TITLE

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

BACKGROUND OF THE INVENTION

1. Modafinil

Modafinil, $C_{15}H_{15}NO_2S$, 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 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 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 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 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 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 reducing adverse symptoms in an animal subject associated with the cessation of antidepressant therapy. The method includes administering an effective amount of one or more analeptics, including but not limited to modafinil, to the animal subject, preferably a

human, to reduce the adverse symptoms associated with antidepressant therapy, wherein the analeptic is administered before and/or during and/or after antidepressant therapy cessation.

In one embodiment, the present invention includes a method of reducing adverse symptoms in an animal subject associated with antidepressant therapy. The method includes administering an effective amount of one or more analeptics, including but not limited to modafinil, to the animal subject, preferably a human, to reduce the adverse symptoms, wherein the analeptic is administered before and/or during and/or after antidepressant therapy.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1A: Mean FSS total scores for baseline and weeks 1 through 6.

Figure 1B: Mean ESS total scores for baseline and weeks 1 through 6.

Figure 2A: Mean VAS scores for "sad mood, lack of pleasure" for baseline and weeks 1 through 6.

Figure 2B: Mean VAS scores for "anxiety, worry, irritability, agitation" for baseline and weeks 1 through 6.

Figure 2C: Mean VAS scores for "low energy, fatigue" for baseline and weeks 1 through 6.

Figure 2D: Mean VAS scores for "lack of motivation" for baseline and weeks 1 through 6.

Figure 2E: Mean VAS scores for "difficulty thinking, concentrating, remembering" for baseline and weeks 1 through 6.

Figure 2F: Mean VAS scores for "sleepiness" for baseline and weeks 1 through 6.

DETAILED DESCRIPTION OF THE INVENTION

1. Analeptic Agents

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 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 ("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: adatanserin hydrochloride; 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 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 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; nisoxetine; nitrafudam hydrochloride; nomifensine maleate; nortriptyline hydrochloride; octriptyline phosphate; opipramol hydrochloride; oxaprotiline hydrochloride; oxypertine; paroxetine; phenelzine sulfate;

pirandamine hydrochloride; pizotyline; pridefine hydrochloride; prolintane hydrochloride; protriptyline hydrochloride; quipazine maleate; rolicyprine; seproxetine hydrochloride; sertraline hydrochloride; sibutramine hydrochloride; sulpiride; suritozole; 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 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 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 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. 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 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 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 or 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 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 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/cm^3 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 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 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. 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 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 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 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, 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 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 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 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 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, 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 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 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 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 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 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 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 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; 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 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 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.

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

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., 50, 75, 100 to 200 mg. doses of modafinil per day and 10, 20, 30, 40, 50 mg. of antidepressant per 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.

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 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 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 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 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 otherwise indicated by a particular method of treatment below.

B. Administration of an Analeptic To Reduce Side Effects Associated With Antidepressant Treatment Cessation

Administration of a combination of an analeptic such as modafinil and one or more antidepressants can significantly reduce the adverse side effects associated with the discontinuation of antidepressant therapy. In such an embodiment, an effective amount of an analeptic such as modafinil can be administered simultaneously with an antidepressant and/or after antidepressant therapy has been discontinued.

In one embodiment, the present invention includes a method of reducing adverse symptoms in an animal subject associated with the cessation of antidepressant therapy. The method includes administering an effective amount of one or more analeptics, including but not limited to modafinil, to the animal subject, preferably a human, to reduce the adverse symptoms, wherein the analeptic is administered before and/or during and/or after antidepressant therapy cessation, according to one or more of the timing schemes set forth above. The amount of analeptic and duration of analeptic therapy can vary from subject to subject.

However, in one embodiment, the amount of analeptic includes an effective amount, typically from about 100 mg to about 200 mg of modafinil administered once or twice daily during antidepressant therapy. In another embodiment, administration of an analeptic can occur within a period of 2 days, preferably less than 10 days, prior to the cessation of therapy of the antidepressant with which it is desired to have a reduction of adverse symptoms. The administration of both modafinil and an antidepressant can significantly reduce the adverse side effects associated with the discontinuation of antidepressant therapy.

In one embodiment, the analeptic can be administered after antidepressant treatment cessation. In such an embodiment, the administration of an analeptic can continue for a period of 1, 2, 5, 10, 20, or 30 days or more after the cessation of antidepressant therapy.

In such an embodiment, the modafinil can be administered orally, nasally, rectally, intravenously, epidurally, intraperitoneally, subcutaneously, intramuscularly or intrathecally.

C. Reduction of Depressive Disorder Side Effects

In one embodiment, the present invention includes a method of treating a subject for depression and other disorders for which antidepressants are indicated, whereby side effects of antidepressant therapy are reduced. The method includes the steps of administering to the subject an effective amount of an analeptic agent in addition to administering to the patient an effective amount of an antidepressant. The therapy can occur according to one or more timing schemes set forth above.

In another embodiment, the present invention includes a method for enhancing activity of an antidepressant, whereby side effects are reduced. The method includes the steps of administering to the subject an effective amount of an analeptic agent in addition to administering to the patient an effective amount of an antidepressant according to one or more of the administration schemes set forth above.

In yet another embodiment, the present invention includes a method of decreasing onset time of an antidepressant, whereby side effects are reduced. The method includes administering to the subject an effective amount of an analeptic agent in addition to administering to the patient an effective amount of an antidepressant according to one or more of the administration schemes set forth above.

In a further embodiment, the present invention includes a method for enhancing activity of an antidepressant and decreasing onset time of an antidepressant, whereby side effects are reduced. The method includes the steps of administering to the subject an effective amount of an analeptic agent in addition to administering to the patient an effective amount of an antidepressant according to one or more of the administration schemes set forth above.

D. Reduction of Adverse Symptoms

In one embodiment, the present invention includes a method of reducing adverse symptoms in an animal subject associated with antidepressant therapy. The method includes administering an effective amount of one or more analeptics, including but not limited to modafinil, to the animal subject, preferably a human, to

reduce the adverse symptoms, wherein the analeptic is administered before and/or during and/or after antidepressant therapy or according to one or more administration schemes set forth above.

Adverse symptoms treatable with the therapy of the present invention include, but are not limited to fatigue, sleepiness, sad mood – lack of pleasure, anxiety, worry, irritability, agitation, excessive sleepiness, somnolence, sedation, low energy, lack of motivation, and difficulty in thinking, concentrating and/or remembering. Some or all of these symptoms can be measured using standard Fatigue Severity Scales (FSS), Visual Analogue Scales (VAS) and Epworth Sleepiness Scales (ESS).

The amount of analeptic and duration of analeptic therapy can vary from subject to subject. However, in one embodiment, the amount of analeptic includes from about 100 mg to about 200 mg of modafinil administered once or twice daily 1, 2, 5, 10, 20 or 30 days or more before, during and/or 1, 2, 5, 10, 20, or 30 days or more after cessation of antidepressant therapy. Preferably, modafinil administration continues during antidepressant therapy.

In certain preferred embodiments, the antidepressant includes fluoxetine and/or paroxetine administered at about 20 mg. per day for the duration of antidepression therapy.

In such an embodiment, the modafinil and/or antidepressant can be administered orally, nasally, rectally, intravenously, 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 antidepression 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.

Example

Eligible patients were previously diagnosed with MDD (single episode or recurrent), four patients had significant fatigue (Fatigue Severity Scale [FSS] score of greater than or equal to 4), and had not taken antidepressant therapy for greater than or equal to 4 weeks. Patients were evaluated at screening, baseline (shown in Table 1), and weeks 1, 2, 3, 4, 5, and 6.

Table 1. Baseline Patient Characteristics

	Modafinil + Fluoxetine or Paroxetine (N=29)
Mean age; years (SD)	36.2 (8.6)
Mean weight; pounds (SD)	173.1(57.5)
Gender; n (%)	
Female	21 (72.4)
Race; n (%)	
Caucasian	19 (65.5)
Mean years with disease (SD)	2.7 (3.9)
Mean HAMD-21 score (SD)	22.6 (4.9)*
Mean HAMD-31 score (SD)	29.9 (7.4)*
Mean FSS score (SD)	5.2 (0.8)*
Mean ESS score (SD)	10.3 (4.9)

* N=28

ESS=Epworth Sleepiness Scale; FSS=Fatigue Severity Scale; HAMD=Hamilton Rating Scale for Depression; SD=standard deviation; VAS=Visual Analogue Scale

Patients were then started on a combination of an SSRI and modafinil.

Modafinil was initiated at 100 mg/day for 3 days and then titrated to 200 mg/day, depending on response and tolerability. SSRI therapy was either fluoxetine or paroxetine administered at 20 mg/day for 6 weeks.

1. Symptom Assessments

Depressive symptom changes were analyzed using HAMD-31, each of which were videotaped and rated independently, and HAMD-21 total score evaluations. HAMD-21 total score analyses were also performed to evaluate response and remission rates. Changes in fatigue were assessed using the FSS. A fatigue response was defined as an FSS score of less than 4 at any post-baseline visit. An FSS score of greater than or equal to 4 denotes pathologic levels of fatigue. Subjective sleepiness was assessed using the Epworth Sleepiness Scale (ESS). An ESS score of greater than or equal to 10 denotes pathologic levels of sleepiness. Symptoms associated

with depression, including fatigue, mood, motivation, and concentration, were evaluated using patient-assessed Visual Analogue Scales (VAS).

2. Safety Monitoring

Safety was assessed by recording all reported adverse events by day of onset, type, severity, and relationship to study medication. Physical exams, vital signs, and clinical laboratory tests were conducted during the study.

3. Statistics

Continuous variables were analyzed using a paired t-test for normally distributed data or Wilcoxon signed rank test for non-normal data.

The numbers of responders (defined as a >50 % decrease in HAMD-21) and remitters (defined as a score of less than or equal to 7 in HAMD-21 at any post-baseline visit) were analyzed using the Wilcoxon signed rank test. Patients receiving at least 1 dose of a study drug were included in the safety analysis.

Descriptive statistics were used to summarize safety measures. Baseline characteristics of all patients are summarized in Table 1. Patients who received at least 1 dose of modafinil and had at least 1 post-baseline efficacy measurement were evaluated for efficacy (N=28). Twenty-nine patients were available for safety evaluation.

4. Treatment Outcomes

Modafinil combined with an SSRI rapidly reduced fatigue, as shown by a significant reduction in mean FSS scores at week 1 that progressed to week 6 (Figure 1A). Modafinil combined with an SSRI rapidly improved wakefulness, as shown by a significant reduction in mean ESS scores at week 1 that progressed to week 6 (Figure 1B). Modafinil combined with an SSRI rapidly improved the patient-rated global impression of mood and concentration, as shown by a significant reduction in mean VAS total scores from baseline to week 1 (-13.07; $p < 0.01$) that progressed to week 6 (-23.17; $p<.01$).

Individual VAS scores showed significant improvements in mood, anxiety, fatigue, and concentration at weeks 1 through 6 (Figures 2A, 2B, 2C, and 2E). Additionally, significant improvements in motivation and sleepiness in individual

VAS scores (Figures 2D and 2F) were found at week 1 and these were progressive to week 6.

5. Safety and Tolerability

Adjunct modafinil was well tolerated. Fifty-nine percent (17/29) of patients reported at least one adverse event. The most frequently reported adverse events were nausea (41%) and headache (24%).

Adverse events were mild to moderate in severity, with no serious adverse events reported during the study. No clinically significant differences were found in vital signs, body weight changes, ECG, or laboratory parameters. Twenty-three of 29 patients (79%) completed the study. Three patients in the modafinil and fluoxetine group discontinued because of treatment-related adverse events: one reported agitation, anorexia, and headache; another reported headache and abnormal thinking; and a third reported insomnia, nausea, and nervousness. One patient was withdrawn due to protocol noncompliance. Two patients were lost to follow-up.

Modafinil can also prove effective as a treatment option for patients who develop fatigue or other residual symptoms which diminish antidepressant effectiveness. Results from this 6-week study show that adjunct treatment with modafinil can enhance the degree and rate of symptom relief achieved in MDD patients with significant fatigue.

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 of reducing adverse symptoms associated with the cessation of antidepressant therapy in an animal subject comprising administering an amount of modafinil sufficient to reduce the adverse symptoms to the subject.

2. The method of claim 1 wherein the antidepressant therapy comprises administration of an antidepressant selected from the group consisting of tricyclics, selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, monoamine oxidase inhibitors, and monoamine oxidase type A to the subject.

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.

4. The method of claim 1 wherein the amount of antidepressant administered during the antidepressant therapy includes 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300 or 400 mg of antidepressant.

5. 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.

6. A method of treating a subject for depression and other disorders for which antidepressants are indicated whereby side effects of the treatment are reduced, which comprises administering an effective amount of an analeptic agent and an antidepressant to the subject .

7. A method of decreasing onset time of an antidepressant upon administration to a subject such that side effects are reduced, comprising administering an effective amount of an analeptic agent and an antidepressant to the subject .

8. The method of claim 6 or 7 wherein the analeptic agent is modafinil.

9. The method of claim 8 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.

10. The method of claim 9 wherein the antidepressant is selected from the group consisting of citalipram, fluoxetine, fluoxetine hydrochloride, paroxetine, paroxetine hydrochloride, and clomipramine hydrochloride.

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

12. The method of claim 8 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.

13. The method of claim 8 wherein the modafinil is administered before or simultaneously with administration of the antidepressant.

14. The method of claim 8 wherein the modafinil is administered after the administration of the antidepressant.

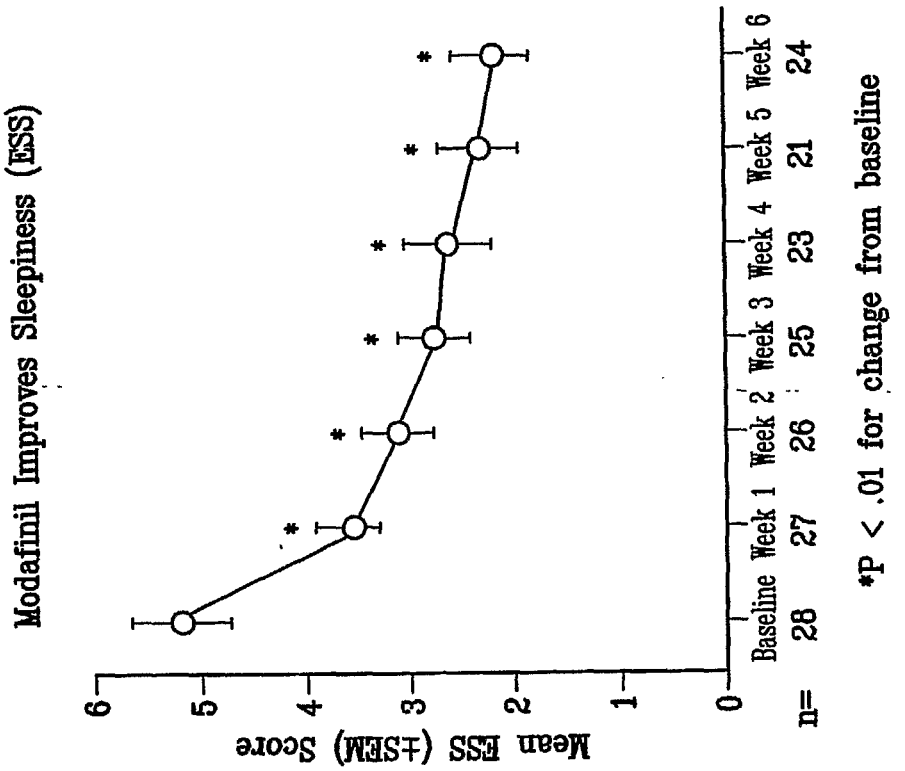

Modafinil Improves Sleepiness (ESS)
Mean ESS (±SEM) Score
0
1
2
3
4
5
6
Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
n= 28 27 26 25 23 21 24
*P < .01 for change from baseline

FIG. 1B

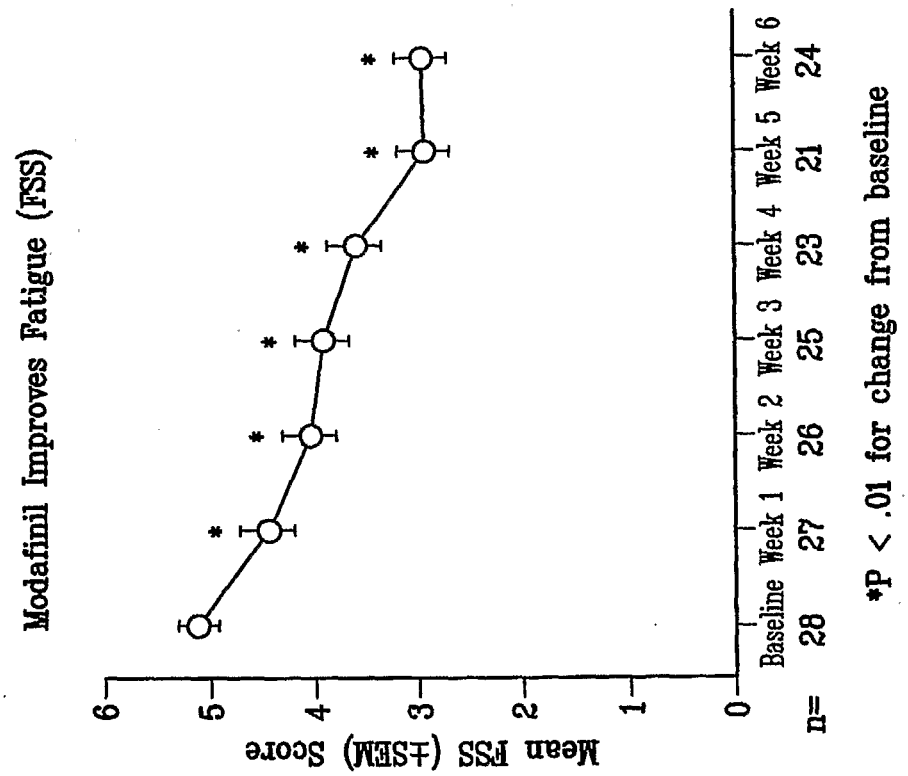

Modafinil Improves Fatigue (FSS)
Mean FSS (±SEM) Score
0
1
2
3
4
5
6
Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
n= 28 27 26 25 23 21 24
*P < .01 for change from baseline

FIG. 1A

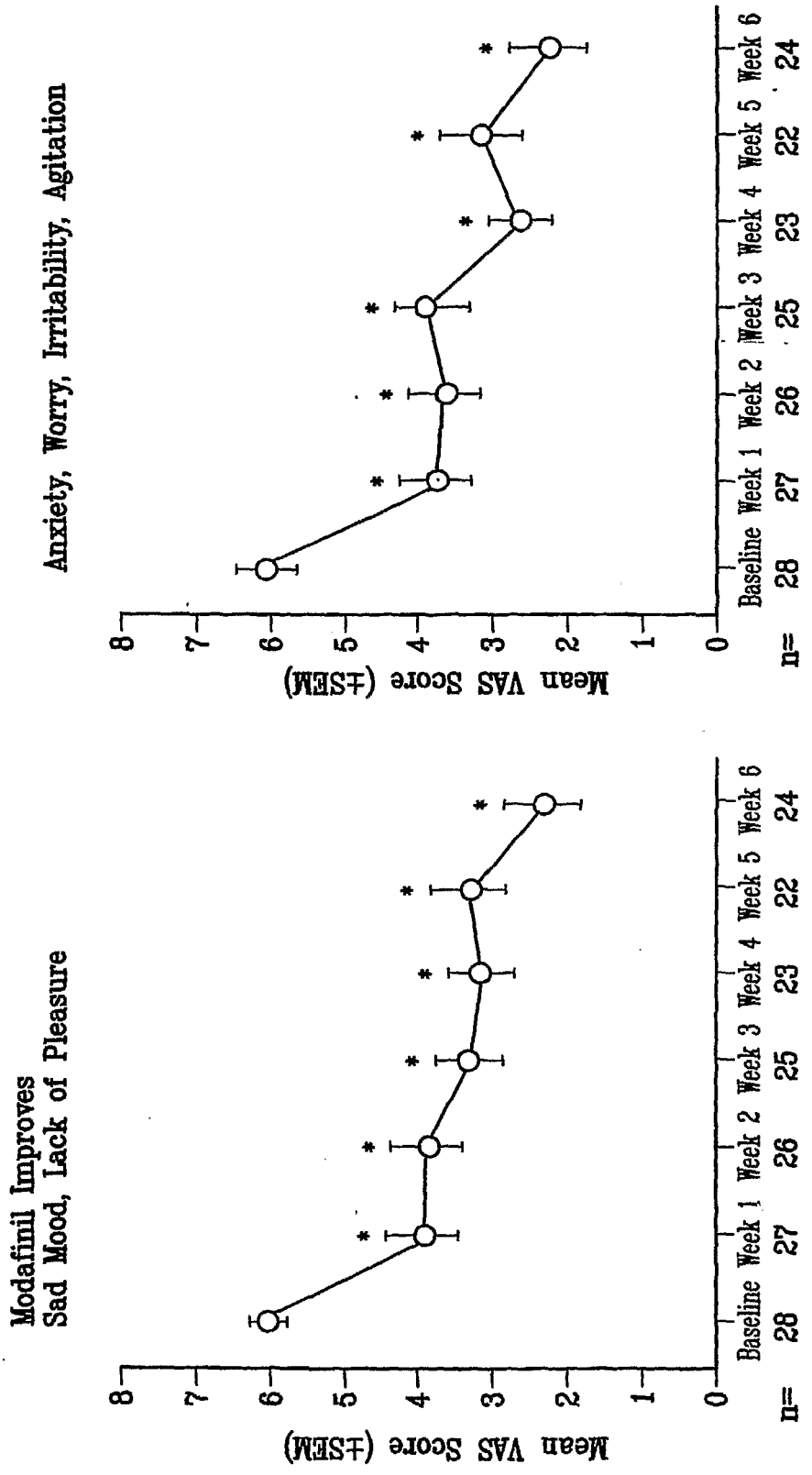

Modafinil Improves
Sad Mood, Lack of Pleasure
Mean VAS Score (±SEM)
0
1
2
3
4
5
6
7
8
Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
n= 28 27 26 25 23 22 24
*P < .01 for change from baseline
Anxiety, Worry, Irritability, Agitation
Mean VAS Score (±SEM)
0
1
2
3
4
5
6
7
8
Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
n= 28 27 26 25 23 22 24
*P < .01 for change from baseline

FIG. 2A

FIG. 2B

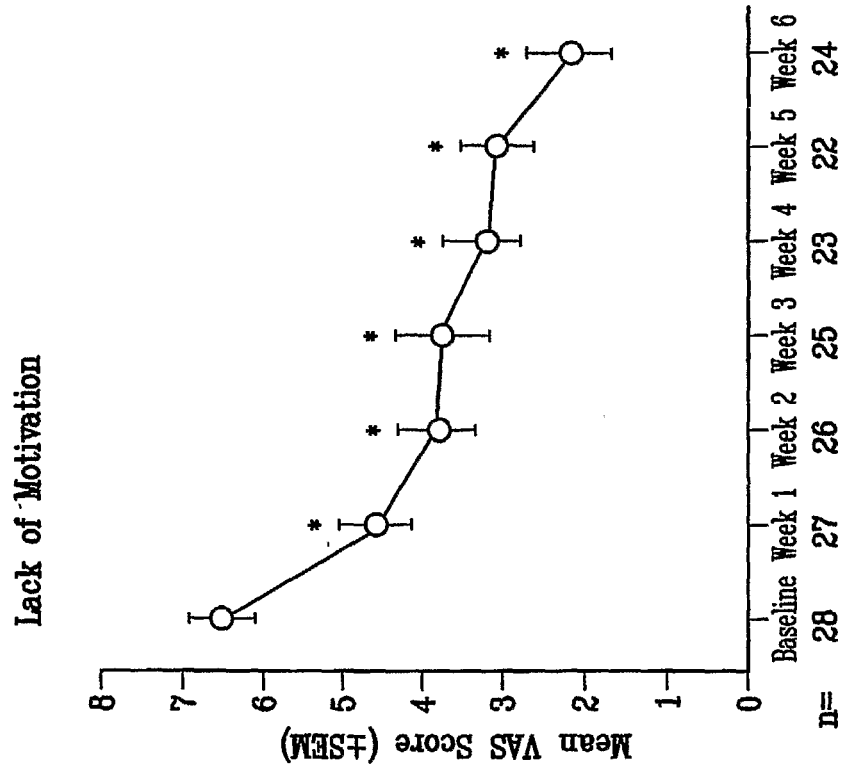

Lack of Motivation
Mean VAS Score (±SEM)
0
1
2
3
4
5
6
7
8
Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
n= 28 27 26 25 23 22 24
*P < .01 for change from baseline

FIG. 2D

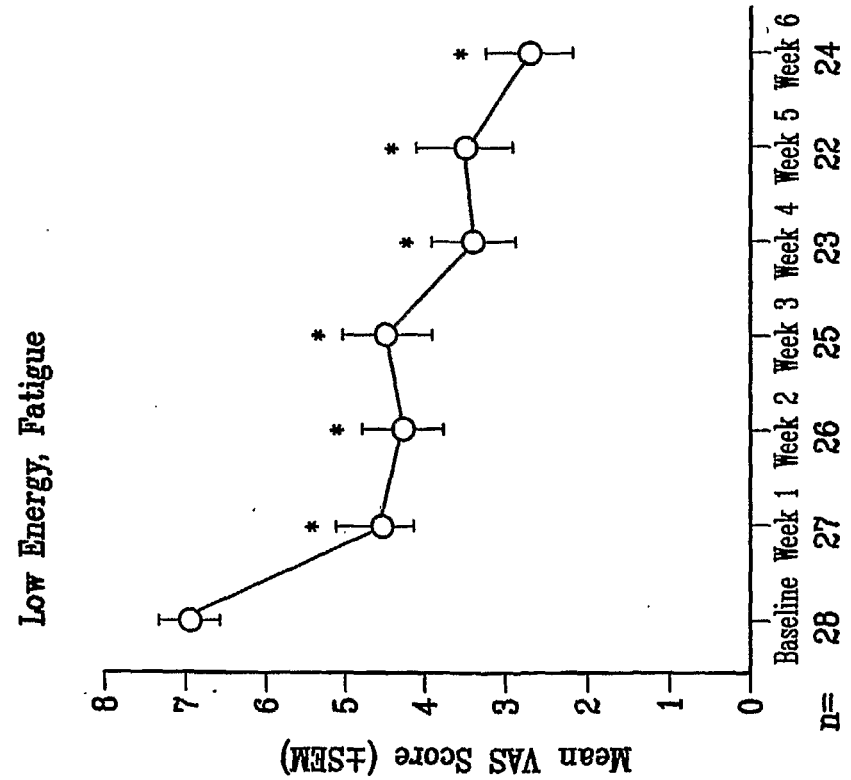

Low Energy, Fatigue
Mean VAS Score (±SEM)
0
1
2
3
4
5
6
7
8
Baseline Week 1 Week 2 Week 3 Week 4 Week 5 Week 6
n= 28 27 26 25 23 22 24
*P < .01 for change from baseline

FIG. 2C

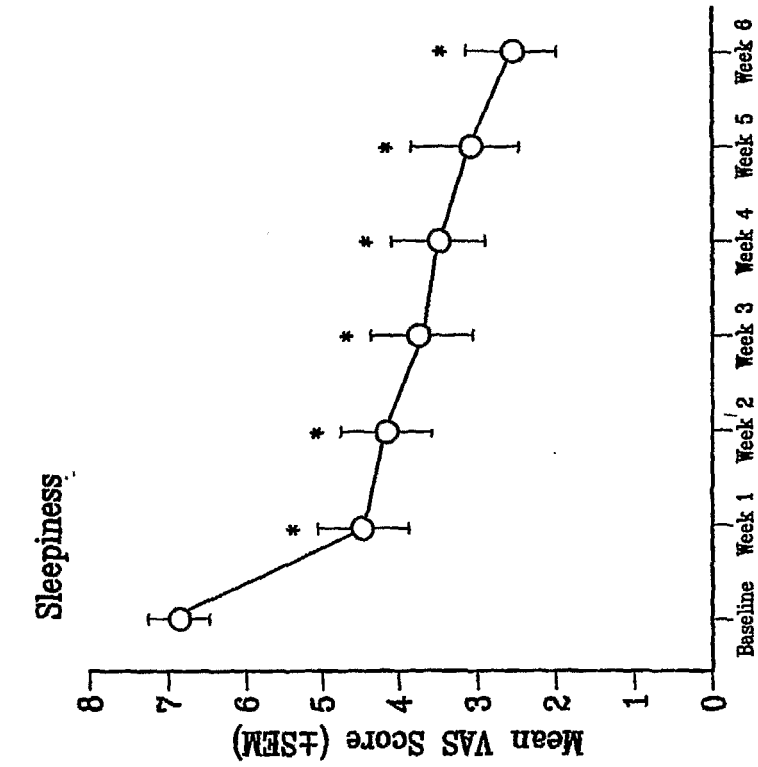

Sleepiness
Mean VAS Score (±SEM)
0
1
2
3
4
5
6
7
8
Baseline
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
n= 28 27 26 25 23 22 24
*P < .01 for change from baseline

FIG. 2F

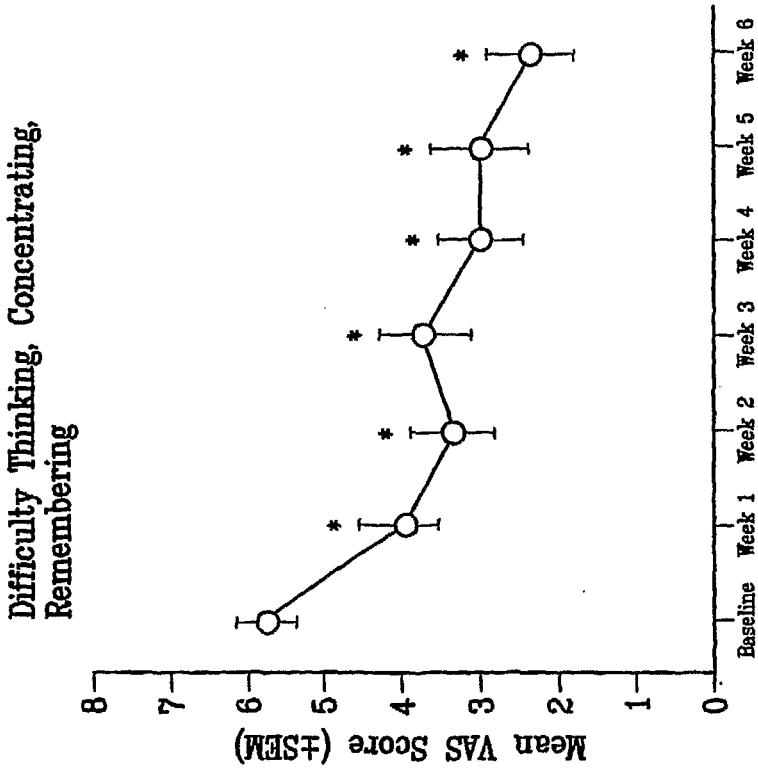

Difficulty Thinking, Concentrating, Remembering
Mean VAS Score (±SEM)
0
1
2
3
4
5
6
7
8
Baseline
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
n= 28 27 26 25 23 22 24
*P < .01 for change from baseline

FIG. 2E