

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
29 November 2007 (29.11.2007)

PCT

(10) International Publication Number
WO 2007/137224 A2

(51) International Patent Classification:
A61K 31/519 (2006.01)

(21) International Application Number:
PCT/US2007/069366

(22) International Filing Date: 21 May 2007 (21.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/747,866 22 May 2006 (22.05.2006) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF TREATMENT

(57) Abstract: Combinations and combination therapies for the treatment of insomnia in patients with psychotic disorders or with psychotic features, patients with bipolar depression, and patients with major depression with psychotic features.

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METHOD OF TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of co-pending US Provisional Patent Application No. 60/747,866, filed 22 May 2006, which is hereby incorporated herein.

BACKGROUND OF THE INVENTION

Psychosis is a psychiatric term for symptoms of mental disorders in which rational thought and perception are severely impaired. Such symptoms include, *e.g.*, hallucinations, delusions such as paranoid delusions, personality changes and disorganized thinking. Patients suffering from psychoses often are incapable of recognizing the unusual or even bizarre nature of their behaviors and suffer difficulties with social interaction and impairments in carrying out daily activities.

Psychosis is not a defined disease but, rather, is a collection of symptoms usually associated with psychotic disorders, such as schizophrenia, bipolar disorder, bipolar mania, and severe clinical depression.

In some cases, a patient who is not diagnosed as having a psychotic disorder, may experience psychotic symptoms. For example, patients suffering from depression that is not severe enough to be characterized as a psychotic disorder sometimes nevertheless have mild or infrequent psychotic episodes.

A wide array of drug therapies have been developed to treat psychoses, *e.g.*, schizophrenia, bipolar disorder, and severe clinical depression, and psychotic episodes in patients who are not diagnosed as having a psychotic disorder, *e.g.*, hallucinations or delusions in patients suffering from depression. A common symptom of the disease, and

sometimes side effect of some such drug therapies, is difficulty in sleeping normally, commonly referred to as insomnia.

Melatonin receptor agonists have been shown to have positive effects on sleep disorders including sleeplessness or insomnia. In addition, melatonin agonists such as VALDOXAN agomelatine (N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide), which is disclosed in US 5,225,442, have been shown to be useful in the treatment of depression. See, e.g., Papp et al., Neuropsychopharmacology 2003 Apr; 28(4):694-703.

SUMMARY OF THE INVENTION

This invention relates to treatment of various disorders relating to sleep and psychoses in human patients in need thereof by co-administering an effective amount of an anti-psychotic medication and a melatonin agonist. The invention in preferred embodiments relates to treatment of patients suffering from insomnia and psychotic disorders, bipolar depression, major depression with psychotic features, and insomnia with psychotic features.

DETAILED DESCRIPTION

Anti-psychotics for use in the invention include all drugs and combinations thereof shown to be useful in the lessening of the severity or frequency of psychotic symptoms, such as delusions or hallucinations. These include anti-psychotics having one or more of the following mechanisms of action: Dopamine (D2) antagonists, dual D2 and serotonin (5-HT1A) antagonists, D2 agonists, Dopamine stabilizers, dual-acting D2 antagonists and SSRIs, Serotonin antagonists, dual-acting D2 antagonists and serotonin agonists, Serotonin inverse agonists, Serotonin agonists, Substance P antagonists, Serotonin 5-HT7 antagonists, Nicotinic agonists, Glycine modulators, Glutamate modulators, CCK2 (cholecystokinin neuropeptide 2) antagonists, Neurokinin antagonists, AMPA (alpha-amino-5-methyl-3-

hydroxy-4-isoxazolepropionic acid) receptor agonists, Muscarinic modulators, Sigma antagonist/agonist, Adrenoreceptor antagonists such as but not limited to α -2 adrenoceptor antagonists, Cannabinoid CB1 modulators, Phospholipase inhibitors, Cox-2 inhibitors, imidazoline agonists, dual-acting imidazoline agonists and α 2 adrenoceptor antagonists and combinations of any one or more of the recited classes of anti-psychotics.

These also include anti-psychotics that are in one or more of the following chemical types: Phenothiazines, Thioxanthenes, Dibenzodiazepines, Benzisoxazoles, Butyrophenones, Dihydroindolones, Diphenylbutylpiperidines, Piperazine phenothiazines, Thienobenzodiazepines, Phenylindole derivatives, Benzisothiazolylpiperazines, and Piperidinylbenzisoxazoles.

Typical anti-psychotics for use in the invention include, for example, Chlorpromazine, Thioridazine, Mesoridazine, Fluphenazine, Perphenazine, Trifluoperazine, Thiothixene, Loxapine, Haloperidol, Molindone, Pimozide, Chlorprothixene, Prochlorperazine, and Sulpiride.

Atypical anti-psychotics for use in the invention include, for example, Iloperidone, Clozapine (US 3539573), Risperidone (US4804663), Olanzapine (US5229382), Quetiapine (US4879288), Sertindole (US4710500, US5112838, US5238945), Ziprasidone (US4831031), Aripiprazole, Amisulpride, Ocaperidone, Paliperidone, Bifeprunox, Asenapine, Blonanserin (US5021421), Osanetant, Dexeferoxsan, D-serine, Secretin, ABT-089, ORG-2448, Miraxion, PLO-255, Eplivanserin, Idazoxan, DAB-452, SLV-313, SLV-310, SM-13496, Talnetant, CX-516, DAR-001, abaperidone (US5736588), belaperidone (US 5475105), perospirone (US4745117), tiospirone (US4411901), and zotapine (US 3704245).

Metabolites, prodrugs, stereoisomers, polymorphs, hydrates, solvates, and salts of the above compounds that are directly or indirectly active can of course also be used in the practice of this invention.

Iloperidone (1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl] ethanone) is disclosed in US Patent 5,364,866, which is incorporated herein by reference. Metabolites of Iloperidone, e.g., P88 (also referred to as P-88-8891), are useful in the present invention. See, e.g., WO03020707, which is incorporated herein by reference. In some cases, it may be advantageous to use iloperidone preferentially in patients with certain genotypes as disclosed, e.g., in WO2006039663 and in WO2003054226, which are incorporated herein by reference.

Iloperidone metabolites include:

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-a-methylbenzenemethanol

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxyphenyl]ethanone

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]-2-hydroxyethanone

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-hydroxy- a-methylbenzene methanol

4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxyl-2-hydroxy-5-methoxy-a-methylbenzenemethanol

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2-hydroxy-5-methoxyphenyl]ethanone

1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-2,5-dihydroxyphenyl]ethanone

See, US 5364866, WO93/09276 and WO95/11680, which are incorporated herein by reference.

P88, a preferred metabolite, is 1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanol.

Iloperidone has moderate to high affinity to a broad spectrum of monoamine receptors and acts as an antagonist at selected dopaminergic, serotonergic, and adrenergic receptors. It has high ($K_d < 10$ nM) affinity for 5-HT_{2A}, Ne_{a1}, Ne_{a2c}, D₂, D₃ and 5-HT_{1A} receptors and moderate (K_d 10-100 nM) affinity for other dopaminergic, adrenergic, and serotonergic receptors including 5-HT_{1A}.

Melatonin agonists that are useful in the invention include any drug that agonizes the human MT₂ receptor, or both the MT₁ and MT₂ receptors, and preferably are highly selectively, even over the MT₃ receptor. Examples include: melatonin, (1R-Trans)-N-[[2-(2,3-dihydro-4benzofuranyl)cyclo-propyl]methyl]propanamide (herein referred to as MA-1), N-[1-(2,3-dihydrobenzofuran-4-yl)pyrrolidin-3-yl]-N-ethylurea] (herein referred to as MA-2), ramelteon ((S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno- [5,4-b] furan-8-yl)ethyl]propionamide), GR196429, LY156735 ((R)-N-(2-(6-chloro-5-methoxy-1H-indol-3yl)propyl)acetamide) (US 4997845), Agomelatine (N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide) (US 5225442), 2-Phenylmelatonin, 8-M-PDOT, 2-Iodomelatonin, and 6-Chloromelatonin.

Additional melatonin agonists are those listed in US 20050164987, which is incorporated herein by reference, specifically:

TAK-375 (Kato, K. et al. Int. J. Neuropsychopharmacol. 2000, 3(Suppl. 1): Abst P.03.130; see also abstracts P.03.125 and P.03.127)

CGP 52608 (1-(3-allyl-4-oxothiazolidine-2-ylidene)-4-methylthiosemicarbazone)
(Missbach et al., J. Biol. Chem. 1996, 271, 13515-22)

GR196429 (N-[2-[2,3,7,8-tetrahydro-1H-furo[2,3-g]indol-1-yl]ethyl]acetamide)
(Beresford et al., J. Pharmacol. Exp. Ther. 1998, 285, 1239-1245)

S20242 (N-[2-(7-methoxy naph-1-yl)ethyl]propionamide) (Depres-Brummer et al.,
Eur. J. Pharmacol. 1998, 347, 57-66)

S-23478 (Neuropharmacology July 2000)

S24268 (Naunyn Schmiedebergs Arch. June 2003)

S25150 (Naunyn Schmiedebergs Arch. June 2003)

GW-290569

Luzindole (2-benzyl-N-acetyltryptamine) (US 5093352)

GR135531 (5-methoxycarbonylamino-N-acetyltryptamine) (US 20010047016)

Melatonin Research Compound A

Melatonin Agonist A (IMSWorld R&D Focus August 2002)

Melatonin Analogue B (Pharmaprojects August 1998)

Melatonin Agonist C (Chem. Pharm. Bull. (Tokyo) January 2002) Melatonin Agonist
D (J. Pineal Research November 2000)

Melatonin Agonist E (Chem. Pharm. Bull. (Tokyo) February 2002) Melatonin Agonist
F (Reprod. Nutr. Dev. May 1999)

Melatonin Agonist G (J. Med. Chem. October 1993)

Melatonin Agonist H (Famaco March 2000)

Melatonin Agonist I (J. Med. Chem. March 2000)

Melatonin Analog J (Bioorg. Med. Chem. Lett. March 2003)

Melatonin Analog K (MedAd News September 2001)

Melatonin Analog L

AH-001 (2-acetamido-8-methoxytetralin) (US 5151446)

GG-012 (4-methoxy-2-(methylene propylamide)indan) (Drijfhout et al., Eur. J. Pharmacol. 1999, 382, 157-66)

Enol-3-IPA

ML-23 (N-2,4-dinitrophenyl-5-methoxy-tryptamine) (US 4880826)

SL-18.1616

IP-100-9 (US 5580878)

Sleep Inducing Peptide A

AH-017 (US 5151446)

AH-002 (8-methoxy-2-propionamido-tetralin) (US 5151446)

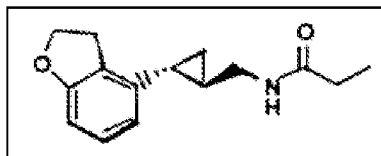
IP-101

Metabolites, prodrugs, stereoisomers, polymorphs, hydrates, solvates, and salts of the above compounds that are directly or indirectly active can of course also be used in the practice of this invention.

MA-1 is an experimental melatonin agonist that is disclosed in US 5,856,529, which is incorporated herein by reference. MA-2 is disclosed in US 6,211,225, which is incorporated herein by reference.

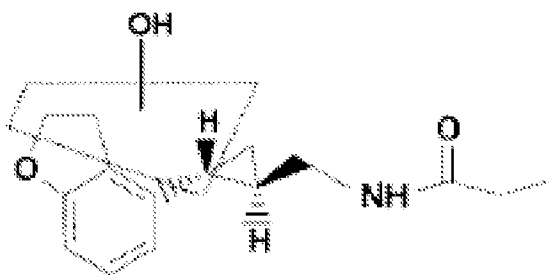
MA-1 is a white to off-white powder with a melting point of about 78°C (DSC) and has the structure illustrated in Formula 1.

Formula 1: MA-1 Chemical Structure

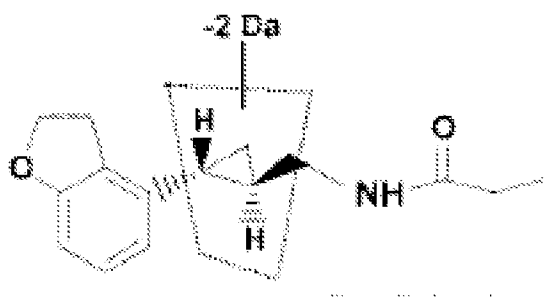


MA-1 is very soluble or freely soluble in 95% ethanol, methanol, acetonitrile, ethyl acetate, isopropanol, polyethylene glycols (PEG-300 and PEG-400), and only slightly soluble in water. The native pH of a saturated solution of MA-1 in water is 8.5 and its aqueous solubility is practically unaffected by pH.

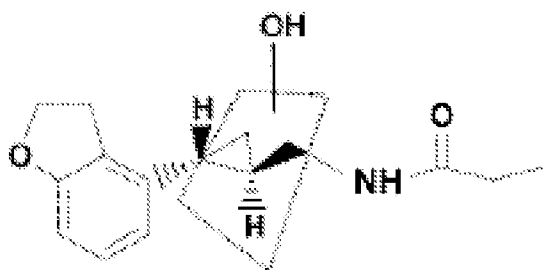
Metabolites of MA-1 include, for example, those described in “Preclinical Pharmacokinetics and Metabolism of BMS-214778, a Novel Melatonin Receptor Agonist” by Vachharajani et al., *J. Pharmaceutical Sci.*, 92(4):760-772, which is hereby incorporated herein by reference. More specifically, these metabolites include hydroxylated and dehydrogenated derivatives of MA-1 as well as glucuronide and diol derivatives of MA-1. The structures of eight such metabolites have Formulae 2-9.



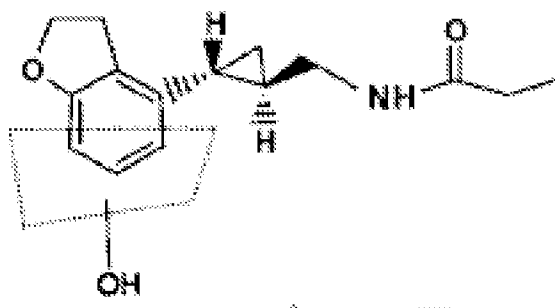
Formula 2 – Hydroxylated MA-1 metabolite 1



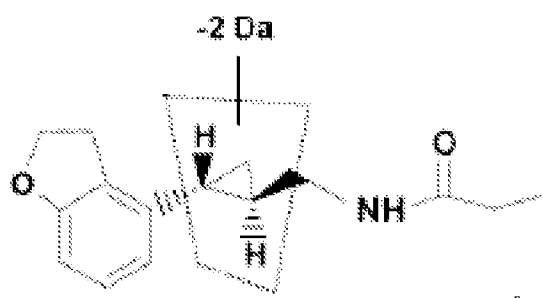
Formula 3 – Dehydrogenated MA-1 metabolite 2



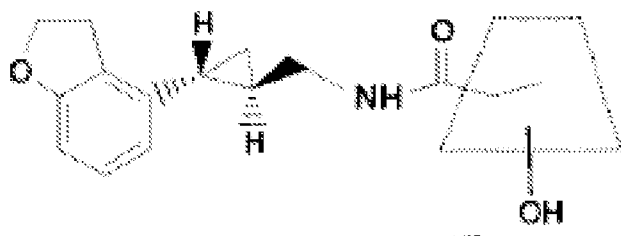
Formula 4 – Hydroxylated MA-1 metabolite 3



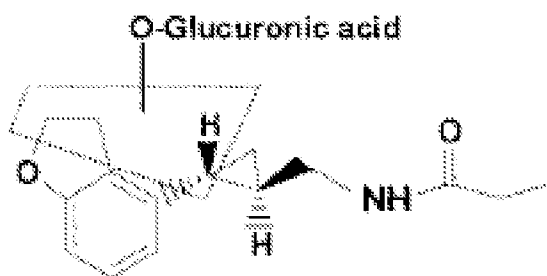
Formula 5 – Hydroxylated MA-1 metabolite 4



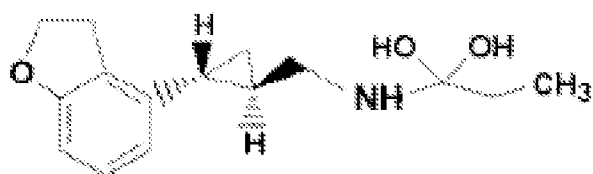
Formula 6 – Dehydrogenated MA-1 metabolite 5



Formula 7 – Hydroxylated MA-1 metabolite 6



Formula 8 – Glucuronic MA-1 metabolite



Formula 9 – Diol MA-1 metabolite

Melatonin agonists are useful in treating insomnia, i.e., difficulty falling asleep, frequent wakings, poor sleep quality, or waking before an adequate period of sleep. Insomnia is a problem encountered by certain patients suffering from psychotic disorders, including but not limited to bipolar disorders, or suffering from psychotic features, i.e., symptoms of psychotic disorders, including patient receiving anti-psychotic drug therapy.

Thus, the invention is useful in treating patients, e.g., human beings, undergoing anti-psychotic drug therapy who suffer from or who are at risk of suffering from difficulty in sleeping normally, i.e., insomnia, either due to the disease itself or while undergoing anti-

psychotic drug therapy. It is also useful in treating patients suffering from bipolar disorder, especially bipolar depression, independently of whether or not the patient is suffering from insomnia. It is also useful in treating patients who are suffering from depression, including but not limited to major depression, and who experience psychotic episodes, i.e., psychotic features, but whose psychotic episodes are not severe enough or frequent enough to warrant a diagnosis with a psychotic disorder, independently of whether or not the patient is suffering from insomnia. The invention is also useful in treating insomnia in patients suffering from insomnia with psychotic features. If a patient suffering bipolar disorder or psychotic episodes not associated with a psychotic disorder is also suffering from insomnia associated with anti-psychotic drug therapy, then the invention will be useful also to treat the insomnia in which case the anti-psychotic drug therapy may be replaced with a combined therapy of an anti-psychotic plus a melatonin agonist, taken together in the same dosage form or taken separately but concomitantly.

In accordance with this invention, patients are treated with effective amounts, i.e., amounts that reduce the severity or frequency of psychotic symptoms or depression, or, in the case of patients who suffer from or at risk of suffering from insomnia, that aid the patient in sleeping restfully and normally. By "treatment" is meant treatment or prevention, e.g., treatment or prevention of psychotic features, depression, or insomnia.

The two agents can be administered more or less simultaneously, i.e., concomitantly (e.g., within about 0 to about 5 minutes of each other, preferably within about a minute apart), or they can be administered at different times. For example, in one aspect, the invention is a pharmaceutical composition comprising both the anti-psychotic agent and the melatonin agonist. This embodiment, for example, comprises a pill or capsule having both active pharmaceutical ingredients either admixed together or having each active pharmaceutical ingredient in a discrete portion of the pill or capsule.

For example, the compositions can be formulated in a unit dosage form, each dosage containing both active ingredients. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired prophylactic or therapeutic effect over the course of a treatment period, in association with the required pharmaceutical carrier. So, for example, an adult patient suffering a depressive disorder could be prescribed 1-4 tablets, such as illustrated below, to be taken once, twice or three times daily and might expect improvement in his or her condition within about one to about 12 weeks.

In another embodiment, the invention comprises administering the anti-psychotic and the melatonin agonist at different time intervals, such that an effective amount of each is maintained in the patient's bloodstream in the appropriate amounts at the appropriate times. In a related embodiment, this invention is a kit comprising pharmaceutical dosage units of the anti-psychotic and distinct pharmaceutical dosage units of the melatonin agonist, allowing the anti-psychotic to be taken at different time intervals than the melatonin agonist. In a related embodiment, the kit comprises pharmaceutical dosage units of one agent alone and other pharmaceutical dosage units comprising both agents. In this way, for example, the anti-psychotic could be taken alone during the day and with the melatonin agonist in the evening.

The agents can be administered in any pharmaceutically acceptable way, e.g., oral, parenteral, nasal, buccal, transdermal, sublingual, intramuscular, intravenous, rectal, vaginal, etc. For example, US 20030091645 discloses a depot formulation of iloperidone and WO2004006886 discloses a formulation of iloperidone in crystalline form. Both are fully incorporated herein by reference. Methods for the administration of iloperidone directed toward, *inter alia*, eliminating or minimizing the prolongation of a corrected electrocardiographic QT (QTc) interval associated with increased concentrations of

iloperidone or iloperidone derivatives are described in U.S. Provisional Application No. 60/614,798, filed September 30, 2004, which is incorporated herein by reference.

In accordance with this invention, the anti-psychotic and the melatonin agonist can also be administered in combination with other agents, e.g., anti-depressants.

The amount of each active pharmaceutical ingredient will vary depending upon the condition and the individual being treated. Generally, an effective amount of each is expected to be approximately the same as, or less than, an effective amount of either alone. For example, each pharmaceutically active ingredient can be administered in doses that are about 20% to about 80% of the dose in which each ingredient would be administered alone. This is especially so in cases in which the melatonin agonist is being administered to alleviate insomnia. In cases in which the melatonin agonist is being administered to treat the underlying disorder, e.g., depression, the amount of the antipsychotic and of the melatonin agonist may be reduced relative to the amount in which either would be administered alone.

In general, in the case of an iloperidone-MA-1 combination, the dose of iloperidone will be in the range of about 2 to about 24 mg/day, preferably about 16 to about 24 mg/day, and the dose of MA-1 will be in the range of about 10 to about 150 mg/day, preferably about 10 to about 100 mg/day. Treatment would be expected to be maintained for as little as one month but can be maintained for longer period, e.g., about 6 to about 24 months, or, in some cases, even longer.

The route of administration is usually oral although other routes of administration, e.g., parenteral, intravenous, intramuscular, buccal, lozenge, transdermal, transmucosal, etc., can be used. Controlled release forms, e.g., sustained, pulsatile, or delayed, including depot forms such as are disclosed in WO2003037337 or WO2004006886, can also be used.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 100 mg of each active ingredient. The term "unit dosage

form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired prophylactic or therapeutic effect over the course of a treatment period, in association with the required pharmaceutical carrier. So, for example, an adult patient suffering a depressive disorder could be prescribed 1-4 tablets, each having about 5 to about 100 mg of MA-1 and about 2 to about 24 mg of iloperidone, to be taken once, twice or three times daily and might expect improvement in his or her condition within about one to about 12 weeks.

In one embodiment of the invention, iloperidone, or the metabolite known as P-88, is co-administered with MA-1 or with MA-2. In accordance with this embodiment, for example, the following illustrative dosage units are contemplated, among others:

1. A tablet, capsule or solution comprising about 2 mg to about 24 mg, preferably about 16 mg to about 24 mg, of iloperidone and about 1 mg to about 500 mg, preferably about 10 mg to about 100 mg, of MA-1;
2. A tablet, capsule or solution comprising about 2 mg to about 24 mg, preferably about 16 mg to about 24 mg, of iloperidone and about 1 mg to about 500 mg, preferably about 10 mg to about 100 mg, of MA-2;
3. A tablet, capsule or solution comprising about 0.5 mg to about 24 mg, preferably about 12 mg to about 16 mg, of P88 and about 1 mg to about 500 mg, preferably about 10 mg to about 100 mg, of MA-1;
4. A tablet, capsule or solution comprising about 0.5 mg to about 24 mg, preferably about 12 mg to about 16 mg, of P88 and about 1 mg to about 500 mg, preferably about 10 mg to about 100 mg, of MA-2.

Controlled release forms, e.g., prolonged (including delayed) or pulsatile release forms, in which the anti-psychotic and the melatonin agonist are administered at the same or

different times and at the same or different rates, are also contemplated by this invention. For example, the anti-psychotic could be released shortly after ingestion, as in an immediate release formulation, while the melatonin agonist could be released over a period of up to about 8 hours, including, e.g., pulsatile releases at 0 and 2, 4, or 6 hours post-administration, or at two or more other prescribed time intervals post-administration.

For example, a controlled release formulation of the invention includes one in which: (i) iloperidone or P-88 dissolves at a rate of between about 3% and about 15% per hour, more preferably between about 4% and about 13% per hour, and most preferably between about 5% and about 7% per hour in a standard dissolution assay (e.g., an aqueous solvent at (1) pH 4.5, (2) pH 6.8 or (3) 0.1N HCl, under ambient conditions), thereby providing a slow, substantially constant dosage of iloperidone or an iloperidone derivative over a period of between about 16 and about 24 hours and (ii) MA-1 or MA-2 is released over a prolonged period of time to provide a substantially steady-state plasma concentration over a period of about 6 to about 10 hours, preferably over a period of about 8 hours. In another embodiment, MA-1 or MA-2 are released in a pulsatile profile, e.g., to release approximately 25% of drug shortly following administration and approximately 25% of drug at more or less 2 hours, 4 hours, and 6 hours post-administration, or to release approximately 50% of drug shortly following administration and approximately 25% of drug at more or less 2 hours and 4 hours post-administration or to release approximately 50% of drug shortly following administration and approximately 25% of drug at more or less 4 hours and 6 hours post-administration.

The invention therefore encompasses, for example, co-administration of an injectable form of an anti-psychotic, such as an injectable depot form of iloperidone or P-88 and an oral form of a melatonin agonist, such as an immediate release or controlled release tablet or capsule comprising MA-1 or MA-2.

While this invention has been described in conjunction with the specific embodiments outlined above, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art or are otherwise intended to be embraced. Accordingly, the embodiments of the invention as set forth above are intended to be illustrative, not limiting. Various changes may be made without departing from the spirit and scope of the invention as defined in the following claims. All patents, patent application, scientific articles and other published documents cited herein are hereby incorporated in their entirety for the substance of their disclosures.

CLAIMS

What is claimed is:

1. A method of treating:
insomnia in a patient suffering therefrom and from a psychotic disorder, or
bipolar depression, or
depression with psychotic features, or
insomnia with psychotic features, or
a combination of the above,
comprising administering to the patient an effective amount of an anti-psychotic and an effective amount of a melatonin agonist.
2. The method of claim 1, wherein the anti-psychotic is selected from the group consisting of: Dopamine (D2) antagonists, dual D2 and serotonin (5-HT1A) antagonists, D2 agonists, Dopamine stabilizers, dual-acting D2 antagonists and SSRIs, Serotonin antagonists, dual-acting D2 antagonists and serotonin agonists, Serotonin inverse agonists, Serotonin agonists, Substance P antagonists, Serotonin 5-HT7 antagonists, Nicotinic agonists, Glycine modulators, Glutamate modulators, CCK2 (cholecystokinin neuropeptide 2) antagonists, Neurokinin antagonists, AMPA (alpha-amino-5-methyl-3-hydroxy-4-isoxazolepropionic acid) receptor agonists, Muscarinic modulators, Sigma antagonist/agonist, Adrenoreceptor antagonists such as but not limited to alpha-2 adrenoceptor antagonists, Cannabinoid CB1 modulators, Phospholipase inhibitors, Cox-2 inhibitors, imidazoline agonists, dual-acting imidazoline agonists and alpha a2 adrenoreceptor antagonists and combinations of any one or more of the recited classes of anti-psychotics.

3. The method of claim 1, wherein the anti-psychotic is selected from the group consisting of Phenothiazines, Thioxanthenes, Dibenzodiazepines, Benzisoxazoles, Butyrophenones, Dihydroindolones, Diphenylbutylpiperidines, Piperazine phenothiazines, Thienobenzodiazepines, Phenylindole derivatives, Benzisothiazolylpiperazines, and Piperidinylbenzisoxazoles.
4. The method of claim 1, wherein the anti-psychotic is a typical anti-psychotic.
5. The method of claim 4, wherein the anti-psychotic is selected from the group consisting of Chlorpromazine, Thioridazine, Mesoridazine, Fluphenazine, Perphenazine, Trifluoperazine, Thiothixene, Loxapine, Haloperidol, Molindone, Pimozide, Chlorprothixene, Prochlorperazine, and Sulpiride and active metabolites of the preceding.
6. The method of claim 1, wherein the anti-psychotic is an atypical anti-psychotic.
7. The method of claim 6, wherein the antipsychotic is selected from the group consisting of Iloperidone, P-88, Clozapine, Risperidone, Olanzapine, Quetiapine, Sertindole, Ziprasidone, Aripiprazole, Amisulpride, Ocaperidone, Paliperidone, Bifeprunox, Asenapine, Blonanserine, Osanetant, Dexeferoxsan, D-serine, Secretin, ABT-089, ORG-2448, Miraxion, PLO-255, Eplivanserin, Idazoxan, DAB-452, SLV-313, SLV-310, SM-13496, Talnetant, CX-516, DAR-001, abaperidone, belaperidone, perospirone, tiospirone, and zotapine and active metabolites of the preceding.

8. The method of any of claims 1-7, wherein the melatonin agonist is selected from the group consisting of melatonin, MA-1, MA-2, LY-156735, Agomelatine, Ramelteon, 2-Phenylmelatonin, 8-M-PDOT, 2-Iodomelatonin, and 6-Chloromelatonin.
9. The method of any of claims 1-8, wherein the antipsychotic and the melatonin agonist are administered by the same or a different route selected from parenteral, intravenous, intramuscular, buccal, lozenge, transdermal, and transmucosal.
10. A pharmaceutical composition for the treatment of a psychotic disorder comprising an anti-psychotic and a melatonin agonist.
11. The pharmaceutical composition of claim 10, which is in unit dose form, which dose form comprises an effective amount of the antipsychotic and of the melatonin agonist when administered as a single dose or when administered in multiple doses.
12. A kit comprising one or more pharmaceutical dosage units of an anti-psychotic and one ore more pharmaceutical dosage units of a melatonin agonist, wherein either or both of the anti-psychotic dosage unit and the melatonin agonist unit can also comprise, respectively, a melatonin agonist or an anti-psychotic, and optionally, one or more additional pharmaceutically active ingredients.