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(54) **Title:** METHOD FOR TREATING SUICIDAL IDEATION

(57) **Abstract:** A method for the rapid treatment of persistent suicidal ideations by administration of ketamine and co-administration or subsequent administration of lithium.



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Method for Treating Suicidal Ideation

FIELD OF THE INVENTION

The present invention pertains to a method for providing rapid relief from suicidal ideations and maintaining the relief for extended time periods.

BACKGROUND OF THE INVENTION

Suicide is a major public health problem worldwide. Every year over 800,000 people lose their lives because of suicide. A 2001 report from the World Health Organization (WHO) indicates that the number of individuals who died by suicide in 2001 exceeded the number of individuals who died by homicide and those who died during war time. Alarming, a 28.4% increase in suicide rate was observed between 1999 and 2010 in individuals aged 35 to 64 years, in the midst of the most productive years of their lives. (See Mann JJ, Kuehn BM. Rate of suicide increases in middle age: primary care key to suicide prevention. *Jama*. Nov 5 2014; 312(17):1727-1728).

The presence of a mental illness is a major risk factor for suicide, as evidenced by psychological autopsy studies that report a diagnosable psychiatric disorder at the time of the suicide in 90–95 percent of cases. Major depressive disorder (MDD) is the most common psychiatric comorbidity among suicide attempters; other mood disorders, anxiety disorders, and substance use disorders additionally represent important co-morbidities. However, the vast majority of patients with MDD or other psychiatric illness do not attempt or complete suicide. Therefore, a vulnerability to suicide and specific treatment for suicide should be considered at least partially independent from MDD or other psychiatric disorders. One-third of these cases are known to have had contact with a mental health professional within a year of their suicide, underscoring the importance of clinical screening and management of suicide risk. A 2014 article in the journal *Nature* advocates defining suicide as a distinct disorder. See Aleman & Denis; A Roadmap for Suicide Research and Prevention; *Nature* May 22, 2014 (509) 421-423.

Suicidal behavior is difficult to predict at the level of the individual and a firm understanding of the biological and psychological factors that lead to suicide remains elusive. The influential

“stress-diathesis” model of suicide proposes that a trait-like diathesis (or vulnerability) towards suicide exists in certain individuals and suicidal behavior results when this diathesis interacts with psychosocial stressors or a psychiatric illness, such as major depression. The diathesis may increase the sensitivity of an individual to social stressors or increase the tendency towards impulsivity, hopelessness, or a failure to successfully regulate one’s emotions. Suicide is known to run in families. Studies have shown higher rates of suicide in the biological parents of adoptees who commit suicide and among monozygotic versus dizygotic twins even after controlling for psychiatric co-morbidities. The vulnerability to suicide cannot be fully accounted for by the presence of MDD or other psychiatric disorders. For this reason, suicidality and suicidal ideation should be considered a separate and distinct disorder apart from underlying mood disorders.

Despite this knowledge, the specific genetic and epigenetic causes of suicide remain to be discovered. Biological alterations that have been linked to suicide include disturbances within the serotonin and glutamate neurotransmitter systems, abnormalities within the hypothalamic-pituitary-adrenal stress axis, and changes in specific brain regions, including medial and lateral aspects of the prefrontal cortex.

There is a lack of available medical interventions with evidence to support a specific therapeutic effect on suicidal ideation or behavior. Some of the scarcity of the literature is due to the complexity of the phenomenon of suicide and to the ethical dilemmas inherent in clinical trial study design, which impose limitations on the feasibility of suicide research. Clozapine (8-chloro-11-(4-methyl-1-piper-aziny)-5H-dibenzo [b,e][1,4] diazepine) is the only drug currently approved for reducing suicidal behavior, and only in patients with schizophrenia or with schizoaffective disorder. However due to the serious safety concerns (possible agranulocytosis) associated with administration, Clozapine is not widely used. At this time there is no approved pharmaceutical for treating suicidal ideations much less one that provides rapid relief from this condition. The time required to obtain relief may be critical because suicidal action (attempted suicide) is a risk for patients suffering from suicidal ideations. Current treatment recommendations for acute worsening of suicidal ideation are primarily environmental and include inpatient hospital admission and close observation. There is lack of evidence from meta-analyses of randomized controlled trials supporting the efficacy of antidepressants in ameliorating suicide risk in mood disorders. Since most clinical trials of antidepressant agents exclude patients with elevated levels of suicidality, the existing data does

not allow for an adequate evaluation of the impact of antidepressants on suicidal behavior. Notably, a black box warning issued by the U.S. FDA in 2004 warned of an increase in suicidal ideation or behavior linked to antidepressant medication in adolescents and young adults. A recent study examining the impact of this regulatory act found a decrease in antidepressant use and a simultaneous increase in suicide attempts among young people subsequent to the issuance of black box warning.

The glutamate N-methyl-d-aspartate (NMDA) receptor antagonist ketamine has shown rapid antidepressant effects (e.g. within 24 hours) in patients with treatment-resistant depression (TRD) (Zarate CA, Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK: *A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression*. Arch Gen Psychiatry 2006; 63:856-864; Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, Iqbal S, Pillemer S, Foulkes A, Shah A, Charney DS, Mathew SJ: *Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial*. Am J Psychiatry 2013; 170:1134-1142); and bipolar depression (Zarate CA, Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, Selter J, Marquardt CA, Liberty V, Luckenbaugh DA: *Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial*. Biol Psychiatry 2012; 71:939-946). Ketamine's rapid onset of therapeutic action makes it a potentially attractive therapeutic candidate for patients who require rapid treatment for suicidal thinking. Post-hoc analyses of ketamine studies in mood disorders provide initial support for the anti-SI effects of ketamine (Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, Soleimani L, Charney DS, Foulkes AL, Mathew SJ: *Effects of ketamine on explicit and implicit suicidal cognition: A randomized controlled trial in treatment-resistant depression*. Depress Anxiety 2014; 31:335-343; and a single open-label proof of concept study of ketamine conducted in an emergency department setting demonstrated that a single intravenous (IV) administration of ketamine reduced the intensity of SI for up to 10 days (Larkin GL, Beautrais AL: *A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department*. Int J Neuropsychopharmacol 2011; 14:1127-1131).

Some evidence supports the efficacy of antidepressant treatments for suicidal ideations but the evidence is inconclusive. The problem of suicidal ideations is particularly concerning for

patients with recurrent suicidal ideations (patients that have responded to adequate treatment for suicidal ideations in the past but are presently experiencing renewed episodes of suicidal ideations) and for patients that are non-responders (patients who have failed to respond to adequate treatment for suicidal ideation and their suicidal ideations have not abated). Suicidal ideation is also a high risk factor for morbidity in a patient that has attempted suicide at least once or has a history of recurrent or chronic suicidal ideations.

Up to now, management of suicidal patients has primarily involved hospitalization, or psychiatric treatment including medication and/or psychotherapy for co-morbid psychiatric/mood disorders. A distinct pharmaceutical treatment for suicidality (as opposed to a co-morbid psychiatric/mood disorder) is a relatively new concept, and attempts at drug development toward this objective have yet to be successful.

Ketamine ((2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist that is currently approved as an anesthetic agent in the U.S. More recently, a growing body of literature supports the rapid antidepressant effect of ketamine in patients with treatment resistant depression (TRD), and major depressive disorder (MDD) and bipolar disorder. The onset of antidepressant effects of ketamine has been reported as early as 40 minutes following a single intravenous administration and peak antidepressant effects have been reported between 4 and 72 hours following treatment. This rapid onset of symptomatic relief is a significant benefit.

Intranasal administration of ketamine to patients afflicted with treatment resistant depression (TRD) is disclosed in US patent 8,785,500 (the disclosure of which is incorporated by reference herein in its entirety).

The rapid and robust antidepressant effects of ketamine, unfortunately, are relatively short-lived, and little research to date has investigated strategies for maintaining the anti-depressant response to ketamine. The duration of antidepressant efficacy following a single administration of ketamine is anywhere from a few days to approximately a week or two following a single intravenous administration and peak antidepressant effects have been reported between 4 and 72 hours following treatment. In addition, several early studies have reported a rapid anti-suicidal ideation effect after administration of ketamine in patients with mood disorder. The rapidity of ketamine's onset of action and the relatively large effect sizes reported to date make ketamine a potentially promising candidate for anti-suicidality.

pharmacotherapy. Because it would be desirable to avoid administering ketamine to the patient each time the ketamine anti-suicidal effect began to fade, several approaches have been tried in an effort to maintain or extend the anti-suicidal effect of ketamine and to prevent relapse of suicidal ideations.

The glutamate-release inhibitor riluzole has been tested as a relapse prevention strategy following ketamine in TRD but the results established that riluzole was not superior to placebo in preventing relapse. In that study, the initial response rate was 65% and the cumulative risk of relapse over the 4- week observation period was 62%.

A second study conducted at the NIMH Intramural Program similarly found no benefit of riluzole beyond placebo for relapse prevention following ketamine and a cumulative probability of relapse during the 4-week assessment period of 73%. Ibrahim L, Diazgranados N, Franco-Chaves J, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. *Neuropsychopharmacology* 2012; 37: 1526-33.

Lithium is unique in that several studies support a specific protective effect of the medication on suicidal behavior in patients with mood disorders (e.g. depression and bipolar disorder). A recent meta-analysis including 6674 participants with MDD, bipolar disorder and schizoaffective disorder compared lithium with placebo or other active treatments on outcomes that included completed suicide and all-cause mortality Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *Bmj.* 2013;346:f3646. Lithium was significantly more effective than placebo in decreasing the number of suicides (odds ratio = 0.13) and deaths from any cause (odds ratio = 0.38). The only other psychotropic medication that has demonstrated clear anti-suicidal effects is the second-generation antipsychotic, clozapine. The International Suicide Prevention Study Trial (InterSePT), a 2-year multi-center randomized study including 980 high risk patients with schizophrenia and schizoaffective disorders, compared treatment with clozapine vs olanzapine on suicidal behavior. The main outcomes of the study included suicide attempts, completed suicide, hospitalization and worsening of suicidality. Compared to olanzapine, fewer patients treated with clozapine made a suicide attempts (hazard ratio = 0.76).

In an initial study of 26 patients with treatment-resistant depression (TRD) treated with a single open-label intravenous (IV) infusion of ketamine (0.5 mg/kg), 65% showed significant alleviation of the depression [defined as a reduction of 50% or more on the Montgomery-Asperg Depression Rating Scale, (MADRS)]. Ketamine specifically showed a large effect on suicidal ideation as measured by the suicidality item of the MADRS (MADRS-SI) ($P < 0.001$; $d = 1.37$). Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biological Psychiatry*. Sep 1 2009;66(5):522-526. Moreover, suicidality measured implicitly using a computer-based task (i.e., the Implicit Association Test, AIT) was also reduced following ketamine ($P < 0.003$; $d = 1.36$).

Zarate et al at the National Institute of Mental Health (NIMH) replicated these results in another cohort of MDD patients where a single ketamine infusion decreased suicide scores as early as 40 minutes post-infusion, as measured by Scale for Suicidal Ideation (SSI). This effect remained significant for the first 4 hours post-infusion and the effect size at the two-time point were noted to be large and moderate, respectively Diazgranados N, Ibrahim L, Brutsche NE, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of general psychiatry*. Aug 2010;67(8):793-802. Ballard et al, in a post-hoc analysis of pooled data from 4 prior ketamine clinical trials in TRD and bipolar depression (single dose, double blind as well as open-label), confirmed a decrease in suicidal ideation 230 minutes post-infusion. Ballard ED, Ionescu DF, Vande Voort JL, et al. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. *Journal of psychiatric research*. Nov 2014;58:161-166.

More recently, a larger two-site randomized controlled trial of a single IV administration of ketamine compared to midazolam (used as an anesthetic “active placebo”) was conducted in 72 patients with TRD (Murrough et al 2013). Antidepressant response rates were 64% and 28% in the ketamine and control condition, respectively. In a follow up analysis focusing on the impact of ketamine on suicidality, Price et al reported that 53% of patients receiving ketamine exhibited a rapid decrease in explicit measures of suicidal thinking compared to 24% of patients receiving midazolam ($P = 0.03$) (Price, Iosifescu et al. 2014).

Suicidality is a psychiatric emergency and the development of effective treatments that can rapidly treat suicidal ideation and lower suicide risk is a major area of unmet need in

medicine. Identifying strategies to provide rapidly effective treatment for suicidal ideation in which the effectiveness of the treatment can be maintained for an extended period of time, particularly for patients that have been refractory to adequate treatments for suicidal ideation and for patients receiving ketamine, represents a critical area of need.

SUMMARY OF THE INVENTION

Methods and compositions for the rapidly effective treatment of suicidal ideations with ketamine and for maintenance of the ketamine anti-suicidal effect are described herein. It has now been discovered that administration of ketamine and lithium to patients is effective to provide rapid abatement of suicidal ideations, to maintain the ketamine effect (in rapidly reducing suicidal ideations) and to provide continued relief from suicidal ideations. The ketamine and lithium may be co-administered or administered serially and can be used to treat patients that currently suffer from suicidal ideations, or that have attempted suicide at least once or that have a history of recurrent or chronic suicidal ideations.

As used herein the term suicidal ideation refers to thinking about, considering, or planning for suicide. This is the same definition of this term adopted by the Centers for Disease Control and Prevention. See <http://www.cdc.gov/violenceprevention/suicide/definitions.html>. Suicidal ideation is sometimes referred to as suicidality.

One measure of active suicidal ideation is a score of greater than 3 out of 5 on the suicidal ideation component of the Columbia-Suicide Severity Rating Scale (C-SSRS). In this test, a psychiatrist assesses the patient for suicide risk and completes the C-SSRS.

As used herein the term "effective amount," or "effective dose" means an amount or dose of the compound that is effective to reduce SI severity to less than 3 out of 5 on the C-SSRS.

In particular embodiments, the invention provides a method of treating a human patient for suicidal ideation by administering a composition comprising ketamine to the patient at a dosage sufficient to reduce or eliminate the suicidal ideations and either co-administering at the same time, or subsequently administering, a daily dose of lithium to the patient to maintain the relief from suicidal ideation provided by ketamine administration. Using this combined treatment, the ketamine effect may be maintained for up to several months or more

after administration of ketamine has been discontinued. In one embodiment, ketamine is administered to the patient and between one and three days following treatment the patient's level of suicidality is evaluated to determine if the patient's suicidal ideation has responded to ketamine. Lithium is then administered to the patients in which suicidal ideations have been reduced or eliminated as measured by one of the accepted scales for measuring suicidality.

The clinical utility of combined ketamine and lithium treatment for mitigating suicide risk is the result of the speed of onset, magnitude of effect and the ability to maintain the effect for an extended period of time up to several months or more, provided by the combined administration of these agents. In essence, lithium extends and maintains the patient's response to ketamine and maintains the suicidality reducing effects of ketamine administration.

Esketamine, an enantiomer of ketamine, S (+)-ketamine, a compound two times more potent than racemic (which is a mixture of the S (+) and R (+)) is also useful in practicing the methods of the present invention.

In more specific embodiments, the ketamine is in a pharmaceutically acceptable carrier and is administered to a patient afflicted with suicidal ideations at an effective amount for treating suicidal ideations (for example less than 3 on the CSSRS) of between about 0.1 mg/kg to about 1.0 mg/kg. Lithium is either co-administered along with the ketamine, or can be administered to the patient subsequent to administration of ketamine. The effective daily amount of lithium for maintaining the ketamine effect is a dose of between about 300 to about 1800 mg/day. The ketamine can be administered intra-nasally, intravenously, or via the trans-dermal route. In one embodiment administration of lithium is begun after it has been established that the ketamine has alleviated the patient's suicidal ideations. The lithium can be administered at any time up to a week after administration of ketamine. Some patients may receive a course of treatment with ketamine that may involve administration of ketamine one or more times per week over a period of weeks or months before beginning treatment with lithium.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein are methods and compositions for treating suicidal ideations by intranasal administration of ketamine and in an alternative embodiment, intravenous administration of ketamine. Ketamine administration is effective to provide rapid relief from suicidal ideations in as little as 40 minutes or less. Relapse can be avoided and the ketamine effect maintained by administration of lithium.

The methods of the invention may be achieved by intranasal or intravenous administration of a single dose of ketamine or esketamine. Alternatively, multiple doses of ketamine or esketamine may be administered at spaced apart intervals. In specific embodiments, a single intranasal administration of an aerosol formulation of ketamine is sufficient to reduce suicidal ideations for up to 7 days or more. In other embodiments ketamine is administered once, twice, or three times per week. The ketamine effect of reducing suicidal ideations can be maintained by administering a daily dose of lithium to the patient. The lithium can either be co-administered with an initial ketamine dose or administered after the ketamine. In a typical treatment regimen, the patient will receive an initial dose of ketamine and beginning within a week after the last dose of ketamine (in the case where multiple doses of ketamine are administered) a daily dose of lithium to maintain the ketamine effect. In another embodiment of the invention the patient is not begun on lithium treatment until after it has been determined (using one of the accepted scales for measuring suicidality) that the patient's suicidality has been reduced or eliminated by treatment with ketamine.

At least twenty-four hours after administration of a first dose of ketamine the patient may be tested to determine if the patient is responding to the ketamine.

The effectiveness of ketamine in reducing suicidal ideation can be measured using any of the available scales for scoring a patient's suicidality-including for example the suicide item of the Montgomery-Asberg Depression Rating Scale (MADRS-SI) or the Columbia-Suicide Severity Rating Scale (C-SSRS). Prior to beginning ketamine therapy for suicidal ideation the patient is tested using one of the standard suicidality rating scales. Examples of other accepted scales for assessing suicidal ideation that are well known to those skilled in the art include the Beck Scale for Suicidal Ideation (BSS), Suicidal Ideation Questionnaire (SIQ),

Suicide Behaviors Questionnaire-Revised (SBQ-R), Concise Associated Symptoms Tracking scale (CAST), Concise Health Risk Tracking scale (CHRT), the Suicide Intent Scale (SIS), the Hamilton Depression Rating Scale© (HDRS) Montgomery-Asberg Depression Rating Scale (HDRS), Mini International Neuropsychiatric Interview (MINI) ; Columbia Classification Algorithm of Suicide Assessment (C CASA), Beck Hopelessness Scale© (BHS) Geriatric Depression Scale (GDS) and Clinical Global Impression scale (CGI). Any of these scales, employed alone or in combination, can be effectively used to assess the patient's pre-treatment level of suicidality as well as the efficacy of the treatment methods and compositions disclosed herein.

A patient is considered to be responding to ketamine if there is at least a fifty percent (50%) improvement in the patients suicidal ideation severity compared to the patients initial (pre-ketamine administration) test score in some cases, such as when the BSS is used. In other cases, a specific score on the scale indicates resolution of clinically significant SI, for example a score of less than 4 on the MADRS-SI or a score of less than 3 on the C-SSRS. If the patient does not respond to the initial ketamine dose, administration of ketamine is continued one, two or three times per week until the patient shows at least a fifty percent improvement in suicidal ideation severity compared to the initial (pre-ketamine administration) test score or otherwise attains a score consistent with amelioration of clinically significant SI (e.g., a score of less than 3 on the C-SSRS). That is to say, the patient is observed after administration of each ketamine dose and a determination made as to whether the patient has responded to the ketamine.

The determination that a patient has responded to the ketamine treatment is made at least one to three days after administration of the initial ketamine dose.

In one embodiment, once it has been established that the patient is responding to ketamine (using one of the accepted scales for measuring suicidal ideation level), lithium (preferably in the form of lithium carbonate) is administered to the patient on a daily basis. The daily dose of lithium is between about 300 and 1800 mg/day and preferably between about 600 and 1200 mg/day and can be administered in a single daily dose or in divided doses.

The lithium can be in tablet or capsule form or administered in a solution. Lithium is also available in an extended release form, which is suitable for this use in the method of the

invention. (US trade names for lithium carbonate and lithium carbonate-extended release include Eskalith, Eskalith-CR and Lithobid).

The therapeutic effect of reducing or entirely eliminating suicidal ideation provided by ketamine may be maintained for several months or longer, as long as the daily administration of lithium is continued. At some point the lithium may lose its maintenance effect i.e. the patients suicidal ideations begin to occur again. At this time the patient is again treated by administration of ketamine (via the intranasal or intravenous route) until it is determined that she is responding to treatment.

The invention provides for administration of a therapeutically effective dose of ketamine, i.e., a dose effective to alleviate suicidal ideation. The actual dose will vary, depending on the body weight of the patient, the severity of the patients suicidal ideations, the route of administration, the nature of medications administered concurrently, the number of doses to be administered per day, and other factors generally considered by the ordinary skilled physician in the administration of drugs.

In a specific embodiment, the amount of ketamine administered to a patient suffering from suicidal ideation is about 10% to about 20% of the amount used to induce anesthesia.

In another specific embodiment, the dose of ketamine for IV administration is about 0.1 mg per kg of body weight (0.1 mg/kg) to about 1 mg/kg; for IN administration the dose is about 0.25 mg/kg to about 3 mg/kg.. In one embodiment lithium is administered at a dose of between 0.1 and 1.0 mg/kg of body weight. In yet another embodiment, the dose ranges from about 1 mg to about 250 mg.

In another specific embodiment intravenous ketamine is administered two or three times a week (on days 1, 3 and 5) at a dose of 0.5 mg/kg of body weight.

Preferably, the effective dose is titrated under the supervision of a physician or medical care provider, so that the optimum dose for the patient's specific condition and disease state are accurately determined.

In one embodiment, the ketamine is introduced into the subject in the aerosol form in an effective amount of between about 0.25 mg per kg body weight of the patient up to about 3.0 mg per kg body weight of the patient. Doses in this range are effective to reduce or eliminate suicidal ideations in less than 8 hours in most instances and often in less than two hours. In another specific embodiment ketamine is intranasally administered three times per week (on days 1, 3 and 5) at a dose of 0.5 mg/kg of body weight (may vary from 0.1 – 1.0 mg/kg). In another specific embodiment, the dosage is administered as needed. One of ordinary skill in the art can readily determine a volume or weight of aerosol corresponding to this dosage based on the concentration of ketamine in an aerosol formulation of the invention.

The present invention provides liquid aerosol formulations and dosage forms for use in treating subjects suffering from suicidal ideations. In general such dosage forms contain ketamine in a pharmaceutically acceptable diluent. Pharmaceutically acceptable diluents in such liquid aerosol formulations include, but are not limited to, sterile water, saline, buffered saline, dextrose solution, and the like. In a specific embodiment, a diluent that may be used in the present invention or the pharmaceutical formulation of the present invention is phosphate buffered saline or a buffered saline solution generally between the pH 7.0-8.0 range, or water.

The liquid aerosol formulation also may optionally include pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, surfactants and excipients.

The formulation may include a carrier. The carrier is a macromolecule which is soluble in the circulatory system and which is physiologically acceptable where physiological acceptance means that those of skill in the art would accept injection of said carrier into a patient as part of a therapeutic regime. The carrier preferably is relatively stable in the circulatory system with an acceptable plasma half- life for clearance. Such macromolecules include but are not limited to Soya lecithin, oleic acid and sorbitan trioleate, with sorbitan trioleate preferred.

The formulations of the present embodiment may also include other agents useful for pH maintenance, solution stabilization, or for the regulation of osmotic pressure. Examples of the agents include but are not limited to salts, such as sodium chloride, or potassium chloride, and carbohydrates, such as glucose, galactose or mannose, and the like.

The aerosol formulation can be prepared as a dry powder formulation comprising a finely divided powder form of ketamine and a dispersant. For example, the dry powder formulation can comprise a finely divided dry powder containing ketamine, a dispersing agent and also a bulking agent.

Bulking agents useful in conjunction with the present formulation include such agents as lactose, sorbitol, sucrose, or mannitol, in amounts that facilitate the dispersal of the powder from the device.

The formulations of the present aerosol embodiment may also include other agents useful for pH maintenance, solution stabilization, or for the regulation of osmotic pressure. Examples of the agents include but are not limited to salts, such as sodium chloride, or potassium chloride, and carbohydrates, such as glucose, galactose or mannose, and the like.

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In another alternative embodiment, the route of administration comprises trans dermal administration. Such treatment may be administered alone or may be supplemented with other suicidal ideation therapies as described herein. Transdermal administration includes passive or active trans dermal or transcutaneous modalities, including, for example, patches and iontophoresis devices, as well as topical application of pastes, salves, or ointments.

Ketamine is formulated into pharmaceutical compositions comprising a carrier suitable for the desired delivery method. Exemplary carriers include, but are not limited to, any of a number of standard pharmaceutical carriers such as sterile phosphate buffered saline solutions, bacteriostatic water, and the like. A variety of aqueous carriers may be used, e.g. water, buffered water, 0.4% saline, 0.3% glycine and the like. Ketamine may be administered alone in a separate dosage form, or co-administered, simultaneously or sequentially, with the lithium agent, or may be formulated with lithium in a single dosage form.

The compositions of the invention may be designed to be short-acting, fast releasing, long-acting, or sustained-releasing as described herein. Thus, the pharmaceutical formulations may also be formulated for controlled release or for slow release. Specific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs. Any of the above dosage forms containing effective amounts are well within the bounds of routine experimentation and therefore, well within the scope of the instant invention.

The invention also provides a device for patient self-administration of ketamine, which device comprises a transdermal patch containing a ketamine formulation and a pharmaceutically acceptable carrier, wherein the device is formulated to disperse an amount of the ketamine formulation that contains a dose of ketamine effective to alleviate suicidal ideations.

Also contemplated herein is a kit comprising a carrier for delivering ketamine intranasally containing in close confinement therein one or more components, wherein a first component contains ketamine, a second component comprises lithium tablets or capsules and a third component comprises instructions for use.

The methods of the invention may be achieved through a method that comprises intravenous or transdermal administration of multiple doses of the ketamine. In specific embodiments, the ketamine is administered at least one, two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine times in fourteen days. In other embodiments, the ketamine is administered at least one, two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine times in twenty-one days.

Patients experiencing suicidal ideations are treated with a course of ketamine (for example administered 0.5 mg/kg IV three times weekly for two weeks). Patients who respond to this treatment, are then started on a regimen of lithium carbonate dosed daily at a range of 300 - 1200 mg daily for the purpose of extending and maintaining the antidepressant effect of ketamine. The therapeutic maintenance effect of lithium following a response to ketamine is expected to last at least 3 months but may last up to one year or longer, as long as the lithium medication is continued. This regime will be especially useful in treating patients currently experiencing suicidal ideations that have failed to respond to at least two adequate

antidepressant treatments for suicidal ideations as well as for patients that have responded to treatment for suicidal ideations in the past but are presently experiencing renewed episodes of suicidal ideations.

The method of treating suicidality is further described in the following examples.

Examples

Example 1:

Patients with major depressive disorder (MDD) diagnosed with the Structured Clinical Interview for DSM who have a history of recurrent suicidal ideation (SI) as measured by the Columbia Suicide Severity Scale (C-SSRS) are eligible for treatment invention. Patients to be treated are men and women between 18-80 years of age with current clinically significant SI, operationalized as a score of ≥ 4 on the suicide item of the Montgomery-Asberg Depression Rating Scale. The patients' SI have not responded to at least 2 previous treatment attempts, for example two adequate trials of antidepressant medication such as an SSRI or SNRI in the case of MDD. The adequacy of prior antidepressant treatment trials is determined using the Antidepressant Treatment History Form.

Exclusion criteria include any unstable medical or neurological condition, substance abuse or dependence in the 6 months before screen, any psychotic disorder, developmental disorder, or lifetime abuse or dependence on ketamine or phencyclidine. Physical examination, vital signs, weight, electrocardiogram, standard blood tests, and urinalysis are used to confirm the absence of unstable medical illnesses. Women of childbearing potential are required to have a negative pregnancy test before treatment begins.

The patients have a history of co-occurring MDD and SI and present for treatment with current SI symptoms. After the medical and psychiatric screening, ketamine in an IV formulation each patient is administered a dose of between 0.1 mg/kg up to 1.0 mg/kg or else an IN formulation of about 0.25 to 3 mg/kg. A typical dose for the IN formulation would be 1 – 1.5 mg/kg. The amount administered to each patient is determined by either a history of prior response to ketamine at a given dose or determined by the physician, typically beginning at 0.5 mg/kg for the IV formulation or 1.0 mg/kg for the IN formulation.

Response to the treatment is assessed initially at 24 hours following the treatment using the suicide item of the Montgomery-Asberg Depression Rating Scale (MADRS-SI) and the Columbia Suicide Severity Scale (C-SSRS). Patients that experience a clinically significant decrease in their SI, operationalized as at least a 50% reduction in SI score or less than 3 on the MADRS-SI or less than 3 on the C-SSRS, are started on lithium carbonate 600 mg by mouth daily, titrated to up to 1200 mg daily or to a therapeutic blood level of greater than 0.6 mEq/L. The lithium is continued daily to maintain the initial anti-suicidal effect of ketamine. The effect is maintained for up to 1 year and SI severity is assessed at least monthly by the C-SSRS

Example 2:

Patients between the ages of 18 and 80 with posttraumatic stress disorder (PTSD) diagnosed by the Structured Clinical Interview for DSM who have a history of recurrent suicidal ideation (SI) as measured by the Columbia Suicide Severity Scale (C-SSRS) are selected for treatment. Patients have current clinically significant SI, operationalized as a score of ≥ 4 on the suicide item of the Montgomery-Asberg Depression Rating Scale. The patients' SI has not have responded to at least 2 previous treatment attempts. In the case of PTSD, treatment attempts may have included adequate trials of antidepressant medication such as an SSRI or SNRI or else adequate trials of exposure therapy, cognitive behavioral therapy or other evidence-based psychological interventions for PTSD. Patients may or may not have experienced a prior suicide attempt.

Exclusion criteria include any unstable medical or neurological condition, substance abuse or dependence in the 6 months before screen, any psychotic disorder, developmental disorder, or lifetime abuse or dependence on ketamine or phencyclidine. Physical examination, vital signs, weight, electrocardiogram, standard blood tests, and urinalysis will confirm the absence of unstable medical illnesses. Women of childbearing potential are required to have a negative pregnancy test before treatment begins.

The patients described above have a history of PTSD, potentially a prior suicide attempt, a history of SI with non-response to prior treatment attempts. These patients are treated with a course of ketamine in an intranasal formulation (ketamine suspended in saline) of between 0.1 mg/kg and 1.0 mg/kg of ketamine either three times per week or twice per week for up to

4 weeks. Simultaneously, the patients receive lithium carbonate started at 600 mg by mouth daily, titrated to up to 1200 mg daily or to a therapeutic blood level of greater than 0.6 mEq/L. In the case of a clinical response to the combination treatment, operationalized as at least a 50% reduction in SI score, following 4 weeks of concurrent lithium and ketamine treatment, the ketamine is discontinued and the lithium is continued for a duration of up to 1 year, SI severity is assessed at least monthly by the C-SSRS.

Example 3

A group of patients between 18 and 80 years of age diagnosed with suicidal ideation as measured by a score of 3 or more on the Columbia Suicide Severity Scale (C-SSRS) are treated with ketamine. Each patient receives 0.5 mg/kg of body weight of intranasal ketamine (ketamine in a buffered saline solution at between pH 7.0 and 8.0). The ketamine is administered once a day, three times per week on days 1, 3 and 5, for a treatment period of two weeks. One to three days after the conclusion of the two week treatment period, the patients are again tested using the Columbia-Suicide Severity Rating Scale (C-SSRS). Patients that have a response according to their C-SSRS test score are considered as having responded to ketamine treatment. These patients are started on a dose of 600 mg/day of Eskalith (lithium carbonate). Patients return for evaluation every four weeks. For most patients the lithium carbonate maintains the ketamine effect of reducing or eliminating their suicidal ideations for at least 3 months.

CLAIMS

1. A method of treating suicidality which comprises administering to a patient that has attempted suicide at least once and has suicidal ideations an effective amount of ketamine to abate suicidal ideation in the patient, determining that the patients suicidal ideation has been reduced after administration of the ketamine and thereafter administering an effective amount of lithium to the patient at predetermined time intervals.
2. The method of claim 1 which comprises determining that the patients suicidal ideation has been reduced using an accepted scale for measuring suicidal ideation.
3. The method of claim 2 wherein the accepted scale is the suicide item of the Montgomery Asberg Depression Rating Scale (MADRS-SI) or the C-SSRS.
4. The method of claim 2 which comprises beginning administration of ketamine when the patient's suicidal ideation is reduced to less than 3 out of 5 on the Columbia-Suicide Severity RatingScale (C-SSRS).
5. The method of claim 1 which comprises determining the patients level of suicidal ideation prior to administering ketamine using an accepted scale for measuring suicidal ideation.
6. A method of treating suicidal ideation which comprises administering an effective amount of ketamine for reducing suicidal ideation to a patient that has previously been treated for attempted suicide and continues to have suicidal ideations, comprising determining that the patients suicidal ideations have been reduced, and thereafter administering an effective amount of lithium for maintaining the suicidal ideation reducing effect of ketamine in the patient at predetermined time intervals.
7. A method of treating recurrent suicidal ideation which comprises administering to a patient that has been treated for at least one suicide attempt an effective amount for reducing the level of suicidal ideation of ketamine, assessing the patient to determine

if the ketamine has reduced the level of suicidal ideation and thereafter administering an effective amount of lithium to maintain the suicidal ideation reduction effect of ketamine in the patient.

8. A method of treating suicidal ideations which comprises administering an effective amount of ketamine for reducing suicidal ideation to a patient suffering from suicidal ideations and thereafter daily administering to the patient an effective amount of lithium for maintaining the reduced suicidal ideation.
9. The method of claim 8 which comprises administering the lithium once a day.
10. The method of claim 8 which comprises co-administering ketamine and lithium.
11. The method of claim 8 which comprises administering the ketamine intranasally.
12. The method of claim 8 which comprises administering the ketamine intravenously.
13. The method of claim 8 which comprises measuring the patient's level of suicidal ideation prior to administering ketamine to the patient.
14. The method of claim 13 which comprises measuring the patient's level of suicidal ideation after administration of ketamine and administering lithium to the patient only if the measured suicidal ideation level has decreased after administration of ketamine.
15. The method of claim 13 which comprises administering lithium to the patient only if the patient's level of suicidal ideation has been reduced by at least fifty percent after receiving ketamine.
16. The method of claim 7 wherein the effective amount of ketamine is between about 0.01 mg per kg of body weight to about 1 mg/kg of body weight.
17. The method of claim 14 wherein the effective amount of lithium is between about 300 and 1800 mg/day.

18. The method of treating suicidal ideations arising from major depressive disorder which comprises administering to a patient in need of such treatment that has been treated unsuccessfully for suicidal ideations after at least one suicide attempt and is still afflicted with suicidal ideation an effective amount for reducing suicidal ideations of ketamine and thereafter administering lithium to the patient daily to maintain the suicidal ideation reducing effects of the ketamine.
19. The method of claim 18 which comprises administering the ketamine via the intranasal route and administering the lithium orally.
20. The method of claim 1 which comprises administering the ketamine intranasally.
21. The method of claim 1 which comprises administering the ketamine intravenously.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/29137

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 31/135; A61K 9/72 (2016.01) CPC - A61K31/135; A61K9/0019; A61K31/137; A61M15/08; A61K9/0043; A61K45/06 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 9/72 (2016.01) CPC: A61K31/135; A61K9/0019; A61K31/137; A61M15/08; A61K9/0043; A61K45/06 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 514/647; 424/600 (Keyword limited, terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, Google Patents, Google Scholar (NPL); Keywords: suicidal ideation, treat, ketamine, intranasal, lithium, intravenous		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/0093592 A1 (Singh et al.) 03 April 2014 (03.04.2014) para [0002], [0003], [0014], [0016], [0019], [0032], [0035], [0048], [0049], [0067], [0069], [0070]-[0072]	1-21
A	US 2014/0256821 A1 (Chamey et al.) 11 September 2014 (11.09.2014) entire document	1-21
A	Niciu et al., 'Glutamate Receptor Antagonists as Fast-Acting Therapeutic Alternatives for the Treatment of Depression: Ketamine and Other Compounds,' Annu Rev Pharmacol Toxicol., 2014, Vol. 54, pg. 119-139. entire document	1-21
A	US 2012/0107396 A1 (Khan) 03 May 2012 (03.05.2012) para [0002], [0006]-[0007], [0026], [0028], [0040]-[0042], [0056]-[0062], [0100], Table 4	1-21
☐ 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 15 June 2016 (15.06.2016)		Date of mailing of the international search report 29 JUL 2016
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