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DESCRIPTION

Field of Invention

[0001] The present invention relates to: 1) A combination of one or more muscarinic agonists and one or more muscarinic antagonists for use in the treatment of diseases that are ameliorated by activation of muscarinic receptors (e.g., schizophrenia and related disorders); 2) A medicament comprising one or more muscarinic agonists and one or more muscarinic antagonists.

Background of the Invention

[0002] The acetylcholine neurotransmitter system plays a significant role in a variety of central nervous system (CNS) and peripheral functions. Acetylcholine signaling occurs through two different families of receptors: nicotinic receptors and muscarinic receptors. Muscarinic cholinergic receptors are G-protein coupled receptors with five different receptor subtypes (M1-M5) (Raedler et al. American Journal of Psychiatry. 160: 118. 2003), each of which are found in the CNS but have different tissue distributions. Activation of the muscarinic system through use of muscarinic agonists has been suggested to have the potential to treat several diseases including Alzheimer's disease, Parkinson's disease, movement disorders and drug addiction. (US 2005/0085463; Langmead et al. Pharmacology & Experimental Therapeutics. 117: 232:2008). Genetic evidence has suggested a direct link between the muscarinic system and both alcohol addiction (Luo X. Et al. Hum Mol Genet. 14:2421. 2005) and nicotine addiction (Mobascher A et al. Am J Med Genet B Neuropsychiatr Genet. 5:684. 2010). M1 and M4 subtypes have been of particular interest as therapeutic targets for various diseases. For instance, the mood stabilizers lithium and valproic acid, which are used to treat bipolar depression, may exert their effects via the muscarinic system particularly through the M4 subtype receptor. (Bymaster & Felder. Mol Psychiatry. 7 Suppl 1:S57. 2002).

[0003] Some of the strongest linkages to the muscarinic system have been with schizophrenia, which is a serious mental illness affecting approximately 0.5-1% of the population. (Arehart-Treichel. Psych News. 40:9. 2005). The disease is characterized by a set of symptoms that are generally divided into three categories: 1) Positive symptoms (e.g., hallucinations, delusional thoughts, etc.); 2) Negative symptoms (e.g., social isolation, anhedonia, etc.); and 3) Cognitive symptoms (e.g., inability to process information, poor working memory, etc.). (Schultz. Am Fam Physician. 75:1821. 2007). Patients who suffer from schizophrenia both experience a major decline in quality of life and are at increased risk for mortality due to a number of factors, such as an increased suicide rate. (Brown et al. British Journal of Psychiatry. 177: 212. 2000). The cost of schizophrenia to society is also significant as sufferers of schizophrenia are much more likely to be incarcerated, homeless or unemployed.

[0004] Today, antipsychotics are the mainstay of treatment for schizophrenia. The first generation of antipsychotics are generally known as "typical antipsychotics" while newer antipsychotics are generally called "atypical antipsychotics." Both typical and atypical antipsychotics have limited efficacy and severe side effects. There is little to no difference in efficacy between typical and atypical antipsychotics, most likely due to the fact that both classes of drugs achieve their therapeutic effect through the same pharmacological mechanisms (e.g., acting as dopamine receptor antagonists). (Nikam et al. Curr Opin Investig Drugs. 9:37. 2008). Side effects of typical antipsychotics include abnormal movement (e.g., rigidity) whereas atypicals have different but equally significant side effects (e.g., major weight gain, cardiovascular effects, etc.). The side effect profile of current antipsychotics further decreases compliance in a patient population that is already frequently non-compliant. Thus, there exists a clear need for new therapeutics to treat schizophrenia and related disorders (e.g., schizoaffective disorder).

[0005] Clozapine is an example of an antipsychotic that has major side effects, including sialorrhea (hypersalivation) which occurs in up to 54% of patients. (Davydov and Botts, Ann Pharmacother. 34:662. 2000). The exact mechanism of hypersalivation remains unknown. (Rogers and Shramko. Pharmacotherapy. 20:109. 2000). Clozapine has a complex pharmacological profile with appreciable activity at a variety of receptors, including dopamine receptors, serotonin receptors, adrenergic receptors, muscarinic receptors and possibly others. (Coward. Br J Psychiatry Suppl. 17:5. 1992). Investigators have tried a variety of pharmacological approaches in an attempt to counteract sialorrhea, including botulinum toxin (Kahl et al. Nervenarzt. 76:205. 2005) as well as the antipsychotics amisulpride (Croissant et al. Pharmacopsychiatry. 38:38. 2005) and sulpiride. (Kreinin et al. Isr J Psychiatry Relat Sci. 42:61. 2005). Efforts have focused mostly on alpha2 adrenergic agonists as well as anti-cholinergic drugs due to clozapine's known interaction with these receptors. Anti-muscarinic drugs such as pirenzepine have shown efficacy in small scale trials (Schneider et al. Pharmacopsychiatry. 37:43. 2004), but other

trials with the same agent found no effect. (Liu et at. J Clin Psychopharmacol. 21.:608. 2001). Alpha2 adrenergic agonist such as clonidine (Singh et al., J Psychopharmacol. 19:426. 2005) have also shown efficacy in reducing sialorrhea in small scale trials. However, Syed et al. reported in a 2008 review that there is inadequate data to guide clinical practice. (Syed et al. Cochrane Database Syst Rev. 16:3. 2008).

[0006] Another approach to the treatment of schizophrenia has been use of muscarinic agonists. Muscarinic receptors are G-protein linked receptors that bind the neurotransmitter acetylcholine. (Eglen RM. Auton Autacoid Pharmacol 26: 219. 2006). To date, five subtypes of muscarinic receptor have been identified and are generally labeled M1, M2, M3, M4, and M5, respectively. (Caulfield MP et al. Pharmacol. Rev. 50: 279. 1998). These muscarinic subtypes vary in terms of the affinity of various agonists and antagonists for the receptors. A number of lines of evidence have suggested that the muscarinic system plays a significant role in the pathology of schizophrenia. In particular, decreased expression of M1 and M4 receptor subtypes has been noted in post-mortem studies in deceased schizophrenic patients. (Dean et al. Mol Psych. 1: 54. 1996). Likewise, SPECT imaging studies have shown decreased muscarinic availability in schizophrenia. (Raedler et al. Am J Psych.160:118. 2003).

[0007] There is also pharmacological evidence implicating activation of muscarinic receptors as a potential therapeutic approach to schizophrenia. For example, the muscarinic antagonist scopolamine, which is used to treat motion sickness, produces cognitive impairment and delusions of the type seen in schizophrenia. (Ellis et al. Int. J. Neuropsychopharmacol. 9:175. 2006). More selective M1 agonists have been suggested to potentiate glutamate signaling which could help exert a therapeutic effect. (Jones et al. J. Neurosci. 28:10422. 2008). In a double-blind placebo controlled trial of schizophrenic patients using xanomeline, which has preferential activity at the M1 and M4 receptors, alleviation of schizophrenia was observed. (Shekhar et al. Am. J. Psych. 165: 1033. 2008). However, because xanomeline also bound to subtypes of receptors other than M1, a number of various serious side effects were observed including GI side effects, cardiac side effects and problems with hyper-salivation.

[0008] To date, nobody has been able to harness the approach of employing muscarinic agonists because of the side effects associated with the agents' binding certain muscarinic receptor subtypes. A need exists for a method of using muscarinic agonists and for a medicament employing such muscarinic agonists that would allow for the therapeutic effects associated with activation of muscarinic receptors, but with fewer side effects.

Summary of the Invention

[0009] The present invention relates to the treatment of diseases or conditions ameliorated by activation of the muscarinic system by administering one or more muscarinic "Activators" (e.g., agonist, partial agonist, co-agonist, physiological agonist, potentiator, stimulator, allosteric potentiator, positive allosteric modulator or allosteric agonist) and one or more muscarinic "Inhibitors" (e.g., antagonist, partial antagonist, competitive antagonist, non-competitive antagonist, uncompetitive antagonist, silent antagonist, inverse agonist, reversible antagonist, physiological antagonist, irreversible antagonist, inhibitor, reversible inhibitor, irreversible inhibitor, negative allosteric modulator, or allosteric antagonist). Such diseases include schizophrenia and related disorders.

[0010] In one aspect, the invention provides a medicament comprising a combination of a muscarinic Activator and a muscarinic Inhibitor selected from: xanomeline and trospium chloride; sabcomeline and trospium chloride; milameline and trospium chloride; xanomeline and tolterodine; milameline and tolterodine; sabcomeline and trospium chloride controlled release; xanomeline and trospium chloride controlled release; milameline and trospium chloride controlled release; xanomeline and darifenacin; xanomeline and solifenacin; sabcomeline and solifenacin; talsaclidine and trospium chloride; cevimeline and trospium chloride; talsaclidine and darifenacin; talsaclidine and solifenacin; talsaclidine and trospium chloride controlled release; talsaclidine and tolterodine; xanomeline and fesoterodine; cevimeline and darifenacin; and cevimeline and trospium chloride controlled release; and a pharmaceutically acceptable carrier.

[0011] In a preferred embodiment, the combination of the Activator and Inhibitor has a score ("Theta score") above 230 as determined by *in silic*o testing using a proprietary algorithm as described herein.

[0012] In an embodiment, the medicament comprises from 10 micrograms to 10 grams of the muscarinic Activator.

[0013] In an embodiment, the medicament comprises from 1 milligram to 1 gram of the muscarinic Activator.

[0014] In an embodiment, the medicament comprises from 10 micrograms to 10 grams of the muscarinic Inhibitor.

[0015] In an embodiment, the medicament comprises from 1 milligram to 1 gram of the muscarinic Inhibitor.

[0016] In an embodiment, the medicament comprises from 1 milligram to 1 gram of the muscarinic Activator and from 1 milligram to 1 gram of the muscarinic Inhibitor.

[0017] In an embodiment, the medicament comprises from 25 to 300 milligrams of xanomeline.

[0018] In an embodiment, the medicament comprises from 6.5 to 200 milligrams of trospium chloride.

[0019] In an embodiment, the medicament comprises: a) 75 milligrams of xanomeline and 20 milligrams of trospium chloride; or b) 225 milligrams of xanomeline and 60 milligrams of trospium chloride.

[0020] In an embodiment, the medicament is in the form of: a) a single capsule formulation comprising 75 milligrams of xanomeline and 20 milligrams of trospium chloride; or b) a single capsule formulation comprising 225 milligrams of xanomeline and 60 milligrams of trospium chloride.

[0021] In an embodiment, the medicament is formulated as an immediate release formulation.

[0022] In an embodiment, the medicament is formulated as a controlled release formulation.

[0023] In an embodiment, the muscarinic Activator is formulated as a controlled release formulation and the muscarinic Inhibitor is formulated as an immediate release formulation.

[0024] In another embodiment, the medicament can be taken orally. The medicament may be given orally in tablets, troches, liquids, drops, capsules, caplets and gel caps or other such formulations known to one skilled in the art. Other routes of administration can include but are not limited to: parenteral, topical, transdermal, ocular, rectal, sublingual, and vaginal.

[0025] In another embodiment, the medicament can be administered in conjunction with other therapies. In one embodiment of the invention, the medicament is used simultaneously or sequentially with psychotherapy. In another embodiment of the invention, the medicament is administered either simultaneously or consecutively with other pharmacological therapy. Such pharmacological therapy could include but is not limited to: antipsychotics, anxiolytics, anti-depressants, sedatives, tranquilizers and other pharmacological interventions known to one skilled in the art.

[0026] In another aspect, the invention provides a medicament as defined in relation to the first aspect of the invention for use in the treatment of a central nervous system disorder selected from schizophrenia, disorders related to schizophrenia, muscarinic disorder, movement disorder, mood disorder, cognitive disorder, attention disorder, and addictive disorder.

[0027] In an embodiment of the invention, the treatment can be applied to a mammal. In another embodiment, the mammal is a human being.

[0028] In one embodiment of the invention, the use of the Inhibitor alleviates the side effects associated with use of the Activator. In another embodiment, use of the Inhibitor allows for a higher maximum tolerated dose of the Activator.

[0029] In one embodiment, the muscarinic Activator may be taken sequentially with the Inhibitor. In another embodiment of the invention, the muscarinic Activator may be taken concurrently with the Inhibitor. In a preferred embodiment of the invention, the Activator and Inhibitor are formulated to be contained in the same dosage form or dosage vehicle. In another embodiment of the invention, the muscarinic Activator and Inhibitor are formulated to be in separate dosage forms or dosage vehicles. In one embodiment, the Activator and Inhibitor are formulated in an immediate release dosage form. In another embodiment, Activator and Inhibitor are formulated in a controlled release dosage form. In another embodiment, either the Activator or the Inhibitor is formulated in an immediate release dosage form, while the other is formulated in a controlled release dosage form.

[0030] In another embodiment of the invention, the muscarinic Activator and Inhibitor can be taken orally. The Activator and Inhibitor may be given orally in tablets, troches, liquids, drops, capsules, caplets and gel caps or other such formulations known to one skilled in the art. Other routes of administration can include but are not limited to: parenteral, topical,

transdermal, ocular, rectal, sublingual, and vaginal.

[0031] In another embodiment of the invention, the muscarinic Activator and Inhibitor are administered either simultaneously or consecutively with other therapies for schizophrenia. In one embodiment of the invention, the muscarinic Activator and Inhibitor are used simultaneously or sequentially with psychotherapy. In another embodiment of the invention, the muscarinic Activator and Inhibitor are administered either simultaneously or consecutively with other pharmacological therapies. Pharmacological therapies could include but are not limited to: antipsychotics, anxiolytics, anti-depressants, sedatives, tranquilizers and other pharmacological interventions known to one skilled in the art.

[0032] These and other embodiments of the invention, and their features and characteristics, will be described in further detail in the description and claims that follow.

Detailed Description of the Invention

Definitions

[0033] For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as would be understood by a person of ordinary skill in the art.

[0034] The articles "a" and "an" are used herein to refer to one or to more than one (*i*.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0035] The terms "comprise" and "comprising" are used in the inclusive, open sense, meaning that additional elements may be included.

[0036] The term "consisting" is used to limit the elements to those specified except for impurities ordinarily associated therewith.

[0037] The term "consisting essentially of" is used to limit the elements to those specified and those that do not materially affect the basic and novel characteristics of the material or steps.

[0038] As used herein, unless otherwise specified, the term "controlled release" is defined as a prolonged release pattern of one or more drugs, such that the drugs are released over a period of time. A controlled release formation is a formulation with release kinetics that result in measurable serum levels of the drug over a period of time longer than what would be possible following intravenous injection or following administration of an immediate release oral dosage form. Controlled release, slow release, sustained release, extended release, prolonged release, and delayed release have the same definitions for the present invention.

[0039] The term "including" is used herein to mean "including but not limited to." "Including" and "including but not limited to" are used interchangeably.

[0040] The term "mammal" is known in the art, and exemplary mammals include humans, primates, bovines, porcines, canines, felines, and rodents (e.g., mice and rats).

[0041] The terms "parenteral administration" and "administered parenterally" are art-recognized and refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

[0042] A "patient," "subject" or "host" to be treated by the subject method may mean either a human or non-human mammal.

[0043] The term "pharmaceutically-acceptable carrier" is art-recognized and refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials that may serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0044] The term "pharmaceutically-acceptable salts," used interchangeably with "salts," is art-recognized and refers to salts prepared from relatively non-toxic acids or bases including inorganic acids and bases and organic acids and bases, including, for example, those contained in compositions of the present invention. Suitable non-toxic acids include inorganic and organic acids such as acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic, hydrochloric, hydrobromic, phosphoric, and sulfuric acids and the like.

[0045] The term "treating" is art-recognized and refers to curing as well as ameliorating at least one symptom of any condition or disorder.

[0046] The term "therapeutic agent" is art-recognized and refers to any chemical moiety that is a biologically, physiologically, or pharmacologically active substance that acts locally or systemically in a subject. Examples of therapeutic agents, also referred to as "drugs," are described in well-known literature references such as the Merck Index (14^{th} edition), the Physicians' Desk Reference (64^{th} edition), and The Pharmacological Basis of Therapeutics (12^{th} edition), and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances that affect the structure or function of the body, or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment.

[0047] The term "psychotherapy" refers to use of non-pharmacological therapies in which those skilled in the art use a variety of techniques that involve verbal and other interactions with a patient to affect a positive therapeutic outcome. Such techniques include, but are not limited to, behavior therapy, cognitive therapy, psychodynamic therapy, psychoanalytic therapy, group therapy, family counseling, art therapy, music therapy, vocational therapy, humanistic therapy, existential therapy, transpersonal therapy, client-centered therapy (also called person-centered therapy), Gestalt therapy, biofeedback therapy, rational emotive behavioral therapy, reality therapy, response based therapy, Sandplay therapy, status dynamics therapy, hypnosis and validation therapy. It is further understood that psychotherapy may involve combining two or more techniques and that a therapist can select and adjust the techniques based on the needs of the individual patient and the patient's response.

[0048] The term "Muscarinic Disorder" refers to any disease or condition that is ameliorated by activation of the muscarinic system. Such diseases include ones in which direct activation of muscarinic receptors themselves or inhibition of cholinesterase enzymes has produced a therapeutic effect.

[0049] The terms "Diseases Related To Schizophrenia" and "Disorders Related To Schizophrenia" include, but are not limited to, schizo-affective disorder, psychosis, delusional disorders, psychosis associated with Alzheimer's disease, psychosis associated with Parkinson's disease, psychotic depression, bipolar disorder, bipolar with psychosis or any other disease with psychotic features.

[0050] The term "Movement Disorders" includes, but is not limited to, Gilles de la Tourette's syndrome, Friederich's ataxia, Huntington's chorea, restless leg syndrome and other diseases or disorders whose symptoms include excessive movements, ticks and spasms.

[0051] The term "Mood Disorders" includes major depressive disorder, dysthymia, recurrent brief depression, minor

depression disorder, bipolar disorder, mania and anxiety.

[0052] The term "Cognitive Disorders" refers to diseases or disorders that are marked by cognitive deficit (e.g., having abnormal working memory, problem solving abilities, etc.). Diseases include but are not limited to Alzheimer's disease, Parkinson's Disease, dementia (including, but not limited to, AIDS related dementia, vascular dementia, age-related dementia, dementia associated with Lewy bodies and idiopathic dementia), Pick's disease, confusion, cognitive deficit associated with fatigue, learning disorders, traumatic brain injury, autism, age-related cognitive decline, and Cushing's Disease, a cognitive impairment associated with auto-immune diseases.

[0053] The term "Attention Disorders" refers to diseases or conditions that are marked by having an abnormal or decreased attention span. Diseases include but are not limited to attention hyperactivity deficit disorder, attention deficit disorder, Dubowitz Syndrome, FG Syndrome, Down's Syndrome, growth delay due to insulin-like growth factor I deficiency, hepatic encephalopathy syndrome, and Strauss Syndrome.

[0054] The term "Addictive Disorders" refers to diseases or conditions marked by addiction or substance dependence as defined by the Diagnostic & Statistical Manual IV. Such disorders are characterized by physical dependence, withdrawal and tolerance to a particular substance. Such substances include but are not limited to alcohol, cocaine, amphetamines, opioids, benzodiazepines, inhalants, nicotine, barbiturates, cocaine and cannabis. Addictive Disorders can also encompass behaviors that a patient does in a compulsive, continual manner despite clear negative consequences. For instance, ludomania is recognized by those skilled in the art as being an addictive behavior that often has devastating consequences.

[0055] The term "Activator" means a molecule that can be described as an agonist, partial agonist, co-agonist, physiological agonist, potentiator, stimulator, allosteric potentiator, positive allosteric modulator, allosteric agonist or a molecule that increases the activity or signaling of muscarinic receptors through direct or indirect means.

[0056] The term "Inhibitor" means a molecule that can be described as an antagonist, partial antagonist, competitive antagonist, non-competitive antagonist, uncompetitive antagonist, silent antagonist, inverse agonist, reversible antagonist, physiological antagonist, irreversible antagonist, inhibitor, reversible inhibitor, irreversible inhibitor, negative allosteric modulator, allosteric antagonist or a molecule that decreases the activity or signaling of muscarinic receptors through direct or indirect means.

[0057] The term "maximum tolerated dose" means the highest dose of a drug or therapeutic that can be taken by patients without the patients' experiencing intolerable side effects. The maximum tolerated dose is typically determined empirically in clinical trials.

[0058] The term "Muscarinic receptors" refers to G-protein linked receptors that bind the neurotransmitter acetylcholine, and to date, five subtypes of muscarinic receptor have been identified. "M1" means the subtype one muscarinic receptor. "M2" means the subtype two muscarinic receptor. "M3" means the subtype three muscarinic receptor. "M4" means the subtype four muscarinic receptor. "M5" means the subtype five muscarinic receptor.

[0059] The term "Antipsychotic" refers to a drug that diminishes psychosis, hallucinations or delusions. Antipsychotics can include, but are not limited to: Haloperidol, droperidol, chlorpromazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, trifluoperazine, mesoridazine, periciazine, promazine, triflupromazine, levomepromazine, promethazine, pimozide, chlorprothixene, flupenthixol, thiothixene, zuclopenthixol, clozapine, olanzapine, risperidone, quetiapine, ziprasidone, amisulpride, asenapine, paliperidone, zotepine, aripiprazole, bifeprunox, and tetrabenazine .

[0060] The term "Anxiolytics" refers to drugs that reduce anxiety, fear, panic or related feelings. Such drugs include, but are not limited to: benzodiazepines (e.g., alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam), buspirone, barbiturates (e.g., amobarbital, pentobarbital, secobarbital, phenobarbitol) and hydroxyzine.

[0061] The term "Anti-depressants" refers to drugs that alleviate depression and related conditions (e.g., dysthymia) and include, but are not limited to: Selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), serotonin- norepinephrine reuptake inhibitors (e.g., desvenlafaxine, duloxetine, milnacipram, venlafaxine), mianserin, mirtazapin, norepinephrine reuptake inhibitors (e.g., atomoxetine, mazindol, reboxetine, viloxazine), bupropion, tianeptine, agomelatine, trycyclic antidepressants (e.g., amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, nortriptyline, protriptyline), monoamine oxidase inhibitors (e.g., isocarboxazid, moclobemide, phenelzine, selegiline, tranylcypromine).

[0062] The terms "Sedatives" or "tranquilizers" refer to drugs that induce somnolence, promote a feeling of being tired or desire to sleep or promote a state of unconsciousness. Such drugs include but are not limited to benzodiazepines, barbiturates (e.g., amobarbital, pentobarbital, secobarbital, phenobarbitol), eszopiclone, zaleplon, zolpidem, zopiclone.

[0063] The term "Theta Score" is defined as the numerical value assigned by an *in silico* algorithm described herein used to predict the overall efficacy and side effects of any given combination of a Muscarinic Activator and a Muscarinic Inhibitor.

Introduction

[0064] The present invention relates to the combination of one or more Activators and Inhibitors of muscarinic receptors for use in the treatment of various disorders that can be ameliorated by activation of the muscarinic system. The present invention also describes a medicament comprising one or more Activators and one or more Inhibitors of muscarinic receptors. Use of muscarinic Activators has previously been hypothesized to be useful for various central nervous system related conditions. In particular, activation of the M1 and M4 receptor subtypes could prove to be of therapeutic value. However, no one has been able to advance M1 and M4 muscarinic Activators through clinical development to receive regulatory approval for CNS indications because of unacceptable side effects. For instance, while Activators of M1 and M4 muscarinic receptors have been suggested to be efficacious treatments for schizophrenia (Shekhar et al. Am J Psychiatry. 165:1033. 2008; Shirey et el. Nature Chem Biol. 4:41. 2007), the binding by those Activators to subtypes of muscarinic receptors besides M1 and M4 results in side effects which have prevented use of muscarinic Activators in the clinic. (Shekhar et al. Am. J. Psych. 165: 1033.2008). For instance, in both phase I and subsequent trials, the muscarinic agonist xanomeline had unacceptable GI side effects as well as other side effects primarily linked to binding of muscarinic receptors besides M1 and M4. (Sramek et al. The Journal of Clinical Pharmacology. 35:800. 1995), (Cutler & Sramek. Eur. J. Clin. Pharmacol. 48:421-428. 1995), (Bodick et al. Arch Neuro 54:465-473. 1997). By combining a muscarinic Activator with an Inhibitor, it is possible to achieve the desired therapeutic effect while diminishing or eliminating the side effects associated with unwanted subtype binding.

[0065] Muscarinic Inhibitors are used for treatment of overactive bladder and pulmonary disorders and have been suggested for treatment of other disorders. (Witte LP et al. Curr. Opin. Urol. 1:13. 2009). Groups have outlined use of muscarinic Inhibitors with drugs in other classes to achieve a greater effect for treatment of a disease. For example, WO 2008/121268 suggests a combination for the treatment of lower urinary tract symptoms (LUTS) consisting of a beta-3 adrenergic agonist, which on its own has been investigated for the treatment of LUTS, and a muscarinic antagonist. Others have suggested combining specific muscarinic Activators or Inhibitors with other specific therapeutic agents other than muscarinic agents to further have a therapeutic effect (e.g., WO 2009/037503, WO 2009/036243, WO 2008/104776, WO 2008/096136, WO 2008/096126, WO 2008/096121, WO 2008/096111, WO 2007/127196, WO 2007/125293, EP 2002843, EP 2002844, US 5744476, US 7524965, US 2005/0267078, US 2006/0189651, and US 2008/0045565). US 2006/0287294 A1 outlines use of aspartyl protease inhibitors with either an M1 agonist or an M2 antagonist for treatment of various diseases, including improvement of cognitive deficit. Both M1 Activators and M2 Inhibitors themselves (Carey et al. Eur J Pharmacol 431:198. 2001.) have been suggested to be useful treatments for cognitive deficit, and the rationale for the combination with the aspartyl protease inhibitor was to enhance the effects of the aspartyl protease inhibitor. No suggestion was made of combining the M1 Activator with the M2 Inhibitor, and both compounds would be capable of reaching and would be active in the central nervous system. US 5480651 discloses use of agents that increase acetylcholine in the synapse or that activate the nicotinic acetylcholine receptors, followed by administration of an acetylcholine receptor antagonist to relieve craving associated with nicotine addiction. The preferred composition uses physostigmine which is an inhibitor of acetylcholinesterase, as opposed to a muscarinic Activator which would not activate the nicotinic acetylcholine receptors. WO 03/092580 discloses compounds that can act simultaneously as muscarinic Activators at certain receptor subtypes and antagonists at others. Groups have used various muscarinic Activators with muscarinic Inhibitors in the context of trying to differentiate the role of various muscarinic subtypes in drug pharmacology or normal physiology without suggesting a therapeutic use of the combination. Such studies include use of cellular assays starting from animal materials. (e.g., Iwanaga K. et al. J. Pharmacol. Sci. 110:306. 2009). In US 2009/0318522, Paborji discloses use of a peripherally-acting muscarinic antagonist targeting the M2 and M3 receptors for the treatment of overactive bladder. The Paborji publication also discloses use of a peripherally-acting muscarinic M2/M3 agonist to counteract dry mouth associated with the peripherally-acting M2/M3 muscarinic antagonist. Paborji's approach does not, however, relate to activity at muscarinic receptors in the CNS, which is of critical importance for the work described herein, nor does it pertain to activity at either the M1 or M4 receptor. Paborji's approach is highly limited to a specific muscarinic inhibitor and does not provide any selection criteria to identify preferred or specific combinations of muscarinic Activators with the muscarinic antagonist, in spite of the prohibitively large number of potential combinations for which experimental testing could be done.

Muscarinic Activators for use in combination with Muscarinic Inhibitors

[0066] In one embodiment of the invention, one or more muscarinic Activators are used in combination with one or more Muscarinic Inhibitors for treatment of Muscarinic Disorders. In a preferred embodiment, such diseases or disorders include schizophrenia and Diseases Related to Schizophrenia. In another embodiment one or more muscarinic Activators are used in combination with one or more Muscarinic Inhibitors for treatment of Mood Disorders. In another embodiment, one or more muscarinic Activators are used with one or more muscarinic Inhibitors to treat Movement Disorders. In another embodiment, one or more muscarinic Activators are used with one or more muscarinic Inhibitors to treat Cognitive Disorders, including using the combination to enhance cognitive function not associated with a specific pathology. For instance, improvement in cognition could be important in undertaking complex tasks. In another embodiment, one or more muscarinic Activators are used with one or more muscarinic Inhibitors to treat Attention Disorders. Outside of disease treatment, enhancement of attention could improve learning and decrease symptoms associated with fatigue due to both lack of sleep and circadian rhythm disturbances such as jet lag. In another embodiment, one or more muscarinic Activators are used with one or more muscarinic Inhibitors to treat Addictive Disorders.

[0067] In another embodiment, the combination of one or more muscarinic Activators with one or more Muscarinic Inhibitors can be used to treat Muscarinic Disorders which are characterized by an amelioration of symptoms in response to inhibitors of cholinesterase enzymes. While cholinesterase inhibitors have proven therapeutic for certain diseases (e.g., Alzheimer's disease), the use of such inhibitors is limited due to toxicity. In fact, powerful chemical weapons such as sarin gas exert their toxic effects by inhibiting acetylcholinesterase (sarin gas material safety data sheet *103d Congress, 2d Session.* United States Senate. May 25, 1994. http://www.gulfweb.org/bigdoc/report/appgb.html). The combination of one or more muscarinic Activators with one or more Muscarinic Inhibitors represents not only a safer method of treatment of those diseases shown to be response to cholinesterase inhibitors, but also a more effective one given the limitations on current cholinesterase inhibitors.

[0068] In one embodiment, the combination of one or more muscarinic Activators with one or more Muscarinic Inhibitors is used to treat an animal. In a further embodiment, the animal is a mammal. In a preferred embodiment, the mammal is a human being. In one embodiment, a single muscarinic Activator and a single muscarinic Inhibitor are used. In another embodiment more than one muscarinic Activator and/or more than one muscarinic Inhibitor is used.

[0069] In one embodiment, use of the Inhibitor decreases the side effects associated with use of the Activator. Such side effects include, but are not limited to, GI side effects, cardiac side effects, excessive sweating and excessive salivation. Use of one or more Inhibitors in combination with one or more Activators may allow the Activators to be used clinically when the Activators may not otherwise be used clinically due to the their side effects. In another embodiment, use of the Inhibitor in conjunction with the Activator allows for the Activator to achieve a higher maximum tolerated dose than the Activator would otherwise achieve.

[0070] Various time and resource intensive methods may be used to demonstrate both the efficacy of combination of the Activator and Inhibitor for the aforementioned embodiments. For example animal models have been used to demonstrate the efficacy of new therapeutics for schizophrenia, including both pharmacological models (e.g., ketamine model) and genetic models. (e.g., DISCI mouse) (Dawe GS et al. Ann Acad Med Singapore. 38:425. 2009; Desbonnet L. Biochem Soc Trans. 37:308. 2009; Geyer MA. Neurotox Res. 14:71. 2008). Likewise, animal models including rodents, dogs and non-human primates can be used to demonstrate the side effect profile of pharmacological agents. Animal models serve as an experimental proxy for humans, but may suffer from deficiencies associated with the physiological differences between human and animals and thus may have limited predictive power for translation to human experiments, particularly for central nervous system disorders. Alternatively, the combination can be tried in controlled clinical trials of people. Standard measures based on patient self-report can be used by those skilled in the art to assess various side effects such as GI discomfort. As another example, objective physiological measures (e.g., EKGs) may be used by those skilled in the art. A set of standard measures has also been developed to assess schizophrenia symptoms including the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI). (Mortimer AM. Br J Psychiatry Suppl. 50:s7. 2007). Typically, clinical trials are conducted in a double blinded manner in which one group of patients receives an inactive placebo and the other group the active intervention.

[0071] In one embodiment of the invention, the muscarinic Activator is administered concurrently with the muscarinic Inhibitor. In another embodiment, the muscarinic Inhibitor is administered consecutively with the Activator. In further embodiment, the muscarinic Activator is administered prior to administration of the muscarinic Inhibitor. In another

embodiment, the muscarinic Inhibitor is administered prior to administration of the muscarinic Activator. In one embodiment, the muscarinic Inhibitor is administered within one hour of administration of the muscarinic Activator. In another embodiment, the muscarinic Inhibitor is administered within 30 minutes of administration of the muscarinic Activator. In another embodiment, the muscarinic Inhibitor is administered within 10 minutes of administration of the muscarinic Activator. In another embodiment, the muscarinic Inhibitor is administered within one minute of administration of the muscarinic Activator. In another embodiment, the muscarinic Inhibitor is administered within 30 seconds of administration of the muscarinic Activator. Prior to the start of a drug regimen of the type outlined above, there may be a lead-in period that lasts from one to fourteen days. During this lead-in period, the muscarinic Inhibitor may be given by itself prior to the start of administration of the combination.

[0072] In one embodiment, from 10 micrograms to 10 grams of Activator is used in the combination with the Inhibitor. In another embodiment, from 1 milligram to 1 gram of Activator is used in the combination with the Inhibitor. In a preferred embodiment, from 5 to 500 milligrams of Activator is used. In one embodiment from 10 micrograms to 10 grams of Inhibitor is used in the combination with the Activator. In another embodiment, from 1 milligram to 1 gram of Inhibitor is used in the combination with the Activator. In a preferred embodiment, from 2.5 milligrams and 200 milligrams of Inhibitor is used.

[0073] In one embodiment, the muscarinic Activator and Muscarinic Inhibitor are administered to a patient 6 times during a 24 hour period. In another embodiment, the muscarinic Activator and Muscarinic Inhibitor are administered to a patient 5 times during a 24 hour period. In another embodiment, the muscarinic Activator and Muscarinic Inhibitor are administered to a patient 4 times during a 24 hour period. In a preferred embodiment, the muscarinic Activator and Muscarinic Inhibitor are administered to a patient 3 times during a 24 hour period. In another preferred embodiment, the muscarinic Activator and Muscarinic Inhibitor are administered to a patient 2 times during a 24 hour period. In another preferred embodiment, the muscarinic Activator and Muscarinic Inhibitor are administered to a patient one time during a 24 hour period.

***In Silico* testing of muscarinic combinations**

[0074] There are 65 unique muscarinic Activators and 114 unique muscarinic Inhibitors that are currently known (Adis R&D Insight™, Pubmed, Web of Science, U.S. FDA Orange Book, US Patent No. 5,852,029). Therefore, there exist 7,410 potential combinations in which a single muscarinic Activator could be paired with a single muscarinic Inhibitor. If one were to combine *more* than one muscarinic Activator with one or more muscarinic Inhibitors, then the number of combinations would be even greater. While a number of animal models exist for relevant diseases such as schizophrenia (Dawe GS et al. Ann Acad Med Singapore. 38:425. 2009; Desbonnet L. Biochem Soc Trans. 37:308. 2009; Geyer MA. Neurotox Res. 14:71. 2008), animal models of complex diseases such as schizophrenia are imperfect, and thus the ability to predict human efficacy and side effect burden based on animal data may be limited. Likewise, it is possible to test combinations in humans suffering from a particular disease such as schizophrenia where there exist standard measuring scales (Mortimer AM. Br J Psychiatry Suppl. 50:s7. 2007) for both efficacy of disease treatment as well as side effects. However, testing such a large number of combinations in either animal models of disease or more importantly in human clinical trials is practically impossible as it would be prohibitively expensive, and could take decades due to limitations in the number of existing skilled investigators and required time for patient recruitment.

[0075] Without a method of testing and predicting the efficacy of a given combination, it is extremely difficult to predict *a priori* if such a combination will be efficacious. For instance, Medina et al. gave the muscarinic agonist xanomeline and the muscarinic antagonist methscopolamine to investigate whether syncope, which is a side effect observed with xanomeline, can be mediated by muscarinic antagonists (Medina et al. Hypertension. 29: 828. 1997). The group observed no effect on syncope, which may reflect the lack of involvement of the muscarinic system in syncope or, alternatively, may reflect the incorrect selection of a muscarinic combination. Likewise, Maral et al. documented use of the muscarinic agonist RS-86 with the anticholinergic agent glycopyrrolate for treatment of Alzheimer's Disease (Maral et al. Neurology. 38:606. 1988). The approach did not result in any improvement in cognition despite use of escalating amounts of RS-86. US 2006/0194831 discloses use of a derivative of clozapine to activate muscarinic receptors. While US 2006/0194831 discloses that the use of the clozapine derivative can be combined with another therapy selected from a broad list of therapies including use of a muscarinic antagonist, the publication provides no guidance or reasoning, for example, as to why a particular agent should be selected from the broad list for combination with the clozapine derivative, or why such a combination would be useful. US 5852029, which discloses a particular muscarinic agonist, mentions potential use of the particular agonist with muscarinic antagonists to help eliminate side effects but does not provide any criteria for selecting an appropriate antagonist.

[0076] Lack of success by groups such as Maral et al. points to the need to carefully select and ideally test combinations of

muscarinic Activators and Inhibitors. Given the impractical nature of physically testing such a large number of combinations, we created an algorithm for *in silico* testing to perform the extremely difficult task of predicting *a priori,* without *in vivo* testing, if a given combination will be efficacious and safe. In order to carry out the *in silico* testing based on the algorithm, we created an extensive database which captured the known information about muscarinic Activators and Inhibitors. The process by which we created this unique algorithm, as well as the database of muscarinic agents and their properties, was both multi-phased and resource-intensive. First, we created a list of all known muscarinic Activators and Inhibitors. Next, we selected properties of muscarinic agents that are useful in predicting an efficacious and safe combination and determined the relative importance of each property. We then embarked on an exhaustive data-collection process to, wherever possible, gather data related to each property for each muscarinic Activator and Inhibitor. With this data on-hand, we then created a computer-based algorithm, whereby a score is calculated for each property and each combination, such that these scores are then used to generate an overall score for each combination. The scoring system was created such that higher total scores ("Theta Scores") are applied to combinations with a higher probability to be efficacious with acceptable side effects. Therefore, by testing each combination with the algorithm, we created a prioritized list of combinations whereby combinations with higher scores are more attractive candidates for clinical testing. Given the impracticality of testing every possible combination *in vivo,* prioritization to select combinations for testing in humans is critical.

[0077] In order to evaluate different combinations of muscarinic Activator and Inhibitors, we created a proprietary database of all known muscarinic Activators and Inhibitors (see Tables 2 and 3). This database was created through systematic reviews of a variety of resources in search of all current and past programs related to muscarinic Activators and Inhibitors. Our reviews included scholarly literature databases, such as Pubmed and Web of Science, patent databases, such as Delphion, and pharmaceutical research and development databases, such as Adis R&D Insight™. We also reviewed drug package inserts, news databases, company websites, and conference abstracts. In all, we reviewed several thousand journal publications, patents, Adis records, and other documents to generate a comprehensive database of 65 muscarinic Activators and 114 muscarinic Inhibitors.

[0078] We then selected properties useful in predicting whether a given combination will be efficacious with acceptable side effects. We determined, in other words, the criteria by which each combination may be evaluated in order to generate a quantitative, predictive assessment. This process of selecting relevant properties was driven by rigorous internal analyses and resulted in the identification of several properties that are typically not considered, and/or that are typically thought to be unfavorable, but which we treated as favorable. The combination therapy approach in this application is significantly different from typical combination therapy approaches, which entail looking for synergistic efficacy of two agents. In the present invention, we look for one agent to eliminate the effects of the other agent, which leads to unorthodox criteria for drug selection. For example, we evaluated each muscarinic Inhibitor based on efficacy data such that, in some cases, *low* or *poor* efficacy data was rewarded. Also, contrary to typical approaches, in some cases we rewarded muscarinic Inhibitors for the side effects they exhibited during clinical development. Since most muscarinic Inhibitors were tested for unrelated indications, such as overactive bladder, efficacy for these unrelated indications may be undesirable and may be predictive of a combination with potentially unacceptable side effects. For instance, excessive urination is not a commonly reported side effect of muscarinic Activators. Therefore, having Inhibitors that have the greatest ability to decrease micturition may present the greatest risk of causing urinary retention without providing a benefit in the combination.

[0079] We rewarded certain side effects, particularly those known to be associated with peripheral anticholinergic effects, because they may counteract or lessen the impact of muscarinic Activator side effects. This combination of rewarding side effects and rewarding poor efficacy leads to the selection of a muscarinic Inhibitor that will have physiological effects throughout the periphery, which is desired for the elimination of muscarinic Activator side effects. For example, if a compound demonstrated efficacy for the treatment of overactive bladder without any side effects, this would suggest that the compound was inhibiting muscarinic receptors in the bladder, but not in the gastrointestinal tract or in the salivary glands to a significant degree. Although such as compound would be ideal for a drug whose intended purpose is the treatment of overactive bladder, such a compound would be unfavorable for the uses described herein. A more favorable Inhibitor for the envisioned combination would demonstrate pharmacological effects (i.e., side effects observed when treating overactive bladder) in the same organs where the Activator causes undesired side effects (e.g., the gastrointestinal tract). The rewarding of side effects and penalizing of efficacy stands in contrast to the typical method for selecting pharmaceutical agents.

[0080] Our intensive selection process resulted in 95 relevant properties, on the basis of which each of the 7,410 combinations of known muscarinic Activators and Inhibitors would be evaluated. The properties fell into three general categories: properties related exclusively to muscarinic Activators; properties related exclusively to muscarinic Inhibitors; and properties that combined attributes of both the Activator and Inhibitor. These classifications are discussed below in detail.

[0081] To collect data for each muscarinic Activator and Inhibitor based on each property, we embarked on a rigorous data collection process using many of the same resources as those used in generating a database of all known muscarinic Activators and Inhibitors. Again, our review spanned scholarly literature databases, such as Pubmed and Web of Science, patent databases, such as Delphion, pharmaceutical research and development databases, such as Adis R&D Insight™ and the U.S. FDA Orange Book, as well as package inserts and other resources. This process differed, however, in the detailed and often quantitative nature of the information extracted. For example, we gathered and categorized all known efficacy and side effect data for each muscarinic Activator and Inhibitor. We also gathered all known data related to pharmacokinetics and pharmacodynamics. As new data becomes available for compounds currently in our database, or as information regarding potential new entries for our database becomes available, database updates may be made, which would yield new theta scores. For example, MCD 386 is a muscarinic Activator for which additional data could result in increased theta scores for muscarinic Activator and Inhibitor combinations that include MCD 386.

[0082] Using these data, we then created a computer-based algorithm to quantify the relative probability that each muscarinic Activator and Inhibitor combination will be efficacious with acceptable side effects. The scoring system functions by applying a score to each combination based on each property, which we call a p-score. Each p-score contributed to an overall calculation, such that a high p-score signified that a combination has an increased likelihood of being efficacious with acceptable side effects based on a given property. Since the algorithm tested a total of 7,410 possible combinations, each of which was evaluated based on 95 p-scores, the algorithm summed a total of 703,950 p-scores in calculating a unique overall score (a "Theta Score") for each combination (see Table 1).

[0083] Given the varied nature of data from one property to the next, a variety of scoring methodologies were used to generate p-scores. In all cases, scoring methodologies were consistent within a given property and generated a maximum value of 10, which was then multiplied by a "weight factor." Weight factors were used to reflect the importance of each property in predicting the probability that a combination is efficacious with acceptable side effects. Some properties, such as those relating to the demonstration of efficacy for an agonist, have a stronger impact in assessing a preferred combination and were thus weighted more heavily. The baseline weight factor for all properties was 1, and the maximum weight factor used was 2.

[0084] The primary methodologies used in generating p-scores were ranking-based scoring, binary scoring, and scoring by value cut-off. The mechanics of each of these methodologies are detailed below:

- **Ranking-based p-scores** were generated using quantitative data, such as efficacy measurements, and awarding the highest value (e.g., a score of 10) to the most preferable data point, and the lowest value (e.g., a score of 0) to the least preferable data point. The remaining values were then distributed linearly, such that less preferable data points were awarded proportionally lower scores. Finally, a weight factor was applied to each value by multiplying each score by a pre-determined weight that reflected the importance of the given property. Take, for example, the case where three muscarinic Inhibitors (Inhibitor A, Inhibitor B, and Inhibitor C) are evaluated based on the demonstrated reduction in urinary frequency (number of micturitions per 24 hours), such that the minimum reduction, or lowest efficacy, is desired. In this case, Inhibitor A shows a reduction of 1 micturition per 24 hours, while Inhibitors B and C show values of 2 and 4 respectively. To calculate each p-score, since Inhibitor A demonstrated the most desirable results, we first must give Inhibitor A a proportionally higher value than B or C (e.g., Inhibitors A, B, and C are given values of 1, ½, and ¼, respectively). We then linearly distribute these values such that Inhibitor A receives a score of 10, Inhibitor B a score of 5, and Inhibitor C a score of 2.5. Finally, these scores are multiplied by a weight factor, which in this case would be 1, giving final p-scores of 10, 5, and 2.5.

- **Binary p-scores** were generated by assigning one of two values relating to a binary property. Take, for example, the case of two muscarinic Activators, A and B, which are evaluated based on whether they have shown efficacy in human trials. Muscarinic Activator A, which has shown efficacy, is awarded a value of 10, while B, which has not, receives a score of 0. Since this important property has a weight factor of 2, muscarinic Activators A and B receive final p-scores of 20 and 0, respectively.
- **Value cut-off p-scores** were applied based on the group into which a given value fell. This methodology was used for non-binary cases where a ranking methodology is not preferred or possible (e.g., scoring qualitative data, or scoring quantitative data in which cut-offs are relevant). In these cases, muscarinic Activators or Inhibitors whose values fall into the most desirable category are awarded values of 10 (prior to multiplication by the corresponding weight factor).

[0085] The p-scores applied to each combination were summed to generate three unique Subscores: the Activator Independent Subscore, the Inhibitor Independent Subscore, and the Combination Subscore. The Activator Independent Subscore represents an evaluation of each agonist based on properties that are independent of the antagonist with which it is combined (e.g., the demonstration of efficacy in human trials). Similarly, the Inhibitor Independent Subscore represents an evaluation of each antagonist based on properties that are independent of the agonist with which it is combined (e.g., level of CNS penetrance). The Combination Subscore, in contrast, represents an evaluation based on properties in which characteristics of both the agonist and antagonist are relevant (e.g., similarity of T_{max} based on pharmacokinetic studies). For both the Activator Independent Subscore and the Inhibitor Independent Subscore, the value was calculated by summing each p-score and then normalizing each score such that the highest ranking entry was given a score of 100. Each lower ranking entry was thus increased or decreased proportionally by the same factor as the highest ranking entry. In calculating the Combination Subscore, the same principle was applied; however, the maximum score given was 50.

[0086] Ultimately, the algorithm generated a final "Theta Score" for each combination such that, as the theta score increased, so did the probability that the combination would produce efficacy with acceptable side effects. The Theta Score was calculated by summing the three Subscores.

Table 1. Algorithm Structure

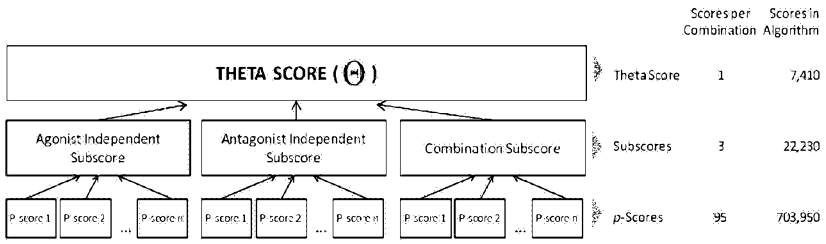

Table 2. List of Muscarinic Activators

Muscarinic Activators			
1	A 72055	37	PDC 008004
2	AF 125	38	Pilocarpine
3	AF 150(S)	39	Pilocarpine - Controlled Therapeutics
4	AF 185	40	PTAC
5	Alvameline	41	Anavex Life Sciences preclinical muscarinic activator
6	Amifostine		
7	Arecoline transdermal - Cogent Pharmaceuticals	42	Eli Lilly preclinical M1 receptor muscarinic activator
8	Cevimeline		
9	CI 1017	43	Eli Lilly preclinical M4 receptor muscarinic activator
10	CMI 1145		
11	CMI 936	44	TorryPines Therapeutics preclinical muscarinic activator
12	CS 932		
13	DM 71	45	Banyu preclinical muscarinic activator
14	FPL 14995		
15	GSK 1034702	46	Mithridion preclinical muscarinic activator
16	Himbacine		
17	Itameline	47	ACADIA/Sepracor preclinical muscarinic activator
18	KST 2818		
19	KST 5410	48	ACADIA preclinical muscarinic activator
20	KST 5452		
21	L 670548	49	RU 35963
22	L 689660	50	Sabcomeline
23	L 696986	51	SDZ 210086
24	L 705106	52	SR 46559A

Muscarinic Activators			
25	LY 316108	53	SR 96777A
26	MCD 386	54	Stacofylline
27	Milameline	55	Talsaclidine
28	Muscarinic receptor agonists - ACADIA/Allergan	56	Tazomeline
29	NC 111585	57	Thiopilocarpine
30	Nebracetam	58	Ticalopride
31	NGX 267	59	U 80816
32	Norclozapine	60	Vedaclidine
33	ORG 20091	61	WAY 131256
34	PD 141606	62	WAY 132983
35	PD 142505	63	Xanomeline
36	PD 151832	64	YM 796
		65	YM 954

Table 3. List of Muscarinic Inhibitors

Muscarinic Inhibitors					
1	Aclidinium bromide	42	Liriodenine	87	RL 315535
2	Aclidinium bromide/formoterol	43	LK 12	88	RO 465934
3	Acotiamide	44	Mequitamium iodide	89	SCH 211803
4	AH 9700	45	Methantheline	90	SCH 57790
5	Alvameline	46	Methantheline bromide	91	Scopolamine intranasal - Nastech
6	AQRA 721	47	Methscopolamine bromide		
		48	N-butylscopolamine	92	Scopolamine transmucosal - Anesta
7	AQRA 741	49	N-methylatropine		
8	AZD 9164	50	NPC 14695	93	Secoverine
9	BIBN 99	51	NX 303		
10	CEB 1957	52	Otenzepad	94	S-ET 126
11	Clozapine extended release - Azur Pharma	53	Oxybutynin - Labopharm	95	Sintropium bromide
12	Darenzepine	54	Oxybutynin - Penwest Pharmaceuticals		
13	Darifenacin	55	Oxybutynin chloride - ALZA	96	Solifenacin
		56	Oxybutynin intravesical - Situs	97	Solifenacin/tamsulosin
14	Darotropium bromide	57	Oxybutynin transdermal - Schwarz Pharma	98	SVT 40776
15	Dextro-mequitamium iodide	58	Oxybutynin transdermal - Watson	99	TD 6301
		59	Oxybutynin transdermal gel - Antares	100	Telenzepine
16	Ebeinone	60	Oxybutynin transmucosal - Auxilium	101	Temiverine
17	Esoxybutynin	61	Oxybutynin vaginal - Barr Laboratories		
		62	PG 1000	102	Tiotropium bromide
18	Espatropate	63	Pirenzepine ophthalmic	103	Tolterodine
		64	Pirmenol	104	Tolterodine/tamsulosin
19	Fesoterodine	65	PNU 200577	105	Tropenzilium
			Promethazine/hydrocodone/paracetamol -	106	Trospium chloride

Muscarinic Inhibitors					
20	Glycopyrrolate/indacaterol	66	Charleston Laboratories	107	Trospium chloride controlled release
		67	Propantheline	108	Trospium chloride inhalation
21	Glycopyrronium bromide	68	Propantheline bromide	109	V 0162
22	GSK 1160724	69	Propiverine	110	YM 35636
23	GSK 202405	70	PSD 506	111	YM 46303
		71	PTAC	112	YM 53705
24	GSK 573719	72	QAT 1370	113	YM 58790
25	GSK 656398	73	Almirall muscarinic Inhibitor	114	Zamifenacin
26	GSK 961081				
27	GYKI 46903	74	Anavex Life Sciences primary muscarinic Inhibitor		
28	Homatropine methylbromide				
29	Imidafenacin	75	Anavex Life Sciences secondary muscarinic inhibitor		
30	Inhaled glycopyrrolate - Novartis	76	FF2 - Nuada		
31	Ipratropium bromide dry-powder inhalation - Dura/Spiros	77	GlaxoSmithKline/Theravance muscarinic Inhibitor		
32	Ipratropium bromide dry-powder inhalation - ML Laboratories	78	Chiesi Farmaceutici/SALVAT muscarinic inhibitor		
33	Ipratropium bromide hydrofluoroalkane inhalation - Boehringer Ingelheim	79	UCB muscarinic Inhibitor		
34	Ipratropium bromide intranasal - Chiesi	80	Theravance primary muscarinic Inhibitor		
35	Ipratropium bromide metered solution inhalation - Sheffield	81	Theravance secondary muscarinic Inhibitor		
36	Ipratropium bromide/xylometazoline	82	Novartis muscarinic Inhibitor		
37	J 104129	83	ACADIA/Sepracor muscarinic Inhibitor		
38	J 106366				
39	L 696986	84	Safetek muscarinic Inhibitor		
40	LAS 35201	85	Revatropate		
41	Levosalbutamol/ipratropium inhalation solution - Arrow International limited/Senracor	86	Rispenzepine		

[0087] The algorithm was structured with inputs according to the following 3 tables. The Property, Scoring Methodology, Criteria for a High Score, and Weight columns in each table represent the underlying inputs and mechanics used in calculating each Subscore.

Table 4. Mechanics of Activator Independent Subscore

Activator Subscore Mechanics					
Count	**Property Category**	**Property**	**Scoring Methodology**	**Criteria for a High Score**	**Weight Factor**
1	Development	Highest Phase	Unique value assigned to each dev. stage	High stage of development	1
2	Development	Highest Phase CNS	Unique value assigned to each dev. stage	High stage of development	1
3	Development	Highest Phase US	Unique value assigned to each dev. stage	High stage of development	1
4	ROA	Route of Administration	Unique value assigned to each ROA	Oral	1
5	Pharmacokinetics	Tmax	Ranked by Tmax value	High Tmax	1
6	Pharmacokinetics	T(1/2)	Ranked by T(1/2) value	High T(1/2)	1
7	Efficacy	Demonstrated Efficacy	Binary scoring	Efficacy shown	2
8	Efficacy	Demonstrated Efficacy in Cognition	Binary scoring	Efficacy shown	2
9	Efficacy	Demonstrated Efficacy in Schizophrenia	Binary scoring	Efficacy shown	2
10	Receptor Selectivity	M2 Agonist?	Binary scoring	Not M2 Agonist	1
11	Receptor Selectivity	M3 Agonist?	Binary scoring	Not M3 agonist	1
12	Receptor Selectivity	M1/M2 ratio	Ranked by ratio value	High ratio	1
13	Receptor Selectivity	M1/M3 ratio	Ranked by ratio value	High ratio	1
14	Receptor Selectivity	M1/M5 ratio	Ranked by ratio value	High ratio	1
15	Receptor Selectivity	M4/M2 ratio	Ranked by ratio value	High ratio	1
16	Receptor Selectivity	M4/M3 ratio	Ranked by ratio value	High ratio	1
17	Receptor Selectivity	M4/M5 ratio	Ranked by ratio value	High ratio	1
18	Receptor Selectivity	M2/M3 ratio	Ranked by ratio value	Close to 1	1
19	Receptor Selectivity	M5/M2 ratio	Ranked by ratio value	Close to 1	1
20	Receptor Selectivity	M5/M3 ratio	Ranked by ratio value	Close to 1	1

Table 5. Mechanics of Inhibitor Independent Subscore

Inhibitor Subscore Mechanics					
Count	**Property Category**	**Property**	**Scoring Methodology**	**Criteria for High Score**	**Weight Factory**
1	Development	Highest Phase	Unique value assigned to each dev. stage	High stage of development	1
2	Development	Highest Phase US	Unique value assigned to each dev. stage	High stage of development	1
3	ROA	Route of Administration	Unique value assigned to each ROA	Oral	1
4	Pharmacokinetics	Tmax	Ranked by Tmax	High Tmax	1

Inhibitor Subscore Mechanics					
Count	**Property Category**	**Property**	**Scoring Methodology**	**Criteria for High Score**	**Weight Factory**
			value		
5	Pharmacokinetics	T(1/2)	Ranked by T(1/2) value	High T(1/2)	1
6	CNS Penetrance	CNS Penetrance	Unique value assigned based on H, M, L penetrance	Low penetrance	2
7	Receptor Selectivity	M2/M1 ratio	Ranked by ratio value	High ratio	1
8	Receptor Selectivity	M2/M4 ratio	Ranked by ratio value	High ratio	1
9	Receptor Selectivity	M3/M1 ratio	Ranked by ratio value	High ratio	1
10	Receptor Selectivity	M3/M4 ratio	Ranked by ratio value	High ratio	1
11	Efficacy	Urinary Frequency (# Micturitions per 24hrs)Reduction	Ranked by efficacy value	Low efficacy	1
12	Efficacy	Urinary Frequency (# Micturitions/24hrs)-% Reduction	Ranked by efficacy value	Low efficacy	1
13	Efficacy	Urinary Frequency (# Micturitions/24hrs)-% Reduction over Placebo	Ranked by efficacy value	Low efficacy	1
14	Efficacy	Urinary Frequency (# Micturitions/24hrs)Reduction over Placebo	Ranked by efficacy value	Low efficacy	1
15	Efficacy	Volume Voided / micturition (mL) -- Reduction	Ranked by efficacy value	Low efficacy	1
16	Efficacy	Volume Voided /micturition (mL) -- % Reduction	Ranked by efficacy value	Low efficacy	1
17	Efficacy	Volume Voided / micturition (mL) -- % Reduction over Placebo	Ranked by efficacy value	Low efficacy	1
18	Efficacy	Volume Voided / micturition (mL) -- Reduction over Placebo	Ranked by efficacy value	Low efficacy	1
19	Efficacy	# of Incontinence Eps / 24 hours -- % Reduction	Ranked by efficacy value	Low efficacy	1
20	Efficacy	# of Incontinence Eps / 24 hours -- Reduction	Ranked by efficacy value	Low efficacy	1
21	Efficacy	# of Incontinence Eps / week - - % Reduction	Ranked by efficacy value	Low efficacy	1
22	Efficacy	# of Incontinence Eps / week - - Reduction	Ranked by efficacy value	Low efficacy	1
23	Efficacy	# Urge incontinence eps / 24 hrs -- % Reduction	Ranked by efficacy value	Low efficacy	1
24	Efficacy	# Urge incontinence eps / 24 hrs -- Reduction	Ranked by efficacy value	Low efficacy	1
25	Efficacy	# Urge incontinence eps / week -- % Reduction	Ranked by efficacy value	Low efficacy	1
26	Efficacy	# Urge incontinence eps / week -- Reduction	Ranked by efficacy value	Low efficacy	1
27	Adverse Events	Dry Mouth -- % increase	Ranked by AE value	Low AE	1

Inhibitor Subscore Mechanics					
Count	**Property Category**	**Property**	**Scoring Methodology**	**Criteria for High Score**	**Weight Factory**
		over placebo		values	
28	Adverse Events	Constipation -- % increase over placebo	Ranked by AE value	Low AE values	1
29	Adverse Events	Dyspepsia -- % increase over placebo	Ranked by AE value	Low AE values	1
30	Adverse Events	Abdominal Pain -- % increase over placebo	Ranked by AE value	Low AE values	1
31	Adverse Events	Dry Mouth -- absolute % values	Ranked by AE value	Low AE values	1
32	Adverse Events	Constipation -- absolute % values	Ranked by AE value	Low AE values	1
33	Adverse Events	Dyspepsia -- absolute % values	Ranked by AE value	Low AE values	1
34	Adverse Events	Abdominal Pain -- absolute % values	Ranked by AE value	Low AE values	1
35	Adverse Events	Constipation aggravated	Ranked by AE value	Low AE values	1
36	Adverse Events	Nausea	Ranked by AE value	Low AE values	1
37	Adverse Events	Abdominal Distension	Ranked by AE value	Low AE values	1
38	Adverse Events	Flatulence	Ranked by AE value	Low AE values	1
39	Adverse Events	Diarrhea	Ranked by AE value	Low AE values	1
40	Adverse Events	Vomiting	Ranked by AE value	Low AE values	1
41	Adverse Events	UTI	Ranked by AE value	Low AE values	1
42	Adverse Events	Upper Respiratory tract infection	Ranked by AE value	Low AE values	1
43	Adverse Events	Influenza	Ranked by AE value	Low AE values	1
44	Adverse Events	Pharyngitis	Ranked by AE value	Low AE values	1
45	Adverse Events	Headache	Ranked by AE value	Low AE values	1
46	Adverse Events	Dizziness	Ranked by AE value	Low AE values	1
47	Adverse Events	Vision Blurred	Ranked by AE value	Low AE values	1
48	Adverse Events	Dry Eyes	Ranked by AE value	Low AE values	1
49	Adverse Events	Urinary Retention	Ranked by AE value	Low AE values	1
50	Adverse Events	Dysuria	Ranked by AE value	Low AE values	1
51	Adverse Events	Edema Lower Limb	Ranked by AE value	Low AE values	1
52	Adverse Events	Edema peripheral	Ranked by AE value	Low AE values	1
53	Adverse Events	Fatigue	Ranked by AE value	Low AE	1

Inhibitor Subscore Mechanics					
Count	**Property Category**	**Property**	**Scoring Methodology**	**Criteria for High Score**	**Weight Factory**
				values	
54	Adverse Events	Depression	Ranked by AE value	Low AE values	1
55	Adverse Events	Insomnia	Ranked by AE value	Low AE values	1
56	Adverse Events	Cough	Ranked by AE value	Low AE values	1
57	Adverse Events	Dry Throat	Ranked by AE value	Low AE values	1
58	Adverse Events	Hypertension	Ranked by AE value	Low AE values	1
59	Adverse Events	Asthenia	Ranked by AE value	Low AE values	1
60	Adverse Events	Nasal dryness	Ranked by AE value	Low AE values	1
61	Adverse Events	Back pain	Ranked by AE value	Low AE values	1
62	Adverse Events	ALT increased	Ranked by AE value	Low AE values	1
63	Adverse Events	GGT increased	Ranked by AE value	Low AE values	1
64	Adverse Events	Rash	Ranked by AE value	Low AE values	1
Note: ALT = Alanine transaminase; GGT=Gamma-glutamyltransferase					

Table 6. Mechanics of Combination Subscore

Combination Subscore Mechanics					
Count	**Property Category**	**Property**	**Scoring Methodology**	**Criteria for High Score**	**Weight Factor**
1	Pharmacokinetics	Tmax	Unique value given based on closeness of Tmax	Close Tmax values	1
2	Pharmacokinetics	T(1/2)	Unique value given based on closeness of T(1/2)	Close T(1/2) values	1
3	Metabolism	Drug-drug interaction potential	Unique value assigned based on H, M, or L degree of interaction, specifically regarding CYP 450	Low overall risk of drug-drug interaction	1
4	Receptor Selectivity	(M1 Activator selectivity / M1 Inhibitor selectivity) ratio	Ranked by ratio value	High ratio value (devalue if Inhibitor acts on M1, Activator is weak M1 Activator)	1
5	Receptor Selectivity	(M4 Activator selectivity / M4 Inhibitor selectivity) ratio	Ranked by ratio value	High ratio value (devalue if Inhibitor acts on M4, Activator is weak M4 Activator)	1
6	Receptor Selectivity	(M3 Activator selectivity / M3 Inhibitor selectivity) ratio	Ranked by ratio value	Low ratio value (With M3 Activator, M3 Inhibitor is desired)	1
7	Receptor Selectivity	(M2 Activator selectivity / M2	Ranked by ratio value	Low ratio value (If M2 Activator, M2 Inhibitor	1

Combination Subscore Mechanics					
Count	**Property Category**	**Property**	**Scoring Methodology**	**Criteria for High Score**	**Weight Factor**
		Inhibitor selectivity) ratio		is desired)	
8	Receptor Selectivity	(M5 Activator selectivity / M5 Inhibitor selectivity) ratio	Ranked by ratio value	High ratio value	1
9	Receptor Selectivity	M2/M3 ratio comparison	Ranked by ratio value	Ratio value close to 1	1
10	Efficacy	Reward specific cases of Inhibitor AEs if "offsetting" an Activator AE	Case specific	Case specific	1
11	Adverse Events	Reward specific cases of Inhibitor AEs if "offsetting" an Activator AE	Case specific	Case specific	1
Note: In cases where Activators inhibits a receptor, or where an Inhibitor activates a receptor, receptor selectivity ratios are changed to equal one divided by the ratio for determining the p-score.					

Table 7. Top 15 Combinations by Theta Score

Combination ID	Combination	Theta Score	Activator Independent Subscore	Inhibitor Independent Subscore	Combination Subscore
6355	Xanomeline & Trospium chloride	250	100	100	50
5003	Sabcomeline & Trospium chloride	245	95	100	50
2611	Milameline & Trospium chloride	243	98	100	45
6346	Xanomeline & Tolterodine	241	100	91	50
2602	Milameline & Tolterodine	239	98	91	50
5005	Sabcomeline & Trospium chloride controlled release	238	95	93	50
6357	Xanomeline & Trospium chloride controlled release	238	100	93	45
2613	Milameline & Trospium chloride controlled release	236	98	93	45
6347	Xanomeline & Darifenacin	235	100	95	40
6348	Xanomeline & Solifenacin	234	100	94	40
4996	Sabcomeline & Solifenacin	229	95	94	40
5523	Talsaclidine & Trospium chloride	224	94	100	30
635	Cevimeline & Trospium chloride	219	89	100	30
5515	Talsaclidine & Darifenacin	219	94	95	30
5516	Talsaclidine & Solifenacin	218	94	94	30
5525	Ttalsaclidine & Trospium chloride controlled release	217	94	93	30
5514	Talsaclidine & Tolterodine	215	94	91	30
6349	Xanomeline & Fesoterodine	215	100	85	30
627	Cevimeline & Darifenacin	214	89	95	30
637	Cevimeline & Trospium chloride controlled release	212	89	93	30

[0088] In a preferred embodiment of the invention, a combination of a muscarinic Activator and a muscarinic Inhibitor with a theta score of 230 or greater as determined by in silico testing using the above described algorithm is used. In another embodiment of the invention, a combination of a muscarinic Activator and a muscarinic Inhibitor with a theta score of 200 or greater as determined by in silico testing using the above described algorithm is used.

[0089] In one embodiment, xanomeline is used as the muscarinic Activator in combination with the muscarinic Inhibitor. In another embodiment, xanomeline is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, xanomeline is administered from one time to three times during a 24 hour period. In another embodiment, from 25 milligrams to 700 milligrams of xanomeline is used during a 24 hour period. In a preferred embodiment, from 75 milligrams to 300 milligrams of xanomeline is used during a 24 hour period.

[0090] In one embodiment, sabcomeline is used as the muscarinic Activator in combination with the muscarinic Inhibitor. In another embodiment, sabcomeline is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, sabcomeline is administered from one to three times during a 24 hour period. In another embodiment, from 50 micrograms to five milligrams of sabcomeline is used during a 24 hour period. In a preferred embodiment, from 150 micrograms to 450 micrograms of sabcomeline is used during a 24 hour period.

[0091] In one embodiment, milameline is used as the muscarinic Activator in combination with the muscarinic Inhibitor. In another embodiment, milameline is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, milameline is administered from one to three times during a 24 hour period. In another embodiment, from 0.5 milligrams to 50 milligrams of milameline is used during a 24 hour period. In a preferred embodiment, from four milligrams to 16 milligrams of milameline is used during a 24 hour period.

[0092] In one embodiment, talsaclidine is used as the muscarinic Activator in combination with the muscarinic Inhibitor. In another embodiment, talsaclidine is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, talsaclidine is administered from one to three times during a 24 hour period. In another embodiment, from five milligrams to 1 gram of talsaclidine is used during a 24 hour period. In a preferred embodiment, from 120 milligrams to 480 milligrams of talsaclidine is used during a 24 hour period.

[0093] In one embodiment, cevimeline is used as the muscarinic Activator in combination with the muscarinic Inhibitor. In another embodiment, cevimeline is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, cevimeline is administered from one to three times during a 24 hour period. In another embodiment, from 45 milligrams to 750 milligrams of cevimeline is used during a 24 hour period. In a preferred embodiment, from 90 milligrams to 360 milligrams of cevimeline is used during a 24 hour period.

[0094] In one embodiment, pilocarpine is used as the muscarinic Activator in combination with the muscarinic Inhibitor. In another embodiment, pilocarpine is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, pilocarpine is administered from one to three times during a 24 hour period. In another embodiment, from 7.5 milligrams to 500 milligrams of pilocarpine is used during a 24 hour period. In a preferred embodiment, from 30 milligrams to 200 milligrams of pilocarpine is used during a 24 hour period.

[0095] In one embodiment, trospium chloride is used as the muscarinic Inhibitor in combination with the muscarinic Activator. In another embodiment, trospium chloride is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, trospium chloride is administered from one time to three times during a 24 hour period. In another embodiment, from five milligrams to 400 milligrams of trospium chloride is used during a 24 hour period. In a preferred embodiment, from 20 milligrams to 200 milligrams of trospium chloride is used during a 24 hour period.

[0096] In one embodiment, trospium chloride extended release is used as the muscarinic Inhibitor in combination with the muscarinic Activator. In another embodiment, trospium chloride extended release is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, trospium chloride extended release is administered from one to three times during a 24 hour period. In another embodiment, from five milligrams to 400 milligrams of trospium chloride extended release is used during a 24 hour period. In a preferred embodiment, from 20 milligrams to 200 milligrams of trospium chloride extended release is used during a 24 hour period.

[0097] In one embodiment, solifenacin is used as the muscarinic Inhibitor in combination with the muscarinic Activator. In another embodiment, solifenacin is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, solifenacin is administered from one time to three times during a 24 hour period. In another

embodiment, from 0.25 milligrams to 100 milligrams of solifenacin is used during a 24 hour period. In a preferred embodiment, from 1 milligram to 30 milligrams of solifenacin is used during a 24 hour period.

[0098] In one embodiment, tolterodine is used as the muscarinic Inhibitor in combination with the muscarinic Activator. In another embodiment, tolterodine is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, tolterodine is administered from one to three times during a 24 hour period. In another embodiment, from one milligram to 16 milligrams of tolterodine is used during a 24 hour period. In a preferred embodiment, from two milligrams to eight milligrams of tolterodine is used during a 24 hour period.

[0099] In one embodiment, fesoterodine is used as the muscarinic Inhibitor in combination with the muscarinic Activator. In another embodiment, fesoterodine is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, fesoterodine is administered from one to three times during a 24 hour period. In another embodiment, from two milligrams to 56 milligrams of fesoterodine is used during a 24 hour period. In a preferred embodiment, from four milligrams to 28 milligrams of fesoterodine is used during a 24 hour period.

[0100] In one embodiment, darifenacin is used as the muscarinic Inhibitor in combination with the muscarinic Activator. In another embodiment, darifenacin is administered to a patient from one time to five times during a 24 hour period. In a preferred embodiment, darifenacin is administered from one to three times during a 24 hour period. In another embodiment, from 3.75 milligrams to 150 milligrams of darifenacin is used during a 24 hour period. In a preferred embodiment, from 7.5 milligrams to 30 milligrams of darifenacin is used during a 24 hour period.

[0101] While the subject is being treated, the health of the patient may be monitored by measuring one or more of the relevant indices at predetermined times during the treatment period. Treatment, including composition, amounts, times of administration and formulation, may be optimized according to the results of such monitoring. The patient may be periodically reevaluated to determine the extent of improvement by measuring the same parameters. Adjustments to the amount(s) of subject composition administered and possibly to the time of administration may be made based on these reevaluations.

[0102] Treatment may be initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum balance between therapeutic effect and side effects is attained.

Dosage forms of the combination

[0103] In one embodiment, the muscarinic Activator and muscarinic Inhibitor are in different dosage forms or dosage vehicles. In a preferred embodiment, the muscarinic Activator and muscarinic Inhibitor are in the same dosage form or dosage vehicles. The dosage forms may include one or more pharmaceutically-acceptable carriers. The dosage forms may also include one or more pharmaceutically-acceptable salts. The dosage forms may be administered orally. The Activator and Inhibitor may be delivered orally using tablets, troches, liquids, emulsions, suspensions, drops, capsules, caplets or gel caps and other methods of oral administration known to one skilled in the art. The muscarinic Activator and Inhibitor may also be administered parentally. Other routes of administration include but are not limited to: topical, transdermal, nasal, ocular, rectal, sublingual, inhalation, and vaginal. For topical and transdermal administration, the Activator and Inhibitor may be delivered in a cream, gel, ointment, spray, suspension, emulsion, foam, or patch or by other methods known to one skilled in the art. For nasal administration, the Activator and Inhibitor may be delivered by sprays, drops, emulsions, foams, creams, ointments or other methods known to one skilled in the art. For nasal administration, formulations for inhalation may be prepared as an aerosol, either a solution aerosol in which the active agent is solubilized in a carrier, such as a propellant, or a dispersion aerosol, in which the active agent is suspended or dispersed throughout a carrier and an optional solvent. For ocular administration, the Activator and Inhibitor may be delivered in drops, sprays, injections, solutions, emulsions, suspensions, or ointments, or by other methods known to one skilled in the art. For rectal administration, the Activator and Inhibitor may be delivered using suppositories, enemas, creams, foams, gels, or ointments or by other methods known to one skilled in the art. For sublingual administration, the Activator and Inhibitor may be delivered in tablets, troches, liquids, emulsions, suspensions, drops, capsules, caplets or gel caps and by other methods of oral administration known to one skilled in the art. For administration by inhalation, the Activator and Inhibitor may be delivered in vapor, mist, powder, aerosol, or nebulized form, or by other methods known to one skilled in the art. For vaginal administration, the Activator and Inhibitor may be delivered in solutions, emulsions, suspensions, ointments, gels, foams, or vaginal rings or by other methods known to one skilled in the art.

[0104] The muscarinic Activator and Inhibitor may be in a dosage form that immediately releases the drug. In an alternative embodiment, the muscarinic Activator and Inhibitor are in a controlled release dosage form. In one embodiment of the controlled release dosage form, the Activator and Inhibitor have similar release kinetics. In another embodiment, the Inhibitor is released prior to the Activator's being released. In another embodiment, a three part release profile is used such that the Inhibitor is released immediately, followed by the Activator in a controlled release fashion and then by the Inhibitor in a controlled release fashion. In one embodiment, the muscarinic Activator and Inhibitor are packaged in liposomes. In a further embodiment, the liposome comprises a phospholipid. In a further embodiment, the phospholipid in the liposome is selected from phosphatidylcholine (PC), phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidic acid (PA), egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), egg phosphatidylinositol (EPI), egg phosphatidylserine (EPS), egg phosphatidylethanolamine (EPE), egg phosphatidic acid (EPA), soy phosphatidylcholine (SPC), soy phosphatidylglycerol (SPG), soy phosphatidylserine (SPS), soy phosphatidylinositol (SPI), soy phosphatidylethanolamine (SPE), soy phosphatidic acid (SPA), hydrogenated egg phosphatidylcholine (HEPC), hydrogenated soy phosphatidylcholine (HSPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylcholine (DOPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylglycerol (DPPG), distearoylphosphatidylcholine (DSPQ), distearoylphosphatidylglycerol (DSPG), dioleoylphosphatidyl-ethanolamine (DOPE), palmitoylstearoylphosphatidyl-choline (PSPC), palmitoylstearolphosphatidylglycerol (PSPG), mono-oleoyl-phosphatidylethanolarnine (MOPE), dilauroyl ethylphosphocholine (DLEP), dimyristoyl ethylphosphocholine (DMEP), dipalmitoyl ethylphosphocholine (DPEP), distearoyl ethylphosphocholine (DSEP), dimyristoylphosphatidic acid (DMPA), dipalmitoylphosphatidic acid (DPPA), distearoylphosphatidic acid (DSPA), dimyristoylphosphatidylinositol (DMPI), dipalmitoylphosphatidylinositol (DPPI), distearoylphosphatidylinositol (DSPI), dimyristoylphosphatidylserine (DMPS), dipalmitoylphosphatidylserine (DPPS), distearoylphosphatidylserine (DSPS), N-acylated phosphorylethanolamine (NAPE), and combinations thereof.

[0105] In a further embodiment, the controlled release formulation comprises a semi-permeable membrane. The muscarinic Activator and muscarinic Inhibitor may be in different membranes in the same formulation. In another embodiment, the muscarinic Activator and muscarinic Inhibitor can be in different membranes in different formulations or dosing vehicles. In a further embodiment, the semi-permeable membrane comprises a polymer. In a further embodiment, the controlled release formulation comprises a matrix that suspends the muscarinic Activator(s) and muscarinic Inhibitor(s). The muscarinic Activator and Inhibitor may be in separate matrices within the same medicament. In a further embodiment, the matrix comprises a polymer. In a further embodiment, the polymer comprises a water soluble polymer. In a further embodiment, the water soluble polymer is selected from Eudragit RL, polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyethylene glycol, and mixtures thereof. In a further embodiment, the polymer comprises a water insoluble polymer. In a further embodiment, the water insoluble polymer is selected from Eudragit RS, ethylcellulose, cellulose acetate, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethane, and mixtures thereof. In a further embodiment, the matrix comprises a fatty compound. In a further embodiment, the fatty compound is a wax or glyceryl tristearate. In a further embodiment, the polymer comprises a water soluble polymer and a water insoluble polymer. In a further embodiment, the matrix further comprises a fatty compound.

[0106] The muscarinic Activator and muscarinic Inhibitor may be in dosage forms that use other methods of controlled release formulation known to one skilled in the art (for example, Dixit & Puthli. J. Control Release. 2:94. 2009; Mizrahi & Domb. Recent Pat Drug Deliv Formul. 2:108. 2008; Forqueri & Singh. Recent Pat Drug Deliv Formul. 3:40. 2009; Kalantzi et al. Recent Pat Drug Deliv Formul. 3:49. 2009; Iconomopoulou et al. Recent Pat Drug Deliv Formul. 2:94. 2008; Panos et al. Curr Drug Discov Technol. 5: 333. 2008; 2008. Wan et al. Nanomed. 2:483. 2007. Wang et al. Drug Delivery: Principles & Applications. Wiley 2005).

[0107] In another embodiment, the combination of the muscarinic Activator and Inhibitor is used in combination with one or more therapies that can include both psychotherapy and drugs. Therapeutic agents include but are not limited to antipsychotics, anxiolytics, anti-depressants, sedatives, tranquilizers and other pharmacological interventions known to one skilled in the art. A therapeutic agent may fall under the category of more than one type of drug. For instance benzodiazepines can be considered anxiolytics, sedatives and tranquilizers.

Medicament containing one or more muscarinic Activators & muscarinic Inhibitors

[0108] One embodiment of the invention is a medicament comprising one or more muscarinic Activators and one or more muscarinic Inhibitors.

[0109] In one embodiment, from 10 micrograms to 10 grams of Activator is used in the combination with the Inhibitor in the medicament. In another embodiment, from 1 milligram to 1 gram of Activator is used in the combination with the Inhibitor. In another embodiment from 10 micrograms to 10 grams of Inhibitor is used in the combination with the Activator. In another embodiment, from 1 milligram to 1 gram of Inhibitor is used in the combination with the Activator.

[0110] In one embodiment, the medicament is administered to a patient 6 times during a 24 hour period. In another embodiment, the medicament is administered to a patient 5 times during a 24 hour period. In another embodiment, the medicament is administered to a patient 4 times during a 24 hour period. In another embodiment, the medicament is administered to a patient 3 times during a 24 hour period. In another embodiment, the medicament is administered to a patient 2 times during a 24 hour period. In another embodiment, the medicament is administered to a patient one time during a 24 hour period. In a preferred embodiment, the medicament is administered from one to 3 times during a 24 hour period.

[0111] In one embodiment of the invention, the medicament contains a combination of a muscarinic Activator and a muscarinic Inhibitor with a theta score of 230 or greater as determined by in silico testing using the above described algorithm. In another embodiment of the invention, the medicament contains a combination of a muscarinic Activator and a muscarinic Inhibitor with a theta score of 200 or greater as determined by in silico testing using the above described algorithm. In a further embodiment, xanomeline is used as the muscarinic Activator in the medicament. In another embodiment, the medicament contains from five milligrams to 700 milligrams of xanomeline. In a preferred embodiment, the medicament contains from 25 milligrams to 300 milligrams of xanomeline.

[0112] In one embodiment, sabcomeline is used as the muscarinic Activator in the medicament. In another embodiment, the medicament contains from 10 micrograms to five milligrams of sabcomeline. In a preferred embodiment, the medicament contains from 50 micrograms to 450 micrograms of sabcomeline.

[0113] In one embodiment, milameline is used as the muscarinic Activator in the medicament. In another embodiment, the medicament contains from 0.1 milligrams to 50 milligrams of milameline. In a preferred embodiment, the medicament contains from one milligram to 16 milligrams of milameline.

[0114] In one embodiment, talsaclidine is used as the muscarinic Activator in the medicament. In another embodiment, the medicament contains from one milligram to one gram of talsaclidine. In a preferred embodiment, the medicament contains from 40 milligrams to 480 milligrams of talsaclidine.

[0115] In one embodiment, cevimeline is used as the muscarinic Activator in the medicament. In another embodiment, the medicament contains from nine milligrams to 750 milligrams of cevimeline. In a preferred embodiment, the medicament contains from 30 milligrams to 360 milligrams of cevimeline.

[0116] In one embodiment, pilocarpine is used as the muscarinic Activator in the medicament. In another embodiment, the medicament contains from 1.5 milligrams to 500 milligrams of pilocarpine. In a preferred embodiment, the medicament contains from 10 milligrams to 200 milligrams of pilocarpine.

[0117] In one embodiment, trospium chloride is used as the muscarinic Inhibitor in the medicament. In another embodiment, the medicament contains from one milligram to 400 milligrams of trospium chloride. In a preferred embodiment, the medicament contains from 6.5 milligrams to 200 milligrams of trospium chloride.

[0118] In one embodiment, trospium chloride extended release is used as the muscarinic Inhibitor in the medicament. In another embodiment, the medicament contains from one milligram to 400 milligrams of trospium chloride extended release. In a preferred embodiment, the medicament contains from 6.5 milligrams to 200 milligrams of trospium chloride extended release.

[0119] In one embodiment, solifenacin is used as the muscarinic Inhibitor in the medicament. In another embodiment, the medicament contains from 0.25 milligram to 100 milligrams of solifenacin. In a preferred embodiment, the medicament contains from 1 milligrams to 30 milligrams of solifenacin.

[0120] In one embodiment, tolterodine is used as the muscarinic Inhibitor in the medicament. In another embodiment, the medicament contains from 0.2 milligrams to 16 milligrams of tolterodine. In a preferred embodiment, the medicament contains from 0.7 milligrams to eight milligrams of tolterodine.

[0121] In one embodiment, fesoterodine is used as the muscarinic Inhibitor in the medicament. In another embodiment, the medicament contains from 0.4 milligrams to 56 milligrams of fesoterodine. In a preferred embodiment, the medicament contains between one milligrams to 28 milligrams of fesoterodine.

[0122] In one embodiment, darifenacin is used as the muscarinic Inhibitor in the medicament. In another embodiment, the medicament contains from n 0.8 milligrams to 150 milligrams of darifenacin. In a preferred embodiment, the medicament contains from 2.5 milligrams to 30 milligrams of darifenacin.

[0123] While the subject is being treated, the health of the patient may be monitored by measuring one or more of the relevant indices at predetermined times during the treatment period. Treatment, including composition, amounts, times of administration and formulation, may be optimized according to the results of such monitoring. The patient may be periodically reevaluated to determine the extent of improvement by measuring the same parameters. Adjustments to the amount(s) of subject composition administered and possibly to the time of administration may be made based on these reevaluations.

[0124] Treatment may be initiated with smaller dosages that are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum balance between therapeutic effect and side effects is attained. This principle of drug titration is well understood by those of skill in the art.

[0125] The medicament may also include one or more pharmaceutically-acceptable salts. The medicament may include one or more pharmaceutically-acceptable carriers. The medicament may be administered orally. The medicament may be delivered orally using tablets, troches, liquids, emulsions, suspensions, drops, capsules, caplets or gel caps and other methods of oral administration known to one skilled in the art. The medicament may also be administered parentally. Other routes of administration include but are not limited to: topical, transdermal, nasal, rectal, ocular, sublingual, inhalation, and vaginal. For topical and transdermal administration, the medicament may be delivered in a cream, gel, ointment, spray, suspension, emulsion, foam, or patch or by other methods known to one skilled in the art. For nasal administration, the medicament may be delivered by sprays, drops, emulsions, foams, creams, or ointments or by other methods known to one skilled in the art. For nasal administration, formulations for inhalation may be prepared as an aerosol, either a solution aerosol in which the active agent is solubilized in a carrier, such as a propellant, or a dispersion aerosol, in which the active agent is suspended or dispersed throughout a carrier and an optional solvent. For rectal administration, the medicament may be delivered using suppositories, enemas, creams, foams, gels, or ointments or by other methods known to one skilled in the art. For ocular administration, the medicament may be delivered in drops, sprays, injections, solutions, emulsions, suspensions, or ointments, or by other methods known to one skilled in the art. For sublingual administration, the medicament may be delivered in tablets, troches, liquids, emulsions, suspensions, drops, capsules, caplets or gel caps and by other methods of oral administration known to one skilled in the art. For administration by inhalation, the medicament may be delivered in vapor, mist, powder, aerosol, or nebulized form, or by other methods known to one skilled in the art. For vaginal administration, the medicament may be delivered in solutions, emulsions, suspensions, ointments, gels, foams, or vaginal rings or by other methods known to one skilled in the art.

[0126] The medicament may be in a dosage form that immediately releases the drug. In an alternative embodiment, the medicament may have a controlled release dosage form. In one embodiment, the medicament is packaged in liposomes. In a further embodiment, the liposome comprises a phospholipid. In a further embodiment, the phospholipid in the liposome is selected from phosphatidylcholine (PC), phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidic acid (PA), egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), egg phosphatidylinositol (EPI), egg phosphatidylserine (EPS), egg phosphatidylethanolamine (EPE), egg phosphatidic acid (EPA), soy phosphatidylcholine (SPC), soy phosphatidylglycerol (SPG), soy phosphatidylserine (SPS), soy phosphatidylinositol (SPI), soy phosphatidylethanolamine (SPE), soy phosphatidic acid (SPA), hydrogenated egg phosphatidylcholine (HEPC), hydrogenated soy phosphatidylcholine (HSPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylcholine (DOPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylglycerol (DPPG), distearoylphosphatidylcholine (DSPQ), distearoylphosphatidylglycerol (DSPG), dioleoylphosphatidyl-ethanolamine (DOPE), palmitoylstearoylphosphatidyl-choline (PSPC), palmitoylstearolphosphatidylglycerol (PSPG), mono-oleoyl-phosphatidylethanolarnine (MOPE), dilauroyl ethylphosphocholine (DLEP), dimyristoyl ethylphosphocholine (DMEP), dipalmitoyl ethylphosphocholine (DPEP), distearoyl

ethylphosphocholine (DSEP), dimyristoylphosphatidic acid (DMPA), dipalmitoylphosphatidic acid (DPPA), distearoylphosphatidic acid (DSPA), dimyristoylphosphatidylinositol (DMPI), dipalmitoylphosphatidylinositol (DPPI), distearoylphosphatidylinositol (DSPI), dimyristoylphosphatidylserine (DMPS), dipalmitoylphosphatidylserine (DPPS), distearoylphosphatidylserine (DSPS), N-acylated phosphorylethanolamine (NAPE), and combinations thereof.

[0127] In a further embodiment, the controlled release formulation comprises a semi-permeable membrane. The muscarinic Activator and muscarinic Inhibitor may be in different membranes in the same formulation. In another embodiment, the muscarinic Activator and muscarinic Inhibitor can be in different membranes in different formulations or dosing vehicles. In a further embodiment, the semi-permeable membrane comprises a polymer. In a further embodiment, the controlled release formulation comprises a matrix that suspends the muscarinic Activator(s) and Inhibitor(s). The muscarinic Activator and Inhibitor may be in separate matrices within the same medicament. In a further embodiment, the matrix comprises a polymer. In a further embodiment, the polymer comprises a water soluble polymer. In a further embodiment, the water soluble polymer is selected from Eudragit RL, polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyethylene glycol, and mixtures thereof. In a further embodiment, the polymer comprises a water insoluble polymer. In a further embodiment, the water insoluble polymer is selected from Eudragit RS, ethylcellulose, cellulose acetate, cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethane, and a mixtures thereof. In a further embodiment, the matrix comprises a fatty compound. In a further embodiment, the fatty compound is a wax or glyceryl tristearate. In a further embodiment, the polymer comprises a water soluble polymer and a water insoluble polymer. In a further embodiment, the matrix further comprises a fatty compound.

[0128] The medicament may be in dosage forms that use other methods of controlled release formulation known to one in the art (for example, Dixit & Puthli. J. Control Release. 2:94. 2009; Mizrahi & Domb. Recent Pat Drug Deliv Formul. 2:108. 2008; Forqueri & Singh. Recent Pat Drug Deliv Formul. 3:40. 2009; Kalantzi et al. Recent Pat Drug Deliv Formul. 3:49. 2009; Iconomopoulou et al. Recent Pat Drug Deliv Formul. 2:94. 2008; Panos et al. Curr Drug Discov Technol. 5: 333. 2008;. Wan et al. Nanomed. 2:483. 2007. Wang et al. Drug Delivery: Principles & Applications. Wiley 2005).

[0129] In another embodiment, the medicament is used in combination with one or more therapies that can include both psychotherapy and drugs. Therapeutic agents include but are not limited to antipsychotics, anxiolytics, anti-depressants, sedatives, tranquilizers and other pharmacological interventions known to one skilled in the art. A therapeutic agent may fall under the category of more than one type of drug. For instance benzodiazepines can be considered anxiolytics, sedatives and tranquilizers.

[0130] The above-described benefits of the novel methods and compositions of the present invention are illustrated by the non-limiting examples that follow.

Examples

Example 1

[0131] In one example, the invention is a single capsule formulation containing 75 milligrams of xanomeline and 20 milligrams of trospium chloride. The capsule consists of a gelatin shell surrounding a fill material composed of the active compounds, a vehicle, a surfactant and a modifier. The vehicle is polyethylene glycol with a molecular weight in the range of from 500 to 10,000 Daltons and is 10% of the fill material by weight. The surfactant is polysorbate 80 and represents 0.1 % by weight of the fill material. The modifier is fumed silica present at 0.25% by weight of the fill material. The total fill material represents 50% of the total capsule weight and the gelatin shell is 50% of the total capsule weight.

Example 2

[0132] A second formulation is the capsule in Example 1 with an additional outer controlled release layer comprising an enteric material (material that is relatively insoluble in the acidic environment of the stomach). There are a variety of enteric materials known to one skilled in the art. For this specific formulation we use hydroxyethylcellulose which would compose 20% of total capsule weight.

Example 3

[0133] A third example is a formulation prepared as in Example 2, with the capsule containing 225 mg of xanomeline and 60 milligrams of trospium chloride.

Example 4

[0134] In one example, the invention is a single capsule formulation containing 75 milligrams of xanomeline and 5 milligrams of solifenacin. The capsule consists of a gelatin shell surrounding a fill material composed of the active compounds, a vehicle, a surfactant and a modifier. The vehicle is polyethylene glycol with a molecular weight in the range of from 500 to 10,000 Daltons and is 10% of the fill material by weight. The surfactant is polysorbate 80 and represents 0.1 % by weight of the fill material. The modifier is fumed silica present at 0.25% by weight of the fill material. The total fill material represents 50% of the total capsule weight and the gelatin shell is 50% of the total capsule weight.

Example 5

[0135] A second formulation is the capsule in Example 41 with an additional outer controlled release layer comprising an enteric material (material that is relatively insoluble in the acidic environment of the stomach). There are a variety of enteric materials known to one skilled in the art. For this specific formulation we use hydroxyethylcellulose which would compose 20% of total capsule weight.

Example 6

[0136] A third example is a formulation prepared as in Example 52, with the capsule containing 225 mg of xanomeline and 10 milligrams of solifenacin.

Equivalents

[0137] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[0138] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

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Patentkrav

1. Medikament omfattende en kombination af en muskarinaktivator og en muskarininhibitor valgt fra:

xanomelin og trospiumchlorid; sabcomelin og trospiumchlorid; milamelin og trospiumchlorid; xanomelin og tolterodin; milamelin og tolterodin; sabcomelin og trospiumchlorid med kontrolleret frigivelse; xanomelin og trospiumchlorid med kontrolleret frigivelse; milamelin og trospiumchlorid med kontrolleret frigivelse; xanomelin og darifenacin; xanomelin og solifenacin; sabcomelin og solifenacin; talsaclidin og trospiumchlorid; cevimelin og trospiumchlorid; talsaclidin og darifenacin; talsaclidin og solifenacin; talsaclidin og trospiumchlorid med kontrolleret frigivelse; talsaclidin og tolterodin; xanomelin og fesoterodin; cevimelin og darifenacin; og cevimelin og trospiumchlorid med kontrolleret frigivelse; og en farmaceutisk acceptabel bærer.

2. Medikament ifølge krav 1, hvor kombinationen af en muskarinaktivator og en muskarininhibitor er xanomelin og trospiumchlorid.

3. Medikament ifølge krav 1 eller 2, hvor kombinationen af muskarinaktivatoren og muskarininhibitoren har en theta-score større end 230.

4. Medikament ifølge krav 1 eller 2, omfattende fra 10 mikrogram til 10 gram af muskarinaktivatoren.

5. Medikament ifølge krav 1 eller 2, omfattende fra 1 milligram til 1 gram af muskarinaktivatoren.

6. Medikament ifølge krav 1 eller 2, omfattende fra 10 mikrogram til 10 gram af muskarininhibitoren.

7. Medikament ifølge krav 1 eller 2, omfattende fra 1 milligram til 1 gram af muskarininhibitoren.

8. Medikament ifølge krav 1 eller 2, omfattende fra 1 milligram til 1 gram af muskarinaktivatoren og fra 1 milligram til 1 gram af muskarininhibitoren.

9. Medikament ifølge krav 1 eller 2, omfattende fra 25 til 300 milligram af xanomelin.

10. Medikament ifølge krav 1 eller 2, omfattende fra 6,5 til 200 milligram af trospiumchlorid.

11. Medikament ifølge krav 2, omfattende:

a) 75 milligram af xanomelin og 20 milligram af trospiumchlorid; eller

b) 225 milligram af xanomelin og 60 milligram af trospiumchlorid.

12. Medikament ifølge krav 2, i form af

a) en enkeltkapselformulering omfattende 75 milligram af xanomelin og 20 milligram af trospiumchlorid; eller

b) en enkeltkapselformulering omfattende 225 milligram af xanomelin og 60 milligram af trospiumchlorid.

13. Medikament ifølge krav 1 eller 2, som er i form af en tablet, pastil, væske, emulsion, suspension, dråber, kapsel, gelkapsel, creme, gel, salve, skum, creme, aerosol, stikpille, lavement eller vaginalring.

14. Medikament ifølge krav 1 eller 2, der er formuleret som en formulering med øjeblikkelig frigivelse.

15. Medikament ifølge krav 1 eller 2, der er formuleret som en formulering med kontrolleret frigivelse.

16. Medikament ifølge krav 1 eller 2, hvor muskarinaktivatoren er formuleret som en formulering med kontrolleret frigivelse og muskarininhibitoren er formuleret som en formulering med øjeblikkelig frigivelse.

17. Medikament som defineret i et hvilket som helst af kravene 1 til 16 til anvendelse i behandlingen af en forstyrrelse i centralnervesystemet valgt fra

skizofreni, forstyrrelser relateret til skizofreni, muskarin forstyrrelse, bevægelsesforstyrrelse, humørforstyrrelse, kognitiv forstyrrelse, opmærksomhedsforstyrrelse og afhængighedssygdom.