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(54) Title: PAIN MEDICINE COMBINATION AND USES THEREOF

(57) Abstract: Embodiments disclosed herein describe, amongst other things, dosage forms, compounds, compositions, pharmaceutical compositions that can be used in the treatment of, for example, pain and pain related disorders or to produce analgesia.

Pain Medicine Combination and Uses Thereof

Cross-Reference to Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 61/774,113, filed March 7, 2013, which is hereby incorporated by reference in its entirety.

Field of the Invention

[0002] Embodiments described herein relate to compositions and pharmaceutical compositions that can be used to treat or prevent pain or to produce analgesia.

Background

[0003] Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be acute or chronic. While acute pain is usually self-limited, chronic pain, which can persist for 3 months or longer and can lead to significant changes in a patient's personality, lifestyle, functional ability and overall quality of life. Pain is often treated opioid agonists, such as morphine, oxycodone and hydromorphone. Unfortunately, opioid agonists can have severe side effects that limit their use and effectiveness as treating and/or preventing pain. Therefore, the embodiments described herein provide for compositions that can be used to treat and/or prevent pain with significant and unexpected advantages over compositions currently used to treat or prevent pain.

Summary

[0004] Embodiments described herein provide pharmaceutical compositions comprising a NMDA antagonist; a CYP2D6 inhibitor; and an opioid agonist. In some embodiments, the NMDA antagonist is chosen from one or more of dextromethorphan, a glycine antagonist, ifenprodil like compound, amantadine, MK-801 (dizocilpine; [5R,10S]-[+]-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine), ketamine, memantine, D-AP5 (D(-)-2-Amino-5-phosphonovaleric acid) , CPP (3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid), or a pharmaceutically acceptable salt thereof, or any combination thereof. In some embodiments, the CYP2D6 inhibitor is chosen from one or more of: quinidine, methadone, bupropion, cinacalcet, fluoxetine, paroxetine, duloxetine, sertraline, terbinafine, amiodarone, cimetidine, or a pharmaceutically acceptable salt thereof, or any combination thereof. In some embodiments, the opioid agonist is chosen from one or more of the agonists described herein.

[0005] Embodiments described herein provide pharmaceutical compositions comprising dextromethorphan, or a pharmaceutically acceptable salt thereof; quinidine, or a

pharmaceutically acceptable salt thereof; and an opioid agonist chosen from one or more of: morphine, oxycodone, and hydromorphone, or a pharmaceutically acceptable salt thereof, or any combination thereof. In some embodiments, the compositions is formulated for simultaneous administration.

[0006] In some embodiments, the ratio of the opioid agonist to NMDA antagonist is about 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.1 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist to CYP2D6 inhibitor is 1:1:0.1-1 (wt:wt:wt). In some embodiments, the composition comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, or about 60 mg of the opioid agonist.

[0007] In some embodiments, the ratio of the opioid agonist to dextromethorphan is about 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.1 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to dextromethorphan to quinidine is 1:1:0.1-1 (wt:wt:wt). In some embodiments, the composition comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, or about 60 mg of the opioid agonist.

[0008] Embodiments described herein provide dosage forms comprising dextromethorphan, or a pharmaceutically acceptable salt thereof; quinidine, or a pharmaceutically acceptable salt thereof; and an opioid agonist chosen from one or more of: morphine, oxycodone, and hydromorphone, or a pharmaceutically acceptable salt thereof, or any combination thereof. In some embodiments, the composition comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, or about 60 mg of the opioid agonist.

[0009] Methods of treating or preventing pain in a subject are also provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition described herein. In some embodiments, the pharmaceutical composition is administered every 4 hours, every 6 hours, every 8 hours, or every 12 hours. In some embodiments, the method does not comprise a risk evaluation mitigation strategy (REMS). In some embodiments, the subject is a subject in need of pain relief. In some embodiments, none of the components are administered for the purpose of avoiding withdrawal symptoms.

Detailed Description

[0010] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. Although methods

and materials similar or equivalent to those described herein can be used in the practice or testing of the compositions and compounds described herein, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only not intended to be limiting. Other features and advantages of the compositions and compounds described herein will be apparent from the following detailed description and claims.

[0011] Various compositions are described herein. Each of the compositions described herein can also be pharmaceutical compositions.

[0012] The present embodiments described herein provide compositions that unexpectedly and surprisingly treat or prevent pain with a lower amount of an opioid agonist and with fewer side effects while providing improved pain relief or analgesia. The surprising results are from the combination of three compounds, an opioid agonist, a CYP2D6 inhibitor, and a NMDA antagonist. The combination of the three types of compounds allow the compounds to stay as effective levels to produce improved pain relief or analgesia compared to the relief obtained with just one or two of the compounds. As shown in the non-limiting examples, the compositions treat or prevent pain relief better than with just the opioid agonist alone or the combination of the opioid agonist with the NMDA antagonist. Additionally, the compositions increase the bioavailability of the opioid agonist to the brain. Without being bound to any particular theory, it is the increase in bioavailability that allows the improvement in pain relief or analgesia. Therefore, a small amount of the opioid agonist should be able to be used, leading to fewer side effects. The compositions also surprisingly and unexpectedly have an effect that is longer in duration than the opioid agonist alone. The compositions also surprisingly and unexpectedly have a lower incidence of tolerance. That is, under certain circumstances increasing amounts of the opioid agonist are necessary to achieve the same level of pain relief. For the compositions described herein, the compositions can have a lower incidence of tolerance, thereby keeping the amount of the opioid agonist to a minimum, which reduces the adverse side effects that are common to the usage of opioid agonists. The advantages described herein apply to having all three components (*e.g.* opioid antagonist, NMDA antagonists, and CYP2D6 inhibitor) administered or present in a composition as opposed to just two of an opioid agonist,

dextromethorphan or quinidine. In some embodiments, the combination of an opioid agonist, NMDA antagonist, and CYP2D6 inhibitor has other reduced side effects compared to any of the components alone or in a combination of just two of them. Examples of opioid side effects include, but are not limited to, weight loss, constipation, diarrhea, nausea, vomiting, stomach pain, loss of appetite, flushing (*e.g.* warmth, redness, or tingly feeling), headache, dizziness, spinning sensation, memory problems, sleep problems (insomnia), or strange dreams. Therefore, the compositions described herein can reduce or lessen the side effects.

[0013] Accordingly, in some embodiments, compositions are provided that comprise an opioid agonist, a NMDA antagonists, and a CYP2D6 inhibitor. In some embodiments, the composition comprises an opioid agonist, dextromethorphan, quinidine, pharmaceutically acceptable salt of each or any of the foregoing, or any combination thereof is provided. Examples of opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papavereturn, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts of each or any of the foregoing, and any mixtures thereof. In some embodiments, the opioid agonist is morphine, oxycodone, and hydromorphone, or a pharmaceutically acceptable salt thereof, or any combination thereof. In some embodiments, the morphine is morphine sulfate.

[0014] In some embodiments, the NMDA antagonist is chosen from one or more of dextromethorphan, a glycine antagonist, ifenprodil or ifenprodil like compounds, amantadine, MK-801 (dizocilpine; [5R,10S]-[+]-5-methyl-10,11- dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine), ketamine, memantine, D-AP5 (D(-)-2-Amino-5-phosphonovaleric acid) , CPP (3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid), or a pharmaceutically acceptable salt thereof,

or any combination thereof. In some embodiments, the NMDA antagonist is dextromethorphan. Examples of glycine antagonist include, but are not limited to, GLYX-13, TK-40, 1-Aminocyclopropanecarboxylic acid (ACPC), 7-Chlorokynurenic acid, DCKA (5,7-dichlorokynurenic acid), kynurenic acid, lacosamide, L-phenylalanine, and the like. The compositions and dosage forms described herein can have one or more of the glycine antagonists. In some embodiments, the dextromethorphan is a hydrate, such as but not limited to, dextromethorphan hydrobromide monohydrate.

[0015] In some embodiments, the CYP2D6 inhibitor chosen from one or more of: quinidine, methadone, bupropion, cinacalcet, fluoxetine, paroxetine, duloxetine, sertraline, terbinafine, amiodarone, cimetidine, or a pharmaceutically acceptable salt thereof, or any combination thereof. In some embodiments, the CYP2D6 inhibitor is quinidine.

[0016] In some embodiments, the composition is formulated for simultaneous administration. As used herein "simultaneous administration," as it refers to a composition comprising more than one active ingredient or therapeutic agent, means that each of the active ingredients or therapeutic agents are administered substantially or exactly at the same time. The agents may be absorbed or become bioavailable at different rates or times, but the administration of the components, ingredients, or agents, is simultaneous. In some embodiments, the administration is not simultaneous. Simultaneous administration can be achieved by having each of the components (*e.g.*, opioid agonist, NDMA antagonist, and CYP2D6 inhibitor) in the same dosage form. Simultaneous administration can also be achieved where each of the components are not in the same dosage form, but are administered substantially or exactly at the same time.

[0017] The ratio of the different components present in the composition can also be altered. In some embodiments, the ratio of the opioid agonist to NMDA antagonist is about 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist is about 0.1 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist is about 0.5 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist is about 0.7 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist is about 0.8 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist is about 0.9 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.1 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.2 to 1:1 (wt:wt). In some embodiments,

the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.3 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.4 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.4 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.5 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.6 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.7 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.8 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.9 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist to CYP2D6 inhibitor is 1:1:0.1-1 (wt:wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist to CYP2D6 inhibitor is about 1:1:0.9-1.5 (wt:wt:wt). In some embodiments, the ratio of the opioid agonist to NMDA antagonist to CYP2D6 inhibitor is about 0.9-1.1:0.9-1.1:0.9-1.5 (wt:wt:wt). In some embodiments, the amount of CYP2D6 inhibitor is in an effective amount to enhance the analgesia of opioid agonist and NMDA antagonist. In some embodiments, the effective amount of the CYP2D6 inhibitor enhances the analgesia of opioid agonist and NMDA antagonist at least 1.5, 2, 2.5, 3, 4, or 5 times. The enhances can be compared in a non-human animal model, such as the tail flick model, or in a human study where subjects are asked to quantify the pain relief. In some embodiments the ratio of the opioid agonist to CYP2D6 inhibitor is about, or at least, 0.1:1, about, or at least, 0.2:1, about, or at least, 0.3:1, about, or at least, 0.4:1, about, or at least, 0.5:1, about, or at least, 0.6:1, about, or at least, 0.7:1, about, or at least, 0.8:1, about, or at least, 0.9:1, about, or at least, 1:1, about, or at least, 2:1, about, or at least, 3:1 and the like. In some embodiments, the ratio of the opioid agonist to CYP2D6 inhibitor is about 0.1-1:1, about 0.2-1:1, about 0.3-1:1, about 0.4-1:1, about 0.5-1:1, about 0.6-1:1, about 0.7-1:1, about 0.8-1:1, about 0.9-1:1, or about 1-2:1, or about 1-3:1, or about 1-4:1, or about 1-5:1.

[0018] In some embodiments, the ratio of the opioid agonist to dextromethorphan is about 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to dextromethorphan is about 0.1 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to dextromethorphan is about 0.5 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to dextromethorphan is about 0.7 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to dextromethorphan is about 0.8 to 1:1 (wt:wt). In some embodiments, the ratio

of the opioid agonist to dextromethorphan is about 0.9 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.1 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.2 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.3 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.4 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.4 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.5 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.6 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.7 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.8 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to quinidine is about 1:0.9 to 1:1 (wt:wt). In some embodiments, the ratio of the opioid agonist to dextromethorphan to quinidine is 1:1:0.1-1 (wt:wt:wt). In some embodiments, the ratio of the opioid agonist to dextromethorphan to quinidine is about 1:1:0.9-1.5 (wt:wt:wt). In some embodiments, the ratio of the opioid agonist to dextromethorphan to quinidine is about 0.9-1.1:0.9-1.1:0.9-1.5 (wt:wt:wt). In some embodiments, the amount of quinidine is in an effective amount to enhance the analgesia of morphine and dextromethorphan without the quinidine. In some embodiments, the effective amount of the quinidine enhances the analgesia of morphine and dextromethorphan at least 1.5, 2, 2.5, 3, 4, or 5 times. The enhances can be compared in a non-human animal model, such as the tail flick model, or in a human study where subjects are asked to quantify the pain relief. In some embodiments the ratio of the opioid agonist to quinidine is about, or at least, 0.1:1, about, or at least, 0.2:1, about, or at least, 0.3:1, about, or at least, 0.4:1, about, or at least, 0.5:1, about, or at least, 0.6:1, about, or at least, 0.7:1, about, or at least, 0.8:1, about, or at least, 0.9:1, about, or at least, 1:1, about, or at least, 2:1, about, or at least, 3:1 and the like. In some embodiments, the ratio of the opioid agonist to quinidine is about 0.1-1:1, about 0.2-1:1, about 0.3-1:1, about 0.4-1:1, about 0.5-1:1, about 0.6-1:1, about 0.7-1:1, about 0.8-1:1, about 0.9-1:1, or about 1-2:1, or about 1-3:1, or about 1-4:1, or about 1-5:1.

[0019] In some embodiments, the composition comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg of the opioid agonist. In some embodiments, the composition comprises from about 10 to about 100 mg, from about 10 to about 90 mg, from about 10 to about 80 mg, from about 10 to about 70 mg, from about 10 to

about 60 mg, from about 10 to about 50 mg, from about 10 to about 40 mg, from about 10 to about 30 mg, from about 10 to about 20 mg, from about 20 to about 100 mg, from about 20 to about 90 mg, from about 20 to about 80 mg, from about 20 to about 70 mg, from about 20 to about 60 mg, from about 20 to about 50 mg, from about 20 to about 40 mg, from about 20 to about 30 mg, from about 30 to about 100 mg, from about 30 to about 90 mg, from about 30 to about 80 mg, from about 30 to about 70 mg, from about 30 to about 60 mg, from about 30 to about 50 mg, from about 30 to about 40 mg, from about 40 to about 100 mg, from about 40 to about 90 mg, from about 40 to about 80 mg, from about 40 to about 70 mg, from about 40 to about 60 mg, from about 40 to about 50 mg, from about 50 to about 100 mg, from about 50 to about 90 mg, from about 50 to about 80 mg, from about 50 to about 70 mg, from about 50 to about 60 mg, from about 60 to about 100 mg, from about 60 to about 90 mg, from about 60 to about 80 mg, from about 60 to about 70 mg, from about 70 to about 100 mg, from about 70 to about 90 mg, from about 70 to about 80 mg, from about 80 to about 100 mg, from about 80 to about 90 mg, or from about 90 to about 100 mg.

[0020] In some embodiments, the composition comprises an opioid antagonist.

[0021] As discussed herein, in some embodiments, the oral dosage form can comprise an opioid antagonist. In some embodiments, the oral dosage form comprises a sequestered opioid antagonist. A sequestered opioid antagonist is one that is not bioavailable unless the oral dosage form is tampered with or adulterated. Opioids can be abused for their euphoric effect and if the dosage form is a controlled release or sustained release dosage form, crushing the dosage form can increase the bioavailability of the opioid agonist. Therefore, to prevent abuse, the dosage form can be made with the opioid antagonist such that the activity of opioid agonist is inhibited if the dosage form is altered, adulterated or tampered with by the subject using the dosage form. Therefore, in some embodiments, the oral dosage form further comprises a sequestered opioid antagonist which is not released when the dosage form is administered intact. In some embodiments, the sequestered opioid antagonist is in an amount which will negate the euphoric effect of the opioid agonist when the dosage form is tampered with and misused by a human. The form can be misused by administering the tampered dosage form orally, parenterally, intranasally or sublingually. In some embodiments, the sequestered antagonist is selected from the group consisting of naltrexone, naloxone, nalmefene, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof. Other examples of sequestered

antagonists and formulations thereof are described in U.S. Patent 8,231,901, which is hereby incorporated by reference.

[0022] Also provided herein are methods of treating or preventing pain comprising administering to a subject a composition or pharmaceutical composition described herein. The compositions, dosage forms, and such described herein, can be used to produce analgesia. In some embodiments, the composition or pharmaceutical composition or dosage form is administered every 4 hours, every 6 hours, every 8 hours, or every 12 hours.

[0023] Due to the potential for abuse, many opioids are administered in conjunction with a risk evaluation mitigation strategy (REMS). A REMS can include a medication guide, patient package insert, a communication plan, elements to assure safe use, an implementation system, or any combination thereof. Because the compositions described herein may use less amounts of the opioid agonist, risk evaluation mitigation strategies may not need to be used. Therefore, in some embodiments, the method does not comprise the use of a risk evaluation mitigation strategy or any element of a REMS, some of which are described herein.

[0024] In some embodiments, in addition to the components described herein, the composition can comprise non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, and pharmaceutically acceptable salts thereof, and mixtures thereof. Examples of other suitable agents that can be used include, but not limited to, the following chemical classes of analgesic, antipyretic, nonsteroidal antiinflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para aminophennol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid, and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more

detailed description of the NSAIDs, see Paul A. Insel, Analgesic Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics 617-57 (Perry B. Molinhoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, Analgesic, Antipyretic and Anti Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II 1196-1221 (A. R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties. Suitable Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Pat. No. 6,136,839. Cox II inhibitors include, but are not limited to, rofecoxib and celecoxib.

[0025] The compositions described herein can also comprise antimigraine agents, which include but are not limited to, alpiropride, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergot, ergotamine, flumedroxone acetate, fonazine, lisuride, lomerizine, methysergide oxetorone, pizotyline, and mixtures thereof.

[0026] The pain treated, ameliorated, or prevented in accordance with the methods described herein can be acute pain or chronic pain, such as, but not limited to, nociceptive pain, neuropathic pain and psychogenic pain, and can be cancer related or not associated with cancer. Example of "nociceptive pain" include, but are not limited to, pain caused by injury to body tissues, including, without limitation, by a cut, bruise, bone fracture, crush injury, burn, surgery, and the like. In some embodiments, the pain is somatic pain. The term "somatic pain" is used to refer to pain arising from bone, joint, muscle, skin, or connective tissue. This type of pain is typically aching or throbbing in quality and is well localized. The term "neuropathic pain" is used herein to refer to pain originating from abnormal processing of sensory input by the peripheral or central nervous system. The pain can also be as a result of surgery, which can be referred to as post-surgical pain. Examples of surgery include, but are not limited to, dental or trauma, orthopedic surgery, and the like. The compositions described herein can be used, in some embodiments, to treat or prevent these types of pain as well as others.

[0027] The compositions described herein can also be administered in a therapeutically effective amount to treat, ameliorate, or prevent pain. The compositions described herein can also be administered in a therapeutically effective amount to produce analgesia. In some embodiments, the compositions described herein are administered to produce effective analgesia within 1 hour of administration. In some embodiments, the compositions described herein are

administered to produce enhanced analgesia as compared to the opioid agonist given alone or in combination with NMDA antagonist, but without a CYP2D6 inhibitor. In some embodiments, the NMDA antagonist is one described herein, including, but not limited to dextromethorphan. In some embodiments, the CYP2D6 inhibitor is one described herein, including, but not limited to, quinidine. In some embodiments, the analgesia or pain relief is increased by at least 2-3 times when the opioid agonist is administered in combination with CYP2D6 inhibitor and NMDA antagonist as compared to just the opioid agonist alone or as compared to the opioid agonist in combination with NMDA antagonist. In some embodiments, none of the components (*i.e.* opioid agonist, NMDA antagonist, or CYP2D6 inhibitor) of a pharmaceutical composition are administered to the subject to avoid withdrawal symptoms. Opioids and/or other pain medications can be addictive. Thus, as medications are changed the subject may be weaned off of a medication to avoid withdrawal symptoms. In some embodiments, for the compositions described herein, the different components are administered to treat, ameliorate, or prevent pain or to produce analgesia and not for the purpose of avoiding and/or treating withdrawal symptoms. That is, in some embodiments, the compositions, or dosage forms are administered with the intent treat or alleviate the symptoms of pain or to produce analgesia and not for the intent to avoid or treat withdrawal symptoms that can be associated with addiction.

[0028] As described herein, the pharmaceutical compositions can be administered in a dosage form. In some embodiments, the dosage form comprises an opioid agonist, a NMDA antagonist and a CYP2D6 inhibitor. In some embodiments, the dosage form comprises each of the components in the ratios described herein. In some embodiments, the dosage form is a pill, capsule, tablet, fast dissolving tablet (*e.g.* reditab and the like), liquid, film, fast dissolving film, which can also be referred to as oral wafers or oral films. Examples of these are described in Int J Pharm Investig. 2013 Apr-Jun; 3(2): 67–76, Curr Drug Deliv. 2013 Dec;10(6):667-84, Curr Drug Deliv. 2013 Feb;10(1):96-108, Curr Drug Deliv. 2011 Jul;8(4):373-80, Curr Drug Deliv. 2009 Oct;6(5):469-76, each of which is hereby incorporated by reference. In some embodiments, the compositions described herein are a dosage form. A dosage form is where each of the active ingredients or components are mixed together prior to administration. Examples of dosage forms are described herein and include, but are not limited to, pills, capsule, liquid, tablet, and the like. The dosage form can have the same components as discussed herein for the compositions. The ratios of the components can also be the same. In some embodiments,

the dosage form is suitable for oral administration, topical administration, or parenteral administration. The compositions or dosage forms can also be administered sublingually, bucally, intranasal, and the like. The compositions described herein can be administered by any suitable method.

[0029] In some embodiments, the composition is swallowed. In some embodiments, the composition is not swallowed. The composition may also be, for example, administered subcutaneously, intramuscularly, intravenously, transdermally or vaginally. In some embodiments, the combination of the opioid agonist, NMDA antagonist, and CYP2D6 inhibitor is administered simultaneously, separately, or a combination thereof. Therefore, in some embodiments, CYP2D6 inhibitor is administered before the opioid agonist or NMDA antagonist. In some embodiments, the CYP2D6 inhibitor is administered with the opioid agonist and then followed by the administration of NMDA antagonist. In some embodiments, CYP2D6 inhibitor is administered with NMDA antagonist and then followed by the administration of the opioid agonist. In some embodiments, each component is administered sequentially in any order. In some embodiments, they are administered concurrently in the same dosage form or in separate dosage forms.

[0030] In some embodiments, the compositions can be administered to a subject, animal, patient, or mammal in need thereof. As used herein, the phrase "in need thereof" means that the animal, subject, patient or mammal has been identified as having a need for the particular method, use, or treatment. In some embodiments, the identification can be by any means of diagnosis. In any of the methods and treatments described herein, the animal or mammal can be in need thereof. In some embodiments, the animal or mammal is in an environment or will be traveling to an environment in which a particular disease, disorder, or condition is prevalent. As described herein, in some embodiments, the need, or intent, is to treat, ameliorate, or prevent pain, or produce analgesia.

[0031] As used herein, the term "mammal" means a rodent (i.e., a mouse, a rat, or a guinea pig), a monkey, a cat, a dog, a cow, a horse, a pig, or a human. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human mammal.

[0032] As used herein, the terms "comprising" (and any form of comprising, such as "comprise", "comprises", and "comprised"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include"), or

"containing" (and any form of containing, such as "contains" and "contain"), are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

[0033] As used herein, the term "about" means that the numerical value is approximate and small variations would not significantly affect the practice of the disclosed embodiments. Where a numerical limitation is used, unless indicated otherwise by the context, "about" means the numerical value can vary by ±10% and remain within the scope of the disclosed embodiments.

[0034] As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0035] By "pharmaceutical formulation" or "pharmaceutical composition" it is further meant that the carrier, solvent, excipients and salt must be compatible with the active ingredient of the formulation (e.g. a compound described herein). It is understood by those of ordinary skill in this art that the terms "pharmaceutical formulation" and "pharmaceutical composition" are generally interchangeable, and they are so used for the purposes of this application. As discussed herein, the composition described herein can be a pharmaceutical composition. The composition can also have a pharmaceutically acceptable salt of the parent compound.

[0036] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic,

lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic. The present disclosure includes pharmaceutically acceptable salts of any compound(s) described herein.

[0037] Pharmaceutically acceptable salts can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, and the like. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA, USA, p. 1445 (1990).

[0038] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0039] As used herein, "treating" or "treatment" includes any effect e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder, etc. "Treating" or "treatment" of a disease state means the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting an existing disease-state, i.e., arresting its development or its clinical symptoms; and/or (c) relieving the disease-state, i.e., causing regression of the disease state. With regards to pain, the treatment of pain would be the reduction in the pain sensation that one would have in the absence of the composition being administered. For example, in some embodiments, the terms "treatment of" and "treating" pain include the lessening of the severity of or cessation of pain. In some embodiments, it refers to decreasing the overall frequency of episodes of pain.

[0040] As used herein, "preventing" means causing the clinical symptoms of the disease state not to develop i.e., inhibiting the onset of disease, in a subject that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state. Preventing pain may also refer to a subject not having as great of a pain sensation as the subject would have had had the composition not been administered.

[0041] As used herein, the phrase "therapeutically effective amount" means the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that

is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician. The therapeutic effect is dependent upon the disorder being treated or the biological effect desired. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disorder and/or inhibition (partial or complete) of progression of the disorder, or improved treatment, healing, prevention or elimination of a disorder, or side-effects. The amount needed to elicit the therapeutic response can be determined based on the age, health, size and sex of the subject. Optimal amounts can also be determined based on monitoring of the subject's response to treatment. The compositions can also be administered in a therapeutically effective amount.

[0042] The present compositions, which includes dosage forms, can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal. Such pharmaceutical excipients can be, but not limited to, liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipients are sterile when administered to an animal. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

[0043] The compositions described herein can, for example, take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (see e.g., U.S. Pat. No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in Remington's Pharmaceutical Sciences 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

[0044] The compositions described herein can also be formulated to be a controlled- or sustained-release pharmaceutical compositions. Advantages of controlled- or sustained-release compositions include extended activity of the drug or combination of drugs, reduced dosage frequency, and increased patient compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the compounds, and can thus reduce the occurrence of adverse side effects.

[0045] For example, controlled- or sustained-release compositions can initially release an amount of the composition or component that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the composition or component to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the composition or components, the composition or the individual components can be released from the dosage form at a rate that will replace the amount of composition or individual components being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

[0046] All percentages and ratios used herein, unless otherwise indicated, are by weight.

[0047] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions described herein also consist essentially of, or consist of, the recited components, and that the processes described herein also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the process remains operable. Moreover, two or more steps or actions can be conducted simultaneously. Compositions can also refers to the dosage forms.

[0048] As used throughout this disclosure, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a composition" includes a plurality of such compositions, as well as a single composition, and a reference to "a therapeutic agent" is a reference to one or more therapeutic and/or pharmaceutical agents and equivalents thereof known to those skilled in the art, and so

forth. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Examples

[0049] The following examples are illustrative, but not limiting, of the methods and compositions described herein. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered in therapy and that are obvious to those skilled in the art are within the spirit and scope of the compounds and methods described herein.

Example 1: Administration of Quinidine/Morphine/Dextromethorphan treats pain.

[0050] The ability of quinidine (Q) to enhance the analgesic effects of MS:DM and reduce tolerance and dependence of MS and MS:DM in rats is determined. Adult Sprague-Dawly rats are used. All experimental protocols are done at a licensed research facility having an institutional animal care and use committee (IACUC) that conforms to the national institute of health (NIH) office of laboratory animal welfare (OLAW).

[0051] Morphine sulfate pentahydrate (MS), Dextromethorphan hydrobromide monohydrate (DM), quinidine (Q), and/or Naloxone hydrochloride are ordered from commercially available suppliers and manufacturers. Each component is administered orally through a rodent feeding tube. Rats exhibiting signs of misfeeding (choking, irritation, and irregular breathing) are assessed following each dose and treated appropriately.

[0052] Drug Administration and Pain Protocol

[0053] The baseline tail-flick latencies of the rats are be set at 3.5 to 4.5 seconds. To minimize tissue damage, and if no tail-flick occurs after 8 seconds, the light (*e.g.* heat) source is automatically turned off. The average of three tail-flick trials separated by a 1 min inter trial interval is used to determine the mean baseline latency (BL). The analgesic effects of MS, MS:DM, and MS:DM:Q and the development of tolerance is determined by measuring test (tail-flick) latencies (TL) after drug administration. The data can be expressed as percent of maximal possible analgesic effect (%MPAE) using the equation (%MPAE = [(TL - *BL)/(8* - BL)] x100).

[0054] Determination of the development of morphine tolerance and physical dependence:

[0055] Tolerance to MS in rats is determined using the tail flick pain model, and is measured as the time difference between baseline tail flick latencies and test tail flick latencies

after MS, MS:DM, and MS:DM:Q administration. Results of the test are that the tricombination of MS:DM:Q have a statistically significant increase in the tail flick latencies compared to baseline and as compared to MS and MS:DM and no drug administration. Additionally, dependence is determined by observing the three physical characteristics of escape jumping, teeth chattering, and wet-dog shakes for 10-15 minutes duration, following intraperitoneal Naloxone challenge.

[0056] ***Dose Dependency***

[0057] The dose dependent analgesic effects of MS in rats is determined using an oral administration of a range of MS doses, using the tail flick pain model described above. Tail flick latencies are measured at 1, 2, and 3 hours after oral treatment of MS to determine maximal analgesic effects of MS and ED_{50}. The oral MS administration is repeated until tolerance and dependence are achieved. This is done by twice daily dosing of MS at the ED_{50} dose (approximately 30 mg/kg) for 5, 10, and 15 days. Tail flick latencies are measured 90 minutes after each treatment until day 15. After tail flick testing, Naloxone is given IP on days 5, 10, and 15 to one group of rats and signs of withdrawal are observed for 10 minutes after injection. One saline treated group of rats will be used as control for all time points.

[0058] Escape jumping, teeth chattering, and wet-dog shaking are used to assess physical dependence on MS compared to MS:DM, or MS:DM:Q. These observations are determined following naloxone challenge (10 mg/kg, subcutaneously). The frequency of attempted escape jumping from containers housing the individual rats, and the frequency of episodes of teeth chattering, or wet-dog shaking are counted for a duration of 10 min after naloxone challenge.

[0059] Effects of MS/DM and MS/DM/Q combination on tolerance and dependence

[0060] A therapeutically effective ratio range of combined administration of MS, DM, and Q that prevents or reduces the development of morphine tolerance and dependence. Three doses of MS (ED90, ED50, and ED30 doses, respectively) are used to determine whether *MS/DM/Q* ratios are similar in preventing the development of morphine tolerance and dependence induced by different dose levels of MS.

[0061] Groups of rats (*e.g.* n = 12 per group) are used. Each group will receive one MS/DM combinations (MS ED90, ED50, and ED30 plus equal amounts of mg/kg DM), DM alone (mg/kg), MS alone (mg/kg), or saline MS ED90-equivalent mg/kg. After the optimal MS tolerance and dependence reducing MS/DM dose is identified, this combination dose is used

with a dose range of Q at 1:1:0.1, 1:1:0.5, and 1:1:1 (MS:DM:Q). The results will show that the tri-combination is more effective at reducing pain.

[0062] In all combination experiments, baseline tail-flick latencies of each rat is obtained before dosing. Each group of rats receives oral administration of one of the drug combinations or saline twice a day for 30 days. The analgesic effects of MS is examined at 90 min after the oral feeding using the tail-flick test on day, 5, 10, 15 or 30 of the treatment schedule. The choice of this 30-day treatment regimen is dependent on results of the time course experiment. After tail-flick testing on Day 15 or 30, 10 mg/kg naloxone is given intraperitoneally to each rat, and withdrawal signs are observed and recorded for 10 min following injection.

[0063] The time course of the DM-mediated increase in the acute analgesic effects of MS and compare it to MS:DM:Q is determined. MS ED30 dose is used in order to avoid maximal analgesic effects of a high MS dose alone. Four groups (n = 12/group) of rats each receive a single oral administration of MS alone, a combination of MS and DM, DM alone, or MS:DM:Q (based upon the optimal combination ratio of MS:DM to Q determined above). The tail-flick test is recorded before and every 30 min after drug administration until tail-flick latencies are back to the baseline level.

[0064] The experiments will demonstrate the superior and synergistic effects on analgesia of the tri-combination compared to the components alone.

[0065] Example 2: The Combination of Morphine, Dextromethorphan, and Quinidine Potentiates Pain Relief as Compared to Morphine alone or Morphine in Combination with Dextromethorphan.

[0066] The addition of quinidine to a pharmaceutical composition of morphine, and dextromethorphan was tested using Ugo Basile Tail Flick method. This method is often used for in vivo screening of multiple drugs with analgesic activity. The animal was placed and held on the Ugo Basile Tail Flick instrument surface with the tail straight back and across an infrared light source. The heat source and timer are turned on by a foot pedal press, and automatically switch off when the animal flicks its tail off the emitter. Latency time is measured and analyzed as an analgesic effect. Each preparation was tested in 7 rats. The preparations tested in the rats were as follows: 1) vehicle (control), 2) morphine (dose of 25 mg/kg); 3) dextromethorphan (dose of 25 mg/kg); 4) morphine/dextromethorphan at a 1:1 ratio (wt:wt); 5) morphine/dextromethorphan/quinidine at a ratio of 1:1:0.1; 6)

morphine/dextromethorphan/quinidine at a ratio of 1:1:0.5; and 7) morphine/dextromethorphan/quinidine at a ratio of 1:1:1. The results shown below indicate that the combination of morphine/dextromethorphan/quinidine at a ratio of 1:1:1 significantly enhanced the analgesic effects of morphine alone and the combination of morphine and dextromethorphan. Additionally, the tri-combination of morphine/dextromethorphan/quinidine at a ratio of 1:1:1 lead to the increased analgesia within 1 hour of administration as compared to morphine alone or the combination of morphine and dextromethorphan. At 1 hour the tri-combination had a mean of 17.90 seconds, whereas the combination of morphine and dextromethorphan had a mean of 6.84. Therefore, the combination had 2.6 times more analgesia than the combination of morphine and dextromethorphan without quinidine. The tri-combination was also more effective at providing analgesia as compared to morphine alone. The mean of all seven animals shows an almost two fold increase in analgesia, however, when one animal is removed, which appears to have been an outlier, the tri-combination increases analgesia by about 2.7 times.

[0067] When looking at the median, morphine alone showed a time of 6.5, the combination of morphine and dextromethorphan showed a time of 5.60, and the tri-combination of morphine/dextromethorphan/quinidine at a ratio of 1:1:1 showed a time of 16.10, which shows that the tri-combination increases analgesia by about 2.5 times versus morphine alone and 2.875 times more analgesia when compared to the combination of morphine and dextromethorphan without quinidine. The increase in analgesia caused by the tri-combination was observed through at least 8 hours after administration. Therefore, these results demonstrate that the addition of quinidine to an opioid pharmaceutical preparation can increase the analgesic effects (*i.e.* pain relief) of the opioid. This significant increase in analgesia was unexpected and could not have been predicted. Table 1 shows the results of the different pharmaceutical preparations provided to the rats in the tail flick model with the mean and median shown for each preparation.

Table 1

		Tail Flick Time (seconds) after administration						
		1h	3h	5h	8h	10h	14h	24h
Vehicle	1	4.60	3.90	6.10	4.90	3.90	6.10	4.90
	2	3.10	3.20	3.90	5.40	3.20	3.80	4.60
	3	3.90	4.50	3.50	4.20	3.70	5.10	4.90

	4	7.50	5.90	5.20	4.30	6.30	4.20	5.30
	5	3.90	4.10	4.10	3.90	4.50	4.10	3.10
	6	4.90	3.30	3.90	3.90	4.90	3.20	3.90
	7	3.50	3.70	2.90	5.40	3.20	3.80	3.60
	Mean	**4.49**	**4.09**	**4.23**	**4.57**	**4.24**	**4.33**	**4.33**
	Median	**3.90**	**3.90**	**3.90**	**4.90**	**3.90**	**4.10**	**4.60**
Morphine 25 mg/kg	1	5.80	6.30	4.80	6.90	4.70	3.50	4.80
	2	5.10	7.60	6.60	10.50	4.10	7.50	7.60
	3	6.50	2.70	5.90	8.30	4.80	5.10	4.30
	4	30.10	9.50	10.90	8.50	6.50	7.80	3.40
	5	6.80	5.30	4.90	6.70	6.20	5.10	4.80
	6	10.50	5.90	4.60	6.30	4.20	2.90	4.90
	7	3.70	4.80	4.60	3.50	2.90	4.10	6.10
	Mean	**9.79**	**6.01**	**6.04**	**7.24**	**4.77**	**5.14**	**5.13**
	Median	**6.50**	**5.90**	**4.90**	**6.90**	**4.70**	**5.10**	**4.80**
Dextromethorphan 25 mg/kg	1	4.10	3.90	4.60	5.40	3.10	3.90	3.50
	2	3.90	4.60	6.40	5.10	5.50	5.20	4.70
	3	3.30	4.50	2.90	3.70	4.30	5.60	3.50
	4	4.80	5.40	6.40	7.30	4.80	3.80	4.30
	5	5.60	4.60	5.10	4.30	4.80	3.90	5.20
	6	3.70	3.30	4.10	3.80	3.90	5.10	3.70
	7	7.30	8.70	4.50	3.60	6.60	4.10	3.10
	Mean	**4.67**	**5.00**	**4.86**	**4.74**	**4.71**	**4.51**	**4.00**
	Median	**4.10**	**4.60**	**4.60**	**4.30**	**4.80**	**4.10**	**3.70**
Morphine/ Dextromethorphan 1:1 ratio (25 mg/kg:25 mg/kg)	1	13.80	3.50	2.90	3.90	5.50	6.30	2.30
	2	5.60	4.90	3.80	5.40	7.20	5.10	7.20
	3	5.20	8.30	6.90	4.60	3.90	4.90	3.50
	4	8.30	6.30	6.40	4.40	3.60	2.70	3.60
	5	4.90	6.40	6.20	3.80	6.90	6.20	4.60
	6	3.90	5.40	4.30	4.10	4.20	6.40	3.50
	7	6.20	4.30	4.70	4.70	4.90	6.60	3.20
	Mean	**6.84**	**5.59**	**5.03**	**4.41**	**5.17**	**5.46**	**3.99**
	Median	**5.60**	**5.40**	**4.70**	**4.40**	**4.90**	**6.20**	**3.50**
Morphine/ Dextromethorphan/ Quinidine 1:1:0.1 (25 mg/kg:25mg/kg:2.5 mg/kg)	1	3.50	4.60	6.10	4.60	3.20	4.30	3.70
	2	5.40	3.50	2.90	4.80	4.20	5.80	3.90
	3	12.80	9.20	3.40	5.20	3.40	6.10	3.40
	4	16.80	7.30	6.90	9.90	3.90	4.90	5.80
	5	5.60	3.90	4.90	3.90	3.50	5.90	4.70
	6	3.50	5.60	4.70	6.50	5.70	4.90	2.90
	7	3.90	3.90	4.50	5.90	9.10	6.10	4.50
	Mean	**5.46**	**5.90**	**4.27**	**5.66**	**3.86**	**4.21**	**4.04**
	Median	**5.40**	**4.60**	**4.70**	**5.20**	**3.90**	**5.80**	**3.90**

Morphine/ Dextromethorphan/ Quinidine 1:1:0.5 (25 mg/kg:25mg/kg:12.5 mg/kg)	1	2.50	4.40	2.50	3.60	2.90	5.80	4.90
	2	5.50	3.90	5.10	7.80	3.80	5.90	4.30
	3	4.60	4.70	5.60	4.90	5.80	4.20	4.20
	4	3.90	5.10	3.40	4.30	2.90	4.80	4.20
	5	5.80	7.40	3.60	5.40	2.80	2.50	2.90
	6	11.80	10.60	3.90	7.30	5.20	3.10	4.90
	7	4.10	5.20	5.80	6.30	3.60	3.20	2.90
	Mean	**5.35**	**5.80**	**4.23**	**5.63**	**3.83**	**4.21**	**4.06**
	Median	**4.60**	**5.10**	**3.90**	**5.40**	**3.60**	**4.20**	**4.20**
Morphine/ Dextromethorphan/ Quinidine 1:1:1 (25 mg/kg:25mg/kg:25 mg/kg)	1	15.10	5.30	7.30	9.20	5.90	5.20	4.40
	2	16.10	5.90	6.40	4.60	3.30	3.90	5.20
	3	6.10	7.90	9.90	5.30	8.20	4.20	5.20
	4	30.10	16.30	5.30	8.80	7.20	4.40	5.50
	5	15.10	9.30	8.90	6.10	7.50	8.20	2.90
	6	17.80	5.40	3.80	6.80	3.90	6.80	3.40
	7	25.00	7.90	7.80	5.70	5.90	3.50	6.80
	Mean	**17.90**	**8.29**	**7.06**	**6.64**	**5.99**	**5.17**	**4.77**
	Median	**16.10**	**7.90**	**7.30**	**6.10**	**5.90**	**4.40**	**5.20**

[0068] While the compounds, composition, and methods described herein have been described with reference to examples, those skilled in the art recognize that various modifications may be made without departing from the spirit and scope thereof.

[0069] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety.

What is claimed is:

1. A pharmaceutical composition comprising:
a NMDA antagonist;
a CYP2D6 inhibitor; and
an opioid agonist.

2. The pharmaceutical composition of claim 1, wherein the opioid agonist is chosen from one or more of: morphine, oxycodone, and hydromorphone, or a pharmaceutically acceptable salt thereof, or any combination thereof.

3. The pharmaceutical composition of claims 1 or 2, wherein the NMDA antagonist is chosen from one or more of dextromethorphan, a glycine antagonist, ifenprodil like compound, amantadine, MK-801 (dizocilpine; [5R,10S]-[+]-5-methyl-10,11- dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine), ketamine, memantine, D-AP5 (D(-)-2-Amino-5-phosphonovaleric acid) and , CPP (3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid), or a pharmaceutically acceptable salt thereof, or any combination thereof.

4. The pharmaceutical composition of any of claims 1-3, wherein the NMDA antagonist is dextromethorphan, or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition of any of claims 1-4, wherein the NMDA antagonist is dextromethorphan hydrobromide monohydrate.

6. The pharmaceutical composition of any of claims 1-5, wherein the CYP2D6 inhibitor is chosen from one or more of: quinidine, bupropion, cinacalcet, fluoxetine, paroxetine, duloxetine, sertraline, terbinafine, amiodarone, and cimetidine, or a pharmaceutically acceptable salt thereof, or any combination thereof.

7. The pharmaceutical composition of any of claims 1-6, wherein the CYP2D6 inhibitor is quinidine, or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of any of claims 1-7, wherein the CYP2D6 inhibitor is quinidine gluconate or quinidine sulfate.

9. The pharmaceutical composition of any of claims 1-8, wherein the pharmaceutical composition is formulated for simultaneous administration.

10. The pharmaceutical composition of any of claims 1-9, wherein the ratio of the opioid agonist to NMDA antagonist is about 1:1 (wt:wt).

11. The pharmaceutical composition of any one of claims 1-10, wherein the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.1 to 1 (wt:wt).

12. The pharmaceutical composition of claim 1, wherein the ratio of the opioid agonist to CYP2D6 inhibitor is about 0.1-1:1 (wt:wt).

13. The pharmaceutical composition of any one of claims 1-9, wherein the ratio of the opioid agonist to NMDA antagonist to CYP2D6 inhibitor is 1:1:0.1-1 (wt:wt:wt).

14. The pharmaceutical composition of claim 1, wherein the ratio of opioid agonist to NMDA antagonist to CYP2D6 inhibitor is about 1:1:1 (wt:wt:wt).

15. The pharmaceutical composition of any one of claims 1-14, wherein the opioid agonist is morphine sulfate.

16. The pharmaceutical composition of any one of claims 1-3 and 6-15, wherein the NDMA antagonist is dextromethorphan, or a pharmaceutically acceptable salt thereof.

17. The pharmaceutical composition of any one of claims 1-6 and 9-16, wherein the CYP2D6 inhibitor is quinidine, or a pharmaceutically acceptable salt thereof.

18. The pharmaceutical composition of any one of claims 1-17, wherein the composition comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, or about 60 mg of the opioid agonist.

19. The pharmaceutical composition of claim 1, wherein the composition comprises an opioid agonist, dextromethorphan, or a pharmaceutically acceptable salt thereof, and quinidine, or a pharmaceutically acceptable salt thereof, wherein the ratio of the morphine, or a pharmaceutically acceptable salt thereof, to dextromethorphan, or a pharmaceutically acceptable salt thereof, to quinidine, or a pharmaceutically acceptable salt thereof is about 1:1:1 (wt:wt:wt),

wherein the opioid agonist is morphine, oxycodone, or hydromorphone, or a pharmaceutically acceptable salt thereof.

20. The pharmaceutical composition of any one of claims 1-19, further comprising an opioid antagonist.

21. A pharmaceutical dosage form comprising:

a NMDA antagonist;

a CYP2D6 inhibitor; and

an opioid agonist.

22. The pharmaceutical dosage form of claim 21, wherein the opioid agonist is chosen from one or more of: morphine, oxycodone, and hydromorphone, or a pharmaceutically acceptable salt thereof, or any combination thereof.

23. The pharmaceutical dosage form of claim of claims 21 or 22, wherein the NMDA antagonist is chosen from one or more of dextromethorphan, a glycine antagonist, ifenprodil like compound, amantadine, MK-801 (dizocilpine; [5R,10S]-[+]-5-methyl-10,11- dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine), ketamine, memantine, D-AP5 (D(-)-2-Amino-5-phosphonovaleric acid) and, CPP (3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid), or a pharmaceutically acceptable salt thereof, or any combination thereof.

24. The pharmaceutical dosage form of any of claims 21-23, wherein the NMDA antagonist is dextromethorphan, or a pharmaceutically acceptable salt thereof.

25. The pharmaceutical dosage form of any of claims 21-24, wherein the NMDA antagonist is dextromethorphan hydrobromide monohydrate.

26. The pharmaceutical dosage form of any of claims 21-25, wherein the CYP2D6 inhibitor is chosen from one or more of: quinidine, bupropion, cinacalcet, fluoxetine, paroxetine, duloxetine, sertraline, terbinafine, amiodarone, and cimetidine, or a pharmaceutically acceptable salt thereof, or any combination thereof.

27. The pharmaceutical dosage form of any of claims 21-26, wherein the CYP2D6 inhibitor is quinidine, or a pharmaceutically acceptable salt thereof.

28. The pharmaceutical dosage form of any of claims 21-27, wherein the CYP2D6 inhibitor is quinidine gluconate or quinidine sulfate.

29. The pharmaceutical dosage form of any of claims 21-28, wherein the opioid agonist is morphine sulfate.

30. The pharmaceutical dosage form of any of claims 21-29, wherein the ratio of the opioid agonist to NMDA antagonist is about 1:1 (wt:wt).

31. The pharmaceutical dosage form of any of claims 21-29, wherein the ratio of the opioid agonist to CYP2D6 inhibitor is about 1:0.1 to 1 (wt:wt).

32. The pharmaceutical dosage form of any of claims 21-29, wherein the ratio of the opioid agonist to CYP2D6 inhibitor is about 0.1-1:1 (wt:wt).

33. The pharmaceutical dosage form of any one of claims 21-29, wherein the ratio of the opioid agonist to NMDA antagonist to CYP2D6 inhibitor is about 1:1:0.1-1 (wt:wt:wt).

34. The pharmaceutical dosage form of any one of claims 21-29, wherein the ratio of opioid agonist to NMDA antagonist to CYP2D6 inhibitor is about 1:1:1 (wt:wt:wt).

35. The pharmaceutical dosage form of claim 34, wherein the NMDA antagonist is dextromethorphan, or a pharmaceutically acceptable salt thereof, the CYP2D6 inhibitor is quinidine, or a pharmaceutically acceptable salt thereof, and the opioid agonist is morphine, oxycodone, or hydromorphone, or a pharmaceutically acceptable salt thereof.

36. The pharmaceutical dosage form any one of claims 21-35, wherein the opioid agonist is morphine sulfate.

37. The pharmaceutical dosage form of any one of claims 21-36, wherein the dosage form comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, or about 60 mg of the opioid agonist.

38. The pharmaceutical dosage form of any one of claims 21-37, further comprising an opioid antagonist.

39. The pharmaceutical dosage form of any one of claims 21-38, wherein said dosage form is an oral dosage form.

40. The pharmaceutical dosage form of any one of claims 21-39, wherein said dosage form is a fast-dissolving film.

41. The oral dosage form of claim 39, further comprising a sequestered opioid antagonist which is not released when the dosage form is administered intact.

42. The oral dosage form of claim 41, wherein said sequestered opioid antagonist is chosen from one or more of: naltrexone, naloxone, nalmefene, cyclazocine, and levallorphan, or a pharmaceutically acceptable salt thereof, or any combination thereof.

43. A method of treating or preventing pain in a subject comprising administering to the subject a pharmaceutical composition of any one of claims 1-20 or a pharmaceutical dosage form of any one of claims 21-42.

44. The method of claim 43, wherein the pharmaceutical composition or pharmaceutical dosage form is administered every 4 hours, every 6 hours, every 8 hours, or every 12 hours.

45. The method of claims 44 or 45, wherein the method does not comprise a risk evaluation mitigation strategy (REMS).

46. The method of any of claims 43-45, wherein the method treats pain.

47. A method of producing analgesia in a subject comprising administering to the subject a pharmaceutical composition of any one of claims 1-20 or a pharmaceutical dosage form of any one of claims 21-42.

48. The method of claim 47, wherein the pharmaceutical composition or pharmaceutical dosage form is administered every 4 hours, every 6 hours, every 8 hours, or every 12 hours.

49. The method of claims 47 or 48, wherein the method does not comprise a risk evaluation mitigation strategy (REMS).

50. The method of claim 47, wherein the analgesia that is produced is increased at least 2 times more compared to a composition that consists of an opioid agonist and NMDA antagonist.

51. The method of claim 50, wherein the opioid agonist is morphine, or a pharmaceutically acceptable salt thereof and the NMDA antagonist is dextromethorphan, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/22050

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 33/02 (2014.01)
USPC - 514/656,859,305
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A01N 33/02 (2014.01)
USPC 514/656,859,305

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC 514/656,859,305 (Keyword limited, terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar (NPL); Keywords: pharmaceutical NMDA antagonist CYP2D6 inhibitor opioid agonist quinidine dextromethorphan morphine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0249045 A1 (Babul) 30 September 2010 (30.09.2010) para [0049], [0091], [0385], [0411], [0414], [0416], [0438]	1-3, 12, 14, 19, 21-23
A	US 2012/0165363 A1 (Yakatan et al.) 28 June 2012 (28.06.2012) entire document	1-3, 12, 14, 19, 21-23

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2014 (23.05.2014)	15 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/22050

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-11, 13, 15-18, 20, 24-51
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.