COMPOSITIONS AND METHODS FOR TREATING OR PREVENTING PAIN

This application claims priority under 35 U.S.C. § 119 (e) from United States Provisional Application Serial No. 60/572,129, filed May 17, 2004 and United States Provisional Application Serial Nos. 60/574,050, 60/574,261, 60/574,167, 60/574,135, 60/574,106, 60/574,049, 60/574, 257, 60/574,262, 60/574,369 and 60/574,023 filed on May 24, 2004.

1. Technical Field

The methods and compositions disclosed herein relate generally to treating or preventing pain in a subject. More specifically, disclosed herein are compositions of nicotinic agonists, salts, hydrates, solvates or prodrugs thereof and opioid agonists salts, hydrates, solvates or prodrugs thereof, pharmaceutical compositions thereof and methods of using these compositions and pharmaceutical compositions thereof to treat or prevent pain in a subject. Also disclosed are methods of treating pain or preventing pain in a subject with nicotinic agonists, salts, hydrates, solvates or prodrugs thereof and opioid agonists, salts, hydrates, solvates or prodrugs thereof.

2. Background

Patient pain, typically after serious injury or surgical procedures, when inadequately treated, often leads to extended hospitalization, increased morbidity, increased mortality, development of chronic pain states and compromised patient prognosis. Opioid agonists are conventionally used to treat pain but despite therapeutic efficacy the effective dosage and hence utility of these narcotics is limited by significant side effects such as respiratory depression, nausea, pruritis, sedation, constipation and ileus. Other serious side effects of opioid agonists are due to central nervous system depression such as, for example, depression of ventilation, blood pressure and alertness.

Accordingly, development of adjuvants such as NSAIDs which reduce opioid dosage and accordingly, opioid side effects have been investigated (O'Hara *et al.*, *Pharmacotherpy* **1997**, 17 (5): 891; Alexander *et al.*, *J. Clin. Anesth.* **2002**, 14 (3): 187; Ng *et al.*, *Br. J. Anaesth* **2002**, 88 (5): 714). However, dosage of traditional NSAIDs is limited by well-known side effects while the use of COX-2 selective agents is compromised by adverse cardiovascular effects.

Nicotinic agonists have been used to treat various conditions including, for example, movement disorders, dysfunction of the central or autonomic nervous systems, neurodegenerative disorders, cardiovascular disorders, convulsive disorders, drug abuse and eating disorders. The pharmacological action of nicotinic agonists is mediated by nicotinic acetylcholine receptors, which are expressed, *inter alia*, in brain and spinal cord (Woolf, *Progress in Neurobiology* **1991**, 37:475-524; MacDermott *et al.*, *Annu Rev Neurosci* **1999**, 22; 443-485). Agonism of nicotinic acetylcholine receptors leads to a broad spectrum of pharmacologic actions including, for example, modest increase in heart rate and blood pressure and moderate analgesia.

Multiple functional nicotinic acetylcholine receptor subtypes are expressed in the human brain and are composed of a combination of α and β subunits arranged in a pentameric ring. Generally, the receptor contains three β and two α subunits or five α subunits. Currently, nine different α subunit types and three different β subunit types have been identified in the brain. Subunits $\alpha_{7\text{-}10}$ can form homopentameric nicotinic receptors.

Ideally, opioid adjuvants will have synergy for the desired therapeutic effects, thus reducing the effective dosage of opioid agonist required for analgesia while counteracting opioid side effects. Accordingly, such adjuvants will lack toxicity at the dosage required to provide therapeutic synergy while reducing the effective dosage of opioid agonist. Thus, what is needed are opioid adjuvants which have analgesic properties and/or anti-inflammatory properties and are central nervous stimulants.

3. Summary

These and other needs are satisfied by compositions comprised of nicotinic agonists, salts, hydrates, solvates, prodrugs or metabolites thereof and opioid agonists salts, hydrates, solvates, prodrugs or metabolites thereof, pharmaceutical compositions thereof and methods of using these compositions and pharmaceutical compositions thereof to treat or prevent pain in a subject. Also disclosed herein are methods of treating pain with nicotinic agonists salts, hydrates, solvates, prodrugs or metabolites thereof and opioid agonists salts, hydrates, solvates, prodrugs or metabolites thereof where the therapeutic index of the combination of nicotinic agonists or salts, hydrates, solvates, prodrugs or metabolites thereof and opioid

agonists, salts, hydrates, solvates, prodrugs or metabolites thereof is substantially similar to or greater than the therapeutic index of the opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof or the therapeutic index of the nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof. In some of the above aspects, the opioid agonist is a rapid onset opioid agonist. Without wishing to be bound by theory, the stimulatory properties and analgesic properties and/or anti-inflammatory properties of nicotinic agonists, respectively, may reduce opioid side effects and synergize therapeutically with opioids.

In a first aspect, a composition comprising a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a therapeutically effective amount of an opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof is provided. In some embodiments, the opioid agonist is a rapid onset agonist.

In another aspect, pharmaceutical compositions are provided. In some embodiments, a pharmaceutical composition comprising a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates prodrugs or metabolites thereof and a therapeutically effective amount of an opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a pharmaceutically acceptable vehicle is provided. In other embodiments, a pharmaceutical composition comprising a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a therapeutically effective amount of a rapid onset opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a pharmaceutically acceptable vehicle is provided.

In still another aspect, methods of treating or preventing pain in a subject are provided. In some embodiments, these methods comprise administering to the subject in need of such treatment or prevention the compositions and pharmaceutical compositions, *supra*. In other embodiments, nicotinic agonists or salts, hydrates, solvates, prodrugs or metabolites thereof and opioid agonists or salts, hydrates, solvates, prodrugs or metabolites thereof are administered to a subject where the therapeutic index of the combination of nicotinic agonists or salts, hydrates, solvates, prodrugs or metabolites thereof and opioid agonists or salts, hydrates, solvates, prodrugs or metabolites thereof is substantially similar to or greater than the therapeutic index of the opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof or the therapeutic index of the nicotinic agonist or salts, hydrates,

solvates, prodrugs or metabolites thereof. In some of the above embodiments, the opioid agonist is a rapid onset opioid agonist.

4. Brief Description Of The Drawings

Figure 1 illustrates the dose response curve for fentanyl and nicotine in the mouse paw incision model;

Figure 2 illustrates the dose response curve for fentanyl in the mouse paw incision model;

Figure 3 illustrates the dose response curve for fentanyl and nicotine in the mouse paw incision model; and

Figure 4 illustrates the dose response curve for morphine and nicotine in the mouse paw incision model where the dose of nicotine is constant and the dose of fentanyl is varied.

5. Detailed Description

5.1 Definitions

"Metabolite" as used herein, refers to any substance produced by metabolism of either an opioid agonist or a nicotinic agonist.

"Pharmaceutically acceptable vehicle" as used herein, refers to a diluent, adjuvant, excipient or carrier with which the nicotinic agonist and/or opioid agonist disclosed herein are administered.

"Preventing" or "prevention" as used herein, refers, in some embodiments, to inhibiting pain, either physically, (*e.g.*, stabilization of a discernible symptom) or physiologically, (*e.g.*, stabilization of a physical parameter) or both. In other embodiments, "preventing" or "prevention" refers to delaying the onset of pain.

"Prodrug" as used herein, refers to a derivative of an opioid agonist or a nicotinic agonist that requires a transformation within the body to release the active

drug. Prodrugs are frequently, although not necessarily, pharmacologically inactive until converted to the parent drug. A hydroxyl containing drug may be converted, for example, to a sulfonate, ester or carbonate prodrug, which may be hydrolyzed *in vivo* to provide the hydroxyl compound. An amino containing drug may be converted, for example, to a carbamate, amide, enamine, imine, N-phosphonyl, N-phosphoryl or N-sulfenyl prodrug, which may be hydrolyzed *in vivo* to provide the amino compound. A carboxylic acid drug may be converted, for example, to an ester (including silyl esters and thioesters), amide or hydrazide prodrug, which be hydrolyzed *in vivo* to provide the carboxylic acid compound. Prodrugs other than those described, *supra*, are well known to the ordinarily skilled artisan and are within the scope of the present disclosure.

"Rapid Onset Opioid Agonist" as used herein, refers to an opioid agonist that takes less than 10 minutes to reach peak effect after bolus intravenous injection. For example, hydromorphone, methadone, meperidine, sufentanil, fentanyl, alfentanil and remifentanil are rapid onset opioids while morphine is not a rapid onset opioid.

"Salt" as used herein, refers to a salt of an opioid agonist or nicotinic agonist which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, *t*-butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth

ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like.

"Subject" as used herein, refers to a mammal, which includes, but is not limited to, domestic animals and humans. In some embodiments, the subject is a human female.

"Treating" or "treatment" as used herein, refers, in some embodiments, to ameliorating the pain (*i.e.*, arresting or reducing the development of pain or at least one of the clinical symptoms thereof). In other embodiments "treating" or "treatment" refers to ameliorating at least one physical parameter of pain, which may not be discernible by the subject.

"Therapeutically effective amount" as used herein, refers to the amount of a nicotinic agonist or opioid agonist that, when administered to a subject for treating or preventing pain, is sufficient to effect such treatment or prevention of pain. The "therapeutically effective amount" will vary depending on the agonist, the disease and its severity and the age, weight, *etc.*, of the subject to be treated.

"Therapeutically effective lifetime" as used herein, refers to the lifetime (*i.e.*, the amount of time) of the nicotinic agonist or opioid agonist where the agonist is effective in treating or preventing pain. The "therapeutically effective lifetime" will vary depending on the agonist, the disease and its severity and the age, weight, *etc.*, of the subject to be treated.

Reference will now be made in detail to various embodiments. It will be understood that the invention is not limited to these embodiments. To the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the allowed claims.

5.2 Compositions of Nicotinic Agonists and Opioid Agonists

Compositions comprised of nicotinic agonists, salts, hydrates, solvates, prodrugs or metabolites thereof and opioid agonists salts, hydrates, solvates, prodrugs or metabolites thereof and pharmaceutical compositions thereof are described herein.

While not wishing to be bound by theory, nicotinic agonists may reduce the dose of opioid agonists required to treat and/or prevent pain *via* either additive or synergistic effect. In general, side effects due to nicotinic agonists involve activation of the central nervous system while side effects of opioid agonists include central nervous system depression. Accordingly, the net toxicities of the two agonists may be offset when delivered as a combination. Thus, the therapeutic window for opioid analgesia may be increased by a composition comprising a nicotinic agonist and an opioid agonist. Additive or synergistic effect may require co-release of the nicotinic agonist and opioid agonist.

Generally, nicotinic agonists are compounds which activate the nicotinic receptor. Nicotinic agonists include, but are not limited to, nicotine, *meta*-nicotine, DMPP, DMAC, 3-2,4-dimethoxybenzylidine anabaseine (DMBX-anabaseine), choline, acetylcholine, cytisine, GTS-21, DMPP, DMAC, epibatidine (Quian *et al.*, United States Patent No. 6,077,846), ABT-418, ABT-594 (Decker *et al.*, *Curr Top Med Chem.* **2004**, 4:369-384; Michelmore *et al. Naunyn Schmiedebergs Arch Pharmacol* **2002**, 366(3): 235-45), SIB-1508 and SIB-1558 (Jain, *Curr Opin Investig Drugs* **2004**, 5(1): 76-81). In some embodiments, the nicotinic agonist is nicotine. In other embodiments, nicotine is the (+) antipode. In still other embodiments, nicotine is the (-) antipode. In still other embodiments, nicotine is a mixture of the (+) antipode and the (-) antipode. In still other embodiments, nicotinic agonists do not include *meta*-nicotine.

In still other embodiments, the nicotinic agonist is selective for a $\alpha 7$ nicotinic receptor. A $\alpha 7$ nicotinic receptor can comprise only $\alpha 7$ subunits or alternatively can consist of $\alpha 7$ subunit(s) in conjunction with subunit(s) of other nicotinic subtypes. Accordingly, in some embodiments, the nicotinic receptor is a homopentamer while in other embodiments, the nicotinic receptor is a heteropentamer.

In some embodiments, a nicotinic agonist is selective for a $\alpha 7$ nicotinic receptor if it activates the $\alpha 7$ nicotinic receptor more than two fold in comparison to any other nicotinic receptor. In other embodiments, a nicotinic agonist is selective for a $\alpha 7$ nicotinic receptor if it activates the $\alpha 7$ receptor more than five fold in comparison to any other nicotinic receptor. In still other embodiments, a nicotinic agonist is selective for a $\alpha 7$ nicotinic receptor if it activates the $\alpha 7$ receptor more than ten fold in comparison to any other nicotinic receptor. In still other embodiments, a nicotinic agonist is selective for a $\alpha 7$ nicotinic receptor if it activates the $\alpha 7$ receptor more than

twenty fold in comparison to any other nicotinic receptor. In still other embodiments, a nicotinic agonist is selective for a α7 nicotinic receptor if it activates the α7 receptor more than fifty fold in comparison to any other nicotinic receptor.

Examples of selective α7 receptor agonists include, but are not limited to, ABT-418, cocaine methiodide, 3-2,4-dimethoxybenzylidine anabaseine (DMXB-A), 3-(4-hydroxybenzylidene)anabaseine, 3-(4-methoxybenzylidene)anabaseine, 3-(4-aminobenzylidene)anabaseine, 3-(4-hydroxy-2-methoxybenzylidene)anabaseine, 3-(4-methoxy-2-hydroxybenzylidene)anabaseine, *trans*-3-cinnamylidene anabaseine, *trans*-3-(2-methoxy-cinnamylidene)anabaseine and *trans*-3-(4-methoxycinnamylidene)anabaseine, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-hydroxyphenoxy)benzamide, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-acetamidophenoxy)benzamide, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(phenylsulfanyl)benzamide, and N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(3-chlorophenylsulphonyl)benzamide, (l-aza-bicyclo[2.2.2]oct-3-yl) carbamic acid 1-(2-fluorophenyl)-ethyl ester and compounds disclosed in Tracey *et al.*, International Publication No. 2004/0502365.

Opioid agonists include, but are not limited to, fentanyl, hydromorphone, alfentanil, remifentanil, carfentanil, sufentanil, butorphanol, buprenorphine, pentazocine, meperidine, oxycodone, oxymorphone, hydrocodone, hydromorphone, codeine, methadone, diacetylmorphine, morphine, etrophine, levorphanol, oxycodone, oxymorphone, naltrexone, nalbuphine, nalorphine, buprenorphine, codeine, diacetylmorphine, dihydrocodeine, dihydroetorphine, diprenorphine, etorphine, levomethadyl actetate hydrochloride, levorphanol, lofentanil, meperidine, naloxone, methyl naltrexone, beta-hydroxy 3-methylfentanyl, N-methylnaltrexone, normorphine, propoxyphene, tilidine, thebaine, nalbuphine, nalmefene, neopine, penomorphone and tramadol. In some embodiments, the opioid agonist is a rapid onset agonist. In other embodiments, the opioid agonist is sufentanil, fentanyl, oxycodone, hydrocodone or hydromorphone. In still other embodiments, the opioid agonist is fentanyl.

In some embodiments, the nicotinic agonist is nicotine and the opioid agonist is sufentanil, oxycodone, hydrocodone or hydromorphone. In other embodiments, the nicotinic agonist is (+) nicotine and the opioid agonist is fentanyl. In still other embodiments, the nicotinic agonist is (-) nicotine and the opioid agonist is fentanyl.

In still other embodiments, the nicotinic agonist is (+) nicotine and the opioid agonist is morphine. In still other embodiments, the nicotinic agonist is (-) nicotine and the opioid agonist is morphine.

As the various names of nicotinic agonists and/or opioid agonists used herein represent only one of the possible tautomeric or conformational forms, it should be understood that any tautomers or conformational isomers of nicotinic agonists and/or opioid agonists as well as mixtures of these various different isomeric forms are encompassed by the present disclosure.

The nicotinic agonists and/or opioid agonists described herein also include isotopically labeled nicotinic agonists and/or opioid agonists where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the nicotinic agonists and/or opioid agonists disclosed herein include, but are not limited to, ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, *etc.* Nicotinic agonists and/or opioid agonists described herein may exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In general, nicotinic agonists and/or opioid agonists may be hydrated, solvated or N-oxides. Certain nicotinic agonists and/or opioid agonists may exist in multiple crystalline or amorphous forms. All physical forms are equivalent for the uses contemplated herein.

Also provided by the instant disclosure is an article of manufacture, which comprises a packaging material having therein, a nicotinic agonist and an opioid agonist with a label indicating a use of the nicotinic agonist as an analgesic adjuvant for pain.

5.3 Therapeutic Methods of Use

In some embodiments, a composition comprising a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a therapeutically effective amount of an opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof or pharmaceutical compositions thereof is administered to a subject to treat and/or prevent pain. Also disclosed herein are methods of treating pain with a combination of nicotinic agonists salts, hydrates, solvates, prodrugs or metabolites thereof and opioid agonists salts, hydrates, solvates, prodrugs or metabolites thereof where the therapeutic index of the combination of nicotinic agonists or salts, hydrates, solvates, prodrugs or metabolites thereof and

opioid agonists, salts, hydrates, solvates, prodrugs or metabolites thereof is substantially similar to or greater than the therapeutic index of the opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof or the therapeutic index of the nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof.

In other embodiments, a composition comprising a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a therapeutically effective amount of a rapid onset opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof or pharmaceutical compositions thereof is administered to a subject to treat and/or prevent pain. In some embodiments, the therapeutic index of the combination of nicotinic agonists or salts, hydrates, solvates, prodrugs or metabolites thereof and rapid onset opioid agonists, salts, hydrates, solvates, prodrugs or metabolites thereof is substantially similar to or greater than the therapeutic index of the rapid onset opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof or the therapeutic index of the nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof.

In still other embodiments, a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a therapeutically effective amount of an opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof is administered to a subject to treat and/or prevent pain where the therapeutic index of the nicotinic agonists or salts, hydrates, solvates, prodrugs or metabolites thereof and opioid agonists, salts, hydrates, solvates, prodrugs or metabolites thereof is substantially similar to or greater than the therapeutic index of the opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof or the therapeutic index of the nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof.

In some embodiments, a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates or prodrugs thereof and a therapeutically effective amount of a rapid onset opioid agonist or salts, hydrates, solvates or prodrugs thereof is administered to a subject to treat and/or prevent pain. In still other embodiments, the therapeutic index of the nicotinic agonists or salts, hydrates, solvates, prodrugs or metabolites thereof and the rapid onset opioid agonists, salts, hydrates, solvates, prodrugs or metabolites thereof is substantially similar to or greater than the therapeutic index of the rapid onset opioid agonist or salts, hydrates, solvates,

prodrugs or metabolites thereof or the therapeutic index of the nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof.

The type of pain which may treated by methods disclosed herein include, but are not limited to, acute pain, chronic pain, neuropathic pain, acute traumatic pain, arthritic pain, osteoarthritic pain, rheumatoid arthritic pain, muscular skeletal pain, post-dental surgical pain, dental pain, myofascial pain, cancer pain, visceral pain, diabetic pain, muscular pain, post-herpetic neuralgic pain, chronic pelvic pain, endometriosis pain, pelvic inflammatory pain and child birth related pain. Acute pain includes, but is not limited to, acute traumatic pain or post-surgical pain. Chronic pain includes, but is not limited to, neuropathic pain, arthritic pain, osteoarthritic pain, rheumatoid arthritic pain, muscular skeletal pain, dental pain, myofascial pain, cancer pain, diabetic pain, visceral pain, muscular pain, post-herpetic neuralgic pain, chronic pelvic pain, endometriosis pain, pelvic inflammatory pain and back pain. In some embodiments, when the subject is a human female, chronic pain includes, in particular, chronic pelvic pain, endometriosis pain, pelvic inflammatory pain and child birth related pain.

In some embodiments, the nicotinic agonist and the opioid agonist are concurrently administered to a subject to treat or prevent pain. For example, the nicotinic agonist may be released over the therapeutically effective lifetime of the opioid agonist. In other embodiments, particularly where the nicotinic agonist and the opioid agonist are not part of the same composition or pharmaceutical composition thereof, the nicotinic agonist and the opioid agonist may be administered sequentially as well as concurrently.

Without wishing to be bound by theory, maintenance of therapeutically effective amounts of nicotinic agonist over the therapeutically effective lifetime of the opioid agonist may be necessary for effective synergy or additivity. Since clearance of nicotinic agonists may be rapid in comparison to that of many opioid agonists, maintenance of therapeutically effective amounts of nicotinic agonists may require frequent nicotinic agonist administration at regular dosing intervals if performed sequentially. Alternatively, maintenance of therapeutically effective amounts of nicotinic agonists may require sustained release or constant infusion of nicotinic agonist when the nicotinic agonist and the opioid agonist are concurrently administered.

5.4 Pharmaceutical Compositions

The pharmaceutical compositions disclosed herein comprise a composition of a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and an opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof with a suitable amount of a pharmaceutically acceptable vehicle, so as to provide a form for proper administration to a subject. Also provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a pharmaceutically acceptable vehicle and a pharmaceutical composition comprising a therapeutically effective amount of an opioid agonist or salts, hydrates, solvates, prodrugs or metabolites thereof and a pharmaceutically acceptable vehicle.

Suitable pharmaceutical vehicles include excipients such as 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 pharmaceutical compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used.

Pharmaceutical compositions may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries, which facilitate processing of compositions and compounds disclosed herein into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

The present pharmaceutical compositions can 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 known to the skilled artisan. In some embodiments, the pharmaceutically acceptable vehicle is a capsule (see *e.g.*, Grosswald *et al.*, United States Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles have been described in the art (see Remington's

Pharmaceutical Sciences, Philadelphia College of Pharmacy and Science, 19th Edition, 1995).

Pharmaceutical compositions for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, slurries, suspensions or elixirs, for example. Orally administered compositions may contain one or more optional agents, for example, sweetening agents such as fructose, aspartame or saccharin, flavoring agents such as peppermint, oil of wintergreen, or cherry coloring agents and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, when in tablet or pill form, the compositions may be coated to delay disintegration and absorption in the gastrointestinal tract, thereby providing a sustained action over an extended period of time. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, sucrose, sorbitol, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP), granulating agents, binding agents and disintegrating agents such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate *etc.*

In some embodiments, pharmaceutical compositions are in the form of lozenges or lollipops where dissolution and release of the active ingredients occurs in the oral cavity, generally through the oral mucosa. For these embodiments, buffering agents may also be used to provide an optimum environment for delivery of the agents or compositions. Additional components may include, for example, sweeteners, binders, diluents, disintegrating agents, lubricating agents, *etc.* In some embodiments, a nicotinic agonist rich coating may be applied to the exterior of the oral transmucosal (lozenge or lollipop) delivery system, accelerating the initial onset of nicotinic agonist effect. The independent rates of delivery with an oral transmucosal delivery system may be achieved by adjusting the relative concentrations of the nicotinic agonist and opioid agonist and/or by using different polymers with the nicotinic agonist and opioid agonist which independently control their release rates into the mouth.

In still other embodiments, the pharmaceutical composition is a dissolving sublingual tablet, where dissolution and release of the active ingredients occurs under

the tongue, and the compositions and/or compounds disclosed herein are absorbed through the oral mucosa. In these embodiments, buffer agents may also be used to provide an optimum environment for delivery of each of the agents. Additional components may include, for example, sweeteners, binders, diluents, disintegrating agents, *etc.* Additionally, a readily dissolvable coating containing the nicotinic agonist may be applied to the exterior of the sublingual tablet, accelerating the initial onset of nicotinic agonist effect. The independent rates of delivery with a sublingual tablet may be achieved by using different polymers with the nicotinic agonist and the opioid agonist, and thus independently controlling release rates of these agents into the mouth.

The methods that involve oral administration of compositions and/or compounds disclosed herein of can also be practiced with a number of different dosage forms, which provide sustained release.

In some embodiments, the dosage form is comprised of beads that on dissolution or diffusion release compositions and/or compounds disclosed herein over an extended period of hours, preferably, over a period of at least 6 hours, more preferably, over a period of at least 8 hours and even more preferably, over a period of at least 12 hours and most preferably, over a period of at least 24 hours. The beads may have a central composition or core comprising compositions and/or compounds disclosed herein and pharmaceutically acceptable vehicles, including optional lubricants, antioxidants and buffers. The beads may be medical preparations with a diameter of about 1 to about 2 mm. Individual beads may comprise doses of the compositions and/or compounds disclosed herein. The beads, in some embodiments, are formed of non-cross-linked materials to enhance their discharge from the gastrointestinal tract. The beads may be coated with a release rate-controlling polymer that gives a timed-release profile.

The time-release beads may be manufactured into a tablet for therapeutically effective administration. The beads can be made into matrix tablets by direct compression of a plurality of beads coated with, for example, an acrylic resin and blended with excipients such as hydroxypropylmethyl cellulose. The manufacture of beads has been disclosed in the art (Lu, *Int. J. Pharm.* **1994**, 112, 117-124; Pharmaceutical Sciences by Remington, 14th ed, pp 1626-1628 (1970); Fincher, *J. Pharm. Sci.* **1968**, 57, 1825-1835; Benedikt, United States Patent No. 4,083,949) as

has the manufacture of tablets (Pharmaceutical Sciences, by Remington, 17th Ed, Ch. 90, pp 1603-1625 (1985).

In other embodiments, an oral sustained release pump may be used (Langer, *supra*; Sefton, **1987**, *CRC Crit Ref Biomed. Eng.* 14:201; Saudek *et al.*, **1989**, *N. Engl. J Med.* 321:574).

In still other embodiments, polymeric materials can be used (See "Medical Applications of Controlled Release," Langer and Wise (eds.), CRC Press., Boca Raton, Florida (1974); "Controlled Drug Bioavailability," Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Langer *et al.*, **1983**, *J Macromol. Sci. Rev. Macromol Chem.* 23:61; Levy *et al.*, **1985**, *Science* 228: 190; During *et al.*, **1989**, *Ann. Neurol.* 25:351; Howard *et al.*, **1989**, *J. Neurosurg.* 71:105). In some embodiments, polymeric materials are used for oral sustained release delivery. Such polymers include, for example, sodium carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and hydroxyethylcellulose (most preferred, hydroxypropylmethylcellulose). Other cellulose ethers have been described (Alderman, *Int. J. Pharm. Tech. & Prod. Mfr.* **1984**, 5(3) 1-9). Factors affecting drug release are well known to the skilled artisan and have been described in the art (Bamba *et al.*, *Int. J. Pharm.* **1979**, 2, 307).

In still other embodiments, enteric-coated preparations can be used for oral sustained release administration. Coating materials include, for example, polymers with a pH-dependent solubility (*i.e.*, pH-controlled release), polymers with a slow or pH-dependent rate of swelling, dissolution or erosion (*i.e.*, time-controlled release), polymers that are degraded by enzymes (*i.e.*, enzyme-controlled release) and polymers that form firm layers that are destroyed by an increase in pressure (*i.e.*, pressure-controlled release).

In yet other embodiments, drug-releasing lipid matrices can be used for oral sustained release administration. For example, solid microparticles of compositions and/or compounds disclosed herein may be coated with a thin controlled release layer of a lipid (*e.g.*, glyceryl behenate and/or glyceryl palmitostearate) as disclosed in Farah *et al.*, United States Patent No. 6,375,987 and Joachim *et al.*, United States Patent No. 6,379,700. The lipid-coated particles can optionally be compressed to form a tablet. Another controlled release lipid-based matrix material which is suitable for sustained release oral administration comprises polyglycolized glycerides as disclosed in Roussin *et al.*, United States Patent No. 6,171,615.

In yet other embodiments, waxes can be used for oral sustained release administration. Examples of suitable sustained releasing waxes are disclosed in Cain *et al.*, United States Patent No. 3,402,240 (carnauba wax, candedilla wax, esparto wax and ouricury wax); Shtohryn *et al.*, United States Patent No. 4,820,523 (hydrogenated vegetable oil, bees wax, caranuba wax, paraffin, candelillia, ozokerite and mixtures thereof); and Walters, United States Patent No. 4,421,736 (mixture of paraffin and castor wax).

In still other embodiments, osmotic delivery systems are used for oral sustained release administration (Verma *et al.*, *Drug Dev. Ind. Pharm.* **2000**, 26:695-708). In some embodiments, OROS® systems made by Alza Corporation, Mountain View, CA are used for oral sustained release delivery devices (Theeuwes *et al.*, United States Patent No. 3,845,770; Theeuwes *et al.*, United States Patent No. 3,916,899).

In yet other embodiments, a controlled-release system can be placed in proximity of the target of the compositions and/or compounds disclosed herein thus requiring only a fraction of the systemic dose (See, *e.g.*, Goodson, in "Medical Applications of Controlled Release," *supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems are discussed in Langer, **1990**, *Science* 249:1527-1533 may also be used.

In still other embodiments, the dosage form comprises compositions and/or compounds disclosed herein coated on a polymer substrate. The polymer can be an erodible, or a nonerodible polymer. The coated substrate may be folded onto itself to provide a bilayer polymer drug dosage form. For example, compositions and/or compounds disclosed herein can be coated onto a polymer such as a polypeptide, collagen, gelatin, polyvinyl alcohol, polyorthoester, polyacetyl, or a polyorthocarbonate and the coated polymer folded onto itself to provide a bilaminated dosage form. In operation, the bioerodible dosage form erodes at a controlled rate to dispense the compositions and/or compounds over a sustained release period. Representative biodegradable polymers comprise a member selected from the group consisting of biodegradable poly(amides), poly (amino acids), poly(esters), poly(lactic acid), poly(glycolic acid), poly(carbohydrate), poly(orthoester), poly (orthocarbonate), poly(acetyl), poly(anhydrides), biodegradable poly(dihydropyrans), and poly(dioxinones) which are known in the art (Rosoff, *Controlled Release of Drugs*,

Chap. 2, pp. 53-95 (1989); Heller *et al.*, United States Patent No. 3,811,444; Michaels, United States Patent No. 3,962,414; Capozza, United States Patent No. 4,066,747; Schmitt, United States Patent No. 4,070,347; Choi *et al.*, United States Patent No. 4,079,038; Choi *et al.*, United States Patent No. 4,093,709).

In other embodiments, the dosage form comprises compositions and/or compounds disclosed herein loaded into a polymer that releases the drug(s) by diffusion through a polymer, or by flux through pores or by rupture of a polymer matrix. The drug delivery polymeric dosage form comprises a concentration of 10 mg to 2500 mg homogenously contained in or on a polymer. The dosage form comprises at least one exposed surface at the beginning of dose delivery. The non-exposed surface, when present, is coated with a pharmaceutically acceptable material impermeable to the passage of the drug(s). The dosage form may be manufactured by procedures known in the art. An example of providing a dosage form comprises blending a pharmaceutically acceptable carrier like polyethylene glycol, with a known dose of compositions and/or compounds disclosed herein at an elevated temperature, (*e.g.*, 37 °C), and adding it to a silastic medical grade elastomer with a cross-linking agent, for example, octanoate, followed by casting in a mold. The step is repeated for each optional successive layer. The system is allowed to set for about 1 hour, to provide the dosage form. Representative polymers for manufacturing the dosage form comprise a member selected from the group consisting of olefin, and vinyl polymers, addition polymers, condensation polymers, carbohydrate polymers, and silicone polymers as represented by polyethylene, polypropylene, polyvinyl acetate, polymethylacrylate, polyisobutylmethacrylate, poly alginate, polyamide and polysilicone. The polymers and procedures for manufacturing them have been described in the art (Coleman *et al.*, *Polymers* **1990**, 31, 1187-1231; Roerdink *et al.*, *Drug Carrier Systems* **1989**, 9, 57-10; Leong *et al.*, *Adv. Drug Delivery Rev.* **1987**, 1, 199-233; Roff *et al.*, *Handbook of Common Polymers* 1971, CRC Press; Chien *et al.*, United States Patent No. 3,992,518).

In other embodiments, the dosage from comprises a plurality of tiny pills. The tiny time-release pills provide a number of individual doses for providing various time doses for achieving a sustained-release drug delivery profile over an extended period of time up to 24 hours. The matrix comprises a hydrophilic polymer selected from the group consisting of a polysaccharide, agar, agarose, natural gum, alkali alginate including sodium alginate, carrageenan, fucoidan, furcellaran, laminaran, hypnea,

gum arabic, gum ghatti, gum karaya, grum tragacanth, locust bean gum, pectin, amylopectin, gelatin, and a hydrophilic colloid. The hydrophilic matrix comprises a plurality of 4 to 50 tiny pills, each tiny pill comprise a dose population of from 10 ng, 0.5mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 5.0 mg, *etc.* The tiny pills comprise a release rate-controlling wall of 0.001 mm up to 10 mm thickness to provide for the timed release of drug(s). Representative wall forming materials include a triglyceryl ester selected from the group consisting of glyceryl tristearate, glyceryl monostearate, glyceryl dipalmitate, glyceryl laureate, glyceryl didecenoate and glyceryl tridenoate. Other wall forming materials comprise polyvinyl acetate, phthalate, methylcellulose phthalate and microporous olefins. Procedures for manufacturing tiny pills are disclosed in Urquhart *et al.*, United States Patent No. 4,434,153; Urquhart *et al.*, United States Patent No. 4,721,613; Theeuwes, United States Patent No. 4,853,229; Barry, United States Patent No. 2,996,431; Neville, United States Patent No. 3,139,383; Mehta, United States Patent No. 4,752,470.

In other embodiments, the dosage form comprises an osmotic dosage form, which comprises a semipermeable wall that surrounds a therapeutic composition comprising compositions and/or compounds disclosed herein. In use within a subject, the osmotic dosage form comprising a homogenous composition, imbibes fluid through the semipermeable wall into the dosage form in response to the concentration gradient across the semipermeable wall. The therapeutic composition in the dosage form develops osmotic pressure differential that causes the therapeutic composition to be administered through an exit from the dosage form over a prolonged period of time up to 24 hours (or even in some cases up to 30 hours) to provide controlled and sustained release. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations.

In other embodiments, the dosage form comprises another osmotic dosage form comprising a wall surrounding a compartment, the wall comprising a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of compositions and/or compounds disclosed herein present in the compartment, a drug-containing layer composition in the compartment, a hydrogel push layer composition in the compartment comprising an osmotic formulation for imbibing and absorbing fluid for expanding in size for pushing the drug composition layer from the dosage form, and at least one passageway in the wall for releasing the composition. The method delivers the compositions

and/or compounds disclosed herein by imbibing fluid through the semipermeable wall at a fluid imbibing rate determined by the permeability of the semipermeable wall and the osmotic pressure across the semipermeable wall causing the push layer to expand, thereby delivering the compositions and/or compounds disclosed herein from the dosage form through the exit passageway to a subject over a prolonged period of time (up to 24 or even 30 hours). The hydrogel layer composition may comprise 10 mg to 1000 mg of a hydrogel such as a member selected from the group consisting of a polyalkylene oxide of 1,000,000 to 8,000,000 weight-average molecular weight which are selected from the group consisting of a polyethylene oxide of 1,000,000 weight-average molecular weight, a polyethylene oxide of 2,000,000 molecular weight, a polyethylene oxide of 4,000,000 molecular weight, a polyethylene oxide of 5,000,000 molecular weight, a polyethylene oxide of 7,000,000 molecular weight and a polypropylene oxide of the 1,000,000 to 8,000,000 weight-average molecular weight; or 10 mg to 1000 mg of an alkali carboxymethylcellulose of 10,000 to 6,000,000 weight average molecular weight, such as sodium carboxymethylcellulose or potassium carboxymethylcellulose. The hydrogel expansion layer comprises 0.0 mg to 350 mg, in present manufacture; 0.1 mg to 250 mg of a hydroxyalkylcellulose of 7,500 to 4,500,00 weight-average molecular weight (*e.g.*, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxybutylcellulose or hydroxypentylcellulose) in present manufacture; 1 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose and sorbitol; 0 to 5 mg of a colorant, such as ferric oxide; 0 mg to 30 mg, in a present manufacture, 0.1 mg to 30 mg of a hydroxypropylalkylcellulose of 9,000 to 225,000 average-number molecular weight, selected from the group consisting of hydroxypropylethylcellulose, hydroxypropypentylcellulose, hydroxypropylmethylcellulose, and hydropropylbutylcellulose; 0.00 to 1.5 mg of an antioxidant selected from the group consisting of ascorbic acid, butylated hydroxyanisole, butylated hydroxyquinone, butylhydroxyanisole, hydroxycoumarin, butylated hydroxytoluene, cephalm, ethyl gallate, propyl gallate, octyl gallate, lauryl gallate, propyl-hydroxybenzoate, trihydroxybutyrophenone, dimethylphenol, dibutylphenol, vitamin E, lecithin and ethanolamine; and 0.0 mg to 7 mg of a lubricant selected from the group consisting of calcium stearate, magnesium stearate, zinc stearate, magnesium oleate, calcium

palmitate, sodium suberate, potassium laurate, salts of fatty acids, salts of alicyclic acids, salts of aromatic acids, stearic acid, oleic acid, palmitic acid, a mixture of a salt of a fatty, alicyclic or aromatic acid and a fatty, alicyclic or aromatic acid.

In the osmotic dosage forms, the semipermeable wall comprises a composition that is permeable to the passage of fluid and impermeable to the passage of compositions and/or compounds disclosed herein. The wall is non-toxic and comprises a polymer selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate. The wall comprises 75 wt % (weight percent) to 100 wt % of the cellulosic wall-forming polymer; or, the wall can comprise additionally 0.01 wt % to 80 wt % of polyethylene glycol, or 1 wt % to 25 wt % of a cellulose ether selected from the group consisting of hydroxypropylcellulose or a hydroxypropylalkylcellulose such as hydroxypropylmethylcellulose. The total weight percent of all components comprising the wall is equal to 100 wt %. The internal compartment comprises the drug-containing composition alone or in layered position with an expandable hydrogel composition. The expandable hydrogel composition in the compartment increases in dimension by imbibing the fluid through the semipermeable wall, causing the hydrogel to expand and occupy space in the compartment, whereby the drug composition is pushed from the dosage form. The therapeutic layer and the expandable layer act together during the operation of the dosage form for the release of compositions and/or compounds disclosed herein to a subject over time. The dosage form comprises a passageway in the wall that connects the exterior of the dosage form with the internal compartment. The osmotic powered dosage form can be made to deliver drug from the dosage form to the subject at a zero order rate of release over a period of up to about 24 hours.

The expression "passageway" as used herein comprises means and methods suitable for the metered release of the compositions and/or compounds disclosed herein from the compartment of the dosage form. The exit means comprises at least one passageway, including orifice, bore, aperture, pore, porous element, hollow fiber, capillary tube, channel, porous overlay, or porous element that provides for the osmotic controlled release of the compositions and/or compounds disclosed herein. The passageway includes a material that erodes or is leached from the wall in a fluid environment of use to produce at least one controlled-release dimensioned passageway. Representative materials suitable for forming a passageway, or a

multiplicity of passageways comprise a leachable poly(glycolic) acid or poly(lactic) acid polymer in the wall, a gelatinous filament, poly(vinyl alcohol), leach-able polysaccharides, salts, and oxides. A pore passageway, or more than one pore passageway, can be formed by leaching a leachable compound, such as sorbitol, from the wall. The passageway possesses controlled-release dimensions, such as round, triangular, square and elliptical, for the metered release of compositions and/or drugs from the dosage form. The dosage form can be constructed with one or more passageways in spaced apart relationship on a single surface or on more than one surface of the wall. The expression "fluid environment" denotes an aqueous or biological fluid as in a human patient, including the gastrointestinal tract. Passageways and equipment for forming passageways are disclosed in Theeuwes *et al.*, United States Patent No. 3,845,770; Theeuwes *et al.*, United States Patent No. 3,916,899; Saunders *et al.*, United States Patent No. 4,063,064; Theeuwes *et al.*, United States Patent No. 4,088,864 and Ayer *et al.*, United States Patent No. 4,816,263. Passageways formed by leaching are disclosed in Ayer *et al.*, United States Patent No. 4,200,098 and Ayer *et al.*, United States Patent No. 4,285,987.

In order to decrease dosing frequency and augment the convenience to the subject and increase subject compliance, the sustained release oral dosage form (regardless of the specific form of the sustained release dosage form) preferably provides therapeutic concentrations of the compositions and/or compounds disclosed herein in the patient's blood over a period of at least about 6 hours, more preferably, over a period of at least about 8 hours, even preferably, over a period of at least about 12 hours and most preferably, over a period of at least 24 hours. \

For oral liquid preparations such as, for example, suspensions, elixirs and solutions, suitable carriers, excipients or diluents include water, saline, alkyleneglycols (*e.g.*, propylene glycol), polyalkylene glycols (*e.g.*, polyethylene glycol) oils, alcohols, slightly acidic buffers between pH 4 and pH 6 (*e.g.*, acetate, citrate, ascorbate at between about 5 mM to about 50 mM), *etc.* Additionally, flavoring agents, preservatives, coloring agents, bile salts, acylcarnitines and the like may be added.

Liquid drug formulations suitable for use with nebulizers and liquid spray devices and EHD aerosol devices will typically include compositions and/or compounds disclosed herein with a pharmaceutically acceptable carrier such as, for example, a liquid (*e.g.*, alcohol, water, polyethylene glycol or a perfluorocarbon).

Optionally, another material may be added to alter the aerosol properties of the solution or suspension of compositions and/or compounds disclosed herein. In some embodiments, this material is liquid such as an alcohol, glycol, polyglycol or a fatty acid. Other methods of formulating liquid drug solutions or suspension suitable for use in aerosol devices are known to those of skill in the art (Biesalski, United States Patent No. 5,112,598; Biesalski, United States Patent No. 5,556,611)

For topical administration a compound of the invention may be formulated as solutions, gels, ointments, creams, suspensions, *etc.* as are well-known in the art.

For buccal administration, the compositions may take the form of tablets, lozenges, lollipops, *etc.* formulated in conventional manner.

Compositions and/or compounds disclosed herein may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

Systemic formulations include those designed for administration by injection, *e.g.*, subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, oral or pulmonary administration. Systemic formulations may be made in combination with a further active agent that improves mucociliary clearance of airway mucus or reduces mucous viscosity. These active agents include but are not limited to sodium channel blockers, antibiotics, N-acetyl cysteine, homocysteine and phospholipids.

For injection, compositions and/or compounds disclosed herein may be formulated in aqueous solutions, such as physiologically compatible buffers such as Hanks' solution, Ringer's solution, physiological saline buffer or in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion). Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (*e.g.*, Tween.TM. 20, 40, 60, 80 or 85) and other sorbitans (*e.g.*, Span.TM. 20, 40, 60, 80 or 85). Compositions with a surface-active agent may comprise between 0.05 and 5% surface-active agent or between 0.1 and 2.5% surface-active agent. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively compositions and compounds may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Suitable emulsions may be prepared using commercially available fat emulsions. The combination (or single components) may be either dissolved in a

pre-mixed emulsion composition or alternatively it may be dissolved in an oil (*e.g.*, soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (*e.g.*, egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. In some embodiments, EDTA is added as a preservative.

In addition to the formulations described previously, compositions and/or compounds disclosed herein may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, compositions and/or compounds disclosed herein may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

5.5 Therapeutic/Prophylactic Administration And Doses

When used to treat and/or prevent pain the nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof may be administered alone or in combination with other pharmaceutical agents including other compositions of nicotinic agonists and opioid agonists. The nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists thereof may be administered or applied *per se* or as pharmaceutical compositions. The specific pharmaceutical composition depends on the desired mode of administration, as is well known to the skilled artisan.

Nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof may be administered to a subject by intravenous bolus injection, continuous intravenous infusion, oral tablet, oral capsule, oral solution, intramuscular injection, subcutaneous injection, transdermal absorption, buccal absorption, intranasal absorption, inhalation, sublingual, intracerebrally, intravaginallly, rectally, topically, particularly to the ears, nose, eyes, or skin or any other convenient method known to those of skill in the art. In some embodiments, nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof are delivered

via sustained release dosage forms, including oral sustained release dosage forms. Administration can be systemic or local. Various delivery systems are known, (*e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, "patient controlled analgesia" drug delivery systems, *etc.*) that can be used to administer nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists and/or pharmaceutical compositions .

Nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists and/or pharmaceutical compositions may also be administered directly to the lung by inhalation. For administration by inhalation, the compositions and/or compounds disclosed herein may be conveniently delivered to the lung by a number of different devices. For example, a Metered Dose Inhaler ("MDI") which utilizes canisters that contain a suitable low boiling propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas may be used to deliver the compositions and/or compounds disclosed herein. .

Alternatively, a Dry Powder Inhaler ("DPI") device may be used to administer the compositions and/or compounds disclosed herein (See, *e.g.*, Raleigh *et al.*, *Proc. Amer. Assoc. Cancer Research Annual Meeting*, **1999**, 40, 397). DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which may then be inhaled by the patient. A popular variation is the multiple dose DPI ("MDDPI") system, which allows for the delivery of more than one therapeutic dose. For example, capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compositions and/or compounds disclosed herein and a suitable powder base such as lactose or starch for these systems.

Another type of device that may be used to deliver the compositions and/or compounds disclosed herein is a liquid spray device supplied, for example, by Aradigm Corporation, Hayward, CA. Liquid spray systems use extremely small nozzle holes to aerosolize liquid drug formulations that may then be directly inhaled.

In some embodiments, a nebulizer device is used to deliver the compositions and/or compounds disclosed herein. Nebulizers create aerosols from liquid drug formulations by using, for example, ultrasonic energy to form fine particles that may be readily inhaled (*e.g.*, Verschoyle *et al.*, *British J. Cancer*, 1999, 80, Suppl. 2, 96; Armer *et al.*, United States Patent No. 5,954,047; van der Linden *et al.*, United States Patent No. 5,950,619; van der Linden *et al.*, United States Patent No. 5,970,974).

In still other embodiments, an electrohydrodynamic ("EHD") aerosol device is used to deliver the compositions and/or compounds disclosed herein. EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions (see *e.g.*, Noakes *et al.*, United States Patent No. 4,765,539; Coffee, United States Patent No. 4,962,885; Coffee, International Publication No. WO 94/12285; Coffee, International Publication No. WO 94/14543; Coffee, International Publication No. WO 95/26234; Coffee, International Publication No. WO 95/26235; Coffee, International Publication No. WO 95/32807). Other methods of intra-pulmonary delivery of a compound of the invention will be known to the skilled artisan and are within the scope of the present disclosure.

Transdermal devices can also be used to deliver the compositions and/or compounds disclosed herein. In some embodiments, the transdermal device is a matrix type transdermal device (Miller *et al.*, International Publication No. WO 2004/041324). In other embodiments, the transdermal device is a multi-laminate transdermal device (Miller, United States Patent Application Publication No. 2005/0037059). In still other embodiments, the transdermal device will have one or more reservoirs with nicotinic agonist, salts, hydrates, solvates or prodrugs thereof either formulated separately, or in combination with an opioid agonist salts, hydrates, solvates or prodrugs thereof. In the embodiments in which separate reservoirs are used, suitable membranes may be used to adjust the delivery rates of the components such that one is delivered prior to or simultaneously with the other. In some embodiments, the opioid agonist is present in the transdermal patch reservoir and the nicotinic agonist is present in the device (*e.g.*, patch) adhesive as well as the reservoir such that delivery of the nicotinic agonist begins immediately upon contact between the patch and the patient's skin.

In some embodiments, the device is intended for acute analgesia, for example post-operative analgesia. In these embodiments, the initial dose of the nicotinic agonist will be delivered very rapidly. The rapid absorption of the nicotinic agonist may be accomplished, in part, by the addition of the agonist to the device adhesive. The opioid agonist may also be added to the adhesive to increase the onset rate of analgesia. The rate of delivery may be controlled by rate limiting membranes separating the reservoir from the skin, or by the use of embedded polymers within the reservoir that control the rate of nicotinic agonist release into the reservoir. In some embodiments, the nicotinic agonist and the opioid agonist are optionally mixed with

separate polymers with distinct release characteristics in a single reservoir. In other embodiments, the nicotinic agonist and the opioid agonist are optionally mixed with separate polymers with distinct release characteristics in different reservoirs. The opioid and the nicotinic agonist may be present in the reservoir in quantities sufficient to provide 24 hours of analgesia following an acutely painful stimulation, such as an operation. As mentioned, *supra*, the nicotinic agonist may be included in the same reservoir as the opioid agonist or in a different reservoir.

In other embodiments the device is intended for chronic analgesia, for example, pain from cancer, debilitating arthritis, *etc.* In some embodiments, the device is changed every three days. The rate of delivery may be controlled by rate limiting membranes separating the reservoir from the skin, or by the use of embedded polymers within the reservoir that control the rate of nicotinic agonist release into the reservoir. In some embodiments, the nicotinic agonist and the opioid agonist are optionally mixed with separate polymers with distinct release characteristics in a single reservoir. In other embodiments, the nicotinic agonist and the opioid agonist are optionally mixed with separate polymers with distinct release characteristics in different reservoirs. As mentioned, *supra*, the nicotinic agonist may be included in the same reservoir as the opioid agonist or in a different reservoir. In some embodiments, the transdermal device provides sufficient nicotinic agonist and opioid agonist for 24-168 hours of sustained delivery. In some embodiments, the transdermal device provides sufficient nicotinic agonist and opioid agonist for 72 hours of sustained delivery.

In some embodiments, particularly, when a transdermal device is used to deliver nicotinic agonists and/or opioid agonists to treat and/or prevent chronic pain, the active agents are delivered in three distinct phases. The first phase commences upon application of the device where the nicotinic agonist and opioid agonist are initially absorbed from the device. In the second phase, the nicotinic agonist and opioid agonist are delivered at a constant rate to maintain constant plasma nicotinic agonist and opioid agonist concentrations. In the third phase, the device is removed, and the nicotinic agonist and opioid agonist wash out of depots in the skin immediately below the patch, into the systemic circulation. The characteristics of this wash out are determined by the agents and by the skin and not by the device.

The rate of the nicotinic agonist and opioid agonist delivery in the first phase, immediately following application of the device may be adjusted to compensate for

declining rate of delivery of the nicotinic agonist and opioid agonist during the third phase, when the active agents are washing out of the patch. In this manner, a newly applied device introduces the nicotinic agonist and opioid agonist to the systemic circulation in a manner that approximately compensates for the decreasing delivery from the removed device. In this manner, the transdermal devices may be changed at regular intervals, as required for subjects with chronic pain, while still maintaining steady drug concentrations and consistent levels of analgesia.

The amount of nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof that will be effective in the treatment or prevention of pain in a subject will depend on the specific nature of the condition and can be determined by standard clinical techniques known in the art. For example, nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof may be titrated to provide adequate analgesia to the subject. The amount of nicotinic agonists, opioid agonists, compositions of nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof administered will, of course, be dependent on, among other factors, the subject being treated, the weight of the subject, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

When administered in combination, either in combination or separately the nicotinic receptor agonist and opioid agonist are presented in a ratio consistent with the manifestation of analgesia. The ratio will vary according to the particular nicotinic receptor agonist and opioid agonist selected for use.

In some embodiments, the ratio by weight of the nicotinic agonist to fentanyl is about 10 to 1 (nicotinic agonist (*e.g.*, nicotine) to fentanyl). In other embodiments, the ratio is between about 0.001 to 1 and about 1000 to 1. In still other embodiments, the ratio is between about 0.01 to 1 and about 100 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to hydrocodone is about 2 to 1 (nicotinic agonist (*e.g.*, nicotine) to hydrocodone). In other embodiments, the ratio is between about 0.001 to 1 and about 1000 to 1. In still other embodiments, the ratio is between about 0.01 to 1 and about 100 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to codeine is about 15 to 1 (nicotinic agonist (*e.g.*, nicotine) to codeine). In other embodiments, the

ratio is between about 0.000007 to 1 and about 67 to 1. In still other embodiments, the ratio is between about 0.0067 to 1 and about 0.7 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to sufentanil is about 60 to 1 (nicotinic agonist (*e.g.*, nicotine) to sufentanil). In other embodiments, the ratio is between about 0.0667 to 1 and about 66667 to 1. In still other embodiments, the ratio is between about 6.6667 to 1 and about 667 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to methadone is about 2 to 1 (nicotinic agonist (*e.g.*, nicotine) to methadone). In other embodiments, the ratio is between about 0.0005 to 1 and about 500 to 1. In still other embodiments, the ratio is between about 0.0500 to 1 and about 5 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to levorphanol is about 3 to 1 (nicotinic agonist (*e.g.*, nicotine) to levorphanol). In other embodiments, the ratio is between about 0.0033 to 1 and about 3333 to 1. In still other embodiments, the ratio is between about 0.3333 to 1 and about 33 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to alfentanil is about 1 to 1.5 (nicotinic agonist (*e.g.*, nicotine) to alfentanil). In other embodiments, the ratio is between about 0.0007 to 1 and about 667 to 1. In still other embodiments, the ratio is between about 0.0667 to 1 and about 7 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to oxycodone is about 1 to 2 (nicotinic agonist (*e.g.*, nicotine) to oxycodone). In other embodiments, the ratio is between about 0.0005 to 1 and about 500 to 1. In still other embodiments, the ratio is between about 0.05 to 1 and about 5 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to remifentanil is about 5 to 1 (nicotinic agonist (*e.g.*, nicotine) to remifentanil). In other embodiments, the ratio is between about 0.005 to 1 and about 5000 to 1. In still other embodiments, the ratio is between about 0.5 to 1 and about 50 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to hydromorphone is about 2 to 1 (nicotinic agonist (*e.g.*, nicotine) to hydromorphone). In other embodiments, the ratio is between about 0.002 to 1 and about 2000 to 1. In still other embodiments, the ratio is between about 0.2 to 1 and about 20 to 1.

In some embodiments, the ratio by weight of the nicotinic agonist to oxymorphone is about 3 to 1 (nicotinic agonist (*e.g.*, nicotine) to oxymorphone). In other embodiments, the ratio is between about 0.0033 to 1 and about 3333 to 1. In still other embodiments, the ratio is between about 0.3333 to 1 and about 33 to 1.

A suitable dosage level for nicotine or a nicotine receptor agonist is between about 1 mg to about 25 mg per day. In some embodiments, the dosage range is about 5 mg to about10 mg per day. The compounds may be administered on a regimen of up to 6 times per day, preferably, 1 to 4 times per day.

Fentanyl can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, fentanyl is administered at reduced dosage levels. In other embodiments, fentanyl is administered at between about 0.1 mg to about 5 mg/day. In still other embodiments, fentanyl is administered at between about 0.2 mg to about 2 mg per day. In still other embodiments, fentanyl is administered at between about 0.25 mg to about 1.5 mg per day. Fentanyl, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, fentanyl is administered between 1 to 4 times per day.

Hydrocodone can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, hydrocodone is administered at reduced dosage levels. In other embodiments, hydrocodone is administered at between about 2 mg to about 100 mg/day. In still other embodiments, hydrocodone is administered at between about 4 mg to about 40 mg per day. In still other embodiments, hydrocodone is administered at between about 5 mg to about 30 mg per day. Hydrocodone, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, hydrocodone is administered between 1 to 4 times per day.

Codeine can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, codeine is administered at reduced dosage levels. In other embodiments, codeine is administered at between about 15 mg to about 750 mg/day. In still other embodiments, codeine is administered at between about 30 mg to about 300 mg per day. In still other embodiments, codeine is administered at between about 38 mg to about 225 mg per day. Codeine, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, codeine is administered between 1 to 4 times per day.

Sufentanil can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, sufentanil is administered at reduced dosage levels. In other embodiments, sufentanil is administered at between about 0.01 mg to about .5 mg/day. In still other embodiments, sufentanil is

administered at between about 0.02 mg to about .2 mg per day. In still other embodiments, sufentanil is administered at between about 0.025 mg to about .15 mg per day. Sufentanil, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, sufentanil is administered between 1 to 4 times per day.

Methadone can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, methadone is administered at reduced dosage levels. In other embodiments, methadone is administered at between about 2 mg to about 100 mg/day. In still other embodiments, methadone is administered at between about 4 mg to about 40 mg per day. In still other embodiments, methadone is administered at between about 5 mg to about 30 mg per day. Methadone, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, methadone is administered between 1 to 4 times per day.

Levorphanol can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, levorphanol is administered at reduced dosage levels. In other embodiments, levorphanol is administered at between about 2 mg to about 100 mg/day. In still other embodiments, levorphanol is administered at between about 4 mg to about 40 mg per day. In still other embodiments, levorphanol is administered at between about 5 mg to about 30 mg per day. Levorphanol, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, levorphanol is administered between 1 to 4 times per day.

Alfentanil can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, alfentanil is administered at reduced dosage levels. In other embodiments, alfentanil is administered at between about 0.1 mg to about 5 mg/day. In still other embodiments, alfentanil is administered at between about 0.2 mg to about 2 mg per day. In still other embodiments, alfentanil is administered at between about 0.25 mg to about 1.5 mg per day. Alfentanil, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, alfentanil is administered between 1 to 4 times per day.

Oxycodone can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, oxycodone is

administered at reduced dosage levels. In other embodiments, oxycodone is administered at between about 2 mg to about 100 mg/day. In still other embodiments, oxycodone is administered at between about 4 mg to about 40 mg per day. In still other embodiments, oxycodone is administered at between about 5 mg to about 30 mg per day. Oxycodone, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, oxycodone is administered between 1 to 4 times per day.

Remifentanil can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, remifentanil is administered at reduced dosage levels. In other embodiments, remifentanil is administered at between about 0.2 mg to about 10 mg/day. In still other embodiments, remifentanil is administered at between about 0.4 mg to about 4 mg per day. In still other embodiments, remifentanil is administered at between about 0.5 mg to about 3 mg per day. Remifentanil, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, remifentanil is administered between 1 to 4 times per day.

Hydromorphone can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, hydromorphone is administered at reduced dosage levels. In other embodiments, hydromorphone is administered at between about 0.5 mg to about 25 mg/day. In still other embodiments, hydromorphone is administered at between about 1 mg to about 10 mg per day. In still other embodiments, hydromorphone is administered at between about 1.3 mg to about 8 mg per day. Hydromorphone, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, hydromorphone is administered between 1 to 4 times per day.

Oxymorphone can be administered at a dosage level up to and above conventional dosage levels for this analgesic. In some embodiments, oxymorphone is administered at reduced dosage levels. In other embodiments, oxymorphone is administered at between about 0.2 mg to about 10 mg/day. In still other embodiments, oxymorphone is administered at between about 0.4 mg to about 4 mg per day. In still other embodiments, oxymorphone is administered at between about 0.5 mg to about 3 mg per day. Oxymorphone, if administered sequentially, may be administered on a regimen of up to 6 times per day. In some embodiments, oxymorphone is administered between 1 to 4 times per day.

5.6 Combination Therapy

In certain embodiments, nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof can be used in combination therapy with at least one other therapeutic agent. The nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof and the therapeutic agent can act additively or, more preferably, synergistically. In some embodiments, nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof are administered concurrently with the administration of another therapeutic agent. For example, nicotinic agonists and opioid agonists and/or pharmaceutical compositions thereof may be administered together with another pain reducing agent or anti-emetic agent. In other embodiments, nicotinic agonists and opioid agonists and/or pharmaceutical composition thereof are administered prior or subsequent to administration of other therapeutic agents.

5.7 Therapeutic Kits

Also provided herein are therapeutic kits comprising the compositions and/or compounds disclosed herein. The therapeutic kits may also contain other therapeutic agents or pharmaceutical compositions of these other agents.

Therapeutic kits may have a single container which contains the compositions and/or compounds or pharmaceutical compositions thereof with or without other components (*e.g.*, other therapeutic agents or pharmaceutical compositions thereof) or may have distinct container for each component. The components of the kit may be pre-complexed or each component may be in a separate distinct container prior to administration to a patient.

The components of the kit may be provided in one or more liquid solutions, preferably, an aqueous solution, more preferably, a sterile aqueous solution. The components of the kit may also be provided as solids, which may be converted into liquids by addition of suitable solvents, which are preferably provided in another distinct container.

The container of a therapeutic kit may be a vial, test tube, flask, bottle, syringe, or any other means of enclosing a solid or liquid. Usually, when there is more than one component, the kit will contain a second vial or other container, which

allows for separate dosing. The kit may also contain another container for a pharmaceutically acceptable liquid.

In some embodiments, a therapeutic kit will contain apparatus (*e.g.*, one or more needles, syringes, eye droppers, pipette, *etc.*), which enables administration of the components of the kit.

6. Examples

Reference is now made to the following examples, which illustrate methods for using opioid agonists and nicotinic agonists for treating pain. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the disclosure.

6.1 Use of Fentanyl and Nicotine to Treat Pain in the Mouse Paw Incision Method

A mouse incision model was used to measure the effectiveness of the combination of opioids and nicotine in treating pain. This model involves making a small cut near the hindpaw of a mouse (six week old C57BL/6J mice), slightly disturbing the underlying tissues, and sewing the skin shut. After surgery at specified timepoints, the baseline withdrawal threshold to pressure stimulus invoked by von Frey fibers is tested on the incised hindpaw, then the mouse is injected subcutaneously with an analgesic drug (or combination of drugs administered sequentially) and the pain withdrawal testing is repeated. Groups of eight mice are used to make the measurements. Cumulative dose response data is collected following sequential doses separated by a washout period sufficient to prevent pharmacodynamic effects resulting from accumulation of either agent.

Under isoflurane anesthesia the right hind paw is treated with betadine, then a 5mm longitudinal incision is made with a no. 15 blade through the skin and fascia of the plantar foot. The incision starts 2 mm from the proximal edge of the heel and extends toward the toes. The underlying muscle is elevated with forceps, leaving the muscle origin and insertion intact. The skin is then apposed with a single polysorb suture, and the wound covered with antibiotic ointment. The procedure takes approximately 15 minutes and the animal is completely recovered from the anesthetic within 1 hour.

Nociceptive testing with von Frey fibers of increasing diameter is used to evaluate the post-operative effects of the analgesic drugs. Mice are placed in a clear plastic

cylinder (20 cm in diameter) on a wire mesh platform and allowed to acclimate for 30 minutes. The paw is tested with 1 of a series of 8 von Frey fibers ranging in stiffness from 0.02 g to 2.1 g. The von Frey fiber is applied against the hindpaw plantar skin just medial to the incision, taking care to avoid the tori pads. The fiber is pushed until it is slightly bowed. Stimuli are presented at an interval of several seconds. Hindpaw withdrawal from the fiber is considered a positive response. The initial fiber presentation is 0.02 g and the fibers are presented in increasing diameter until a positive withdrawal response is noted; this sequence is repeated several times and an average response threshold is calculated. The response data is reported in terms of percent maximum possible effect whereby maximum (100 %) effect is defined by increasing the withdrawal threshold from the baseline fiber strength to the maximum strength fiber.

Figure 1 illustrates the results when incised mice were treated with nicotine (1 mg/kg) alone and then treated with increasing doses of fentanyl plus nicotine (1 mg/kg). Fentanyl (or a saline control when assessing the effects of nicotine alone) is dosed 10 minutes prior to the nicotine dose, which is dosed 5 minutes prior to withdrawal response testing. Sequential doses are separated by a washout period sufficient to prevent pharmacodynamic effects resulting from accumulation of either agent. These data indicate the dose response curve of fentanyl in the presence of nicotine (1 mg/kg). For comparison, the dose response curve for fentanyl in the absence of nicotine is presented in Figure 2.

Figure 3 illustrates the results when incised mice were treated with fentanyl (50 ug/kg) alone, and then treated with increasing doses of nicotine plus fentanyl (50 ug/kg). Fentanyl is dosed 10 minutes prior to the nicotine dose (or a saline control when assessing the effects of fentanyl alone), which is dosed 5 minutes prior to withdrawal response testing. Sequential doses are separated by a washout period sufficient to prevent pharmacodynamic effects resulting from accumulation of either agent. These data indicate the dose response curve of nicotine in the presence of fentanyl (50 ug/kg). Again, for comparison the dose response curve for fentanyl in the absence of nicotine is presented in Figure 2.

6.2 Use of Morphine and Nicotine to Treat Pain in the Mouse Paw Incision Model

Figure 4 illustrates the results when incised mice were treated with increasing doses of morphine (50 ug/kg) alone, and then a single dose of morphine plus nicotine

(3 mg/kg). Morphine is dosed 10 minutes prior to the nicotine dose (or a saline control when assessing the effects of morphine alone), which is dosed 5 minutes prior to withdrawal response testing conducted at both 15 and 30 minutes post morphine dose. Sequential doses are separated by a washout period sufficient to prevent pharmacodynamic effects resulting from accumulation of either agent. These data indicate the dose response curve of morphine alone and morphine (3 mg/kg) in the presence of nicotine (3 mg/kg). Also, indicated is the timecourse of the morphine + nicotine synergy which appears to be dependent on the pharmacokinetic profile of nicotine.

It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of this disclosure. Accordingly, the present embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the allowed claims.

All publications and patents cited herein are incorporated by reference in their entirety.

CLAIMS

What Is Claimed Is:

1. A composition comprising a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates or prodrugs thereof and a therapeutically effective amount of an opioid agonist or salts, hydrates, solvates or prodrugs thereof.

2. A pharmaceutical composition comprising the composition of Claim 1 and a pharmaceutically acceptable vehicle.

3. A composition comprising a therapeutically effective amount of a nicotinic agonist or salts, hydrates, solvates or prodrugs thereof and a therapeutically effective amount of a rapid onset opioid agonist or salts, hydrates, solvates or prodrugs thereof.

4. A pharmaceutical composition comprising the composition of Claim 3 and a pharmaceutically acceptable vehicle.

5. The composition of any one of Claims 1-4 in which the nicotinic agonist is nicotine, *meta*-nicotine, DMPP, DMAC, ABT-418, DMBX-anabaseine, choline, acetylcholine, epibatidine, cytisine or GTS-21.

6. The composition of any one of Claims 1-4 in which the nicotinic agonist is nicotine.

7. The composition of any one of Claims 1-4 in which the opioid agonist is fentanyl, hydromorphone, alfentanil, remifentanil, carfentanil, sufentanil, butorphanol, buprenorphine, pentazocine, meperidine, oxycodone, oxymorphone, hydrocodone, hydromorphone, codeine, methadone, diacetylmorphine, etrophine, levorphanol, oxycodone, oxymorphone, naltrexone, nalbuphine, nalorphine, buprenorphine, codeine, diacetylmorphine, dihydrocodeine, dihydroetorphine, diprenorphine, etorphine, levomethadyl actetate hydrochloride, levorphanol, lofentanil,

meperidine, naloxone, methyl naltrexone, beta-hydroxy 3-methylfentanyl, N-methylnaltrexone, normorphine, propoxyphene, tilidine, thebaine, nalbuphine, nalmefene, neopine, penomorphone or tramadol.

8. The composition of any one Claims 1-4 in which the opioid agonist is sufentanil, fentanyl, oxycodone, hydrocodone or hydromorphone.

9. The composition of any one of Claims 1-4 in which the opioid agonist is fentanyl.

10. The composition of any one of Claims 1-4 in which the nicotinic agonist is nicotine and the opioid agonist is oxycodone, hydrocodone, sufentanil or hydromorphone.

11. The composition of any one of Claims 1-4 in which the nicotinic agonist is nicotine and the opioid agonist is fentanyl.

12. The composition of any one of Claims 1-4 comprising a sustained release dosage form.

13. The composition of Claim 12 in which the sustained release dosage form is an oral dosage form.

14. The composition of Claim 12 in which the sustained release dosage form is a transdermal patch.

15. The composition of any one of Claims 1-4 in which the nicotinic agonist is released over the therapeutically effective lifetime of the opioid agonist.