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(54) **TOPICAL COMPOSITIONS AND METHODS FOR TREATING PAIN**

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(57) **ABSTRACT**

Topical compositions and methods for treating pain. The invention provides oil-in-water emulsions comprising an antidepressant; an NMDA-receptor antagonists; a lipophilic component; water; and a surfactant. The compositions induce a local-anesthetic effect when topically administered to intact skin thereby treating or preventing pain, for example, neuropathic pain.

**9 Claims, No Drawings**

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# TOPICAL COMPOSITIONS AND METHODS FOR TREATING PAIN

## I. FIELD OF THE INVENTION

The present invention relates to methods for treating or preventing pain via topical formulations that induce a local-anesthetic effect when applied to intact skin. The compositions comprise an antidepressant and a N-methyl-D-aspartate-receptor antagonist.

## II. BACKGROUND OF THE INVENTION

Pain results from the noxious stimulation of nerve endings. Nociceptive pain is caused by noxious stimulation of nociceptors (e.g., a needle stick or skin pinch), which then transmit impulses over intact neural pathways to the spinal neurons and then to the brain. Neuropathic pain is caused by damage to neural structures, such as damage to peripheral nerve endings or nociceptors, which become extremely sensitive to stimulation and can generate impulses in the absence of stimulation (e.g., herpes zoster pain after the rash has healed). Peripheral nerve damage can lead to pathological states where there is a reduction in pain threshold (i.e., allodynia), an increased response to noxious stimuli (hyperalgesia), or an increased response duration (persistent pain). GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 529 (Joel G. Hardman et al. eds., 9th ed. 1996); HARRISON'S PRINCIPLES OF INTERNAL MEDICINE 53–58 (Anthony S. Fauci et al. eds., 14th ed. 1998).

In contrast to pain treatment with systemic agents, pain can be treated locally by topically administering a local anesthetic directly to the painful area to block the nociceptive mechanistic pathway. Local anesthetics prevent the generation and conduction of nociceptive nerve impulses. Thus, for example, a local anesthetic can be injected intradermally (non-systemic injection within the skin) or topically applied at the pain area. Advantages of topical local-anesthetic administration over systemic administration of pain relievers include decrease or preclusion of side effects, improved patient compliance, and reversible action (i.e., the action can be reversed by removing the anesthetic from the application site). TRANSDERMAL AND TOPICAL DRUG DELIVERY SYSTEMS 33–112 (Tapash K. Ghosh et al. eds., 1997).

A variety of drug classes have local-anesthetic properties and can be administered in topical formulations. Traditional local anesthetics or sodium-channel blockers, such as lidocaine prevent the generation and conduction of nerve impulses by decreasing or preventing the large transient increase in the permeability of excitable membranes to Na+. Other agents with local-anesthetic properties include analgesics, such as non-steroidal anti-inflammatories ("NSAIDs"), see, for example, TRANSDERMAL AND TOPICAL DRUG DELIVERY SYSTEMS 87–93 (Tapash K. Ghosh et al. eds., 1997) and opioids, such as morphine. See e.g., U.S. Pat. No. 5,948,389 (issued Sept. 7, 1999); Christoph Stein & Alexander Yassouridis 71 Pain 119 (1997).

N-methyl-D-aspartate ("NMDA") receptor antagonists, such as ketamine have local-aesthetic properties and topical administration is as an effective neuropathic pain treatment. See, for example, U.S. Pat. No. 5,817,699 (issued Oct. 6, 1998). In another example, topical administration of antidepressant medications, such as amitriptyline, has been reported effective for neuropathic pain treatment. See, for example, U.S. Pat. No. 6,211,171 (issued Apr. 3, 2001); J. Sawynok et al., 82 PAIN 149 (1999). In addition, topical administration of a combination of a tricyclic antidepressant and an NMDA-receptor antagonist is reported to have excellent local-anesthetic properties when topically applied and is useful for treatment of neuropathic pain, U.S. Pat. No. 6,197,830 (issued Mar. 6, 2001).



But even though topical local-anesthetic administration to intact skin is routinely used to treat minor indications, it has not found significant use for treating more severe nociceptive and neuropathic pain because it is difficult to get significant concentrations through the skin barrier. Because of the skin's drug-permeation resistance, as little as about 1 percent and usually no more than about 15 percent of a drug in a topical formulation is bioavailable (TRANSDERMAL AND TOPICAL DRUG DELIVERY SYSTEMS 7 (Tapash K. Ghosh et al. eds., 1997)). Another problem with topical administration of pain relievers is stability of the composition. Local-anesthetics emulsion compositions are inherently unstable, and phase separation can occur during shipment and storage. Furthermore, many topical local-anesthetic compositions suffer from oxidative instability. Lecithin compositions are routinely used as bases for topical local-aesthetic compositions, but are highly oxidatively unstable (AM. PHARM. ASSOC., HANDBOOK OF PHARMACEUTICAL EXCIPIENTS 292–294, 292 (Arthur H. Kibbe ed., 3rd ed. 2000)). For example, U.S. Pat. No. 6,197,830 (issued Mar. 6, 2001) describes a lecithin-based composition for topically administering a combination of an NMDA-receptor antagonist and a tricyclic antidepressant and U.S. Pat. No. 5,817,699 (issued Oct. 6, 1998) and U.S. Pat. No. 6,017,961 (issued Jan. 25, 2000) describe topical administration of ketamine in pluronic lecithin organogel.

In sum, topical local-anesthetic administration has advantages over systemic administration of pain relievers. Unfortunately, topical local-anesthetic compositions suffer from instability and poor skin-penetration properties, which limit their use to less severe pain. What are needed are stable topical local-anesthetic compositions with good skin-penetration properties. Particularly, stable, skin-penetrating compositions comprising a combination of an antidepressant and an NMDA-receptor antagonists are needed.

Citation or identification of any reference in the Background section of this application is not an admission that such reference is prior art to the present invention.

## III. SUMMARY OF THE INVENTION

The invention provides methods and topical compositions for treating or preventing pain. The compositions of the invention can be topically administered to intact skin to provide a local-anesthetic effect thereby treating or preventing pain, for example, neuropathic pain. In one embodiment, the invention provides stable, skin penetrating compositions for topical administration comprising a combination of an antidepressant and an NMDA-receptor antagonist.

In a second embodiment, the invention provides an emulsion comprising:

(a) an antidepressant or a pharmaceutically acceptable salt thereof;

(b) an NMDA-receptor antagonists or a pharmaceutically acceptable salt thereof;

(c) a lipophilic component;

(d) water; and

(e) a surfactant, wherein the emulsion is an oil-in-water emulsion.

Preferably, the mean oil-droplet size is within the range of about 0.01 microns to about 100 microns, more preferably, within the range of about 0.1 microns to about 10 microns.

In another embodiment, the invention relates to a patch comprising:

(a) an antidepressant or a pharmaceutically acceptable salt thereof;

(b) an NMDA receptor antagonists or a pharmaceutically acceptable salt thereof;

(c) a lipophilic component;

(d) water; and

(e) a surfactant, wherein the emulsion is an oil in water emulsion.

In still another embodiment, the invention provides a method of treating or preventing pain in a mammal comprising topically administering to the skin of a mammal in need thereof an emulsion comprising:

(a) a therapeutically effective amount of an antidepressant or a pharmaceutically acceptable salt thereof;

(b) a therapeutically effective amount of an NMDA-receptor antagonists or a pharmaceutically acceptable salt thereof;

(c) a lipophilic component;

(d) water; and

(e) a surfactant,

wherein the emulsion is an oil-in-water emulsion.

In still another embodiment, the invention relates to a method of inducing local anesthesia in a mammal comprising topically administering to the skin of a mammal in need thereof an emulsion comprising:

(a) a therapeutically effective amount of an antidepressant or a pharmaceutically acceptable salt thereof;

(b) a therapeutically effective amount of an NMDA-receptor antagonists or a pharmaceutically acceptable salt thereof,

(c) a lipophilic component;

(d) water; and

(e) a surfactant,

wherein the emulsion is an oil-in-water emulsion.

The present invention may be understood more fully by reference to the following figures, detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

## IV. DEFINITIONS

As used herein, the phrase "composition of the invention" refers to an oil-in-water emulsion having a mean droplet size within the range of 0.01 microns to 100 microns comprising:

(1) a therapeutically effective amount of an antidepressant, a pharmaceutically acceptable salts thereof, a complex thereof (e.g., hydrates, solvates, and clathrates), a prodrug thereof, or any stereoisomeric forms or mixtures of stereoisomeric forms thereof (e.g., geometrical isomers, enantiomers, diastereomers, racemates, or mixtures thereof);

(2) a therapeutically effective amount of an NMDA-receptor antagonists, a pharmaceutically acceptable salts thereof, a complex thereof (e.g., hydrates, solvates, and clathrates), a prodrug thereof, or any stereoisomeric forms or mixtures of stereoisomeric forms thereof (e.g., geometrical isomers, enantiomers, diastereomers, racemates, or mixtures thereof);

(3) a lipophilic component;

(4) water; and

(5) a surfactant.

As used herein, a "therapeutically effective amount" of an antidepressant or an NMDA-receptor antagonist means the amount of the antidepressant or the NMDA-receptor antagonist required in a composition of the invention to induce a local-anesthetic effect sufficient to treat or ameliorate pain in a mammal.

As used herein, the term mammal means any mammal, for example, but not limited to humans; pets, such as dogs and cats; farm mammals, such as horses, cows, pigs, and sheep; and laboratory animals, such as monkeys, guinea pigs, rats, and mice. Preferably, a "mammal" is a human.

As used herein, the term "intradermal administration" means administration of a pharmaceutical to the skin of a mammal, preferably a human, to deliver the pharmaceutical to the local tissue under and around the site of administration. Preferably, intradermal administration is effected without absorption of the pharmaceutical into the mammal's blood stream. The purpose of intradermal administration is to elicit a local affect in contrast to transdermal administration where the objective is to transfer the pharmaceutical through the skin and into the blood stream for a systemic effect.

As used herein, the term "topical administration" or "topical delivery" means intradermal administration of a pharmaceutical by administration of the pharmaceutical or a composition comprising the pharmaceutical to intact skin. For example, by rubbing a composition of the invention onto an area of intact skin or by placing an intradermal patch comprising a composition of the invention onto an area of intact skin.

The term "topical composition" means a pharmaceutical composition designed for topical administration and containing a pharmaceutical.

As used herein, the phrase "intradermally-acceptable" means any pharmaceutical, excipient or other component of a topical formulation that is safe or approved for intradermal or topical administration in mammals.

The phrase "pharmaceutically acceptable salt(s)," as used herein includes, but is not limited to, salts of acidic or basic groups that may be present in the compounds of the invention. Compounds of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable salts of such basic compounds are those that form salts comprising pharmacologically acceptable anions including, but not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, bromide, iodide, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydroxynaphthoate, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, muscate, napsylate, nitrate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, succinate, sulfate, tannate, tartrate, teoclate, triethiodide, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)). Compounds of the invention that include an amino moiety also can form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds of the invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts.

As used herein, the term "solvate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for topical administration to humans.

As used herein, the term "hydrate" means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

The term "clathrate" means a compound of the invention or a salt thereof in the form of a crystal lattice that contains spaces (e.g., channels) that have a guest molecule (e.g., a solvent or water) trapped within.

The term "prodrug" refers to a compound that, following administration in a mammal, converts, via a biotransformation, into an antidepressant or an NMDA-receptor antagonist in vivo. Prodrugs can be synthesized using well-known methods, such as those described by 1 BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY, 172–178, 949–982 (Manfred E. Wolff ed., 5th ed. 1995).

As used herein, an "emulsion" means a dispersed system containing at lease two immiscible phases (a lipophilic phase and a hydrophilic or aqueous phase), wherein one immiscible phase is dispersed within the other in the form of droplets. Emulsions are thermodynamically unstable as a result of excess free energy associated with the surface of the droplet. A stable emulsion must contain at least three components, i.e., a dispersion medium, a dispersed phase, and an emulsifying agent. As used herein, a "oil-in-water type emulsion" is a stable emulsion in which the aqueous phase is the dispersion medium and the lipophilic component is the dispersed phase. Several tests are available to determine whether an emulsion is an oil-in-water type emulsion or a water-in-oil type emulsion: for example, the dilution test, the conductivity test, and the dye solubility test, which tests are described in 1 REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 282–291 (Alfonso R. Gennaro ed., 19th ed. 1995), hereby expressly incorporated herein by reference.

## V. DETAILED DESCRIPTION OF THE INVENTION

The compositions of the invention comprise an antidepressant and an NMDA-receptor antagonist in a colloidal dispersion (emulsion). The colloidal dispersion comprises an aqueous phase, a lipophilic phase, and a surfactant system, wherein the lipophilic phase is dispersed within the aqueous phase (oil-in-water emulsion) and the mean-droplet size is within the range of about 0.01 microns to about 100 microns, preferably about 0.1 microns to 10 about microns. In a preferred embodiment, the compositions of the invention further comprise a stiffening agent and a hydrophobic surfactant. When topically administered to a mammal, the compositions of the invention can deliver a combination of an antidepressant and an NMDA-receptor antagonist through intact skin at a high flux rate to induce local anesthesia and thereby treat, ameliorate, or prevent neuropathic pain. Furthermore, the compositions of the invention are stable both physically (resists coalescing of droplets and Ostwald ripening) and chemically stable (e.g., resist oxidation) and impart a soothing feeling when administered.

### A. Pain Indications

The compositions and methods of the invention can be used to treat or prevent any indication resulting from noxious stimulation of peripheral nociceptors. The compositions and methods of the invention are effective to induce local anesthesia and to treat neuropathic pain. As used herein the term "neuropathic pain" refers to neuropathic-pain syndromes, that is, pain due to lesions or dysfunction in the nervous system. The compositions and methods of the invention can be used to treat or prevent pain related to or induced by the following diseases, trauma, or conditions: general neuropathic conditions, such as peripheral neuropathy, phantom pain, reflex-sympathetic dystrophy, causalgia, syringomyelia, and painful scar; specific neuralgias at any location of the body; back pain; diabetic neuropathy; alcoholic neuropathy; metabolic neuropathy; inflammatory neuropathy; chemotherapy-induced neuropathy, herpetic neuralgias; traumatic odontalgia; endodontic odontalgia; thoracic-outlet syndrome; cervical, thoracic, or lumbar radiculopathies with nerve compression; cancer with nerve invasion; traumatic-avulsion injuries; mastectomy, thoracotomy pain; spinal-cord-injury; stroke; abdominal-cutaneous nerve entrapments; tumors of neural tissues; arachnoiditis; stump pain; fibromyalgia; regional sprains or strains; myofascial pain; psoriatic arthropathy; polyarteritis nodosa; osteomyelitis; bums involving nerve damage; AIDS-related pain syndromes; connective tissue disorders, such as systemic lupus erythematosis, systemic sclerosis, polymyositis, and dermatomyositis; and inflammatory conditions, such as acute inflammation (e.g. trauma, surgery and infection) or chronic inflammation (e.g., arthritis and gout).

### B. Antidepressants

The term "antidepressant" means any compound or composition known or to be discovered that, when tested according to standard in vivo or in vitro assays, displays receptor-binding properties or other mechanistic properties associated with the clinically approved antidepressants or any compound or composition known or to be discovered that has demonstrated clinical efficacy in treating depression in mammals including those compounds and compositions that have been approved for treating depression in humans.

Classes of antidepressant agents include norepinephrine-reuptake inhibitors (NRIs"), selective-serotonin-reuptake inhibitors (SSRIs), monoamine-oxidase inhibitors (MAOIs), serotonin-and-noradrenaline-reuptake inhibitors ("SNFIs); corticotropin-releasing factor (CRF) antagonists, α-adrenoreceptor antagonists; NK1-receptor antagonists, 5-$HT_{1A}$-receptor agonist, antagonists, and partial agonists, atypical antidepressants, and other antidepressants.

An antidepressant can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, or diastereomers. As used herein, the term "antidepressant" encompass all such enantiomers and stereoisomers, that is, both the stereomerically-pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. The term "antidepressant" further encompasses all pharmaceutically acceptable salts, all complexes (e.g., hydrates, solvates, and clathrates), and all prodrugs of antidepressants.

Notably, the methods of the invention involve topical administration, thus "antidepressants" unsuitable for systemic administration in mammals, because of toxicity or otherwise, may still be suitable for topical administration in combination with an NMDA-receptor antagonist according to the compositions and methods of the invention. Antidepressants suitable for use in the invention can be identified by testing antidepressant compounds for local-anesthetic

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