-amino-3-p-halophe-nylbutyric acid. U.S. Patent No. 4,415,871 describes the prevention of treatment tolerance and physical dependence in chronic morphine treatment by combining the morphine with any of the specific dipeptides indicated therein. U.S. Patent No. 5,041,446 discloses inhibiting the development of tolerance to morphine by combining the morphine with dapiprazole. U.S. Patent No. 5,057,519 achieves a reduction in morphine tolerance by combining the morphine with a benzamide antagonist for a subtype of the serotonin receptor, 5-HT3. Trujillo et al., "Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801", Science, 251 (4969), pp. 85-87, January 4, 1991; Tanganelli et al., "Glutamate antagonists prevent morphine withdrawal in mice and guinea pigs", Neuroscience Letters, 122(2), pp. 270-272, January 28, 1991; Marek et al., "Excitatory amino acid antagonists prevent morphine withdrawal in mice and guinea pigs", Neuroscience Letters, 45(2), pp. 77-81, April 26, 1991; and, Marek et al., "Delayed application of MK-801 attenuates development of morphine tolerance in rats", Brain Research, 547(1), pp. 77-81, April 26, 1991; and, Marek et al., "Delayed application of MK-801 attenuates development of morphine tolerance in rats", Brain Research, 558(1), pp. 163-165, August 30, 1991 discuss the role of MK-801 (the compound 5-methyl-10,11-dihydro-SH-dibenzo[a,d]cyclohepten-5,10-imine), an NMDA receptor antagonist or blocker, in reducing morphine dependence in laboratory animals. However, MK-801 has been found to be toxic and is therefore unsuitable for pharmaceutical use.

In accordance with the present invention, a pharmaceutical composition is provided which comprises an addictive substance and at least one nontoxic substance that blocks the N-methyl-D-aspartate receptor and/or at least one substance that inhibits the development of tolerance to and/or dependence on the addictive substance and selected from the group consisting of morphinans, their mixtures and their pharmaceutically acceptable salts.

The term "nontoxic" as used herein shall be understood in a relative sense and is intended to designate any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to humans or, in keeping with established criteria, is susceptible to approval by the FDA for administration to humans.

Figs. 1-2 are graphical representations of experimental data demonstrating the effectiveness of specific nontoxic substances that block the N-methyl-D-aspartate receptor or a major consequence of N-methyl-D-aspartate receptor activation for inhibiting morphine tolerance and dependence in rats.

A particularly important category of addictive substances with which the present invention is concerned are the narcotic analgesics, e.g., opiates, opiate derivatives, opioids and their pharmaceutically acceptable salts. Specific examples of narcotic analgesics include alfentanil, alphaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphanol, metazocine, methadone, metopon, morphine, oxymorphone, pethidine, phentazocine, piminozidine, racemorphor, racemorphan, thebaine and pharmaceutically acceptable salts thereof. For a detailed discussion of these and other narcotic analgesics, reference may be made to Jaffe et al., "Opioid Analgesics and Antagonists" in "Goodman and Gilman's Pharmacological Basis of Therapeutics", Goodman et al., eds. 7th ed., 1985, MacMillan and Company, New York pp. 491-531.

Other addictive substances that can be utilized herein include acetophene, acetyldihydrocodeine, acetylmethadol, allylprodine, alphacetylmethadol, alphameprodine, alphamethadol, benzethidine, benzylmorphine, betacetylmethadol, betameprodine, betame-
nerve cells: ing sequences, or cascades, of events occurring within sequences of NMDA receptor activation include the follow-
particular, their capacity for excitability or inhibition in the excitatory amino acid receptors, induces a number of thereof. Activation of the NMDA receptor, a subtype of ns, their mixtures or pharmaceutically acceptable salts and is selected from the group consisting of morphina-
cance to and/or dependence on the addictive substance is administered before, with or following the administra-
ane. However, even with activation of the NMDA receptor, it is still pos-
sual consequences of NMDA receptor activation include the follow-
ing sequences, or cascades, of events occurring within nerve cells:
a) translocation and activation of protein kinases such as protein kinase C → phosphorylation of sub-
strate proteins such as cytosolic enzymes, channel proteins, receptor proteins, etc. → changes in func-
tional activity;
b) initiation of early gene (c-fos, c-jun, zif-268, etc.) expression by either increased intracellular Ca++ or Ca++-activated protein kinases → expression of functional genes responsible for production of cell-
lar enzymes (such as protein kinases), receptor proteins (such as the NMDA receptor), ion channel proteins (such as K+, Na+, Ca++ channels), neu-
peptides (such as dynorphin), etc. → changes in functional activity;
c) Ca++/calmodulin (or other Ca++ binding pro-
tains) induced activation of enzymes and other cell-
lar components → activation of Ca++/calmodulin-
protein kinase systems such as Ca+++/calmodulin kinase II → autophosphorylation of enzymes (e.g., Ca+++/calmodulin kinase II) or other functional pro-
tains → changes in functional activity;
d) Ca++/calmodulin induced activation of constitu-
tive nitric oxide synthase as well as induction of in-
ducible nitric oxide synthase → production of nitric oxide → i) production of cyclic guanosine mono-
phosphate via activation of guanosine cyclase re-
sulting in activation of protein kinases and early gene expression; ii) direct protein modification such as enzymes, receptor and/or channel proteins; iii) lipid membrane modification and/or nucleic acid modification via scavenge of free radicals; iv) induc-
tion of neurotoxicity at higher nitric oxide levels; v) retrograde actions in adjacent neurons or glial cells such as facilitation of glutamate release/NMDA re-
ceptor activation and/or inhibition of post-synaptic NMDA receptors → changes in functional activity; e) interactions with the cyclic adenosine monophos-
phate/protein /protein kinase A system, the phospholipase C-inositol triphosphate-Ca++/diacylglyc-
erol-protein kinase system, the phospholipase A2-arachidonic acid/prostanoids/leukotrienes sys-
tem → changes in functional activity induced by second messenger systems other than NMDA re-
ceptor/Ca++/Ca++-calmodulin/protein kinase systems; and, f) interactions with other excitatory amino acid re-
ceptor subtypes including non-NMDA receptors and metabotropic receptors as well as intracellular events subsequent to the activation of these exci-
tatory amino acid receptor subtypes → changes in functional activity induced by the non-NMDA and metabotropic receptor activation.

A substance that blocks the NMDA receptor will effectively prevent all of the foregoing major intrac-
ellar sequences of events from taking place. However, such a substance interferes with translocation and activation of protein kinase C or with calmodulin induced activation of constitutive nitric oxide
synthase as well as induction of inducible nitric oxide synthase is also useful for the practice of this invention.

[0011] Among the nontoxic substances that block the NMDA receptor and as such are useful in the practice of the present invention are morphinans such as dextromethorphan (\(\pm\)-3-hydroxy-N-methylmorphinan) and dextrorphan (\(\pm\)-3-hydroxy-N-methylmorphinan), their mixtures and the pharmaceutically acceptable salts thereof. Other useful nontoxic substances that block the NMDA receptor include ketamine (2-(2-chlorophenyl)-2-(methylamino)cyclohexanone), pyrroloquinoline quinone and cis-4-(phosphonomethyl)-2-piperidinocarboxylic acid.

[0012] Administration of the composition of this invention can be in the form of a single dosage unit containing both the addictive substance and the nontoxic substance that blocks the NMDA receptor or the two substances can be administered separately provided both are ultimately present in effective amounts in the patient. Introduction of the composition into the patient can be by way of oral administration or by intravenous, intra-muscular, subcutaneous, intrathecal, epidural or intracerebroventricular injection.

[0013] The preferred dosage of addictive substance and the nontoxic substance that blocks the NMDA receptor can vary widely, e.g., from about 0.25 to about 250 mg/day, but actual amounts will vary according to the particular active substances being used, the particular formulation containing the active substances and the state and circumstances of the host being treated. As those skilled in the art recognize, many factors that modify the action of the active substances herein will be taken into account by the treating physician such as the age, body weight, sex, diet and condition of the subject, the time of administration, the rate and route of administration, and so forth. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage determination tests in view of the experimental data provided herein.

[0014] In alleviating withdrawal symptoms in addicted subjects deprived of the addictive substance, the substance that blocks the NMDA receptor can be administered to the subject, together with the addictive substance, at a dosage rate of about 0.25 to about 250 mg/day, again, specific dosage levels and routes of administration being selected in accordance with the subject's circumstances. As a result of this treatment, the subject will experience a reduced level of dependence on the addictive substance eventually reaching the point where total withdrawal of the substance will result in at most mild withdrawal symptoms.

[0015] The composition herein can be formulated as a liquid, powder, elixir, injectable solution, etc. Formulations for oral use can be provided as hard gelatin capsules wherein the composition is mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the composition is mixed with an oleaginous medium, e.g., liquid paraffin or olive oil.

[0016] Aqueous suspensions can contain the composition in admixture with pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkylene oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, e.g., heptadecaethylenoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monooleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monooleate. Such aqueous suspensions can also contain one or more preservatives, e.g., ethyl- or n-propyl-p-hydroxy benzoate, one or more flavoring agents, one or more coloring agents, and one or more sweetening agents, such as sucrose, saccharin or sodium or calcium cyclamate.

[0017] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the composition in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, e.g., sweetening, flavoring and coloring agents, can also be present. Syrups and elixirs can be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents.

[0018] The composition of this invention or either of its principal active ingredients can be provided in sustained release dosage form of which many kinds are known, e.g., as described in U.S. Patent Nos. 4,788,055; 4,816,264; 4,828,836; 4,834,965; 4,834,985; 4,996,047; 5,071,646; and, 5,133,974.

[0019] The example which follows is illustrative of the invention.

**EXAMPLE 1**

[0020] The effect of systemic dextrorphan on prevention of the development of morphine tolerance and dependence was examined in Sprague-Dawley rats weighing 350-400 gm. Morphine tolerance was developed in the rats by twice daily subcutaneous injection of 10 mg/kg morphine sulfate. The analgesic effect of the morphine was examined by using the well known tail-flick test which measures the latency of tail-flick upon radiant heat stimulation. The latency of tail-flick test is defined as the time elapsed from the onset of radiant heat to the flick of the rat's tail. In order to examine the effect of dextrorphan on the development of morphine
tolerance, each morphine-treated rat also received intraperitoneal administration of either dextrorphan (1.56, 3.13, 6.25, 12.5 mg/kg, n=5/group) or saline (n=6) given 30 minutes prior to each morphine administration.

**[0021]** Fig. 1 shows the effects of systemic doses of dextrophan (DEX) on tolerance to morphine analgesia produced by twice daily subcutaneous administration of 10 mg/kg morphine. Each symbol represents mean tail-flick latency scores (those above 4.5 seconds reflect analgesia) for each group of rats (N=5-6) and vertical bars are standard errors in this and the other figures. Baseline scores were between 4 and 5 seconds (at Day 0) and post-drug scores measured 1 hour after drug administration were close to 10 seconds for the first 5 days of daily drug administration. The control group (open triangles) show marked reduction in response to morphine (i.e., tolerance) at 7 and 9 days. In contrast, dextrophan potently prevented the development of morphine tolerance as shown by no significant decreases in tail flick latencies, i.e., remaining analgesic during the whole course of repeated morphine administration. Asterisks indicate mean scores that were significantly different from those of the control group. All tested doses of dextrophan were effective in preventing development of morphine tolerance with optimal doses ranging from 3.13 mg/kg to 12.5 mg/kg.

**[0022]** Fig. 2 shows the effects of systemic doses of dextrophan on jumping, a withdrawal symptom produced by subcutaneous naloxone (2 mg/kg) in rats previously injected with morphine (10 mg/kg) twice daily for 9 days. Asterisks indicate median number of jumps in dextrophan treatment groups (MOR + DEX) that were significantly less than that of the control group (MOR + SAL). Vertical bars refer to the range of the numbers of jumps. Thus, 3.13 and 6.25 mg/kg dextrophan (but not 1.56 mg/kg) significantly reduced the incidence of jumping in morphine tolerant rats, a behavioral manifestation of morphine dependence, brought about following subcutaneous injection with 2 mg/kg naloxone. Thus, coadministration of dextrophan with morphine greatly inhibits the development of both tolerance to and dependence on morphine while the analgesic effect of the morphine remains substantially unaffected.

**Claims**

1. A pharmaceutical composition comprising, in combination, an addictive substance selected from the group consisting of narcotic analgesics, sedatives, hypnotics, barbiturates and pharmaceutically acceptable salts thereof, and at least one non-toxic substance that blocks the N-methyl-D-aspartate receptor and/or at least one substance that inhibits the development of tolerance to and/or dependence on the addictive substance and selected from the group consisting of morphinans, their mixtures and their pharmaceutically-acceptable salts.

2. The composition of Claim 1 wherein the addictive substance is selected from the group consisting of alfentanyl, alphanorphine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydromorphone, isomethadone, levomentorphan, levophenol, metazocine, methadone, metopon, morphine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, pethidine, phenazonine, piminodine, racemethorphan, racemorph, thebaine, acetorphine, acetyldihydrocodeine, acetylmethadol, allylprodine, alphacetylaminomethadol, alphanorphine, alphamethadol, benzethidione, benzylmorphine, benzetamethadol, betamprodine, betamethadol, betaprodine, clonitazene, codeine, codeine methylbromide, codeine-N-oxide, cyproerpinorphine, desomorphine, dextromoramide, diampromide, diethylthiambutene, dihydromorphine, dimenoxadol, dimepeptanol, dimethylthiambutene, dioxyphyl butyrate, dipipanone, drotendol, ethylmethytiambutene, etonitazene, etorphine, ctexeridine, furethidine, hydromorphonil, hydroxyphethidine, ketobemidone, levomoramidone, levophencyclidine, methadone, methadonel, methylmorphine, morpheridine, morphine methylpromide, morphine methylsulfonate, morphan-N-oxide, pyrophan, nicocodeine, nicomorphine, nicotine, noracymethadol, norlevorphanol, normethadone, normorphine, norpipanone, phenadoxone, phenampromide, phenomorph, phenoperidine, piritramide, pholcodine, proheptazoline, properidine, propipan, racemoramide, thebagon, trimeperidine, chloralhydrate, clorazepate, diazepam, flurazepam, halazepam, ketazolam, borazepam, oxazepam, prazepam, temazepam, triazolam amobarbital, ambobarbital, barbital, butabartital, mephobarbital, methohexital, pentobarbital, phe nobarbitol, secobarbital, talbutal, thiamylal, thiopen tal chloralhydrate, meprobamate, methaqualone, me tylpyrrol and pharmaceutically acceptable salts thereof.

3. The composition of claims 1 or 2, wherein the morphinan is dextromethorphan, dextrophan or mixtures or pharmaceutically acceptable salts thereof.

4. A pharmaceutical composition according to claim 1 comprising, in combination, a narcotic analgesic and an NMDA receptor antagonist selected from dextromethorphan, dextrophan, mixtures thereof and/or pharmaceutically acceptable salts thereof.

5. The composition of Claim 4 wherein the narcotic analgesic is selected from the group consisting of alfentanyl, alphanorphine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydromor-
The use according to Claim 5 wherein the addictive substance is selected from the group consisting of narcotics, their mixtures and their pharmaceutically acceptable salts thereof.

6. The use of at least one non-toxic substance that blocks the N-methyl-D-aspartate receptor in the production of a composition effective in inhibiting the development of tolerance to and/or dependence on an addictive substance in mammals, and comprising the step of combining both said addictive substance and non-toxic substance prior to administration, wherein the non-toxic substance is selected from the group consisting of morphinans, their mixtures and their pharmaceutically acceptable salts, and wherein the addictive substance is selected from the group consisting of narcotic analgesics, sedatives, hypnotics, barbiturates and pharmaceutically acceptable salts thereof.

7. The use according to Claim 5 wherein the addictive substance is selected from the group consisting of alfentanil, alfaphrodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levoamphetamine, metazocine, methadone, metopon, morfine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphine, thebeaine, acetorphine, acetyldihydrocodeine, acetylmethadone, allylprodine, alphacracyethylmorphine, alphanorphine, alphanmethadon, benzethidine, benzylmorphine, betacetylmethadol, betamethadone, codeine, dihydrocodeine, diphenoxylate, ethylmorphone, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levoamphetamine, metazocine, methadone, metopon, morphine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphine, thebeaine and pharmaceutically acceptable salts thereof.

8. The use according to claims 6 or 7 wherein the morfine is dextromethorphan, dextrimorphan or pharmaceutically acceptable salts thereof.

9. The use according to claim 6 wherein the non-toxic substance that blocks the NMDA receptor is dextromethorphan, dextrorphan, mixtures thereof and/or pharmaceutically acceptable salts thereof and the addictive substance is a narcotic analgesic.

10. The use according to Claim 9 wherein the narcotic analgesic is selected from the group consisting of alfentanil, alphiaprodine, anileridine, bezitramide, codeine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levoamphetamine, metazocine, methadone, metopon, morfine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, pethidine, phenazocine, piminodine, racemethorphan, racemorphine, thebeaine and pharmaceutically acceptable salts thereof.

Patentansprüche


2. Zusammensetzung gemäß Anspruch 1, wobei die süchtigmachende Substanz ausgewählt ist aus der Gruppe Alfentantil, Alphaphrodine, Anileridine, Bezitramide, Codein, Dihydrocodein, Diphenoxylate, Ethylmorphine, Fentanyl, Heroin, Hydrocodon, Hydromorphon, Isomethadon, Levomethorphan, Levopha-
8. Verwendung gemäß Anspruch 6 oder 7, wobei das Morphinan Dextromethorphan, Dextrophan oder pharmazeutisch annehmbare Salze davon ist.

9. Verwendung gemäß Anspruch 6, wobei die nicht-toxische Substanz, die den NMDA-Rezeptor blockiert, Dextromethorphan, Dextrophan, Mischungen davon und/oder pharmazeutisch annehmbare Salze davon ist, und die süchtigmachende Substanz ein narkotisches, schmerzlinderndes Mittel ist.


Revendications

1. Composition pharmaceutique comprenant, en association, une substance pouvant créer une dépendance choisie dans le groupe consistant en les antalgiques narcotiques, les sédatifs, les hypnotiques, les barbituriques et les sels pharmaceutiquement acceptables correspondants, et au moins une substance non toxique qui bloque le récepteur de N-méthyl-D-aspartate et/ou au moins une substance qui empêche le développement de tolérance et/ou de dépendance vis-à-vis d'une substance pouvant créer une dépendance et choisie dans le groupe consistant en les morphinanes, leurs mélanges et leurs sels pharmaceutiquement acceptables.

2. Composition selon la revendication 1, dans laquelle la substance pouvant créer une dépendance est choisie dans le groupe consistant en l'alfentanyle, l'alphaprodine, l'anileridine, le bétazitramide, la codéine, la dihydrocodéine, le dipéphénylalyle, l'éthylmorphine, le fentanyl, l'héroline, l'hydroycodone, l'hydromorphine, l'isométhadone, le levométhorphane, le levorphanol, la métazocine, la méthadone, la méthapone, la morphine, les extraits d'opium, les extraits fluides d'opium, l'opium en poudre, l'opium en granulés, l'opium brut, la teinture d'opium, l'oxydodone, l'oxymorphine, la pédithidine, la phénazocine, les pimédione, le racémétophane, le racémorphane, la thébaïne, l'acétorphine, l'acétylhydrocodéine, l'acétylméthadon, l'allyproméphine, l'alphacétylméthadon, l'alphamétophine, l'alphamétophine, la benzéthidine, la benzylmorphine, le bétacétylméthadon, la bétabéthadon, le bétaproméphine, le bétaphénéphrine, le clonitazénone, la cocaine, le méthylbromure de codéine, le codéine-N-oxyde, la cyprénorphine, la desomorphine, le dextromoramide, le dixyhydromorphine, le diméthylthiamethbétanne, la dihydromorphine, le diméthopéptanol, le diméthylthiamuthbétanne, le butyrate de dioxyphényle, la dipipanone, le drotébanol, l'ethylméthyliambetane, l'éthylmorphine, la desomorphine, la fu-réthidine, l’hydroxymorphinol, l’hydroxyxypéthidine, le ketobémidone, le lévométhadone, le lévoxyphénacynorphane, la méthyldesmorphine, la méthylid hydromorphine, la morphérédione, le méthylbromure de morphine, le méthylsulfonate de morphine, la morphine-N-oxyde, la myrophine, la nicocodéine, la niconormorphine, la nicotine, le noracétylméthadon, le norlevorphanol, la normorphine, la normorphine, la norpipanone, la phénadoxone, le phénanpromide, le phénopromorphane, la phénopéridine, le piriramida, la pirodoline, la proheptazoline, la propéridine, la propipane, le racémoramide, la thébacone, la trimépéridine, le chloridiazépoxide, le clorazépate, le diazépam, le flurazépam, l'halazépam, le ketozala lam, le borazépam, l'oxazépam, le prazépam, le té-mazépam, le triazolam amobarbital, l'ambobarbital, le barbital, le butabarbital, le méphobarbital, le méthoxépide, le pentobarbital, le phénobarbital, le se cobarbital, le talbutal, le thiamyl, le thiopental hydrate, le mépronamate, la méthaqualone, la méthylprodine et leurs sels pharmaceutiquement acceptables.

3. Composition selon la revendication 1 ou la revendication 2, dans laquelle le morphinane est le dextrométhorphan, le dextrophan ou leurs mélanges ou les sels pharmaceutiquement acceptables correspondants.

4. Composition pharmaceutique selon la revendication 1, comprenant, en association, un antalgique narcotique et un antagoniste du récepteur NMDA choisi parmi le dextrométhorphan, le dextrophan ou leurs mélanges et/ou les sels pharmaceutiquement acceptables correspondants.

5. Composition selon la revendication 4, dans laquelle l'antalgique narcotique est choisi dans le groupe consistant en l'alfentanyle, l'alphaprodine, l'anileridine, le bétazitramide, la codéine, la dihydrocodéine, le dipéphénylalyle, l'éthylmorphine, le fentanyl, l'héroline, l'hydroycodone, l'hydromorphine, l'isométhadone, le levométhorphane, le levorphanol, le
métazocine, la méthadone, la métopone, la morphine, les extraits d’opium, les extraits liquides d’opium, l’opium en poudre, l’opium en granulés, l’opium brut, la teinture d’opium, l’oxydodéine, l’oxymorphine, la pétidine, la phénazocine, la pimédone, le racémorphéphane, le racémorphane, la thébaïne et leurs sels pharmaceutiquement acceptables.

6. Utilisation d’au moins une substance non toxique qui bloque le récepteur de N-méthyl-D-aspartate dans la production d’une composition capable de supprimer efficacement le développement de tolérance et/ou la dépendance vis-à-vis d’une substance pouvant créer une dépendance et substance non toxique avant administration, dans laquelle la substance non toxique est choisie dans le groupe constitué de morphinanes, leurs mélanges et leurs sels pharmaceutiquement acceptables, et dans laquelle la substance pouvant créer une dépendance est choisie dans le groupe constitué d’antalgiques narcotiques, de sédatifs, d’hypnotiques, de barbituriques et des sels pharmaceutiquement acceptables correspondants.

7. Utilisation selon la revendication 5, dans laquelle la substance pouvant créer une dépendance est choisie dans le groupe constitué en l’alfentanyle, l’alphaprodine, l’aniléridine, le bézitramide, la codéine, la dihydorcodéine, le diphénoxylate, l’éthylmorphine, le fentanyl, l’héroïne, l’hydroxycodéone, l’hydroxyxymorphéphane, l’isométhadone, le levoéthorphane, le levorphanol, la métazocine, la méthadone, la morphine, les extraits d’opium, les extraits liquides d’opium, l’opium en poudre, l’opium en granulés, l’opium brut, la teinture d’opium, l’oxydodéine, l’oxymorphéphane, la pétidine, la phénazocine, la pimédone, le racéméthorphane, le racémorphane, la thébaïne et leurs sels pharmaceutiquement acceptables.

8. Utilisation selon la revendication 6 ou la revendication 7, dans laquelle le morphinane est le dextrométhorphane, le dextrorphan ou des sels pharmaceutiquement acceptables correspondants.

9. Utilisation selon la revendication 6, dans laquelle la substance non toxique qui bloque le récepteur de NMDA est le dextrométhorphane, le dextrorphan, leurs mélanges et/ou les sels pharmaceutiquement acceptables correspondants et la substance pouvant créer une dépendance est un antalgique narcotique.

10. Utilisation selon la revendication 9, dans laquelle l’antalgique narcotique est choisi dans le groupe consistant en l’alfentanyle, l’alphaprodine, l’aniléridine, le bézitramide, la codéine, la dihydorcodéine, le diphénoxylate, l’éthylmorphine, le fentanyl, l’héroïne, l’hydroxycodéone, l’hydroxyxymorphéphane, l’isométhadone, le levorphanol, la morphéphane, la méthadone, la méthadone, la morphine, les extraits d’opium, les extraits liquides d’opium, l’opium en poudre, l’opium en granulés, l’opium brut, la teinture d’opium, l’oxydodéine, l’oxymorphéphane, la pétidine, la phénazocine, la pimédone, le racéméthorphane, le racémorphane, la thébaïne, et les sels pharmaceutiquement acceptables correspondants.