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(54) Title: COMBINATION OF THE ANALEPTIC MODAFINIL AND AN ANTIDEPRESSANT FOR THE TREATMENT OF DEPRESSION

(57) Abstract: Compositions and methods for the treatment of depressive disorders through the administration of modafinil with antidepressants.



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TITLE

COMBINATION OF THE ANALEPTIC MODAFINIL AND AN ANTIDEPRESSANT FOR THE TREATMENT OF DEPRESSION

BACKGROUND OF THE INVENTION

1. Modafinil

5 Modafinil, C₁₅H₁₅NO₂S, also known as 2-(benzhydrylsulfinyl) acetamide, or 2-[(diphenylmethyl) sulfinyl] acetamide, is a synthetic acetamide derivative with wake-promoting activity, the structure of which has been described in French Patent No. 78 05 510 and in U.S. Patent No. 4,177,290 ('290), and which has been approved by the United States Food and Drug Administration for use in the treatment of
10 excessive daytime sleepiness associated with narcolepsy. A method of preparation of a racemic mixture is described in the '290 patent and a method of preparation of a levorotatory isomer is described in U.S. Patent No. 4,927,855 (both incorporated herein by reference). The levorotatory isomer is reported to be useful for treatment of hypersomnia, depression, Alzheimer's disease and to have activity towards the
15 symptoms of dementia and loss of memory, especially in the elderly.

The primary pharmacological activity of modafinil is to promote wakefulness. Modafinil promotes wakefulness in rats (Touret et al., 1995; Edgar and Seidel, 1997), cats (Lin et al., 1992), canines (Shelton et al., 1995) and non-human primates (Hernant et al, 1991) as well as in models mimicking clinical situations, such as sleep
20 apnea (English bulldog sleep disordered breathing model) (Panckeri et al, 1996) and narcolepsy (narcoleptic canine) (Shelton et al, 1995).

Modafinil has also been described as an agent with activity in the central nervous system, and as a useful agent in the treatment of Parkinson's disease (U.S. Patent No. 5,180,745); in the protection of cerebral tissue from ischemia (U.S. Patent
25 No. 5,391,576); in the treatment of urinary and fecal incontinence (U.S. Patent No. 5,401,776); and in the treatment of sleep apneas and disorders of central origin (U.S. Patent No. 5,612,379). U.S. Patent No. 5,618,845 describes modafinil preparations of a defined particle size less than about 200 microns. In addition, modafinil may be used in the treatment of eating disorders, or to promote weight gain or stimulate
30 appetite in humans or animals (U.S. Patent No. 6,455,588, incorporated herein by reference), or in the treatment of attention deficit hyperactivity disorder (ADHD) (U.S. Patent No. 6,346,548, incorporated herein by reference), or fatigue, especially

fatigue associated with multiple sclerosis (U.S. Patent No. 6,488,164, incorporated herein by reference).

Modafinil has been shown to be effective in treating narcolepsy, sleepiness, excessive sleepiness (e.g., sleepiness associated with disorders of sleep and wakefulness), excessive daytime sleepiness associated with narcolepsy, Parkinson's disease, urinary incontinence, multiple sclerosis fatigue, ADHD, Alzheimer's disorder, sleep apnea, obstructive sleep apnea, depression, and ischemia.

Narcolepsy is a chronic disorder characterized by intermittent sleep attacks, persistent, excessive daytime sleepiness and abnormal rapid eye movement ("REM") sleep manifestations, such as sleep-onset REM periods, cataplexy, sleep paralysis and hypnagogic hallucinations, or both. Most patients with narcolepsy also have disrupted nocturnal sleep. Pathological somnolence, whether due to narcolepsy or other causes, is disabling and potentially dangerous. Causes of pathological somnolence, other than narcolepsy, include chronic sleep loss; sleep apnea; and other sleep disorders. Whether due to narcolepsy or other causes, pathological somnolence produces episodes of unintended sleep, reduced attention, and performance errors. Consequently, it is linked to a variety of transportation and industrial accidents. A therapeutic agent that reduces or eliminates pathological somnolence would have important implications not only for individual patients, but also for public health and safety.

Other uses of modafinil have been presented. U.S. Pat. No. 5,180,745 discloses the use of modafinil for providing a neuroprotective effect in humans, and in particular for the therapy of Parkinson's disease. The levorotatory form of modafinil, i.e., (-) benzhydrylsulfinyl-acetamide, may have potential benefit for therapy of depression, hypersomnia and Alzheimer's disease (U.S. Pat. No. 4,927,855). European Published Application 547952 discloses the use of modafinil as an anti-ischemic agent. European Published Application 594507 discloses the use of modafinil to treat urinary incontinence.

U.S. Pat. No. RE37,516 discloses pharmaceutical compositions having a defined particle size, and in particular compositions wherein 95% of the cumulative total of the effective amount of modafinil particles in the composition have a diameter less than about 200 microns.

2. Antidepressants

Antidepressants, including selective serotonin reuptake inhibitors (SSRIs) have become first choice therapeutics in the therapy of depression, certain forms of anxiety and social phobias. In some instances, SSRIs can be more favored because they are effective, well tolerated and have a favorable safety profile compared to the classic tricyclic antidepressants.

However, there can be problems associated with any anti-depressant. Current antidepressant therapy can exhibit a delayed onset and modest proportion in achieving response or remission. For example, the response at 6 weeks to the selective serotonin reuptake inhibitor (SSRI) fluoxetine is about 50%. Remission rates with SSRIs at 8 weeks are about 35%. Delayed, incomplete and lack of response of a major depressive disorder to antidepressant therapy can be problematic for numerous reasons, including premature treatment discontinuation. Sometimes symptoms even worsen during the first weeks of therapy. In other cases, non-compliance can be related to side effects, including sexual dysfunction.

Fatigue and excessive sleepiness are among the symptoms of a major depressive disorder, and can be adverse experiences associated with antidepressant therapy and are often residual symptoms inadequately treated with SSRI antidepressant therapy.

In addition, patients sometimes suffer side effects associated with antidepressant therapy and withdrawal of antidepressant therapy.

Because residual symptoms to antidepressant therapy predisposes patients with depression to a greater risk of relapse and greater probability of recurrence, rapid achievement of remission is an important consideration in choosing the most appropriate treatment strategy.

New therapies that address one or more of these problems are needed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention includes a method of enhancing the activity of an antidepressant in an animal subject, preferably a human. The method includes the step of pre-treating the subject with an effective amount of one or more analeptics, including but not limited to modafinil and/or co-administering an effective

amount of one or more analeptics, including but not limited to modafinil, with an antidepressant.

DETAILED DESCRIPTION OF THE INVENTION

1. Analeptic Agents

5 Analeptics are drugs that principally act as or are used as a central nervous system stimulant. Preferred for use in the practice of the invention are analeptics that operate on the sleep-wake centers of the brain and that lack the pharmacological effects of amphetamines. Preferred analeptic agents have the pharmacological profile of modafinil. Thus, in a preferred embodiment of the invention, the analeptic used in
10 the practice of the invention is Provigil® (modafinil).

2. Antidepressants

Useful antidepressants include but are not limited to tricyclic antidepressants ("TCAs"), Selective Serotonin Reuptake Inhibitors ("SSRIs"), Serotonin and Noradrenaline Reuptake Inhibitors ("SNRIs"), Dopamine Reuptake Inhibitors
15 ("DRIs"), Noradrenaline Reuptake Inhibitors ("NRUs"), Dopamine, Serotonin and Noradrenaline Reuptake Inhibitors ("DSNRIs") and Monoamine Oxidase Inhibitors ("MAOIs") including reversible inhibitors of monoamine oxidase type A (RIMAs).

In certain embodiments, a suitable antidepressant can include, but is not limited to, one or more of the following antidepressants: adatsanerin hydrochloride;
20 adinazolam; adinazolam mesylate; alaproclate; aletamine hydrochloride; amedalin hydrochloride; amitriptyline hydrochloride; amoxapine; aptazapine maleate; azaloxan fumarate; azepindole; azipramine hydrochloride; bipenarnol hydrochloride; bupropion hydrochloride; butacetin; butriptyline hydrochloride; caroxazone; cartazolate; ciclazindol; cidoxepin hydrochloride; cilobamine mesylate; citalipram; clodazon
25 hydrochloride; clomipramine hydrochloride; cotinine fumarate; cyclindole; cypenamine hydrochloride; cyprolidol hydrochloride; cyproximide; daledalin tosylate; dapoxetine hydrochloride; dazadrol maleate; dazepinil hydrochloride; desipramine hydrochloride; dexamisole; deximafen; dibenzepin hydrochloride; dioxadrol hydrochloride; dothiepin hydrochloride; doxepin hydrochloride; duloxetine
30 hydrochloride; eclanamine maleate; encyprate; etoperidone hydrochloride; fantridone hydrochloride; fehmetozole hydrochloride; fenmetramide; fezolamine fumarate;

fluotracen hydrochloride; fluoxetine; fluoxetine hydrochloride; fluparoxan hydrochloride; gamfexine; guanoxyfen sulfate; imafen hydrochloride; imiloxan hydrochloride; imipramine hydrochloride; indeloxazine hydrochloride; intriptyline hydrochloride; iprindole; isocarboxazid; ketipramine fumarate; lofepramine hydrochloride; lortalamine; maprotiline; maprotiline hydrochloride; melitracen hydrochloride; milacemide hydrochloride; minaprine hydrochloride; mirtazapine; moclobemide; modaline sulfate; napactadine hydrochloride; napamezole hydrochloride; nefazodone hydrochloride; nisooxetine; nitrafudam hydrochloride; nomifensine maleate; nortriptyline hydrochloride; octriptyline phosphate; opipramol hydrochloride; oxaprotiline hydrochloride; oxypertine; paroxetine; phenelzine sulfate; pirandamine hydrochloride; pizotiline; pridfine hydrochloride; prolintane hydrochloride; protriptyline hydrochloride; quipazine maleate; rolicyprine; seproxetine hydrochloride; sertraline hydrochloride; sibutramine hydrochloride; sulpiride; suritazole; tametraline hydrochloride; tampramine fumarate; tandamine hydrochloride; thiazesim hydrochloride; thozalinone; tomoxetine hydrochloride; trazodone hydrochloride; trebenzomine hydrochloride; trimipramine; trimipramine maleate; venlafaxine hydrochloride; viloxazine hydrochloride; zimeldine hydrochloride; zometapine.

In certain embodiments, the antidepressant includes citalipram, fluoxetine, fluoxetine hydrochloride, paroxetine, paroxetine hydrochloride, and/or clomipramine hydrochloride, with citalipram, paroxetine, fluoxetine and fluoxetine hydrochloride preferred, with citalipram most preferred.

Other drugs which are useful in treating depressive disorders, e.g., tiagabine, can also be used in the practice of the invention.

3. Variants, Analogs, Salts, Different Forms

Antidepressants not listed above, including but not limited to structural analogs of the above compounds, that are safe and effective, are also useful in the practice of the invention.

Included within the scope of this invention are the various individual stereoisomers, including diastereomers and enantiomers (e.g., the L and/or R-isomer of modafinil) as well as mixtures thereof. In addition, compounds useful in this invention also include any pharmaceutically acceptable salts, for example: alkali

metal salts, such as sodium and potassium; ammonium salts; monoalkylammonium salts; dialkylammonium salts; trialkylammonium salts; tetraalkylammonium salts; and tromethamine salts. Hydrates, solvates, and polymorphs of the compounds described above are included within the scope of this invention. Combinations of analeptics and
5 of antidepressants can also be employed. The compounds can be substantially pure or mixed with other ingredients.

4. Depressive Disorders

The invention is useful in the treatment of depression, including mild to severe or acute depression, that may be caused by any of a number of factors, including, for
10 example, depression associated with alcohol or drug abuse. The invention is also useful in the treatment of other disorders for which antidepressants are sometimes prescribed. These include, for example, anxiety, stress, social phobia, panic, obsession, compulsive behavior, pain (e.g., neuropathic and inflammatory pain) etc. Such disorders, for which antidepressants have been shown to have clinically
15 beneficial effects, are herein referred to collectively as "depressive disorders."

5. Therapeutically Effective Amounts of Analeptics and Antidepressants

In one embodiment of the present invention, an amount of analeptic, e.g. modafinil, administered to a patient can include 5, 10, 15, 20, 30, 40, 50, 60, 70, 75, 80, 90, 100, 200, 300 and/or 400 mg. of modafinil, or combinations thereof.
20 Typically, modafinil can be administered in 50, 75, 100 and 200 mg. amounts. However, when used in combination with one or more antidepressants, as described herein, the amount of modafinil necessary to alleviate all or a portion of the symptoms associated with antidepressant therapy can be reduced. Accordingly, one embodiment of the present invention includes 100 mg. or less of modafinil when administered with
25 an antidepressant, either as a combined unit dose with the antidepressant or as a separate dose. A single unit dose containing both modafinil and an antidepressant is a preferred composition of the present invention, as described below.

Typically, one or more antidepressants can be administered in the amounts known to be effective for each antidepressant. More specifically, in the present
30 invention, an antidepressant can be administered in an amount effective to alter the depressive state of an animal subject, i.e., the amount of antidepressant that would be administered to the animal subject if the antidepressant was administered alone.

Suitable amounts can include 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300 and/or 400 mg. of a particular antidepressant, and combinations thereof. However, in the present invention, when used in combination with one or more analeptics such as modafinil, the overall amount of an administered antidepressant can be reduced by
5 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80%, while still providing an antidepressant effect. Accordingly, one embodiment of the present invention includes administering less than an amount of antidepressant relative to the amount of antidepressant administered to an animal subject if administered alone.

Generally, for daily oral doses of active compounds, the combined total of one
10 or more analeptics and one or more antidepressants will be from about 0.01 mg/kg per day to about 2000 mg/kg per day. It is expected that IV doses in the range of about 1 to 1000 mg/cm³ per day will be effective.

In some embodiments of the present invention, the respective weight ratio of analeptic to antidepressant can be from 0.01: 1 to 1:1 to 100:1, possibly 1000:1. In
15 some embodiments the weight ratio can be 1:1 to 7:1 or 10:1, most preferably 1:1 to 5:1.

A dosage form containing an above described amount of an analeptic (e.g., modafinil) and one or more antidepressants can provide to a patient improved fatigue symptoms, as well as improve waking functioning, as demonstrated by the effects of
20 fatigue, energy, alertness and cognitive function (e.g. psychomotor retardation).

6. Preparation of a Composition of the Present Invention

To prepare a pharmaceutical composition of this invention, an analeptic, including but not limited to modafinil, and an antidepressant, including but not limited to one or more of the antidepressants described above, can be intimately admixed.
25 The mixture can further optionally include a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. The amount of each active component in the composition can correspond to the amounts described above. Pharmaceutically
30 acceptable carriers include, e.g., stabilizers binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, colors, diluents, etc. Such a composition, when used for

the therapy of a depressive disorder preferably can include therapeutically effective amounts of an analeptic and antidepressant.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as
5 for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in
10 administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques.

For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation,
15 may be included. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

In one embodiment, a pharmaceutical composition of the present invention can be administered in a tablet or capsule form or other suitable unit dose form. A tablet or capsule of the present invention can contain one or more of the following
20 inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80, etc.

Accordingly, a pharmaceutical compositions herein will contain, per dosage
25 unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 5 to about 1000 mg, or more, of an analeptic and antidepressant. In one embodiment of the invention, each single dosage unit (or unit dose) includes both an amount of an analeptic and an amount of an antidepressant. In such embodiment, it is not necessary that each single dosage unit include an effective amount so long as the
30 total amount of drug administered to a patient is an effective amount of each. Therefore, for example, a patient may require 2 or more single dosage units to receive effective amounts of both agents.

When administered, the formulations of the invention are applied in pharmaceutically acceptable amounts and in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When
5 used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric,
10 hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: acetic acid and a salt (1-2% W/V); citric
15 acid and a salt (1-3% W/V); boric acid and a salt (0.5-2.5% W/V); and phosphoric acid and a salt (0.8-2% W/V). Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V).

Dosage may be adjusted appropriately to achieve desired drug levels, locally
20 or systemically. As noted above, generally, daily oral doses of active compounds will be from about 0.01 mg/kg per day to 2000 mg/kg per day. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous IV dosing over, for example 24
25 hours or multiple doses per day is contemplated to achieve appropriate systemic levels of compounds.

A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state(s) being treated and the dosage required for therapeutic efficacy. The methods
30 of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse

effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion.

The compositions may conveniently be presented in unit dosage form and may
5 be prepared by any of the methods well known in the art of pharmacy. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete
10 units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the
15 active compounds of the invention, increasing convenience to the subject and the physician. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel release systems; silastic systems;
20 peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

Another embodiment of the present invention provides a kit or device which can facilitate the administration of an amount of an analeptic and an antidepressant to
25 treat a depressive disorder. Specifically, a kit according to the present invention includes at least one dosage form containing an analeptic, including but not limited to modafinil, and a separate dosage form containing at least one antidepressant. One suitable kit of the present invention includes a blister pack having a unit dose of modafinil and a separate unit dose of an antidepressant. Most preferably, the unit
30 dose of modafinil includes a 50, 75, 100 or 200 mg. tablet of modafinil and the unit dose of antidepressant includes a 10, 20, 30, 40 or 50 mg. tablet of antidepressant. The kit or device can also include instructions concerning administration of the

analeptic and antidepressant. Preferably, the instructions provide administration guidance according to one or more of the administration schemes set forth below.

The analeptic and/or antidepressant can be in any suitable dosage form, including but not limited to solid dosage forms including tablets, capsules, pills, troches, cachets, and the like, and/or liquid dosage forms such as an oral elixir or an IV fluid. The dosage form of the analeptic can be the same type or a different type than the antidepressant.

In yet another embodiment, the present invention includes a transdermal drug delivery system ("TDDS"). A TDDS suitable for use with the invention in patch form typically contains at least: (1) a backing layer and (2) a carrier formulated with an effective amount of an antidepressant and optionally modafinil.

Preferred patches include (1) the matrix type patch; (2) the reservoir type patch; (3) the multi-laminate drug-in-adhesive type patch; and (4) the monolithic drug-in-adhesive type patch. These patches are generally available commercially.

For practice of the invention, the matrix type and the drug-in-adhesive type patches are especially preferred. The more preferred drug-in-adhesive patch is the monolithic type.

Transdermal drug delivery systems other than standard patches can also be used. These include, for example, osmotic pump systems, ultrasonic systems, ointments, pastes, gels, medicated powders, creams, lotions, aerosols, sprays, foams, medicated adhesives and the like.

7. Method of Treatment/Therapy

A. Administration Schemes and Timing of Treatment of an Analeptic and Antidepressant

An analeptic and an antidepressant can be combined together into a single unit dose, but can also be administered separately as two or more distinct doses.

Thus, in some embodiments of the invention, a treatment of a disorder related to depression can be through the use of separate dosage forms – one or more analeptic doses and one or more antidepressant doses. Accordingly, a dose of an analeptic can be administered at a different time relative to the antidepressant dose or simultaneously (i.e., analeptic dose administration within less than 1 hour before or

after administration of the antidepressant). However, if simultaneous administration is desired, the administration of the analeptic and antidepressant can also be through the use of a single unit dose including both an analeptic and antidepressant.

5 In patients that are beginning antidepressant therapy, i.e. patients that are substantially free of antidepressants or patients that have been free of antidepressant therapy for about 1 week, 2 weeks, more preferably about 4 or more weeks, the dosage form containing the analeptic can be administered before and/or at about the same time as an initial administration of the antidepressant. In such an embodiment, one or more administrations of an analeptic can be within 72 hours, preferably within 10 48 hours, more preferably within 24 hours, most preferably within 1 hour or moments before an initial administration/dosing of an antidepressant. After the initial administration of the analeptic and antidepressant, subsequent dosings of the analeptic and antidepressant can continue at a typical rate, e.g., typically one or two 50, 75, 100 to 200 mg. doses of modafinil per day and 10, 20, 30, 40, 50 mg. of antidepressant per 15 day. Further, after the initial administration of the antidepressant, the dosings of the analeptic and antidepressant can be in separate dosage forms or in a single unit dose. However, if a dose of an analeptic is to be administered before a subsequent dose of an antidepressant, separate dosage forms for each are preferred.

20 Additionally, in patients that are substantially free of antidepressants, the initial administration of the analeptic can coincide with or be nearly simultaneous with the initial administration of an antidepressant. This can be accomplished through the use of separate dosage forms of an analeptic and antidepressant which can then be administered together simultaneously (i.e., within 1 hour or less, before or after the antidepressant) or through the use of a single unit dose including both an analeptic 25 and an antidepressant, as noted above.

Further, an analeptic, including but not limited to modafinil, can also be administered to a patient that has already received at least an initial dose of an antidepressant. In one embodiment, the initial administration of an analeptic can be within 72 hours, preferably within 48 hours, more preferably within 24 hours, most 30 preferably within 1 hour or within moments after the initial administration of an antidepressant. In this timing scheme, modafinil is administered at about the same time as an antidepressant, but subsequent to at least one administration of an

antidepressant. After the initial dosing of an analeptic, the dosing of the analeptic and antidepressant can continue in a typical manner. In one particularly preferred embodiment, initial administration of an analeptic and subsequent administrations of an analeptic can be accomplished through the use of a single unit dose including both
5 an analeptic and an antidepressant.

In a further embodiment, initial administration of an analeptic to a patient can occur and/or continue after antidepressant therapy has ended. Preferably, this is accomplished by administering an amount of the analeptic to the patient and the administration of which can continue for 1, 2, 5, 10, 20, or 30 days, or more, after
10 antidepressant therapy cessation.

In embodiments where the analeptic and antidepressant are in separate dosage forms, the administration of the analeptic can preferably occur within moments, or in less than 1 hour, or less than 5 hours, or less than 24 hours or less than 48 hours, or less than 72 hours before or after administration of the antidepressant, unless
15 otherwise indicated by a particular method of treatment below.

B. Enhancing Antidepressant Activity

In one embodiment, the present invention includes a method of enhancing the activity of an antidepressant in an animal subject, preferably a human. The method includes the step of pre-treating the subject with an effective amount of one or more
20 analeptics, including but not limited to modafinil. The amount of analeptic and duration of pretreatment can vary from subject to subject, but typically conforms to the amounts described above and one or more of the timing schemes set forth above.

However, in one particular embodiment, the amount of analeptic includes an effective amount, typically from about 100 mg to about 200 mg of modafinil
25 administered once or twice daily for a period of less than 2 days, preferably less than 10 days, prior to the initiation of antidepressant therapy. The administration of the analeptic can also optionally continue during antidepressant therapy and also continue for a period of time after the cessation of antidepressant therapy, as described above.

The analeptic can be administered orally, nasally, rectally, intravenously,
30 epidurally, intraperitoneally, subcutaneously, intramuscularly or intrathecally.

DEFINITIONS

“Particle,” as used herein, refers to an aggregated physical unit of the acetamide compound, i.e., a piece or a grain of acetamide.

As used herein, “about” means plus or minus ten percent of the indicated value, such that "about 20 mg" indicates 18 to 22 mg.

As used herein, “consisting essentially of” refers to excluding other active ingredients but including excipients and additional amounts of the active ingredient to account for degradation or otherwise.

An “effective amount,” as used herein, is an amount of modafinil and/or antidepressant that is effective for treating a depressive state, i.e., an amount of modafinil and/or antidepressant that is able to reduce, alleviate or eliminate certain symptoms associated with depression and/or antidepressant therapy.

A “pharmaceutical composition,” as used herein, means a medicament for use in treating a mammal that comprises modafinil prepared in a manner that is appropriate for administration to a mammal. A pharmaceutical composition according to the invention may also, but does not of necessity, include a non-toxic pharmaceutically acceptable carrier. A pharmaceutical composition can also include bulk active modafinil for use in preparing dosage forms. A pharmaceutical composition can also include modafinil in combination with another active, preferably and antidepressant, more preferably an SSRI.

While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations. Further, the contents of all references cited herein are hereby incorporated by reference.

What is claimed is:

1. A method for enhancing the activity of an antidepressant in an animal subject comprising administering an effective amount of modafinil to the subject.

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2. The method of claim 1 wherein the antidepressant is selected from the group consisting of tricyclics, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, monoamine oxidase inhibitors, and monoamine oxidase type A.

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3. The method of claim 2 wherein the antidepressant is selected from the group consisting of citalipram, fluoxetine, fluoxetine hydrochloride, paroxetine, paroxetine hydrochloride, and clomipramine hydrochloride.

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4. The method of claim 3 wherein the antidepressant is fluoxetine or paroxetine.

5. The method of claim 1 wherein the modafinil is administered before or simultaneously with an administration of an antidepressant to the subject.

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6. The method of claim 1 wherein the modafinil is administered after the cessation of administration of the antidepressant to the subject.

7. The method of claim 1 wherein an amount of antidepressant to be administered includes 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300 or 400 mg of antidepressant.

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8. The method of claim 1 wherein the amount of modafinil includes 5, 10, 15, 20, 30, 40, 50, 60, 70, 75, 80, 90, 100, 200, 300 or 400 mg of modafinil.

INTERNATIONAL SEARCH REPORT

national Application No

PCT/US2004/015199

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/165 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DEBATTISTA C ET AL: "A Prospective Trial of Modafinil as an Adjunctive Treatment of Major Depression" JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY 2004 UNITED STATES, vol. 24, no. 1, 2004, pages 87-90, XP009035457 ISSN: 0271-0749 the whole document ----- -/--	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

28 September 2004

Date of mailing of the international search report

06/10/2004

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Authorized officer

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INTERNATIONAL SEARCH REPORT

national Application No

PCT/US2004/015199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	NINAN PHILIP T ET AL: "Adjunctive modafinil at initiation of treatment with a selective serotonin reuptake inhibitor enhances the degree and onset of therapeutic effects in patients with major depressive disorder and fatigue." THE JOURNAL OF CLINICAL PSYCHIATRY. MAR 2004, vol. 65, no. 3, March 2004 (2004-03), pages 414-420, XP009035454 ISSN: 0160-6689 the whole document	1-8
X	MENZA M A ET AL: "Modafinil augmentation of antidepressant treatment in depression" JOURNAL OF CLINICAL PSYCHIATRY 2000 UNITED STATES, vol. 61, no. 5, 2000, pages 378-381, XP009035452 ISSN: 0160-6689 abstract page 380, column 2, lines 1-16; table 1 page 381, column 1, lines 1-7	1-8
X	KOGEORGOS J (REPRINT) ET AL: "Modafinil as augmentation of antidepressant therapy" EUROPEAN NEUROPSYCHOPHARMACOLOGY, (OCT 2002) VOL. 12, SUPP. '3', PP. S211-S212. PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0924-977X., vol. 12, no. S3, October 2002 (2002-10), XP002293250 abstract	1-8
X	MARKOVITZ P J ET AL: "An open-label trial of modafinil augmentation in patients with partial response to antidepressant therapy '2'" JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY 2003 UNITED STATES, vol. 23, no. 2, April 2003 (2003-04), pages 207-209, XP009035470 ISSN: 0271-0749 the whole document	1-8

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INTERNATIONAL SEARCH REPORT

ational Application No

.../US2004/015199

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOLDER G ET AL: "Reduction of daytime sleepiness in a depressive patient during adjunct treatment with modafinil" JOURNAL OF PSYCHIATRIC RESEARCH 2002 UNITED KINGDOM, vol. 36, no. 1, 2002, pages 49-52, XP002293252 ISSN: 0022-3956 page 50, column 2, line 16 - page 51, column 1, line 20 page 51, column 2, lines 10-23; table 1 -----	1-8
X	SCHILLERSTROM JASON E ET AL: "Modafinil augmentation of mirtazapine in a failure-to-thrive geriatric inpatient." INTERNATIONAL JOURNAL OF PSYCHIATRY IN MEDICINE. 2002, vol. 32, no. 4, 2002, pages 405-410, XP009035480 ISSN: 0091-2174 abstract page 406, lines 24-35 page 408, lines 8-19 page 408, lines 31-36 -----	1-8
X	SCHWARTZ THOMAS L ET AL: "Modafinil in the treatment of depression with severe comorbid medical illness." PSYCHOSOMATICS. 2002 JUL-AUG, vol. 43, no. 4, July 2002 (2002-07), pages 336-337, XP009035497 ISSN: 0033-3182 the whole document -----	1-8
A	KAUFMAN K R ET AL: "Modafinil monotherapy in depression" EUROPEAN PSYCHIATRY 2002 FRANCE, vol. 17, no. 3, 2002, pages 167-169, XP002293253 ISSN: 0924-9338 the whole document -----	
A	WO 01/13921 A (OCKERT DAVID M) 1 March 2001 (2001-03-01) the whole document -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/015199

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

national Application No

PCT/US2004/015199

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0113921	A	01-03-2001	AU	6528400 A		19-03-2001
			WO	0113921 A1		01-03-2001
			US	6503950 B1		07-01-2003