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(54) Title: METHOD FOR THE TREATMENT OF DEPRESSION

(57) Abstract: The present invention is directed to a method for the treatment of depression, for example, treatment of resistant depression; wherein the treatment regimen is adjusted depending on the patient's genotype at single nucleotide polymorphism (SNP) rs4306882. Specifically, the method comprising determining the presence of a G or T allele at rs4306882, and administering a dosing regimen of ketamine or esketamine, wherein the dosing regimen is adjusted to provide a higher dose and/or greater frequency of the ketamine or esketamine to those patients with the G allele (rather than T allele) at the polymorphic site of rs4306882. Further disclosed is a method for predicting whether a patient suffering from depression is genetically predisposed to poorly respond to antidepressants which block the reuptake of monoamine neurotransmitters, comprising genotyping said patient to determine the patient's genotype at SNP rs4306882.

METHOD FOR THE TREATMENT OF DEPRESSION

Cross Reference to Related Applications

This application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Application 62/036,896, filed August 13, 2014, the disclosure of which is herein incorporated by reference in its entirety.

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 11, 2015, is named "PRD3345WOPCT_SeqListing.txt" and is 56 kilobytes in size.

Field of the Invention

The present invention is directed to method for the treatment of depression, for example, treatment resistant depression; wherein the treatment regimen is adjusted depending on the patient's genotype at SNP rs4306882.

Background of the Invention

Major Depressive Disorder is defined as the presence of one of more major depressive episodes that are not better accounted for psychotic disorder or bipolar disorder. A major depressive episode is characterized by meeting five or more of the following criteria during the same 2 week period which represent a change in functioning and include at least depressed/ sad mood or loss of interest and pleasure, indifference or apathy, or irritability and is usually associated with a change in a number of neurovegetative functions, including sleep patterns, appetite and body weight, motor agitation or retardation, fatigue, impairment in concentration and decision making, feelings of shame or guilt, and thoughts of death or dying (Harrison's Principles of Internal Medicine, 2000). Symptoms of a depressive episode include depressed mood; markedly diminished interest or pleasure in all, or almost all, activities most of the day; weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day; insomnia or hypersomnia nearly every day; psychomotor agitation or retardation nearly every day; fatigue or loss of energy nearly every day; feelings of worthlessness or excessive or inappropriate guilt nearly every day; diminished ability to think or concentrate, or indecisiveness, nearly every

day; recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. Further, the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. (*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, American Psychiatric Association, 1994)

Current treatment options for unipolar depression include monotherapy or combination therapy with various classes of drugs including mono-amine oxidase inhibitors (MAOI), tricyclic antidepressants (TCA), serotonin specific reuptake inhibitors (SSRI), serotonin noradrenergic reuptake inhibitors (SNRI), , noradrenaline reuptake inhibitor (NRI), "natural products" (such as Kava-Kava, St. John's Wort), dietary supplement (such as s-adenosylmethionine) and others. More specifically, drugs used in the treatment of depression include, but are not limited to imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, maprotiline, amoxapine, trazodone, bupropion, chlomipramine, fluoxetine, citalopram, sertraline, paroxetine, tianeptine, nefazadone, venlafaxine, desvenlafaxine, duloxetine, reboxetine, mirtazapine, phenelzine, tranylcypromine, and / or moclobemide. Several of these agents including, but not limited to, serotonin reuptake inhibitors are also used when depression and anxiety co-exist, such as in anxious depression.

In the clinic, 40-50% of depressed patients who are initially prescribed antidepressant therapy do not experience a timely remission of depression symptoms. This group typifies level 1 treatment-resistant depression, that is, a failure to demonstrate an "adequate" response to an "adequate" treatment trial (that is, sufficient intensity of treatment for sufficient duration). Moreover, about approximately 30% of depressed patients remain partially or totally treatment-resistant to at least two antidepressant treatments including combination treatments. Increasingly, treatment of treatment-resistant depression includes augmentation strategies including treatment with pharmacological agents such as, antipsychotics (such as quetiapine, aripiprazole, olanzapine, risperidone, and the like), lithium, carbamazepine, and triiodothyronine, and the like; adjunctive electroconvulsive therapy; adjunctive transcranial magnetic stimulation; etc.

Suicide, also known as completed suicide, is the "act of taking one's own life". Attempted suicide or non-fatal suicidal behavior is self-injury with the desire to end one's life that does not result in death. Suicidal ideations are thoughts of ending one's life but not taking any active efforts to do so.

Suicidal ideation is the medical term for thoughts about or an unusual preoccupation with suicide. The range of suicidal ideation varies greatly from fleeting to detailed planning, role playing, and unsuccessful attempts, which may be deliberately constructed to fail or be discovered, or may be fully intended to result in death. Although most people who undergo suicidal ideation do not go on to make suicide attempts, a significant proportion do. Suicidal ideation is generally associated with depression; however, it seems to have associations with many other psychiatric disorders, life events, and family events, all of which may increase the risk of suicidal ideation.

Suicidal ideation —may include, for example, suicidal thoughts — but may also include other related signs and symptoms. Some symptoms or co-morbid conditions may include unintentional weight loss, feeling helpless, feeling alone, excessive fatigue, low self-esteem, presence of consistent mania, excessively talkative, intent on previously dormant goals, feel like one's mind is racing. The onset of symptoms like these with an inability to get rid of or cope with their effects, a possible form of psychological inflexibility, is one possible trait associated with suicidal ideation. They may also cause psychological distress, which is another symptom associated with suicidal ideation. Symptoms like these related with psychological inflexibility, recurring patterns, or psychological distress may in some cases lead to the onset of suicidal ideation. Other possible symptoms and warning signs include: hopelessness, anhedonia, insomia, depression, severe anxiety, angst, impaired concentration, psychomotor agitation, panic attack and severe remorse.

Scales used in the evaluation of suicidal ideation include Beck Scale for Suicide Ideation (BSS), Columbia Suicide Severity Rating Scale and The Kessler Psychological Distress Scale (K10, which test does not measure suicidal ideation directly, but there may be value in its administration as an early identifier of suicidal ideation. High scores of psychological distress are also, in some cases associated with suicidal ideation.

There are also several psychiatric disorders that appear to be comorbid with suicidal ideation or considerably increase the risk of suicidal ideation. The following disorders have been shown to be the strongest predictors of suicidal ideation /disorders in which risk is increased to the greatest extent: major depressive disorder (MDD), dysthymia, bipolar disorder, post traumatic stress disorder (PTSD), personality disorders, psychosis (anxiety or detachment from reality), paranoia, schizophrenia and drug abuse.

The main treatments for suicidality and / or suicidal ideation include: hospitalization, outpatient treatment, and medication. Hospitalization allows the patient to be in a secure, supervised environment to prevent their suicidal ideation from turning into suicide attempts. In most cases, individuals have the freedom to choose which treatment they see fit for themselves. However, there are several circumstances in which individuals can be hospitalized involuntarily, including circumstances where an individual poses danger to self or others and where an individual is unable to care for one's self.

Outpatient treatment allows individuals to remain at their place of residence and receive treatment when needed or on a scheduled basis. Before allowing patients the freedom that comes with outpatient treatment, physicians evaluate several factors of the patient. These factors include the patient's level of social support, impulse control and quality of judgment. After the patient passes the evaluation, they are often asked to consent to a "no-harm contract". This is a contract formulated by the physician and the family of the patient. Within the contract, the patient agrees not to harm themselves, to continue their visits with the physician, and to contact the physician in times of need. These patients are then checked on routinely to assure they are maintaining their contract and staying out of troublesome activities.

There are also a number of different pharmacological treatment options for those experiencing suicidal ideation. However, prescribing medication to treat suicidal ideation can be difficult. One reason for this is because many medications lift patients' energy levels before lifting their mood. This puts them at greater risk of following through with attempting suicide. Additionally, if a patient has a co-morbid psychiatric disorder, it may be difficult to find a medication that addresses both the psychiatric disorder and suicidal ideation.

Therefore, the medication prescribed to one suicidal ideation patient may be completely different than the medication prescribed to another patient. However, there are several medications that seem to work fairly well for treating suicidal ideation, more particularly antidepressants, including fluoxetine (PROZAC), sertraline (ZOLOFT), paroxetine (PAXIL), fluvoxamine (LUVOX), venlafaxine (EFFEXOR) and nefazodone (SERZONE).

Although research is largely in favor of the use of antidepressants for the treatment of suicidal ideation, in some cases antidepressants are claimed to be associated with increased suicidal ideation. Upon the start of using antidepressants, many clinicians will note that sometimes the sudden onset of suicidal ideation may accompany treatment. This has caused the Food and Drug Administration (FDA) to issue a warning stating that sometimes the use of antidepressants may actually increase the thoughts of suicidal ideation.

Ketamine (a racemic mixture of the corresponding S- and R-enantiomers) is an NMDA receptor antagonist, with a wide range of effects in humans, including analgesia, anesthesia, hallucinations, dissociative effects, elevated blood pressure and bronchodilation. Ketamine is primarily used for the induction and maintenance of general anesthesia. Other uses include sedation in intensive care, analgesia (particularly in emergency medicine and treatment of bronchospasms. Ketamine has also been shown to be efficacious in the treatment of depression (particularly in those who have not responded to other anti-depressant treatment). In patients with major depressive disorders, ketamine has additionally been shown to produce a rapid antidepressant effect, acting within two hours.

The *S*-ketamine enantiomer (or *S*-(+)-ketamine or esketamine) has higher potency or affinity for the NMDA reception and thus potentially allowing for lower dosages; and is available for medical use under the brand name KETANEST S.

There remains a need to provide an effective treatment for depression, more particularly treatment resistant depression and / or for the treatment of suicidality, suicidal ideations, and for the prevention of suicide, particularly in the first hours and days after the onset of a major depressive episode.

Summary of the Invention

The present invention is directed to a method for predicting whether a patient suffering from depression, preferably treatment resistant depression, is genetically predisposed to poorly respond to antidepressants, for example antidepressants which block the reuptake of monoamine neurotransmitters such as serotonin, norepinephrine, dopamine, and the like, comprising genotyping of said patient to determine the patient's genotype at SNP rs4306882 (on chromosome 3).

The present invention is further directed to a method for genotyping a patient to determine the patient's polymorphism at SNP rs4306882, comprising the steps of:

Step A: obtaining a biological sample comprising genetic material of the subject, wherein the subject is undergoing or is to undergo antidepressant pharmacotherapy;

Step B: determining the presence of a G ot T allele at rs4306882.

In an embodiment, the present invention is directed to a method for genotyping further comprising extracting DNA from the biological sample. In an embodiment, the present invention is directed to a method for genotyping wherein the biological sample is a blood sample. In an embodiment, the present invention is directed to a method for genotyping further comprising reporting the determination to the subject, a health care provider, a physician, a pharmacist, a pharmacy benefits manager or an electronic system.

The present invention is directed to a method for the treatment of depression, preferably treatment resistant depression (TRD), comprising:

Step A: genetically testing (or genotyping) a patient suffering from depression (preferably treatment resistant depression) to determine the patient's genotype at SNP rs4306882;

Step B: administering a dosing regimen of ketamine or esketamine, wherein the dosing regimen is adjusted to provide a higher dose and / or greater frequency of the ketamine or esketamine to those patients with a G allele (rather than a T allele) at the polymorphic site of SNP rs4306882.

In an embodiment of the present invention, the methods further comprise genetically testing (or genotyping) the patient suffering from depression, preferably treatment resistant depression, to determine the patient's genotype at one or more of the SNPs as listed in Table 3 which follows herein.

In an embodiment of the present invention, the patient suffering from depression, or in need of treatment for depression, is suffering from treatment resistant depression (TRD).

In an embodiment of the present invention, the dosing regimen comprises administration of esketamine, preferably intranasal esketamine. In an embodiment of the present invention, the esketamine is administered at a therapeutically effective amount. In another embodiment, the esketamine is administered as co-therapy in combination with one or more anti-depressants. In another embodiment of the present invention, the co-therapy is administered in a therapeuticaly effective amount.

In an embodiment of the present invention, wherein the patient in need of treatment is a patient carrying the G allele at SNP rs4306882, the dosing regimen comprises administration of intranasal esketamine at a dose of between about 28 mg and about 32 mg (preferably 28 mg), at an interval of one to four (preferably one to three, more preferably one to two, more preferably one) times per week, for a period of up to about eight weeks.

In another embodiment of the present invention, wherein the patient in need of treatment is a patient carrying the T allele at SNP rs4306882, the dosing regimen comprises administration of intranasal esketamine at a dose of between about 28 mg and about 32 mg (preferably 32 mg), at an interval of two to five (preferably three to five, more preferably four to five) times per week, for a period of up to about eight weeks.

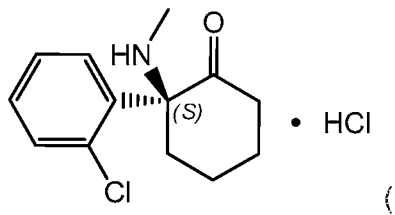
In an embodiment of the present invention, the dosing regimen is administered for one to eight weeks, preferably for one to six weeks. In another embodiment of the present invention, the dosing regimen is administered for two to eight weeks, preferably for two to six weeks, preferably two to four weeks. In additional embodiments of the present invention, the

dosing regimen is administered for one, two, three, four, five, six, seven or eight weeks.

Detailed Description of the Invention

The present invention is directed to methods for the treatment of depression, more particularly treatment resistant depression, and / or for the treatment and / or prevention of suicidality (e.g. suicidal ideations) comprising genotyping a patient in need thereof (e.g. suffering from depression, preferably treatment resistant depression) and administering ketamine, preferably esketamine, preferably intranasally, according to a dosing regimen which is selected (preferably optimized) for said patient, based on the patient's genotype at SNP rs4306882, alone or in combination with one or more SNPs, as described in more detail herein.

As used herein, unless otherwise noted, the term "**esketamine**" shall mean the (S)-enantiomer of ketamine, as its corresponding hydrochloride salt, a compound of formula (I)



(I)

also known as (*S*)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.

As used herein, unless otherwise noted, the term "**antidepressant**" shall mean any pharmaceutical agent which can be used to treat depression. Suitable examples include, but are not limited to mono-amine oxidase inhibitors such as phenelzine, tranylcypromine, moclobemide, and the like; tricyclics such as imipramine, amitriptyline, desipramine, nortriptyline, doxepin, protriptyline, trimipramine, chlomipramine, amoxapine, and the like; tetracyclics such as maprotiline, and the like; non-cyclics such as nomifensine, and the like; triazolopyridines such as trazodone, and the like; serotonin reuptake inhibitors such as fluoxetine, sertraline, paroxetine, citalopram, citolapram, escitolapram, fluvoxamine, and the like; serotonin receptor antagonists such as nefazadone, and the like; serotonin noradrenergic reuptake inhibitors such as venlafaxine, milnacipran, desvenlafaxine, duloxetine and the like; noradrenergic and specific

serotonergic agents such as mirtazapine, and the like; noradrenaline reuptake inhibitors such as reboxetine, edivoxetine and the like; atypical antidepressants such as bupropion, and the like; natural products such as Kava-Kava, St. John's Wort, and the like; dietary supplements such as s-adenosylmethionine., and the like; and neuropeptides such as thyrotropin-releasing hormone and the like; compounds targeting neuropeptide receptors such as neurokinin receptor antagonists and the like; and hormones such as triiodothyronine, and the like. Preferably, the antidepressant is selected from the group consisting of fluoxetine, imipramine, bupropion, venlafaxine and sertaline.

Therapeutically effective dosage levels and dosage regimens for antidepressants (for example, mono-amine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors, serotonin noradrenergic reuptake inhibitors, noradrenergic and specific serotonergic agents, noradrenaline reuptake inhibitor, natural products, dietary supplements, neuropeptides, compounds targeting neuropeptide receptors, hormones and other pharmaceutical agents disclosed herein), may be readily determined by one of ordinary skill in the art. For example, therapeutic dosage amounts and regimens for pharmaceutical agents approved for sale are publicly available, for example as listed on packaging labels, in standard dosage guidelines, in standard dosage references such as the Physician's Desk Reference (Medical Economics Company or online at http://www.pdrel.com) or other sources.

As used herein the term "**antipsychotic**" includes, but is not limited to:

(a) typical or traditional antipsychotics, such as phenothiazines (e.g., chlorpromazine, thioridazine, fluphenazine, perphenazine, trifluoperazine, levomepromazin), thioxanthenes (e.g., thiothixene, flupentixol), butyrophenones (e.g., haloperidol), dibenzoxazepines (e.g., loxapine), dihydroindolones (e.g., molindone), substituted benzamides (e.g., sulpride, amisulpride), and the like; and

(b) atypical antipsychotics, such as paliperidone, clozapine, risperidone, olanzapine, quetiapine, zotepine, ziprasidone, iloperidone, perospirone, blonanserin, sertindole, ORG-5222 (Organon), and the like; and others such as sonepiprazole, aripiprazole, nemonapride, SR-31742 (Sanofi), CX-516 (Cortex), SC-111 (Scotia), NE-100 (Taisho), and the like.

In an embodiment, the "**atypical antipsychotic**" is selected from the group consisting of aripiprazole, quetiapine, olanzapine, risperidone and paliperidone. In another embodiment, the atypical antipsychotic is selected from the group consisting of aripiprazole, quetiapine, olanzapine and risperidone; preferably, the atypical antipsychotic is selected from the group consisting of aripiprazole, quetiapine and olanzapine.

As used herein, the term "**depression**" shall be defined to include major depressive disorder, unipolar depression, treatment resistant depression, depression with anxious distress, bipolar depression and dysthymia (also referred to as dysthymic disorder). Preferably, the depression is major depressive disorder, unipolar depression, treatment resistant depression, depression with anxious distress, or bipolar depression. More preferably, the depression is major depressive disorder, unipolar depression, treatment resistant depression and bipolar depression.

As used herein, the term "**treatment-refractory or treatment-resistant depression**" and the abbreviation "**TRD**" shall be defined as major depressive disorder that does not respond to adequate courses of at least two antidepressants. One skilled in the art will recognize that the failure to respond to an adequate course of a given antidepressant may be determined retrospectively or prospectively. In an embodiment, at least one of the failures to respond to an adequate course of antidepressant is determined prospectively. In another embodiment, at least two of the failures to respond to an adequate course of antidepressant are determined prospectively. In another embodiment, at least one of the failures to respond to an adequate course of antidepressant is determined retrospectively. In another embodiment, at least two of the failures to respond to an adequate course of antidepressant are determined retrospectively.

As used herein, unless otherwise noted, the terms "**treating**", "**treatment**" and the like, shall include the management and care of a subject or patient (preferably mammal, more preferably human) for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present invention to prevent the onset of the symptoms or

complications, alleviate the symptoms or complications, or eliminate the disease, condition, or disorder.

As used herein, unless otherwise noted, the term "**prevention**" shall include (a) reduction in the frequency of one or more symptoms; (b) reduction in the severity of one or more symptoms; (c) the delay or avoidance of the development of additional symptoms; and / or (d) delay or avoidance of the development of the disorder or condition.

One skilled in the art will recognize that wherein the present invention is directed to methods of prevention, a subject in need of thereof (i.e. a subject in need of prevention) shall include any subject or patient (preferably a mammal, more preferably a human) who has experienced or exhibited at least one symptom of the disorder, disease or condition to be prevented. Further, a subject in need thereof may additionally be a subject (preferably a mammal, more preferably a human) who has not exhibited any symptoms of the disorder, disease or condition to be prevented, but who has been deemed by a physician, clinician or other medical profession to be at risk of developing said disorder, disease or condition. For example, the subject may be deemed at risk of developing a disorder, disease or condition (and therefore in need of prevention or preventive treatment) as a consequence of the subject's medical history, including, but not limited to, family history, pre-disposition, co-existing (comorbid) disorders or conditions, genetic testing, and the like.

As used herein, unless otherwise noted, the terms "**subject**" and "**patient**" refer to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. Preferably, the subject or patient has experienced and / or exhibited at least one symptom of the disease or disorder to be treated and / or prevented.

The term "**therapeutically effective amount**" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Wherein the present invention is directed to therapy with a combination of agents, "**therapeutically effective amount**" shall mean that amount of the

combination of agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of combination therapy comprising esketamine and a serotonin reuptake inhibitor would be the amount of esketamine and the amount of the serotonin reuptake inhibitor that when taken together or sequentially have a combined effect that is therapeutically effective, more preferably where the combined effect is synergistic. Further, it will be recognized by one skilled in the art that in the case of combination therapy with a therapeutically effect amount, the amount of each component of the combination individually may or may not be therapeutically effective.

Wherein the present invention is directed to the administration of a combination, the compounds may be co-administered simultaneously, sequentially, separately or in a single pharmaceutical composition. Where the compounds are administered separately, the number of dosages of each compound given per day, may not necessarily be the same, e.g. where one compound may have a greater duration of activity, and will therefore, be administered less frequently. Further, the compounds may be administered via the same or different routes of administration, and at the same or different times during the course of the therapy, concurrently in divided or single combination forms. The instant invention is therefore understood as embracing all regimens of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

As used herein, the terms "**co-therapy**", "**combination therapy**", "**adjunctive treatment**", "**adjunctive therapy**" and "**combined treatment**" shall mean treatment of a patient in need thereof by administering esketamine in combination with one or more antidepressant(s), and further, optionally in combination with one or more atypical antipsychotics wherein the esketamine and the antidepressant(s) are administered by any suitable means, simultaneously, sequentially, separately or in a single pharmaceutical formulation. Where the esketamine and the antidepressant(s) are administered in separate dosage forms, the number of dosages administered per day for each compound may be the same or different. The esketamine and the antidepressant(s) may be administered via the same or different routes of

administration. Examples of suitable methods of administration include, but are not limited to, oral, intravenous (iv), intranasal (in) intramuscular (im), subcutaneous (sc), transdermal, and rectal. Compounds may also be administered directly to the nervous system including, but not limited to, intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal and / or peri-spinal routes of administration by delivery via intracranial or intravertebral needles and / or catheters with or without pump devices. The esketamine and the antidepressant(s) may be administered according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound or compounds used, the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient's sex, age, weight, diet, time of administration and concomitant diseases, will result in the need to adjust dosages.

One skilled in the art will recognize that, both *in vivo* and *in vitro* trials using suitable, known and generally accepted cell and / or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and / or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

As used herein, the term "**composition**" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "**about**". It is understood that whether the term "**about**" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably

be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value.

To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that wherein a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any amount or range therein.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "**pharmaceutically acceptable salts**." Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate.

Representative acids which may be used in the preparation of pharmaceutically acceptable salts include, but are not limited to, the following: acids including acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucoronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hipuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinc acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebaic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid.

Representative bases which may be used in the preparation of pharmaceutically acceptable salts include, but are not limited to, the following: bases including ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

Examples

The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Example 1 – Retrospective Analysis

We performed a genetic association meta-analysis of treatment resistant depression case control genetic association analyses from two independent

cohorts of European ancestry. Irrespective of the definition provided above, in the meta-analysis described in this Example, cases with treatment resistant depression (TRD) were defined as subjects failing two trials of antidepressant treatment regimens and were drawn either from a Cohort J consisting of patients enrolling in antidepressant clinical studies (n=232) genotyped using Ilumina Omni5MExome or from a cohort based on STAR*D study (n=315) genotyped using either Affymetrix 500K or Affymetrix 5.0. Controls were drawn from either the cognitively normal subjects from the ADNI study (n=255) genotyped using Illumina Omni2.5M or the psychiatrically screened healthy controls from NIMH (n=584) genotyped using Affymetrix 500K, respectively. We imputed genotypes based on the reference haplotypes from the 1,000 Genomes prior to meta-analysis to enable direct comparison of variants across the study.

More specifically, for Cohort J, we started with the Illumina Omni5MExome dataset (n~538) comprising subjects from the following studies: (a) RIS-INT-93 (~458 Caucasian subjects including 24 Hispanic subjects); (b) ESKETIV-TRD-2001(n~26, all races); (c) KETIV-TRD-2002 (n~61, all races). Only the patients meeting TRD criteria were defined as cases and only subjects of European ancestry were included in the analysis leading to this invention. Standard SNP-level and subject-level quality control criteria were applied prior to imputation of sites not directly genotyped. SNP-level quality control criteria included 1) Minor Allele Frequency > 1%; 2) SNP-wise genotype missing rate < 5%; 3) Hardy-Weinberg Equilibrium p-value > 1e-06. Subject-level quality control criteria included 1) subject-wise genotype missing rate < 5%; 2) excluded population outliers, cryptic related subject, and subjects with genetically derived gender differing from gender captured in the case report form (CRF) or phenotype file (if exists). The controls for Cohort J were ADNI CN (genotyped using Illumina Omni2.5M, n~281). For the 2nd cohort, the Affymetrix 500K Mapping Array/Affymterix 5.0 comprised the STAR*D (n~ 1851 all races) and NIMH controls (n~ 1727 all races). Similar case definition criteria and similar quality control criteria were applied. The 2 analysis cohorts matched by genotyping platforms were: 1) Cohort J TRD (Omni2.5M using a subset of markers) vs. ADNI CN (Omni2.5M) and 2) STAR*D TRD vs. NIMH

controls screened by Composite International Diagnostic Interview (CIDI-SF) self-report modified to screen for lifetime diagnoses (The Internet-Based MGS-2 Control Samples).

Treatment resistant depression (TRD) was defined as follows: 2 antidepressant failures (1 retrospective and 1 prospective failure for RIS-INT-93; 2 prospective antidepressant failures for STAR*D; or 2 retrospective antidepressant failures for ESKETIV-TRD-2001 & KETIV-TRD-2002). Prospective antidepressant failure was defined by using HAM-D-17 clinical scale for patients with percentage of change in HAM-D-17 score greater than -50%. The minimal treatment length was 6 weeks for RIS-INT-93 and 8-12 weeks for STAR*D.

The associated markers in the meta-analysis (directly genotyped marker $P=8.51 \times 10^{-7}$; imputed marker $P=3.56 \times 10^{-8}$ passing the conventional genome-wide significance threshold ($P=5 \times 10^{-8}$)) were located in a 50kb interval (3p24.3) in chromosome 3 with only unannotated spliced EST reported, within a linkage interval implicated in a linkage meta-analysis (3p25.3-3p22.1). The genetic data from each TRD sample independently supported this association, with uncorrected significance levels of $P=2.37 \times 10^{-5}$ for the STAR*D cohort and P=0.005 for the Cohort J. (See Table 1 and Table 2, below). Minor allele G was determined to occur at a lower frequency in TRD than in a generally healthy population. Patients with each copy of the G allele had ~0. 7x lower odds of exhibiting treatment resistant depression (TRD). rs4306882 was directly genotyped in Cohort J; and imputed in the STAR*D cohort.

Table 1

Cohort	CHR	SNP	BP	A1	A2
Cohort J vs. ADNI CN	3	rs 4306882	21062584	G	T
STAR*D TRD vs. NIMH Controls	3	rs 4306882	21062584	G	T

Cohort	FRQ	INFO	OR	SE	P
Cohort J vs. ADNI CN	0.386	0.9777	0.6754	0.14	0.005078
STAR*D TRD vs. NIMH Controls	0.3771	1.0139	0.5249	0.1525	2.37E-05

Abbreviations in Table 1 are as follows:

CHR Chromosome code, if map file specified

SNP	SNP code
BP	Base-pair position, if map file specified
A1	Allele 1 code
A2	Allele 2 code
FRQ	Frequency of A1, from dosage data
INFO	R-squared quality metric / information content
OR	Odds ratio for association
SE	Standard error of effect estimate
P	p-value for association tests

Table 2:

For Chromosome 3, SNP rs4306882 at Base pair position 21062587

A1	F_A	F_U	A2	CHISQ	P	OR
G	0.3378	0.4321	T	10.16	1.43E-03	0.6703

Abbreviations in Table 2 are as follows:

A1	Minor allele name (based on whole sample)
F_A	Frequency of this allele in cases
F_U	Frequency of this allele in controls
A2	Major allele name
CHISQ	Basic allelic test chi-square (1df)
P	Asymptotic p-value for this test
OR	Estimated odds ratio (for A1, i.e. A2 is reference)

The sequence ID for SNP rs4306882 is as follows:

SEQ. ID. 1:

GGATGCCACA TGCAGATGTA TTTTCTTTGG TCCACATATG GCATCCAACC CATGAGCTAT
AGAAAATATG GATTTCTGGA TTTCTTTGAA ACACTGAAAG ATCTGGAGCC TCTGGGCCAC
TGTTACTGGA TAATAGCAAC AGCCTGAGTG TTTGCATTTA TAACCTGTAA TAAGAGACGC
ATGTCTCCTT GCTGCTCAAG TTATAGATCT GACAGCCCAG GATATGATTA ATCAGAGCTC
AGGGCTCAGG AAGCCATTCT CCACATCTGG CAGAGCCCGA CAAAATCTTT GCAATCAGAT
TAACGAAGCA GTGACATGAT GTTCTATTAG TGGGGGCATG GACATGCAAA ATCATTATGC
AGAACAATTC ATTATCATAG CTGACCATGT ACAGGGTTTT AGCTGCATGT CGATGTGGCA
CAGCTCACTG AAGATGCATG GATAAACGCT GTGGCTAAGG CATTGTGAGA GCAATTGGTA
GGAGCTAGAA AGCTAGCTCT

K

AAGCCAAGCT AGAAGAGAAA CACAGTTCTG GGATCACCAT TCATTTTGCT CTTTCTGGGT
CCTTTTATAT CTGCTTTAGC AAGGTACCTG CTTTAACAAT GTACATTCTT GCATGAATGT
TTTCTTTTCT CTTTCAATTC TTCTTCCATC CTGGTGTTTA GGATATCACT GGGGTGGGAT
AGTGGGAGAG GTGGCAGTTT TATTTTGTTT TTAAGTATAT CAGTTCTCCT TTTTGATATC
AGCTTTTCTT TTTGAATAGT CCAGGATATA CTTGCCTCTC AAGCAGCTTT TTTTTTTCTC
AAAGCCAGTT CTTCTTATGC AACAGACTTA CTATATCATT CACAGATTGT ACCATGAGGG
TTCACTTTCT TGCACCTATA TTAGGCCACA ACCTCTAAGC ACAAAGGTCT TTTCATGACT

GTTTATTGAA ATACCCAGCA AGAATTTTCA TCAGACAGAG TTTTAGTCAT GCTTTAACTC TGCAACTTAT TAAAATGGGA

>gnl|dbSNP|rs4306882|allelePos=501|totalLen=1001|taxid=9606|snpclass=1|alleles='G/T'|mol=Genomic|build=138

SNP rs4306882 was further determined to be in linkage disequilibrium (LD) with an array of the SNPs in the close by genomics region as shown in Table 3, below.

In certain embodiments, the present invention is directed to methods (as described herein) wherein the patient's genotype is determined at any single SNP listed in Table 3 below, alone or in combination with a determination of the patient's genotype at SNP rs4306822. In certain embodiments, the present invention is directed to methods (as described herein) wherein the patient's genotype is determined at any subset of SNPs selected from the list in Table 3 below, alone or in combination with a determination of the patient's genotype at SNP rs4306822.

Table 3

Chromosome 2 (CHR)										
BP	SNP	A1	A2	N	P	P(R)	OR	OR(R)	Q	I
119536884	rs1551133	C	A	2	2.85E-07	1.68E-04	0.4418	0.4392	0.1699	46.91
Chromosome 3 (CHR)										
BP	SNP	A1	A2	N	P	P(R)	OR	OR(R)	Q	I
21061286	rs869495	G	A	2	5.54E-07	0.0006712	0.5941	0.5898	0.1367	54.84
21061473	rs869494	T	A	2	6.68E-07	0.001478	0.5967	0.5914	0.1129	60.21
21062584	rs4306882	G	T	2	8.51E-07	4.85E-05	0.6019	0.5997	0.2233	32.57
21063058	rs4465961	T	C	2	8.85E-07	0.000537	0.5939	0.5897	0.1513	51.43
21063578	rs7625772	T	G	2	6.24E-07	0.00096	0.5947	0.5897	0.1263	57.21
21063804	rs7633632	G	A	2	6.21E-07	5.14E-06	0.5963	0.5954	0.2733	16.68
21063919	rs7612422	C	G	2	1.43E-07	1.64E-07	0.5804	0.5803	0.3149	1
21067747	rs7646153	G	C	2	8.42E-07	0.0004885	0.5984	0.5947	0.1539	50.81
21069166	rs1391144	G	A	2	9.95E-07	9.95E-07	0.6022	0.6022	0.3234	0
21072614	rs2047387	G	A	2	2.04E-07	2.04E-07	0.5822	0.5822	0.3415	0
21077201	rs6769146	G	A	2	4.83E-07	4.83E-07	0.5911	0.5911	0.3302	0
21077685	rs6550565	G	C	2	7.97E-07	6.70E-06	0.5866	0.5856	0.272	17.12
21081507	rs56871503	C	T	2	6.99E-07	0.0004664	0.5965	0.593	0.1525	51.14
21085039	rs11295121	TG	T	2	9.11E-07	9.11E-07	0.6007	0.6007	0.3262	0

21087408	rs4858288	A	G	2	3.76E-07	3.76E-07	0.5893	0.5893	0.3634	0
21088048	rs1391138	G	T	2	2.82E-07	2.82E-07	0.5852	0.5852	0.3252	0
21088878	rs9881998	C	T	2	5.63E-07	3.08E-05	0.5918	0.59	0.228	31.2
21089069	rs9811079	G	A	2	2.62E-07	2.62E-07	0.5843	0.5843	0.3787	0
21093953	rs13097458	C	A	2	9.97E-07	9.97E-07	0.597	0.597	0.389	0
21097393	rs973870	C	A	2	6.85E-07	0.0004483	0.5957	0.5918	0.1531	51.01
21099489	rs7652147	G	A	2	7.14E-07	0.0004306	0.5958	0.5921	0.1551	50.52
21099939	rs141786492	TTTTC	T	2	4.54E-07	0.0008831	0.5822	0.5771	0.1245	57.63
21100108	rs7644744	A	G	2	6.62E-07	0.000343	0.5943	0.5908	0.1612	49.05
21102620	rs985536	G	A	2	6.54E-07	6.54E-07	0.5921	0.5921	0.4025	0
21106260	rs9865061	T	A	2	2.28E-07	8.84E-05	0.58	0.5773	0.184	43.35
21106404	rs11128983	G	A	2	5.11E-07	5.42E-05	0.589	0.5868	0.211	36.07
21107235	rs9850499	C	T	2	3.45E-07	2.87E-05	0.5798	0.5779	0.221	33.23
21107330	rs71935600	CAG	C	2	2.39E-07	0.0001414	0.5709	0.5676	0.1714	46.55
21108963	rs200621794	AAAG	A	2	3.56E-08	3.56E-08	0.5581	0.5581	0.3527	0
21108964	rs67575809	AAG	A	2	2.80E-08	2.51E-07	0.5549	0.5546	0.2812	13.9
21109078	rs7372757	G	A	2	2.25E-07	2.25E-07	0.5801	0.5801	0.7251	0
Chromosome 4 (CHR)										
BP	**SNP**	**A1**	**A2**	**N**	**P**	**P(R)**	**OR**	**OR(R)**	**Q**	**I**
148693230	rs2164527	C	T	2	4.17E-07	4.17E-07	0.451	0.451	0.6757	0
Chromosome 11 (CHR)										
BP	**SNP**	**A1**	**A2**	**N**	**P**	**P(R)**	**OR**	**OR(R)**	**Q**	**I**
86572384	rs12285365	G	A	2	4.43E-07	4.43E-07	0.5116	0.5116	0.6906	0

Abbreviations in Table 3 above, are as follows:

CHR	Chromosome code, if map file specified
BP	Base-pair position, if map file specified
SNP	SNP code
A1	Allele 1 code
A2	Allele 2 code
N	Number of valid studies for the SNP
P	p-value for association tests
P(R)	Random-effectsmeta-analysis p-value
OR	Odds ratio for association
OR(R)	Random effects OR estimate
Q	p-value for Cochrane's Q stratistic
I	I^2 heterogeneity index (0-100)

Thus, we believe that we have identified a candidate genetic marker for TRD with association p-value passing genome wide significance using a relatively small sample size by GWAS standard. The identification of genetic

markers associated with resistance to biogenic amine-based antidepressant drugs holds the potential to guide researchers toward unprecedented targets in the discovery of novel treatments for TRD.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

We Claim:

1. A method for the treatment of depression comprising:

Step A: genetically testing (or genotyping) a patient suffering from depression to determine the patient's genotype at rs4306882;

Step B: administering a dosing regimen of ketamine or esketamine, wherein the dosing regimen is adjusted to provide a higher dose and / or greater frequency of the ketamine or esketamine to those patients with the G allele (rather than T allele) at the polymorphic site of rs4306882.

2. A method as in Claim 1, wherein the depression is treatment resistant depression (TRD).

3. A method as in Claim 1, wherein the dosing regimen comprises administration of esketamine.

4. A method as in Claim 1, wherein the patient in need of treatment is a patient carrying the G genotype at SNP rs4306882; wherein the dosing regimen comprises administration of esketamine; wherein the esketamine is administered intranasally; and wherein the esketamine is administered at a dosage of about 28 mg to about 32 mg, one to three times per week for up to eight weeks.

5. A method as in Claim 1, wherein the patient in need of treatment is a patient carrying the T genotype at SNP rs4306882; wherein the dosing regimen comprises administration of esketamine; wherein the esketamine is administered intranasally; and wherein the esketamine is administered at a dosage of about 28 mg to about 32 mg, two to five times per week for up to eight weeks.

6. A method for predicting whether a patient suffering from depression is genetically predisposed to poorly respond to antidepressants which block the

reuptake of monoamine neurotransmitters, comprising genotyping said patient to determine the patient's genotype at SNP rs4306882.

7. A method as in Claim 6, wherein the depression is treatment resistant depression.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/44830

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/44830

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/135; A61K 31/137; A61M 11/00; A61K 31/35 (2015.01)
CPC - A61K 31/135; A61K 31/137; A61M 15/08; A61K 31/35
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/135; A61K 31/137; A61M 11/00; A61K 31/35 (2015.01)
CPC - A61K 31/135; A61K 31/137; A61M 15/08; A61K 31/35; USPC - 514/646; 514/647; 128/200.14; 514/456

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 31/135; A61K 31/137; A61M 11/00; A61K 31/35 (2015.01) - see keyword below
CPC - A61K 31/135; A61K 31/137; A61M 15/08; A61K 31/35; USPC - 514/646; 514/647; 128/200.14; 514/456 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: treating, depression, resistant-depression, administering, esketamine, ketamine, 28, 32 mg, mg/kg, intranasal, SNP, single nucleotide polymorphism, rs4306882, G allele, T allele, predict, response, respond, block, reuptak, uptake, predisposition, genotyping, week, antidepressant, monoamine, n

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007/0287753 A1 (CHARNEY et al.) 13 December 2007 (13.12.2007), Abstract, para [0003], and [0050]	1-7
A	CLINICALTRIALS.GOV_NCT01998958, A Study to Evaluate the Safety and Efficacy of Intranasal Esketamine in Treatment-resistant Depression. ClinicalTrials.gov Identifier: NCT01998958. 14 July 2014 [online]. [Retrieved on 2015.09.23]. Retrieved from the Internet: <URL: https://clinicaltrials.gov/archive/NCT01998958/2014_07_14> PDF File: pg 1-40. pg 1, Brief Summary, Phase, and the last para; and pg 2, para 1 and 3	1-7
A	US 2013/0172361 A1 (FAVA et al.) 04 July 2013 (04.07.2013), Abstract, para [0006], [0137], [0142], and [0391]	1-7
A	GENBANK_AC099753, Homo sapiens chromosome 3 clone RP11-466A13, complete sequence. 20 March 2002, [online]. [Retrieved on 2015.10.01]. Retrieved from the Internet: <URL: http://www.ncbi.nlm.nih.gov/nuccore/19551144/> PDF file: pg 1-40. pg 1, Definition; pg 3, Origin, pg 27, the nucleotide sequence between 113924-112924, especially the nucleotides between 113444- 113405; and the nucleotide at the position of 113424	1-7
A	US 2013/0236573 A1 (SINGH et al.) 12 September 2013 (12.09.2013), Abstract, para [0002], [0009], [0016], and [0033]	1-7

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 October 2015 (02.10.2015)	23 NOV 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)