Title: COMBINATION OF ATYPICAL ANTIPSYCHOTIC AND SEROTONIN REUPTAKE INHIBITOR FOR THE TREATMENT OF CHRONIC PAIN

Abstract: This invention relates to the use of the combined action of an atypical antipsychotic and a serotonin reuptake inhibitor for the treatment of chronic pain.
COMBINATION OF ATYPICAL ANTIPSYCHOTIC AND SEROTONIN REUPTAKE INHIBITOR FOR THE TREATMENT OF CHRONIC PAIN

TECHNICAL FIELD

This invention relates to the use of the combined action of an atypical antipsychotic and a serotonin reuptake inhibitor for the treatment of chronic pain.

BACKGROUND ART

Chronic pain conditions are debilitating diseases affecting at least 5-10 percent of the population at some point in their lives. For the patient suffering from a chronic pain disease, disturbance of, or disruption to their daily life is almost inevitable with a greatly increased risk of developing comorbid psychiatric illness such as depression.

Available drug treatments for chronic pain conditions are subject to various limitations. Non-steroidal anti-inflammatory drugs such as ibuprofen and aspirin and opiates such as morphine, can be effective at treating chronic pain with a predominant inflammatory component, but are much less effective against chronic pain disorders associated with nerve damage (neuropathic pain). In addition the pain relief that can be obtained with opiates is often associated with tolerance and dependence, with increased risk of developing undesirable side effects.

Thus, although some chronic pain conditions are relatively well treated at present, significant unmet needs remain. There is a continued requirement to develop more selective and effective therapies that are better tolerated, for the treatment of patients with chronic pain conditions.

WO 99/61027 and Zhang, W. et al in Neuropsychopharmacology, 23(3), 250-262, 2000 describe the use of an atypical antipsychotic, such as olanzapine, and a serotonin reuptake inhibitor, such as fluoxetine, for the treatment of treatment-resistant depression.

DETAILED DISCLOSURE OF THE INVENTION

According to the invention it has now been found that the action of an atypical antipsychotic in combination with a serotonin reuptake inhibitor can be used for the treatment of chronic pain.

Accordingly, in its first aspect, the invention provides the use of an effective amount of an atypical antipsychotic in combination with an effective amount of a
serotonin reuptake inhibitor for the manufacture of a medicament for the treatment, prevention or alleviation of chronic pain.

In another aspect, the invention provides a method of treatment, prevention or alleviation of chronic pain in a subject, which method comprises administering to said subject a therapeutically effective amount of an atypical antipsychotic in combination with a therapeutically effective amount of a serotonin reuptake inhibitor.

In one embodiment, the atypical antipsychotic is selected from the group consisting of olanzapine, clozapine, risperidone, serindole, quetiapine, ziprasidone and pharmaceutically acceptable addition salts thereof. In a special embodiment, the atypical antipsychotic is olanzapine or a pharmaceutically acceptable salt addition thereof. In a further special embodiment, the atypical antipsychotic is risperidone or a pharmaceutically acceptable salt addition thereof.

In a further embodiment, the serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran, duloxetine and pharmaceutically acceptable addition salts thereof. In a special embodiment, the serotonin reuptake inhibitor is fluoxetine or a pharmaceutically acceptable addition salt thereof.

In a special embodiment, the atypical antipsychotic is olanzapine and the serotonin reuptake inhibitor is fluoxetine.

In a further special embodiment, the atypical antipsychotic is olanzapine and the serotonin reuptake inhibitor is venlafaxine.

In a still further special embodiment, the atypical antipsychotic is olanzapine and the serotonin reuptake inhibitor is citalopram.

In a further special embodiment, the atypical antipsychotic is olanzapine and the serotonin reuptake inhibitor is fluvoxamine.

In a still further special embodiment, the atypical antipsychotic is olanzapine and the serotonin reuptake inhibitor is paroxetine.

In a further special embodiment, the atypical antipsychotic is olanzapine and the serotonin reuptake inhibitor is sertraline.

In a still further special embodiment, the atypical antipsychotic is olanzapine and the serotonin reuptake inhibitor is milnacipran.

In a further special embodiment, the atypical antipsychotic is olanzapine and the serotonin reuptake inhibitor is duloxetine.

In a still further special embodiment, the atypical antipsychotic is clozapine and the serotonin reuptake inhibitor is fluoxetine.

In a further special embodiment, the atypical antipsychotic is risperidone and the serotonin reuptake inhibitor is fluoxetine.
In a still further special embodiment, the atypical antipsychotic is sertindole and the serotonin reuptake inhibitor is fluoxetine.

In a further special embodiment, the atypical antipsychotic is quetiapine and the serotonin reuptake inhibitor is fluoxetine.

In a still further special embodiment, the atypical antipsychotic is ziprasidone and the serotonin reuptake inhibitor is fluoxetine.

In a further embodiment, the chronic pain is inflammatory pain, neuropathic pain, fibromyalgia, chronic fatigue syndrome, tension-type headache or any pain arising as a consequence of or associated with depressive illness.

In a special embodiment, the chronic pain is an inflammatory pain. In a further embodiment, the chronic pain is a neuropathic pain. In a still further embodiment, the chronic pain is fibromyalgia. In a further embodiment, the chronic pain condition is chronic fatigue syndrome. In a still further embodiment, the chronic pain is chronic tension-type headache. In a further embodiment, the chronic pain is any pain arising as a consequence of or associated with depressive illness.

The subject to be treated according to this invention is a living body, preferably a mammal, most preferably a human, in need for such treatment.

**Atypical antipsychotics**

The essential feature of an atypical antipsychotic is less acute extrapyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Clozapine, the prototypical atypical antipsychotic, differs from the typical antipsychotics with the following characteristics:

1. greater efficacy in the treatment of overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics; 2. greater efficacy in the treatment of negative symptoms of schizophrenia; and 3. less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy (Beasley, et al., Neuropsychopharmacology, 14(2), 111-123, 1996). Atypical antipsychotics include, but are not limited to the following compounds:

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in US patent 5,229,382. A special form of olanzapine is the “Form II” as described in WO 99/61027 is preferred. However, the term “olanzapine” as used herein embraces all solvate and polymorphic forms, unless specifically indicated.

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]-diazepine, is described in US patent 3,539,573.
Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one, is described in US patent 4,804,663.

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in US patent 4,710,500.

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, is described in US patent 4,879,288. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt.

Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in US patents 4,831,031 and 5,312,925. Included are also any pharmaceutically acceptable salt or the free base, and any racemate or enantiomer of the above compounds.

The above examples of atypical antipsychotics are not intended to be in any way limiting to the scope of the invention as claimed.

**Serotonin reuptake inhibitors**

The potential of a given substance to act as a serotonin reuptake inhibitor may be determined using standard *in vitro* binding assays and/or standard *in vivo* functionality tests. Serotonin reuptake inhibitors include, but are not limited to:

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. US patent 4,314,081 is an early reference on the compound. The separation of the R and S enantiomers of fluoxetine is described by Robertson et al. in J. Med. Chem, 31, 1412, 1988.

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It is described in US patent 4,956,388.

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor or serotonin and noradrenaline reuptake is described in US patent 4,761,501. Venlafaxine is identified as compound A in that patent.

Milnacipran, N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide, is described in US patent 4,478,836 (example 4).

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in US patent 4,136,193. The S-enantiomer of citalopram, escitalopram, is described in US patent 4,943,590.

Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone O-(2-aminoethyl)oxime, is described in US patent 4,085,225.
Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yl)oxy]methyl]-4-(4-
fluorophenyl)piperidine is described in US patents 3,912,743 and 4,007,196.
Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-
naphthylamine hydrochloride is disclosed in US patent 4,536,518.

Included are also any pharmaceutically acceptable salt or the free base,
and any racemate or enantiomer of the above compounds.

The above examples of serotonin reuptake inhibitors are not intended to be
in any way limiting to the scope of the invention as claimed.

Pharmaceutically Acceptable Salts

The compounds for use according to the invention may be provided in any
form suitable for the intended administration. Suitable forms include pharmaceutically
(i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical
compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without
limitation, the non-toxic inorganic and organic acid addition salts such as the
hydrochloride derived from hydrochloric acid, the hydrobromide derived from
hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from
perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from
sulphuric acid, the formate derived from formic acid, the acetate derived from acetic
acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid,
the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from
benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric
acid, the embonate derived from embonic acid, the enantate derived from enanthic
acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic
acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the
maleate derived from maleic acid, the malonate derived from malonic acid, the
mandelate derived from mandelic acid, the methanesulphonate derived from methane
sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic
acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid,
the sorbate derived from sorbic acid, the stearate derived from stearic acid, the
succinate derived from succinic acid, the tartrate derived from tartaric acid, the
toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts
may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered
pharmaceutically acceptable, may be useful in the preparation of salts useful as
intermediates in obtaining a chemical compound of the invention and its
pharmaceutically acceptable acid addition salt.
Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts (aza-onium salts). Preferred aza-onium salts include the alkyl-onium salts, in particular the methyl- and the ethyl-onium salts; the cycloalkyl-onium salts, in particular the cyclopropyl-onium salts; and the cycloalkylalkyl-onium salts, in particular the cyclopropyl-methyl-onium salts.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvents such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

**Chronic pain conditions**

In the context of the present invention, the term "chronic pain" includes inflammatory pain, neuropathic pain, fibromyalgia, chronic fatigue syndrome, chronic tension-type headache, and any pain arising as a consequence of or associated with depressive illness.

Inflammatory pain includes without limitation, osteoarthritis, rheumatoid arthritis, back pain, cancer pain, irritable bowel pain, post-operative pain, pain associated with viral infection or diseases with a recognised peripheral or central inflammatory component.

Neuropathic pain includes without limitation, pain arising from any disease state causing damage to the peripheral or central nervous systems, back pain, cancer pain, chemotherapy induced neuropathy, irritable bowel pain, post-stroke pain, post-operative pain, sympathetically-maintained pain, phantom-limb pain, pain associated with viral infection such as postherpetic neuralgia, trigeminal neuralgia, dental pain, myofacial pain, diabetic neuropathy, pain associated with autoimmune disease such as HIV infection and multiple sclerosis, phantom-limb pain, arthritis, or drug-induced neuropathy.

**Pharmaceutical Compositions**

While the active compounds for use according to the invention in therapy may be administered in the form of the raw chemical compounds, it is preferred to introduce the active ingredient, optionally in the form of physiologically acceptable
salts, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

The active compounds for use according to the invention may be administered separately or in combination. Thus the pharmaceutical compositions for use according to the invention may comprise the active compounds for use separately or in combination.

In one embodiment, the invention provides pharmaceutical compositions comprising the active compounds of the invention, or pharmaceutically acceptable salts or derivative thereof, together with one or more pharmaceutically acceptable carriers, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The chemical compounds for use according to the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound for use according to the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.
For preparing pharmaceutical compositions from a chemical compound for use according to the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term “preparation” is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compound for use according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or
emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the chemical compound for use according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be conveniently also contain of a metered valve.
Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington’s Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.01 to about 500 mg of each of the active ingredients per individual dose, preferably of from about 0.1 to about 100 mg, are suitable for therapeutic treatments.

**Methods of Therapy**

In another aspect the invention provides a method of treatment, prevention or alleviation of chronic pain in a subject, which method comprises administering to said subject a therapeutically effective amount of an atypical antipsychotic in combination with a therapeutically effective amount of a serotonin reuptake inhibitor.
The active ingredients may be administered separately or in combination in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 \( \mu \text{g/kg} \) i.v. and 1 \( \mu \text{g/kg} \) p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 \( \mu \text{g/kg} \) to about 10 mg/kg/day i.v., and from about 1 \( \mu \text{g/kg} \) to about 100 mg/kg/day p.o.

Any possible combination of two or more of the embodiments described herein is comprised within the scope of the present invention.
CLAIMS

1. The use of an effective amount of an atypical antipsychotic in combination with an effective amount of a serotonin reuptake inhibitor for the manufacture of a medicament for the treatment, prevention or alleviation of chronic pain.

2. The use according to claim 1, wherein the atypical antipsychotic is selected from the group consisting of olanzapine, clozapine, risperidone, serindole, quetiapine, ziprasidone and pharmaceutically acceptable addition salts thereof.

3. The use according to claims 1, wherein the atypical antipsychotic is olanzapine or a pharmaceutically acceptable salt addition thereof.

4. The use according to any one of claims 1-3, wherein the serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran, duloxetine and pharmaceutically acceptable addition salts thereof.

5. The use according to any one of claims 1-3, wherein the serotonin reuptake inhibitor is fluoxetine or a pharmaceutically acceptable addition salt thereof.

6. The use according to any one of claims 1-5, wherein the chronic pain is inflammatory pain, neuropathic pain, fibromyalgia, chronic fatigue syndrome, tension-type headache or any pain arising as a consequence of or associated with depressive illness.

7. A method of treatment, prevention or alleviation of chronic pain in a subject, which method comprises administering to said subject a therapeutically effective amount of an atypical antipsychotic in combination with a therapeutically effective amount of a serotonin reuptake inhibitor.