



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/00	A2	(11) International Publication Number: WO 00/06140 (43) International Publication Date: 10 February 2000 (10.02.00)
(21) International Application Number: PCT/US99/17417 (22) International Filing Date: 30 July 1999 (30.07.99) (30) Priority Data: 60/094,985 31 July 1998 (31.07.98) US (71) Applicant (for all designated States except US): JANUS PHARMACEUTICALS, INC. [US/US]; 35th floor, 12 East 49th Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KLEIN, Donald, F. [US/US]; 1016 5th Avenue, New York, NY 10028 (US). LEDERMAN, Seth [US/US]; Suite 1A, 143 East 95th Street, New York, NY 10128 (US). (74) Agents: HALEY, James, F., Jr. et al.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: METHODS AND COMPOSITIONS FOR TREATING AND PREVENTING CERTAIN PSYCHIATRIC AND MEDICAL DISORDERS USING MOCLOBEMIDE (57) Abstract Methods and compositions are disclosed utilizing moclobemide, a moclobemide metabolite, a moclobemide derivative or moclobemide composition to assist in treating or preventing low affect disorders, adolescent depression, partial therapy-refractory depression, partial therapy-refractory atypical depression, eating problems and symptoms thereof. The invention also relates to treating somatised symptoms, learning disabilities and conduct disturbances using moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

**METHODS AND COMPOSITIONS FOR TREATING AND
PREVENTING CERTAIN PSYCHIATRIC
AND MEDICAL DISORDERS USING MOCLOBEMIDE**

5 This application incorporates by reference herein
United States application 60/094,985, filed July 31, 1998.

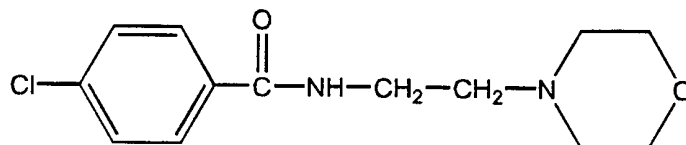
1. FIELD OF THE INVENTION

10 This invention relates to methods and compositions
for treating or preventing low affect disorders, which are
characterized by malaise and lethargy. Such low affect
disorders may be associated with a general psychological or
medical condition. This invention also relates to treating
partial therapy-refractory depression, partial therapy-
refractory atypical depression, and adolescent depression.
15 The invention further relates to a method for treating
malaise, lethargy, hypersomnia, weight gain, carbohydrate
craving, obesity, overeating, leaden paralysis, rejection
sensitivity, sexual inhibition, somatoform disorder,
somatised symptoms, learning disability, conduct disorder,
20 oppositional defiant disorder or conduct disturbance either
individually or in combination, with moclobemide, a
moclobemide metabolite, a moclobemide derivative, or a
moclobemide composition.

2. BACKGROUND OF THE INVENTION

25 **2.1. CHEMISTRY AND PHARMACOKINETICS OF MOCLOBEMIDE**

Moclobemide, or p-chloro-N-(2-morpholinoethyl)-
benzamide, which is represented by the formula:



is described in U.S. Patent No. 4,210,754, to Burkard et al.

Moclobemide is a selective and reversible monoamine oxidase (MAO) subtype A inhibitor. Kettler, R. et al., 1990, Acta Psychiatr. Scand., Supp. 360(82):101-103. Unlike other
5 monoamine oxidase inhibitors, which irreversibly and non-selectively bind MAO and can have severe food and drug interactions that limit their therapeutic utility, moclobemide is part of a distinct class of selective MAO
10 inhibitors that inhibit predominantly or selectively either monoamine oxidase A (MAO-A) or monoamine oxidase B (MAO-B). Compounds that selectively inhibit MAO-B, and thereby inhibit the degradation of dopamine, are useful for the treatment of neurological and neurodegenerative diseases of the
15 dopaminergic pathway, such as Parkinson's disease. Livingston, M.G. and Livingston, H.M., 1996, Drug Safety, 14(4):218-227. Compounds that selectively inhibit MAO-A predominantly affect the degradation of serotonin and norepinephrine, leading to increased concentrations of these neurotransmitters in synapses, and are useful for depression.
20 Livingston and Livingston, 1996.

The *in vitro* binding of moclobemide to MAO-A is weak, but more than 167-fold more selective than for the MAO-B isozyme. The *ex vivo* binding of moclobemide to MAO-A has been demonstrated to be reversible, with sufficient
25 dissociation to result in recovery of enzyme activity within 16 hours. Fulton, B. and Benfield, P., 1996, Drugs, 52(3):451. This is in contrast to older, nonselective and irreversible MAO inhibitors (also referred to herein as "irreversible MAOIs" or "IMAOIs"), which irreversibly bind to
30 either or both MAO-A and MAO-B isozymes and exhibit enzyme inhibition lasting several days. Da Prada, M. et al., 1990. As the MAO-A inhibition *in vivo* is relatively short in duration, it is generally accepted to be reversible. Da

Prada et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):103-105.

5 The effects of moclobemide on monoamine metabolism and/or activity of monoaminergic neurons have been indirectly demonstrated in humans by reductions in plasma levels of the catecholamine metabolites homovanillic acid, 3,4-dihydroxyphenylacetic acid, and 3-methoxy-4-hydroxyphenylglycol and the serotonin (5-hydroxytryptamine) metabolite 5-hydroxyindoleacetic acid. In vitro, moclobemide has no appreciable affinity for muscarinic, dopaminergic, serotonergic, adrenergic, H₁-histaminergic, benzodiazepine or opioid receptors. Da Prada et al., 1981, Excerpta Medica, 183-196; Da Prada et al., 1983, Mod. Probl. Pharmacopsych., 19:231-245; Da Prada et al., 1984, Clin. Neuropharmacol., 7 (Suppl. 1):684-685.

10 Moclobemide is extensively distributed in the body and rapidly eliminated from plasma by metabolic conversion in the liver. After single-dose oral administration, moclobemide is almost completely absorbed; however, bioavailability ranges from 44% to 69% because of substantial first-pass metabolism. Guentert, T.W. et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):91-93. After multiple administrations, moclobemide displays increased bioavailability (approx. 85%), possibly due to saturation of first-pass metabolism. Id. Moclobemide is metabolized to at least 19 different metabolites, one of which has moderate MAO-A inhibitory activity. Jauch, R. et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):87-90. Age and renal function are reported to have no significant effect on the pharmacokinetics of moclobemide; however, elimination is impaired in patients with hepatic dysfunction. Stoeckel et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):94-97. Thus, patients suffering from liver impairment should receive only 50% of the normal dosage. Id.

One of the most attractive features of moclobemide is its impressive safety profile. Because it does not permanently inhibit the monoamine oxidase enzyme, it has a relatively brief pharmacological action that contributes to its clinical safety. Moclobemide's short plasma half life (1 to 2 hours) also contributes to its safety because it promptly degrades in the tissues thereby preventing local over-accumulations. Stoeckel et al., 1990. Moclobemide appears to produce fewer adverse events in normal clinical use than other reversible MAOI compounds. Priest, R.G., et al., 1995, J. Clin. Psychopharm., 15(4), Suppl. 2: 1S-3S. The most frequently reported adverse events were psychiatric, neurologic, and gastrointestinal disorders, with hepatobiliary events occurring only rarely (Hilton, S. et al., 1995, J. Clin. Psychopharmacol., 15(4 Suppl. 2):76S-83S), and the effects of moclobemide on the sleep of healthy volunteers appear weak in comparison to other MAO inhibitors. Blois, R. et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):73-75.

Although moclobemide has not been extensively used in the United States, it has been used in Europe and in other countries and it is not known to produce any clinically relevant interactions with commonly prescribed drugs. Zimmer, R. et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):84-86. Moreover, moclobemide is far less likely than traditional MAO inhibitors to induce hypertensive reactions with the concomitant administration of sympathomimetic drugs, or consumption of tyramine-rich foods. Hilton, S.E., 1997, Eur. Arch. Psychiatry Clin. Neurosci., 247:113-119; Zimmer, 1990, Acta Psychiatr. Scand., Suppl. 360(82):81-83; Zimmer, Fischbach et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):76-77; Zimmer, Puech et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):78-80; Da Prada et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):106-107. A number of studies also suggest that moclobemide is better tolerated

than other compounds with anti-depressant activity. Priest, R.G., et al., 1995. Perhaps most impressively, the fatal toxicity index of moclobemide approaches zero. Hilton et al., 1995.

5 Initially, the recommended doses for moclobemide therapy (i.e., to treat depression) were approximately 100 mg to 150 mg three times daily. Guentert, T.W. et al., 1990. Subsequent experience has suggested that, in view of the positive dose-response curve found with moclobemide, doses as
10 high as 600 mg daily are increasingly efficacious and remain well-tolerated. Fitton, A. et al., 1992, Drugs, 43(4):561-596.

 Moclobemide's excellent safety and positive tolerance profile have made it a popular anti-depressive in
15 Canada, Europe, Australia, New Zealand, South Africa, and Latin America. Angst J. et al., 1996, Int. Clin. Psychopharmacol., 11(Suppl. 3):3-7; Glick, I.D. et al., 1995 Schatzberg, A.F. and Nemeroff, C.B. (Ed.), The American Psychiatric Press Textbook of Psychopharmacology, Washington,
20 DC, pp. 839-846)). Prescribing medications such as irreversible MAOI's with potentially harmful or deadly side effects to treat depression has traditionally caused some measure of concern among physicians, who worry that depressed patients may attempt suicide with the very medicines they are
25 prescribing. Although moclobemide is an MAO inhibitor, as an anti-depressive, it appears to be less prone to deadly drug and food interactions and less toxic in overdose. Patients taking other MAO inhibitors must adhere to restrictive diets which require the avoidance of, *inter alia*, red wines, beer,
30 aged cheese and meats, liver, yeast extracts and fava or broad beans.

 Furthermore, because moclobemide's side-effect profile is so benign, it enjoys good compliance rates. Priest, R.G., 1990, Acta Psychiatr. Scand., Suppl.
35 360(82):39-41. Compliance is an integral component of

successful treatment because the morbidity and mortality rates associated with untreated psychiatric illness are high. If a patient persistently rejects medical treatment for psychiatric illness because the initial experience in pharmacological intervention was bad, then the prognosis can be just as poor as if the patient had not been treated at all. When used in the treatment of major depression, moclobemide has proved itself an effective, gentle, patient-friendly drug.

2.2. THERAPEUTIC EFFICACY OF MOCLOBEMIDE

Moclobemide, sold under the tradename AURORIX™ or MANERIX™ (F. Hoffman-La Roche, Basel, Switzerland), has been shown to be effective in the treatment of various psychiatric disorders. For example, moclobemide is marketed in Canada, Europe, Australia, New Zealand, South Africa, and Latin America as an antidepressive agent, for which it has demonstrated significant therapeutic effect in certain patient populations. Angst J. et al., 1996; Glick, I.D. et al., 1995. A review of the pharmacological properties and therapeutic use of moclobemide in depressive illness was published by Fulton and Benfield in Drugs, 52(3):450-478, 1996, updating a previous review of Fitton et al., 1992, Drugs, 43(4):561-596.

The preparation and use of moclobemide as an antidepressant is described in United States Patent No. 4,210,754 to Burkard et al. In the treatment of depression, moclobemide has been shown to have similar efficacy to tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and nonselective, irreversible MAO inhibitors. Fulton and Benfield, 1996; Fitton et al., 1992. In particular, moclobemide has been shown to be effective in treating elderly patients suffering from depression or age-related dementia. Wesnes, K. et al., 1990,

Acta Psychiatr. Scand., Suppl. 360(82):71-72; United States Patent No. 4,906,626 to Amrein et al.

Moclobemide has also been reported to be effective in the management of tobacco addiction (PCT publication WO 95/28934; PCT publication WO 90/04387), attention deficit disorder (Trott, G.E. et al., 1992, Psychopharmacol., 106 Suppl.:134-136), and anxiety disorders such as social phobia, obsessive-compulsive disorder and panic (United States Patent No. 5,371,082 to Versiani et al.; Liebowitz, M.R. et al., 1990, Acta Psychiatr. Scand., Suppl. 360(82):29-34; Angst, J. et al., 1996, Int. Clin. Psychopharm., 11(Suppl. 3):3-7; Pollack, M.H. and Gould, R.A., 1996, Int. Clin. Psychopharm., 11(Suppl. 3):71-75).

The use of irreversible monoamine oxidase inhibitors (MAOIs) has been limited by the wide range of MAOI-drug and MAOI-food interactions that are possible, particularly with sympathomimetic medications or tyramine-containing foods, resulting in hypertensive reactions. Despite their clinical benefits, this has led to a reduction in use of such medications. Even when MAOI efficacy is documented for a given condition, many practitioners are reluctant to prescribe drugs from this class because of the risk of serious adverse reactions. This appears to be so even when MAOIs are more effective than other available treatments. Perhaps due to its classification as a monoamine oxidase inhibitor, moclobemide has not been extensively studied in the United States. In fact, moclobemide is not approved by the U.S. Food and Drug Administration. Further, there remains a great need in the field of psychiatry for additional therapies to better treat the growing number of psychiatric and psychological disorders presently described in the Diagnostic and Statistical Manual of Mental Disorders, Ed. 4, (DSM-IV), American Psychiatric Association, 1994, Washington, DC. There also remains a need in the field of medicine for additional therapies to treat psychiatric or

psychological illnesses or manifestations of other medical illnesses that are not defined by DSM-IV, such as some mood disturbances, conduct disturbances, etc.

2.3. DEPRESSION

5 The term "depression" is a clinically discernable condition generally known in the art as a depressed mood or a marked loss of interest or pleasure in nearly all activities lasting for a period of time (i.e., weeks, months, or years). Depression (also known as "major depression") is defined in
10 DSM-IV as five or more symptoms present over at least a two week period, wherein at least one of the symptoms must be depressed mood or loss of interest or pleasure and the other symptoms are selected from the group consisting of: (1) depressed mood most of the day, nearly every day; (2)
15 markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly everyday; (3) significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day; (4) insomnia or hypersomnia nearly every day; (5) psychomotor
20 agitation or retardation nearly every day; (6) fatigue or loss of energy nearly every day; (7) feelings of worthlessness or excessive or inappropriate guilt nearly every day; (8) diminished ability to think or concentrate or indecisiveness nearly every day; and (9) recurrent thoughts
25 of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

 A condition that presents similar symptoms but arises from, for example, a general medical condition or a
30 direct physiological effect of taking a substance should not necessarily be considered depression. In DSM-IV, for example, a Mood Disorder Due to a General Medical Condition is a diagnosis made based on history, laboratory findings, or physical examination, wherein the mood disturbance is judged

to be a direct physiological consequence of a specific general medical condition (e.g., multiple sclerosis, stroke, hyperthyroidism) (pp. 325, and 366-367 of DSM-IV).

Similarly, a Substance-Induced Mood Disorder is distinguishable from depression by the fact that a substance (i.e., a drug of abuse, a medication, or a toxin) is judged to be etiologically related to the mood disturbance (pp. 325-326, and 370-371 of DSM-IV). DSM-IV also distinguishes an Adjustment Disorder With Depressed Mood due to, for example, Bereavement, or periods of sadness from depression.

The criteria for diagnosing depression does not include the appearance of the symptoms: malaise or lethargy. There is a need for methods and compositions for treating illnesses, characterized by the symptoms malaise and lethargy, especially in patients who are not clinically depressed or are subclinically depressed. Applicants have solved this problem by providing methods and compositions for treating and preventing illnesses characterized by malaise and lethargy. Illnesses characterized by malaise and lethargy are described herein as low affect disorders or LAD, described in more detail below.

2.4. ATYPICAL DEPRESSION

The diagnosis term referred to as "atypical depression" (AD) has undergone dramatic changes since its initial exposition. As initially applied to depression, atypical was synonymous with nonmelancholic, i.e., absent the usual features of depression such as weight loss and insomnia, and displaying other symptoms normally absent in depression, such as anxiety. Lam, R.W. and Stewart, J.N., 1996, Comprehensive Psychiatry, 37(6):375-383.

Accordingly, the term "atypical depression" (AD) was originally used to describe depressed patients who were agitated, psychotic, and responsive to electroconvulsive therapy. Huston, P.E., and Locker, L.M., 1948, Arch. Neurol.

5 Psychiatry, 60:37-48. West and Dally later applied the term
to a different subset of depressed patients with prominent
phobic anxiety and lack of melancholic vegetative symptoms
such as insomnia and weight loss. West, E.D. and Dally,
10 P.J., 1959, Br. J. Med., 1:1491-94. They found that such
patients were responsive to the MAOI iproniazid. Id. A
similar patient group was described by Klein, in Liebowitz,
M.R. and Klein, D.F., 1979, Psychiatr. Clin. North Am.,
2:555-575, as suffering from "hysteroid dysphoria," a
15 syndrome characterized by marked dysphoric responses to
interpersonal rejection. Along with dysphoria, these
patients also experienced hypersomnia, hyperphagia, and/or
leaden paralysis.

20 Despite a developing clinical interest in AD, and
advances in defining criteria of inclusion, DSM-III did not
include any specific concept of AD. American Psychiatric
Association, Diagnostic and Statistical Manual of Mental
Disorders, Ed. 3, Washington, D.C., American Psychiatric
Association, 1980. Rather, the modifier "atypical" was used
25 to denote depression that did not meet the formal criteria
for any depressive diagnostic category. The revised edition,
DSM-III-R, eliminated all reference to atypical depression.
American Psychiatric Association, Diagnostic and Statistical
Manual of Mental Disorders, Ed. 3 Rev., Washington, D.C.,
30 American Psychiatric Association, 1987.

35 Even though AD has been recognized as a distinct,
clinically-identifiable syndrome, conflicting definitions
continue to be used in the literature. Some groups use the
term AD to describe depression with phobic anxiety, while
others use AD to describe depression with reverse vegetative
features. Davidson et al. formalized these two definitions
into A-type and V-type AD, respectively. Davidson, et al.,
1982, Arch. Gen. Psychiatry, 39:527-534. A-type atypical
depressives were described as anxious phobic, tense, and more
prone to atypical pain, whereas V-type depressives had

increased appetite and weight, increased libido, increased sleep, mood lability, and irritability. Id.

Research interest in defining AD subsequently shifted away from a concept primarily involving a lack of features normally associated with depression, and towards one defined by the presence of so-called "reverse" vegetative symptoms, such as weight gain and hyposomnia. Lam and Stewart, 1996. Accordingly, more recent work on AD has identified the following clinical criteria: (1) Research Diagnostic Criteria (RDC) for major, minor, or intermittent depression, (2) mood reactivity, and (3) two or more of hypersomnia, weight gain, leaden paralysis, and rejection sensitivity (hereinafter referred to as the "Columbia criteria AD"). Stewart, J.W. et al., 1989, Arch. Gen. Psychiatry, 46:1080-1087; Quitkin, F.M. et al., 1984, J. Clin. Psychiatry, 45:19-21; Quitkin, F.M. et al., 1993, Br. J. Psychiatry, 163(Suppl):30-34; Stewart, J.W. et al., 1993, Psychiatr. Clin. North Am., 16:479-495.

With two revisions, these criteria have been incorporated into the DSM-IV; increased appetite is included alongside weight gain as an alternative symptom within the third class of symptoms, and a long-standing pattern of interpersonal rejection sensitivity replaces acute hypersensitivity during episodes of mood disturbance ("DSM-IV AD"). Thus, DSM-IV defines AD as a mood reactive depression with associated reverse vegetative symptoms or marked interpersonal rejection sensitivity. DSM-IV includes AD as an episode specifier for major depressive episodes or dysthymia. The AD mood specifier can be used for depressive episodes occurring either in unipolar and bipolar mood disorders. As referred to herein, "DSM-IV AD" is used interchangeably with "Columbia Criteria AD" to refer to AD meeting the criteria identified in either or both of the foregoing paradigms.

Some studies have found earlier onset of illness in DSM-IV AD as compared to patients with typical depression (Stewart et al., 1993; Davidson, J. et al., 1989, Compr. Psychiatry, 30:357-368; Thase, M.E. et al., 1991, Psychopharmacol. Bull., 27:17-22), but others have found no difference (Asnis, G.M. et al., 1995, Am. J. Psychiatry, 152:31-36). Similarly, index episode duration has been reported as longer and more chronic in some studies (Stewart et al., 1993; Davidson et al., 1989), but not in others (Asnis et al., 1995). In part, these conflicting and inconsistent results may be due to the use of different criteria of inclusion for AD. A longitudinal study of 29 inpatients with AD defined by Columbia criteria found that only 59% continued to meet these criteria after a 1- to 2-year follow-up. Ebert, D. and Barocka, A., 1991, Eur. Arch. Psychiatry Clin. Neurosci., 241:131-132.

The criteria for diagnosing atypical depression, like those for major depression, does not include the appearance of the symptoms of malaise and lethargy.

2.4.1. PHARMACOLOGICAL TREATMENT OF ATYPICAL DEPRESSION

Early antidepressant studies suggested that atypical depressives who met the DSM-IV criteria were unlikely to respond to tricyclic antidepressants (Bielecki, R.J. and Friedel, R.O., 1976, Arch. Gen. Psychiatry, 33:1479-1489; Joyce, P.R. and Paykel, E.S., 1989, Arch. Gen. Psychiatry, 46:89-99), but showed a good response to MAOI's (Quitkin, F. et al., 1979, Arch. Gen. Psychiatry, 36:749-760). However, some studies have not shown differential responses between MAOI's and tricyclic antidepressants. Paykel, E.S. et al., 1982, Arch. Gen. Psychiatry, 39:1041-49. Again, it appears that conflicting criteria may be responsible for the disparate results. Lam and Stewart, 1996.

There are few studies on the efficacy of newer antidepressant medications in treating DSM-IV AD. Moclobemide has been shown to be effective in treating Columbia criteria AD or DSM-IV AD in studies comparing it to other antidepressants, e.g., isocarboxazide and clomipramine (Larsen, J.K. et al., 1991, Acta Psychiatr. Scand., 84:564-570), diazepam (Tiller, J. et al., 1989, J. Affective Disord., 16:181-187; Schweitzer, I. et al., 1989, Int. J. Clin. Pharm. Res., IX(2):111-117), and fluoxetine and imipramine (Stratta, P. et al., 1991, Int. Clin. Psychopharmacol., 16:193-196; Lonngqvist, J. et al., 1994, J. Affective Disord., 32:169-177).

There is a need for methods and compositions for treating illnesses characterized by malaise and lethargy, especially in patients who are not clinically atypical depressive.

2.5 REFRACTORY DEPRESSION AND ATYPICAL DEPRESSION

Resistance to antidepressants is an important problem in treating depressive disorders, involving up to 20% of patients. Konig and Wolfersdorf, 1997, Pharmacopsychiat., 30:93-96. Although the term "therapy resistance" is defined differently in various studies, it generally describes patients who show little to no attenuation of symptoms, or remission, despite treatment with medication at a therapeutic dosage and duration, and is used accordingly herein. Zajecka J.M., Annual Meeting of American Psychiatric Association, May 21, 1995, Miami, Florida.

MAOI's have traditionally presented a significant risk of negative drug interactions with common antidepressants. Thus, they are generally considered to have limited utility for the treatment of antidepressant therapy resistant patients. As discussed above, MAOI's are prone to negative interactions with sympathomimetic medications,

resulting in hypertensive shock. The most serious of such interactions may be fatal. Livingston and Livingston, 1996.

In addition to the threat of hypertensive shock, MAOI's tend to interact negatively with drugs that enhance serotonin production or release, such as TCA's. Although the exact mechanism of interaction is unknown, the co-administration of the two serotonergic compounds is thought to cause serotonin syndrome. Sternbach, H., 1991, Am. J. Psychiatry, 148:705-13. This syndrome is characterized by restlessness, shivering, diaphoresis, tremor, hyperreflexia and myoclonus. Drugs that are likely to cause this syndrome with co-administered conventional MAOIs, in addition to the TCAs (especially the more serotonin-specific clomipramine), are the selective serotonin reuptake inhibitors (SSRI), citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Some opioids, such as pethidine (meperidine), may also cause symptoms of the serotonin syndrome when co-administered with conventional MAOIs, and, sometimes such combinations cause a central depression syndrome that involves excessive sedation and ultimately coma and death. Livingston and Livingston, 1996.

Unlike many MAOI's, moclobemide can be safely and effectively used in alone or in combination with tricyclic and tetracyclic antidepressants to treat therapy-resistant or refractory depression (RD). Stabl, M. et al., 1995; Konig and Wolfersdorf, 1997. Initial results involving the coadministration of moclobemide and SSRIs have been varied. One pilot study described the effective coadministration of moclobemide and fluvoxamine (SSRI) to therapy-resistant patients. [Ebert et al. (1995)] On the other hand, five cases of fatal intoxications from "serotonin syndrome" after coadministration of moclobemide and an SSRI have been reported. [Neuvonen et al., (1993)]

In addition to refractory depression, therapy-resistant atypical depression or refractory atypical

depression (RAD) also presents a significant pharmacological challenge due to the dangerous potential for adverse drug interactions as described above (e.g., with SSRI's and TCA's). A patient with RD or RAD can not readily be switched from the drug to which he has failed to respond or to another antidepressant. Rather, switching between antidepressants typically entails a "wash-out period" of several weeks, due to the relatively long half-lives of many common antidepressants, to ensure elimination of the prior drug from the patient's system. Throughout this delay, the therapy-resistant patient remains untreated, potentially leading to increased severity of depression and serious psychological and physiological complications.

Further, there is a need for methods for treating depressive and atypical depressive patients who partially respond to antidepressive treatment (hereinafter "partial RD" or "partial RAD" patients, or PRD or PRAD patients, respectively), i.e., patients who after antidepressive therapy experienced a decrease or elimination of some but not all of their depressive or atypical depressive symptoms such that they cannot be described as depressive or atypically depressive under the criteria in DSM-IV. Such PRD or PRAD patients include those patients who: (1) experience transient complete recovery from depression or atypical depression; (2) subsequently develop depression or atypical depression that is only partially responsive to treatment after 6 months or who develop one or more of the symptoms of depression or atypical depression; and (3) cannot be described as depressive or atypically depressive under the criteria in DSM-IV. To the best of applicant's knowledge, the efficacy of moclobemide alone or in combination with other antidepressants such as TCAs, tetracyclic antidepressants or SSRIs in treating PRD or PRAD patients has not yet been demonstrated.

2.6 ADOLESCENT DEPRESSION

The DSM-IV recognizes that adolescents are susceptible to certain distinct disorders, such as adolescent antisocial behavior (DSM-IV, p. 684), attention deficit/hyperactivity disorder (pp. 78-85), adolescent-onset type Conduct Disorder (pp. 85-91), and Oppositional Defiant Disorder (pp. 91-94).

However, "adolescent depression" is a not well-characterized disorder that afflicts adolescents and includes specialized symptoms of mood reactivity, social anxiety, and mood-associated rejection sensitivity or hypersensitivity to interpersonal rejection. Thus, depressive episodes in adolescents typically differ in character from those experienced by adult depressives (DSM-IV, pp. 320-327).

It should be appreciated that, to some extent, the above-identified symptoms of adolescent depression are characteristic of adolescence itself, and, in most cases, are not of an intensity or duration warranting pharmaceutical intervention. However, in identifying a new syndrome marked by the above-identified characteristics, it is contemplated by applicant that adolescents who suffer the above symptoms to a degree that interferes with their social, psychological, and interpersonal functioning may be treated without the need to "wait and see" whether a clinically identifiable diagnosis develops.

Thus, despite the knowledge about adult depression and treatments for depression known in the art, there exists a need for better and alternative methods for treating adolescent depression, which is different from adult depression and from known adolescent syndromes described above. To the best of applicants' knowledge, the use of moclobemide to treat or prevent depression in adolescents and especially treat symptoms which may develop into adolescent depression if left untreated has never been reported.

2.7 SEXUAL INHIBITION

The human sexual response can generally be divided into three phases: libido, excitement, and orgasm. It has been shown that certain antidepressants can have deleterious effects on any of these three phases. Problems with excitement may include impotence, painful erection, spontaneous erection, penile or clitoral priapism, and difficulty with vaginal lubrication. Problems with orgasm encompasses delayed orgasm, painful orgasm, anorgasmia, spontaneous ejaculation, retrograde ejaculation, and anhedonic ejaculation (ejaculation without orgasm). [Margolese, H.C. and P. Assalian, J. Sex Marital Ther. 22:209-217 (1996)].

Moclobemide given to healthy volunteers has been reported to have no effect on sexual desire and function over placebo. [Kennedy, S.H., et al., Euro. Neuropsychopharmacol. 6:177-181 (1996)]. Other antidepressants are known to induce sexual dysfunction in patients with depression. In one study, depressive patients treated with fluoxetine experienced diminished libido, orgasm and/or erection which was alleviated after fluoxetine treatment ended and moclobemide treatment began. [Ramasubbu, R., 1999]. In another case, a patient treated with moclobemide directly followed by doxepin (an antidepressant) experienced overreactivity to sexual stimulation 5-7 days after starting moclobemide treatment and up to 6 days following the cessation of moclobemide treatment. [H. Lauerma, Int. Clin. Psychopharmacol. 10:123-124 (1995)]. In yet another case, a major depressive patient was reported to experience sexual hyperarousal after treatment with moclobemide. [Philipp, M. et al., Int. Clin. Psychopharmacol. 7:149-53 (1993)].

Thus, although moclobemide has been suggested to be involved in the sexual hyperarousal of some patients with major depression, to the best of applicant's knowledge, the

use of moclobemide to treat sexual inhibition in patients who are subclinically depressed or who are not clinically depressed has never been reported.

5

3. SUMMARY OF THE INVENTION

The present invention relates to the use of moclobemide, a metabolite of moclobemide, or a derivative of moclobemide for treating or preventing certain psychiatric and medical disorders. Moclobemide, or moclobemide metabolite, or moclobemide derivative according to this invention may be in the form of a pharmaceutically acceptable salt, hydrate, or solvate. Hereinafter, the term "moclobemide, moclobemide metabolite or moclobemide derivative," includes moclobemide, a metabolite of moclobemide, or a derivative of moclobemide; or a prodrug of moclobemide, a metabolite of moclobemide, or a derivative of moclobemide; or pharmaceutically acceptable salt, hydrate, solvate of moclobemide, a metabolite of moclobemide, a derivative of moclobemide; or prodrug thereof. The present invention also encompasses the use of a composition in the methods of this invention, wherein the composition comprises moclobemide, a metabolite of moclobemide, or a derivative of moclobemide together with a pharmaceutically acceptable carrier. Moclobemide metabolites according to this invention are those with MAO-A inhibitor activity, such as moclobemide-N-oxide.

The invention encompasses the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition in treating or preventing certain disorders associated with low affect as defined herein. Thus, one embodiment of the present invention relates to the treatment of low affect disorders by administration of a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a

5 moclobemide composition. Another embodiment of the present invention is the treatment of disorders associated with LAD, by administration of a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.

The invention also encompasses the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to treat or prevent adolescent depression.

10 The invention also encompasses the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to treat the symptoms of malaise and lethargy.

15 The invention also encompasses the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition in treating PRD or PRAD by administration to a patient exhibiting, at a sub-syndromal level, symptoms commonly associated with the development of depression or atypical depression, either alone or in conjunction with psychotherapy. Thus, the present invention also encompasses methods for treating PRD or PRAD in a human by administering a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to said human.

25 The invention also encompasses the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to treat individual symptoms commonly associated with atypical depression, such as hypersomnia, weight gain, leaden paralysis, and rejection sensitivity, in patients who are not clinically depressed or who are subclinically depressed. Accordingly, one embodiment of the present invention is a method for treating a human with hypersomnia, weight gain, leaden paralysis, and/or rejection sensitivity by administering a therapeutically

30

35

effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition, to said human.

5 The invention relates to the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to treat a LAD patient, suffering from sexual inhibition, somatization, somatoform disorder, carbohydrate cravings, obesity or overeating, who is not clinically depressed or who is subclinically depressed.

10 Another object of this invention is to provide a method for treating or preventing an illness selected from the group consisting of a learning disability, conduct disorder, oppositional defiant disorder, or a conduct disturbance, in a human who is in need of treatment for said illness and who does not suffer from attention deficit
15 hyperactivity disorder, comprising the step of administering moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition thereof.

20 The present invention further encompasses the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to treat patients who are immunocompromised or immunosuppressed, as a result of, for example, viral infection including HIV, cancer, medication, or post-operative trauma. Accordingly, one embodiment of the
25 present invention is a method for treating LAD in an immunocompromised or immunosuppressed patient by administering a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to said human.

30 The use of other moclobemide derivatives is also encompassed by the present invention. In particular, the use of p-iodo-N-(2-morpholinoethyl)-benzamide, p-fluoro-N-(2-morpholinoethyl)-benzamide, p-bromo-N-(2-morpholinoethyl)-benzamide, and p-chloro-N-(2-morpholinoethyl)-benzamide-N'-
35 oxide is contemplated. Each of these compounds, and salts

thereof, is structurally similar to moclobemide and can be used with the present methods, although moclobemide is preferred.

5 According to this invention, moclobemide, a
moclobemide metabolite, a moclobemide derivative or a
moclobemide composition may be administered before, along
with, or after other psychoactive compounds, particularly
those with antidepressant activity. Accordingly, the present
10 invention encompasses the use of moclobemide, a moclobemide
metabolite, a moclobemide derivative or a moclobemide
composition to treat or prevent LAD, adolescent depression,
or the above-identified individual symptoms commonly
associated with AD, in conjunction with other known
antidepressants, such as tricyclic antidepressants,
15 serotonin-reuptake inhibitors, atypical antidepressants and
other monoamine oxidase inhibitors. Such known
antidepressant compounds include, without limitation,
tricyclic antidepressants such as amitriptyline,
clomipramine, doxepin, imipramine, (+)-trimipramine,
20 amoxapine, desipramine, maprotiline, nortriptyline, and
protryptiline; serotonin-reuptake inhibitors such as (+)-
fluoxetine, (+)-fluoxetine, fluvoxamine, paroxetine,
sertraline, and (+)-venlafaxine or an active optical isomer
thereof; atypical antidepressants such as bupropion,
25 nefazodone, and trazodone; and other monoamine oxidase
inhibitors, such as phenelzine, tranylcypromine, and (-)-
selegiline, either singly or in combination. In particular,
the present invention encompasses the use of moclobemide, a
moclobemide metabolite, a moclobemide derivative or a
30 moclobemide composition in conjunction with other known
antidepressants without the resulting negative drug
interactions commonly associated with MAOI's.

The present invention further encompasses the use
of moclobemide, a moclobemide metabolite, a moclobemide
35 derivative or a moclobemide composition in conjunction with

traditional psychotherapy to treat or prevent LAD, adolescent depression, PRD or PRAD in a human by administering moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to said human, before, during, or after psychotherapeutic intervention.

The invention provides for methods for using moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition either alone or in conjunction with psychotherapy, antidepressants, or additional psychoactive medication such as lithium, in all potential human patient populations, including men, women, children and the elderly.

In one embodiment, the humans to be treated do not have depression, atypical depression and/or attention deficit hyperactivity disorder. One preferred class of patients to be treated with moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition thereof is immunocompromised or immunosuppressed patients.

4. DEFINITIONS

As used herein, the terms "malaise" and "lethargy" are as known in the art. For example, malaise can be characterized by a feeling of discomfort, and lethargy can be characterized as drowsiness.

As used herein, the term "affect" is defined as emotional feeling, tone, or mood, including its external manifestations.

As used herein, the term "low affect" is defined as emotional tone tending towards sadness, lethargy, malaise, melancholy, dejection, listlessness, or withdrawal in the absence of external stimuli, such as reactive depression that is inappropriate or is abnormally protracted or prolonged (e.g., wherein the initial cause of the depression is bereavement) commonly associated with such emotions.

As used herein, the term "low affect disorder" (LAD) is an affliction with the hallmark characteristics of malaise and lethargy. LAD is distinguished from depression, as defined in DSM-IV, by the presence of these characteristic symptoms, which do not appear in the DSM-IV definition of "depression". LAD may be present in conjunction with a general medical or psychological condition, or may be independent of any additional symptoms. For example, LAD may be accompanied by symptoms meeting the criteria for RD or RAD.

As used herein, the terms "not clinically depressed" or "subclinical depression" refers to a condition which does not meet the criteria of major depression or atypical depression according to DSM-IV. The term "subclinical depression" additionally refers to a condition as readily known in the art and can be characterized by low affect.

As used herein, the term "refractory depression" or "RD" is defined as a syndrome that (1) meets the RDC for major, minor, or intermittent depression and (2) is resistant

to treatment with SSRI's, TCA's, or other standard antidepressant medications after a period of 6 months.

As used herein, the concept of AD has been further refined to describe a subset of patients nonresponsive to treatment for AD, as defined by the Columbia criteria or the DSM-IV criteria. As used herein, "refractory AD" or "RAD" is defined as a syndrome that: (1) meets the Research Diagnostic Criteria (RDC) for major, minor, or intermittent depression, (2) includes mood reactivity, (3) includes two or more of hypersomnia, weight gain, increased appetite, leaden paralysis, acute, mood-associated rejection sensitivity, or a long-standing pattern of hypersensitivity to interpersonal rejection, and (4) is resistant to treatment with selective serotonin reuptake inhibitors (SSRI's), tricyclic antidepressants (TCA's), or other standard antidepressant medications after a period of 6 months. For example, a patient with RAD, as defined herein, may be depressed, display mood reactivity, have an increased appetite and hypersomnia, and be SSRI-refractory or nonresponsive after 6 months of treatment with at least one SSRI, either alone or in combination with other pharmacological or psychotherapeutic interventions.

As used herein, the term partial RD (or PRD) refers to a patient who after antidepressive therapy experience decrease or elimination of some but not all of his/her depressive symptoms such that he/she cannot be described as depressive under the criteria of DSM-IV. Such PRD patients include those patients who: (1) experience transient complete recovery from depression; (2) subsequently develop depression that is only partially responsive to treatment after 6 months or who develop one or more of the symptoms of depression; and (3) cannot be described as depressive under the criteria in DSM-IV.

As used herein, the term partial RAD (or PRAD) refers to a patient who after antidepressive therapy

experience decrease or elimination of some but not all of his/her atypical depressive symptoms such that he/she cannot be described as atypically depressive under the criteria of DSM-IV. Such PRAD patients include those patients who: (1) experience transient complete recovery from atypical depression; (2) subsequently develop atypical depression that is only partially responsive to treatment after 6 months or who develop one or more of the symptoms of atypical depression; and (3) cannot be described as atypically depressive under the criteria in DSM-IV.

As used herein, the term "adolescent depression" describes a novel subset of depressed individuals with unique manifestations of depression thought to be related to the complicated social, psychological, and biochemical environment of adolescence. Thus, adolescent depression is defined as a syndrome that (1) begins between the ages of 9 and 19, and that includes (2) mood reactivity, (3) social anxiety, and (4) mood-associated rejection sensitivity or hypersensitivity to interpersonal rejection. Adolescent depression according to this invention is distinct from known adolescent syndromes as described in DSM-IV.

As used herein, the term "sexual inhibition" describes an inhibition of or deficiency in a sexual response, i.e., libido, excitement, or orgasm. Sexual inhibition as used herein does not include inhibition of or deficiency in a sexual response directly caused by a physical defect which makes a sexual response physically impossible.

As used herein, the term "somatoform disorder" is used to describe a group of disorders having clinically significant physical symptoms that suggest a general medical condition and are not fully explained by a general medical condition, by the effects of a substance, or by another mental disorder (i.e., results in medical treatment or causes significant impairment in functioning), as defined in DSM-IV (*supra*).

As used herein, the term "somatization" is used to describe an unconscious process in a patient not afflicted with a "somatoform disorder" as defined in DSM-IV, whereby psychological distress or anxiety is expressed as a physical symptom (hereinafter "somatised symptom"). The term "somatised symptom" according to this invention refers to any symptom resulting from somatization or a somatoform disorder which is a physical expression of psychological distress or anxiety. For example, a somatised symptom can be a lack of energy or the presence of fatigue, muscular aches and pains or a symptom that occurs in a somatoform disorder such as nausea, impaired coordination/balance, paralysis, blindness, deafness, seizures, dissociative symptoms, loss of consciousness and pain during sexual intercourse, menstruation or urination.

The term "carbohydrate craving" according to this invention refers to a clinically significant tendency to frequently crave carbohydrate-containing foods (particularly, carbohydrate-rich containing snack foods such as potato chips, pastries, cookies), which is well known in the art (e.g., Wurtman, R.J. et al., Obes. Res. Suppl 4:477S-480S (1995)). Patients suffering from this tendency do not necessarily suffer from obesity.

The term "conduct disorder" according to this invention refers to a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as defined in DSM-IV (*supra*). As used herein, a patient experiencing a conduct disorder does not have Attention-Deficit/Hyperactivity Disorder as defined in DSM-IV.

The term "oppositional defiant disorder" according to this invention refers to a recurrent pattern of negativistic, defiant, disobedient, and hostile behavior toward authority figures that persists for at least six months, as defined in DSM-IV. As used herein, a patient

experiencing an oppositional defiant disorder does not have Attention-Deficit/Hyperactivity Disorder as defined in DSM-IV.

5 The term "conduct disturbance" according to this invention refers to a clinically significant behavior in patient which is repetitive and persistent, in which the basic rights of others or major age-appropriate societal norms or rules are violated, wherein said patient's behavior does not meet the criteria of a conduct disorder or
10 oppositional defiant disorder as defined in DSM-IV. As used herein, a patient experiencing a conduct disturbance does not have Attention-Deficit/Hyperactivity Disorder as defined in DSM-IV. The term "conduct disturbance" according to this invention refers to a clinically significant behavior in a
15 patient experiencing conduct disorder, oppositional defiant disorder or conduct disturbance, which is repetitive and persistent and violates the basic rights of others or major age-appropriate societal norms or rules. Said conduct disturbances according to this invention include aggressive
20 conduct; causes or threatens physical harm to humans or animals; non-aggressive conduct that causes property loss or damage; deceitfulness or theft; serious violations of rules; and negativistic, defiant, disobedient, and hostile behavior toward authority figures. In one embodiment, said human
25 having a conduct disturbance or a conduct disorder or oppositional defiant disorder, does not have Attention-Deficit/Hyperactivity Disorder.

 The term "learning disability" is as known in the art. In one embodiment, a human with a learning disability
30 according to this invention does not suffer from attention deficit hyperactivity disorder.

5. DETAILED DESCRIPTION OF THE INVENTION

"Low Affect Disorder" (LAD) is a heretofore uncharacterized affliction with the hallmark characteristics

of malaise and lethargy. LAD is distinguished from depression, as defined in DSM-IV, by the presence of these characteristic symptoms, which do not appear in the DSM-IV definition of "depression". In a one embodiment, the LAD patient being treated in the methods of this invention is not clinically depressed or is subclinically depressed.

In identifying a new, clinically significant constellation of symptoms under the diagnosis LAD, it is hoped that patients with this distinct group of symptoms may be treated promptly and effectively, without the need to "wait and see" if another, clinically significant syndrome develops. Thus, the main advantage of treating LAD is the avoidance of resultant psychological syndromes such as depression, of which LAD may be a precursor syndrome.

It should be appreciated that a diagnosis of LAD can include patients who suffer from these symptoms as part of clinically defined syndromes such as depression or atypical depression. Thus, LAD, as used herein, is meant to encompass patients with malaise and lethargy who are suffering from a concomitant medical condition, such as an autoimmune disorder in which "malaise" is a diagnostic feature, e.g., systemic lupus. Accordingly, it should be understood that LAD patients may also suffer from concomitant psychiatric problems. However, it should also be noted that LAD is not the same disorder as "depression" known in the art or defined in DSM-IV. To the best of applicant's knowledge, the use of moclobemide to treat LAD has never been reported.

The invention encompasses the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to treat the symptoms of malaise and lethargy. In one preferred embodiment, the patient suffering from malaise and lethargy is not clinically depressed or is subclinically depressed.

The present invention also provides a method of treating LAD in a human, which comprises administering to

said human suffering from LAD a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.

5 The present invention encompasses a method of treating PRAD or PRD in a human, which comprises administering to said human suffering from PRAD or RAD, respectively, a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition either alone or in
10 conjunction with psychotherapy or additional psychoactive medication, in a manner designed to minimize or eliminate any symptoms associated with depression or atypical depression, respectively, of a subsyndromal intensity. In one preferred embodiment, the PRD or PRAD patient is administered a
15 therapeutically affective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition with another therapeutic agent such as a TCA, a SSRI, a antipsychotic drug.

20 The present invention encompasses a method of treating adolescent depression in a human, which comprises administering to said human suffering from adolescent depression a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.

25 The present invention also encompasses the use of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to treat individual symptoms commonly associated with atypical depression, such as hypersomnia, weight gain, leaden paralysis, and rejection
30 sensitivity, in patients who are not clinically depressed or who are subclinically depressed.

35 As used herein, the concept of AD has been further refined to describe a subset of AD patients, those with refractory AD ("RAD"), who are nonresponsive to conventional treatment with well-known antidepressants, such as SSRI's,

TCA's or other known antidepressants. Thus, a patient with RAD, as defined herein, would continue to meet the DSM-IV or Columbia criteria for AD after 6 months of treatment with at least one antidepressant.

5 The invention provides a method for using moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to a patient, who is not clinically depressed or who is subclinically depressed, and who is suffering from sexual inhibition, somatization, 10 somatoform disorder, carbohydrate cravings, obesity or overeating. The invention also provides a method for treating a somatised symptom comprising the step of administering moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition to a 15 human who in need of treatment for a somatised symptom. In a preferred embodiment the human is not clinically depressed or is subclinically depressed. Such method may be useful for preventing the onset of depression or AD. The somatised symptoms can be selected from the group consisting of lack of 20 energy, fatigue, muscular aches and pains or a symptom that occurs in a somatoform disorder such as nausea, impaired coordination/balance, paralysis, blindness, deafness, seizures, dissociative symptoms, loss of consciousness and pain during sexual intercourse, menstruation or urination.

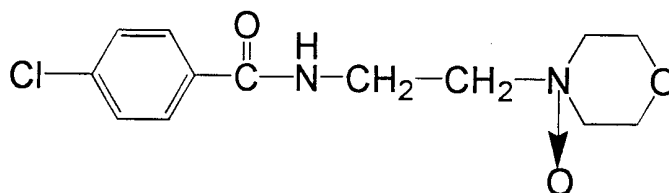
25 Another object of this invention is to provide a method for treating or preventing an illness selected from the group consisting of a learning disability, conduct disorder, oppositional defiant disorder, or a conduct disturbance, in a human who is in need of treatment for said 30 illness and who does not suffer from attention deficit hyperactivity disorder, comprising the step of administering moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition. The invention also provides a method for treating a conduct disturbance 35 comprising the step of administering moclobemide, a

5 moclobemide metabolite, a moclobemide derivative or a
moclobemide composition to a human in need of treatment for a
conduct disturbance. Said conduct disturbance can be
selected from the group consisting of aggressive conduct;
causes or threatens physical harm to humans or animals; non-
aggressive conduct that causes property loss or damage;
deceitfulness or theft; serious violations of rules; and
negativistic, defiant, disobedient, and hostile behavior
toward authority figures.

10 Further, the present invention encompasses the use
of moclobemide, a moclobemide metabolite, a moclobemide
derivative or a moclobemide composition to treat patients who
are immunocompromised or immunosuppressed.

15 Moclobemide, as well as certain other moclobemide
derivatives, can be synthesized according to the method
described in United States Patent No. 4,210,754 to Burkard et
al., and in United States Patent No. 4,906,626 to Amrein et
al., which are incorporated by reference herein in their
entirety.

20 The moclobemide metabolite known as moclobemide-N-
oxide, which can be represented by the formula:



has been shown to have MAO-A inhibitory activity, and its use
is also encompassed by the present invention.

25 Prodrugs, i.e. drugs that are metabolized in vivo
into the active agent, and methods for making prodrugs are
readily known in the art (e.g., Balant, L.P., "Prodrugs for
the Improvement of Drug Absorption Via Different Routes of
Administration," Eur. J. Drug Metab. Pharmacokinet.
15:143-153 (1990); and Bundgaard, H., "Novel Chemical

Approaches in Prodrug Design," Drugs of the Future 16:443-458 (1991); incorporated by reference herein). In one embodiment, derivatives according to this invention have MAOI activity.

5 The magnitude of a prophylactic or therapeutic dose of the active ingredient (e.g., moclobemide, a moclobemide metabolite, a moclobemide derivative) in accordance with the present invention will vary with the severity of the patient's affliction and the route of administration. The
10 dose and dose frequency will also vary according to the age, weight and response of the individual patient. In general, the recommended daily dose range for the conditions described herein lies within the range of from about 50 mg to about
15 1200 mg per day, generally divided equally into doses given one to four times a day. Preferably, a daily dose range should be between 150 mg and 900 mg per day, usually divided
20 equally into a two to four times a day dosing. Most preferably, a daily dose range should be between 150 mg and 600 mg per day, usually divided equally into a two to four
25 times a day dosing. It may be necessary to use dosages outside these ranges in some cases, and the treating physician will know how to increase, decrease or interrupt treatment based upon patient response. The various terms described above such as "therapeutically effective amount,"
are encompassed by the above-described dosage amounts and dose frequency schedule.

 For use in accordance with the present invention, the treating physician will generally prescribe the period of treatment and frequency of dose of moclobemide, a moclobemide
30 metabolite, a moclobemide derivative or a moclobemide composition on a patient-by-patient basis. In general, however, treatment with moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition may be carried out for as long a period as
35 necessary, either in a single, uninterrupted session, as is

preferred for LAD, adolescent depression, RD, and RAD, or in discrete sessions timed to coincide with exposure to biochemical or hormonal stimuli likely to trigger symptoms, as is preferred for treating the symptoms commonly associated with AD, in the absence of depression. Most preferably, moclobemide, a moclobemide metabolite, or a moclobemide derivative therapy may be carried out for a period of at least 4 weeks.

When used for treating or preventing LAD, adolescent depression, or the symptoms commonly associated with depression or AD in patients who do not have depression or AD by DSM-IV criteria, moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition may be administered before, along with, or after psychoactive compounds without antidepressant activity, such as lithium.

Moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition may also be administered before, along with, or after traditional psychotherapy. Thus, moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition may be utilized in accordance with the present invention as an adjunct to conventional behavioral therapy that aims to eliminate, minimize, or prevent depressive symptoms commonly associated with the above-described disorders.

Any suitable route of administration may be employed for providing the patient with an effective dosage of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition. For example, oral, rectal, parenteral, transdermal, subcutaneous, sublingual, intranasal, intramuscular, intrathecal and the like may be employed as appropriate. Dosage forms include tablets, coated tablets, caplets, capsules (e.g. hard gelatin capsules), troches, dragées, dispersions, suspensions, solutions, patches and the like, including sustained release

formulations well known in the art. See, e.g. Introduction to Pharmaceutical Dosage Forms, 1985, Ansel, H.C., Lea and Febiger, Philadelphia, PA; Remington's Pharmaceutical Sciences, 1995, Mack Publ. Co., Easton, PA.

5 The compositions of the present invention may also comprise other therapeutic ingredients. The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

10 Since the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Such acids include maleic, acetic, benzene-sulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric,
15 gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are hydrobromic, hydrochloric, maleic, phosphoric,
20 and sulfuric acids.

 The compositions include compositions suitable for oral, rectal, transdermal, sublingual, and parenteral administration (including subcutaneous, intramuscular, intrathecal and intravenous), although the most suitable
25 route in any given case will depend on the nature and severity of the condition being treated. The most preferred route of administration of the present invention is the oral route. The composition may be conveniently presented in unit dosage form and prepared by any of the methods well-known in
30 the art of pharmacy.

 In the case where an oral composition is employed, a suitable dosage range for use is, e.g., from about 50 mg to about 1200 mg per day, generally divided equally into a one to four times a day dosing, preferably from about 150 mg to
35 about 900 mg per day, generally divided equally into a two to

four times a day dosing and most preferably from about 150 mg to about 600 mg per day, generally divided equally into a two to four times a day dosing. Patients may be upward titrated from below to within this dose range to achieve satisfactory control or prevention of symptoms as appropriate.

In practical use, moclobemide, a moclobemide metabolite, or a moclobemide derivative can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous injections or infusions). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, for example, suspensions, elixirs and solutions; or aerosols; or carriers such as starches, sugars, microcrystalline cellulose, stabilizers, diluents, granulating agents, lubricants, binders, fillers, disintegrating agents and the like in the case of oral solid preparations such as, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. The preferred solid oral preparation is tablets. The most preferred solid oral preparation is coated tablets. Because of their ease of 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 coated by standard aqueous or nonaqueous techniques. The preparation of coated tablets, sachets, and hard gelatin capsules containing moclobemide as the active ingredient is described in United States Patent No. 4,906,626, which is incorporated herein by reference.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release or sustained release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200, 4,008,719, 4,687,660, and 4,769,027, the disclosures of which are hereby incorporated by reference. Preferred controlled release or sustained release tablets suitable for use with moclobemide are described in U.S. Patent No. 5,427,798, which is incorporated herein by reference.

Pharmaceutical stabilizers may also be used to stabilize compositions containing moclobemide or salts thereof; acceptable stabilizers include but are not limited to L-cysteine hydrochloride, glycine hydrochloride, malic acid, sodium metabisulfite, citric acid, tartaric acid and L-cysteine dihydrochloride. See, e.g. U.S. Patent No. 5,358,970, which is incorporated herein by reference.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients.

Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with one or more of a binder, filler, stabilizer, lubricant, inert diluent, and/or surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 50 mg to about 300 mg of the active ingredient, and each cachet or capsule contains from about 50 mg to about 300 mg of the active ingredient. In a preferred embodiment, the tablet, cachet or capsule contains one of four dosages: about 50 mg, about 75 mg, about 100 mg, and about 150 mg of active ingredient.

The invention is further defined by reference to the following examples describing in detail the preparation of the compound and compositions of the present invention. It will be apparent to those skilled in the art that many modifications, both to materials and to methods, may be practiced without departing from the purpose and interest of this invention.

6. EXAMPLES6.1. EXAMPLE 1ORAL FORMULATIONCoated Tablets:

Formula	Quantity per Tablet (mg.)
moclobemide	50.0
Lactose	74.0
Corn Starch	35.0
Water (per thousand Tablets)	30.0 ml *
Magnesium Stearate	1.0
Corn Starch	25.0

*

The water evaporates during manufacture.

The active ingredient (moclobemide) is blended with the lactose until a uniform blend is formed. The smaller quantity of corn starch is blended with a suitable quantity of water to form a corn starch paste. This is then mixed with said uniform blend until a uniform wet mass is formed. The remaining corn starch is added to the resulting wet mass and mixed until uniform granules are obtained. The granules are then screened through a suitable milling machine, using a 1/4 inch stainless steel screen. The milled granules are then dried in a suitable drying oven until the desired moisture content is obtained. The dried granules are then milled through a suitable milling machine using 1/4 mesh stainless steel screen. The magnesium stearate is then blended and the resulting mixture is compressed into tablets of desired shape, thickness, hardness and disintegration.

Tablets are coated by standard aqueous or nonaqueous techniques. For example, 2.5 mg of hydroxypropylmethylcellulose can be dissolved in 25 mg of deionized water. An aqueous (10 mg) suspension of 1.88 mg

talco, 0.5 mg of titanium dioxide, 0.1 mg of yellow iron oxide, and 0.02 mg of red iron oxide is stirred into this solution. The coating suspension is sprayed on the tablets and the coated tablets are dried overnight at 45°C.

6.2. EXAMPLE 2

ORAL FORMULATION

Capsules:

10	Formula	Quantity per capsule in mg.		
		<u>A</u>	<u>B</u>	<u>C</u>
	Active ingredient moclobemide	25	50	75
15	Lactose	149.5	124.5	374
	Corn Starch	25	25	50
	Magnesium Stearate	0.5	0.5	1.0
	Compression Weight	200.0	200.0	500.0

20 The active ingredient (moclobemide), lactose, and corn starch are blended until uniform; then the magnesium stearate is blended into the resulting powder. The resulting mixture is encapsulated into suitably sized two-piece hard gelatin capsules.

6.3. EXAMPLE 3
ORAL FORMULATION

Tablets

5	Formula	Quantity per Tablet in mg.		
		<u>A</u>	<u>B</u>	<u>C</u>
	Active ingredient, moclobemide	20	40	100
10	lactose BP	134.5	114.5	309.0
	starch BP	30.0	30.0	60.0
	Pre-gelatinized Maize Starch BP	15.0	15.0	30.0
	magnesium stearate	0.5	0.5	1.0
15	Compression Weight	200.0	200.0	500.0

20 The active ingredient (moclobemide) is sieved through a suitable sieve and blended with lactose, starch, and pre-gelatinized maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using punches.

25 Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit. In particular, single unit dosage forms of moclobemide in 50, 100, 150, and 200 mg are preferred and can be easily manufactured by those of skill in the art. For example, tablets of the following
30 composition, as described in U.S. Patent No. 4,210,754,

incorporated herein in its entirety, may be prepared by methods known to those of skill in the art:

Tablets

5	Formula	Quantity per Tablet in mg.
10	Active ingredient, moclobemide Lactose Maize starch Talc Magnesium stearate Weight per tablet	50.0 95.0 100.0 4.5 0.5 250.0

15 The embodiments of the present invention described above
are intended to be merely exemplary and those skilled in the
art will recognize, or be able to ascertain using no more
than routine experimentation, numerous equivalents to the
specific procedures described herein. All such equivalents
20 are considered to be within the scope of the present
invention and are covered by the following claims.

 The contents of all references described herein are
hereby incorporated by reference. Throughout this
specification and claims, the word "comprise," or variations
25 such as "comprises" or "comprising," will be understood to
imply the inclusion of a stated integer or group of integers
but not the exclusion of any other integer or group of
integers.

Other embodiments are within the following claims.

What is claimed is:

1. A method of treating or preventing low affect disorder in a human, which comprises administering to a human in need of treatment for or prevention of developing malaise and lethargy a therapeutically effective amount of
5 moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.

2. A method of treating or preventing a conduct disturbance or a conduct disorder in a human, which comprises
10 administering to a human in need of treatment for a conduct disturbance or a conduct disorder or prevention of a conduct disturbance or a conduct disorder a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.

3. A method of treating or preventing
15 oppositional defiant disorder in a human, which comprises administering to a human in need of treatment for an oppositional defiant disorder for or prevention of oppositional defiant disorder a therapeutically effective
20 amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.

4. A method of treating or preventing a
25 somatoform disorder in a human, which comprises administering to a human in need of treatment for a somatoform disorder or prevention of somatoform disorder a therapeutically effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.

5. A method of treating or preventing malaise and
30 lethargy in an immunocompromised or immunosuppressed human, which comprises administering to said human a therapeutically

effective amount of moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition.

5 6. A method of treating or preventing a symptom
selected from the group consisting of malaise, lethargy,
hypersomnia, weight gain, obesity, carbohydrate craving,
overeating, leaden paralysis, rejection sensitivity, sexual
inhibition, and a somatised symptom, in a human, either
10 individually or in combination, which comprises administering
to said human who is subclinically depressed or not
clinically depressed, and who is suffering from or who is in
danger of developing said symptom a therapeutically effective
amount of moclobemide, a moclobemide metabolite, a
moclobemide derivative or a moclobemide composition.

15 7. A method of treating partial refractory
atypical depression in a human, which comprises administering
to a partial refractory atypical depressive (PRAD) human a
therapeutically effective amount of moclobemide, a
moclobemide metabolite, a moclobemide derivative or a
20 moclobemide composition.

 8. A method of treating partial refractory
depression in a human, which comprises administering to a
partial refractory depression (PRD) human a therapeutically
25 effective amount of moclobemide, a moclobemide metabolite, a
moclobemide derivative or a moclobemide composition.

 9. The method according to any one of claims 1 to
5, wherein said human is not clinically depressed or is
subclinically depressed.

30 10. The method according to claim 2 or claim 3,
wherein said human is not suffering from Attention
Deficit/Hyperactivity Disorder.

11. The method according to claim 6, wherein the human is suffering from an illness selected from the group consisting of viral infection, rheumatoid arthritis, systemic lupus, post-operative trauma or cancer.

5 12. The method according to claim 6, wherein the somatised symptom is selected from the group consisting of: lack of energy, fatigue, muscular aches, pains, nausea, impaired coordination/balance, paralysis, blindness, deafness, seizures, dissociative symptoms, loss of
10 consciousness and pain during sexual intercourse, menstruation and urination.

13. The method according to claim 6, wherein the sexual inhibition is decreased libido or decreased excitement.

15 14. The method according to claim 6, wherein the sexual inhibition is caused by an SSRI.

20 15. The method according to claim 6, wherein said conduct disturbance is be selected from the group consisting of aggressive conduct; causing or threatening physical harm to humans or animals, non-aggressive conduct that causes property loss or damage, deceitfulness, theft, serious violations of rules, negativistic behavior, defiant behavior, disobedient behavior, and hostile behavior toward authority figures.

25 16. The method according to any one of claims 1-8, wherein the moclobemide derivative is selected from the group consisting of p-iodo-N-(2-morpholinoethyl)-benzamide, p-fluoro-N-(2-morpholinoethyl)-benzamide, p-bromo-N-(2-morpholinoethyl)-benzamide, a pharmaceutically acceptable

salt thereof, or p-chloro-N-(2-morpholinoethyl)-benzamide-N'-oxide.

5 17. The method according to any one of claims 1-8 further comprising treating said human with a second antidepressant.

 18. The method according to any one of claims 1-8 wherein said second antidepressant is a tricyclic antidepressant.

10 19. The method according to claim 18 wherein the tricyclic antidepressant is selected from the group consisting of amitriptyline, clomipramine, doxepin, imipramine, (+)-trimipramine, amoxapine, desipramine, maprotiline, nortriptyline and protryptiline.

15 20. The method according to claim 17 wherein said second antidepressant is selected from the group consisting of (±)-fluoxetine, (+)-fluoxetine, fluvoxamine, paroxetine, sertraline, (±)-venlafaxine, an active optical isomer of (±)-venlafaxine, bupropion, nefazodone, trazodone, phenelzine,
20 tranylcypromine, maprotiline and (-)-selegiline.

 21. The method according to any one of claims 1-8 wherein moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition is administered orally or parentally.

25 22. The method according to claim 20 wherein moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition is administered orally as a tablet or a capsule.

30 23. The method according to any one of claims 1-8 wherein moclobemide, a moclobemide metabolite, a moclobemide

derivative or a moclobemide composition is administered via a transdermal patch.

5 24. The method according to any one of claims 1-8 wherein the amount administered is from about 50 mg to about 1200 mg.

 25. The method according to any one of claims 1-8 wherein the amount administered is from about 150 mg to about 900 mg.

10 26. The method according to any one of claims 1-8 wherein the amount administered is from about 150 mg to about 600 mg.

 27. The method according to any one of claims 1-8 wherein the amount of moclobemide, a moclobemide metabolite, a moclobemide derivative is administered together with a
15 pharmaceutically acceptable carrier.

 28. The method according to any one of claims 1-8 wherein moclobemide is administered as the hydrochloride salt.

20 29. The method according to any one of claims 1-8 wherein moclobemide, a moclobemide metabolite, a moclobemide derivative or a moclobemide composition is administered in a sustained or controlled release formulation.

 30. The method according to any one of claims 1-8 wherein said administration is made one to four times per
25 day.

31. The method according to any one of claims 1-8 wherein said administration continues for a period of at least 4 weeks.

5 32. The method according to any one of claims 1-8 further comprising treating said human with a psychoactive compound.

33. The method according to claim 32 wherein the psychoactive compound is lithium.