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Wolters Kluwer

Ketamine and esketamine for treating unipolar depression in adults: Administration, efficacy, and adverse effects

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Jun 2019. | **This topic last updated:** Jul 06, 2019.

INTRODUCTION

Ketamine is a racemic mixture of two enantiomers, S-ketamine (esketamine) and R-ketamine [1]. Ketamine is a standard anesthetic drug that is also administered for analgesia and sedation [2,3]. In addition, ketamine and esketamine can rapidly and transiently alleviate treatment resistant unipolar major depression, including suicidal ideation [4,5]. Although use of ketamine to treat depression has increased [6,7], we suggest that clinicians prescribe ketamine or esketamine cautiously for this indication, only after exhausting other recommended non-electroconvulsive therapy treatments for resistant depression. This approach is consistent with clinical guidance from the American Psychiatric Association and other experts [8,9].

This topic discusses treatment of resistant depression with ketamine and esketamine, including their administration, efficacy, and adverse effects. Separate topics discuss the general principles of treating resistant depression; choosing a specific treatment for resistant depression; and the epidemiology, risk factors,

assessment, and prognosis of treatment resistant depression, as well as using ketamine to induce general anesthesia.

- (See "Unipolar depression in adults: General principles of treating resistant depression".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar treatment resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis".)
- (See "General anesthesia: Intravenous induction agents", section on 'Ketamine'.)

CHEMICAL STRUCTURE

Ketamine is a racemic mixture of two enantiomers that are mirror images of each other and thus not identical in that they cannot be superimposed upon each other (similar to one's hands) [1]. One of the enantiomers, S-ketamine (esketamine), binds more potently to the N-methyl-D-aspartate receptor than the other enantiomer, R-ketamine. (See 'Mechanism of action' below.)

MECHANISM OF ACTION

The mechanism of action for the rapid antidepressant effects of ketamine and esketamine is not known [3]. However, several studies indicate that ketamine has an affinity for multiple receptors [2,10], which has given rise to the hypothesis that the drug binds to, or secondarily affects, different types of receptors that initiate cascading effects acting in concert [10]. The receptors that may be involved include the following:

- **Opioid receptor** – Ketamine is an opioid receptor agonist, which may explain its efficacy for acute pain [2,6,11,12]. Evidence that indicates activation of opioid receptors is involved in ketamine's antidepressant effects includes a randomized crossover trial that compared naltrexone 50 mg with placebo, which were given prior to ketamine 0.5 mg/kg infused over 40 minutes [13]. Naltrexone

is an opioid receptor antagonist. Patients with treatment resistant depression were randomly assigned to the order in which they received each study treatment (naltrexone-ketamine or placebo-ketamine), each study treatment was administered once separated by at least 14 days, and patients were depressed at the time of receiving each study treatment. Among the 12 patients who completed both ketamine infusions, improvement was far less with naltrexone-ketamine than placebo-ketamine on postinfusion days 1 and 3. Use of ketamine for acute pain is discussed separately. (See "Management of acute perioperative pain", section on 'Ketamine'.)

- **N-methyl-D-aspartate (NMDA) receptor** – Glutamate is the primary excitatory neurotransmitter in the brain and binds to several types of receptors, including the NMDA receptor [14]. Although it is established that ketamine is an NMDA receptor antagonist, it is not clear whether NMDA antagonism mediates the drug's antidepressant effects [15]. Evidence that suggests NMDA antagonism may be involved includes randomized trials that found intravenous racemic ketamine 0.2 mg/kg was not effective, whereas 0.2 mg/kg of the stereoisomer esketamine, which is more potent at NMDA receptors [2,16], was effective [16,17] However, other NMDA antagonists such as memantine are not effective for treatment resistant depression [4,10]. (See "Unipolar depression in adults: Management of highly resistant (refractory) depression", section on 'Potential drug therapies'.)

- **Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor** – The AMPA receptor is also involved in glutamate neurotransmission, and ketamine's antidepressant effects may be due at least partially to activation of the AMPA receptor by the ketamine metabolite (2R, 6R)-hydroxynorketamine. In a preclinical study, mice received ketamine, the metabolite (2R, 6R)-hydroxynorketamine, or the metabolite (2S, 6S)-hydroxynorketamine [18]. Antidepressant-like effects were assessed using the forced swim test, learned helplessness test, and novelty suppressed feeding test. Ketamine and (2R, 6R)-hydroxynorketamine each generated antidepressant responses that did not occur with (2S, 6S)-hydroxynorketamine. In addition, the investigators found that (2R, 6R)-hydroxynorketamine activates AMPA receptors, but does not bind

to or inhibit (antagonize) the NMDA receptor, and that blocking the AMPA receptors blocked the antidepressant effects of the metabolite.

Other studies have examined ketamine's mechanism of action at the level of brain structures. As an example, functional neuroimaging studies in patients with treatment resistant depression suggest that ketamine may improve depression by activating of the anterior cingulate cortex [19] and by increasing connectivity between the insula and default mode network.

In addition, a rodent study suggested that neuronal vascular endothelial growth factor signaling in the prefrontal cortex may mediate the rapid antidepressant actions of ketamine [20]. Another preclinical study administered ketamine to rodents with depression-like behaviors (eg, immobility in the forced swim test) induced genetically or by exposure to chronic stress, and found that neuronal activity in the habenula diminished to the level observed in control rodents, and that the depressed-like rodents behaved like the control rodents [21].

KETAMINE

Administration

Setting — Randomized trials of intravenous ketamine for treatment resistant depression have typically occurred in academic hospital settings in which psychiatrists collaborated with anesthesiologists [22-24]. However, ketamine infusions are becoming increasingly available at freestanding outpatient clinics, in which treatment is dispensed by physicians such as often anesthesiologists, who often have limited to no experience treating depression [6]. In addition, outpatients have been treated with oral ketamine ingested at home [25].

Route (formulation) — The optimal method of administering ketamine for treatment resistant depression has not been established [26]. Although most studies have given ketamine intravenously, it can also be administered with intramuscular, intranasal, oral, subcutaneous, and sublingual formulations [2,12,25,27-29]. The route of administration affects patient comfort and convenience, as well as bioavailability, serum concentrations, and duration of effect [26,29]. As an example, oral ketamine is more convenient than other routes, but tastes bad and its

bioavailability is relatively low due to first pass hepatic metabolism [29]. Intranasal delivery can be problematic because of nasal cavity conditions that impede administration or absorption (eg, mucosal inflammation or deviated septum) and patient difficulty with self-administration [30-32].

Evidence comparing different routes of administration includes one open-label trial that randomly assigned patients (n = 27) with new onset or treatment resistant major depression to a single dose of ketamine given intravenously 0.5 mg/kg, intramuscularly 0.5 mg/kg, or intramuscularly 0.25 mg/kg; response was comparable across the three groups [33]. However, interpreting the results is difficult due to the small and heterogeneous sample, lack of a placebo control, and lack of blinding.

Dose — The dose of ketamine for treatment resistant depression varies depending upon the route and frequency of administration [26,29]. For any particular route of administration, no one dose has been established among the different doses tested.

Intravenous — The optimal dose of intravenous ketamine for treatment resistant depression is not established. Nevertheless, small randomized trials that compared different doses of ketamine suggest that generally, the preferred dose may be 0.5 mg/kg of body weight:

- A one-month trial enrolled 99 patients with treatment resistant unipolar major depression who were currently treated with antidepressant drugs, and randomly assigned them to add-on midazolam or four different doses of ketamine [34]. Study drugs were administered as a single intravenous infusion over 40 minutes. Ketamine 0.5 mg/kg and 1 mg/kg were each superior to midazolam 0.045 mg at day 1, whereas ketamine 0.1 mg/kg and 0.2 mg/kg were not. The efficacy of the two higher doses was comparable, but dissociation and elevated blood pressure during infusion each appeared to be worse with ketamine 1 mg/kg than 0.5 mg/kg, suggesting a dose response effect.

- Another one-month trial randomly assigned patients (n = 71) to a single dose of adjunctive ketamine 0.5 mg/kg, ketamine 0.2 mg/kg, or placebo; study drugs were infused over 40 minutes [16]. Improvement was greater with the 0.5 mg/kg dose than placebo, whereas improvement was comparable for the 0.2 mg/kg

dose and placebo. However, improvement with the 0.5 mg/kg and 0.2 mg/kg doses was also comparable.

In addition, short-term randomized trials, which compared ketamine with placebo or active controls and established the efficacy of ketamine, typically used 0.5 mg/kg, infused over 40 minutes (see 'Short-term efficacy' below).

However, dose adjustments may be appropriate for specific patients [8]:

- A dose of 0.75 or 1 mg/kg may be suitable for patients not responsive to 0.5 mg/kg [29].

- For patients who are obese, as indicated by a body mass index ≥30 kg/m^2 (calculator 1), it may be safer to calculate the dose according to ideal body weight and not the actual weight. Limited evidence supporting this approach includes a pooled analysis of three randomized trials, which included 97 patients who received a total of 205 infusions; transient blood pressure >180/100 mmHg or pulse >110 beats/minute occurred in 30 percent of patients [35]. These changes were more likely to occur in obese patients and patients who received larger average doses of ketamine (46 versus 42 mg).

Although the standard rate of infusion appears to be 40 minutes [8], across different studies the rate has varied from 2 to 100 minutes [29]. Relatively slower rates may mitigate sedation and other adverse effects.

The expected peak serum concentration of ketamine 0.5 mg/kg over 40 minutes ranges from 70 to 200 ng/mL [8].

The intravenous dose used for depression is typically less than the dose used for inducing general anesthesia. (See "General anesthesia: Intravenous induction agents", section on 'Dosing'.)

Other formulations — The dose of oral and intranasal ketamine is as follows:

- **Oral** – The optimal dose of oral ketamine for treatment resistant depression is not established. In one small randomized trial that compared ketamine with placebo, the dose of ketamine was 1 mg/kg of body weight [25]. (See 'Other formulations' below.)

- **Intranasal** – The preferred dose of intranasal ketamine for treatment resistant depression is not established. In one small randomized trial that compared ketamine with placebo, the dose of ketamine was 50 mg [28]. (See 'Other formulations' below.)

Frequency — It is not clear how frequently ketamine should be administered [26].

- **Intravenous** – Although the number of times that intravenous ketamine 0.5 mg/kg is administered per week for treatment resistant depression is not established, the evidence suggests that the drug should be given once or twice per week. In most randomized trials, the drug was given only one time and the benefit appeared to diminish over the following week. In one trial that infused ketamine twice weekly or thrice weekly for up to six weeks, improvement of depression with the two dosing frequencies was comparable [36]. (See 'Repeated intravenous infusions' below.)

- **Oral** – The number of times that oral ketamine is administered per week for treatment resistant depression is not established (nor is the dose established). One randomized trial administered ketamine 1 mg/kg thrice weekly because of the low and variable bioavailability of oral ketamine [25]. (See 'Other formulations' below.)

Concurrent treatment — The patient's current medications, including prescription, over-the-counter, and complementary or alternative drugs should be reviewed prior to use of ketamine. The psychiatrist, anesthesiologist, or general medical consultant should decide which to continue and which to taper and discontinue.

It appears that ketamine can be used concurrently with most standard antidepressants without reducing efficacy or increasing side effects [37]. Across randomized trials, ketamine has been administered either as monotherapy or as add-on therapy to antidepressants and antipsychotics [4,16,25,34,36,38-40]. However, low quality studies report that concomitant benzodiazepines may interfere with response to ketamine [41,42], and one randomized trial withheld benzodiazepines 24 hours prior to infusing ketamine [40].

Ketamine is metabolized primarily by hepatic cytochrome P450 2B6 and 3A4 [37]. Concomitant drugs that induce these enzymes may decrease exposure to ketamine and drugs that inhibit these enzymes may increase exposure; these effects may necessitate adjusting ketamine doses. Specific interactions of ketamine with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

During short-term treatment with ketamine, ongoing administration of prestudy antidepressants may help transition patients from ketamine to continuation and maintenance treatment [43]. In addition, concurrent treatment with psychotherapy, such as cognitive-behavioral therapy, may also help the transition [44].

Short-term efficacy — For unipolar major depression, the efficacy of ketamine and esketamine appear to be comparable [1]. However, no head-to-head trials comparing the two drugs have been published.

Randomized trials have demonstrated that intravenous ketamine can rapidly improve treatment resistant depression, including symptoms of suicidal ideation. However, most trials administered only a single infusion, and the benefit diminished within two weeks. It is not known how efficacy is influenced by serum concentrations and the interplay of different factors related to administration [26].

Single intravenous infusion — Multiple randomized trials demonstrate that for treatment resistant depression, a single infusion of ketamine produces a rapid and robust response (eg, within 40 to 120 minutes) in at least 50 percent of patients [45-49]. However, the effect dissipates by day 10 to 14. As an example:

- One pooled analysis of seven trials compared ketamine with placebo (saline) or active medication in 172 patients with unipolar or bipolar major depression [4]. A single dose of ketamine (0.5 mg/kg) or the control was administered intravenously (six trials) or intranasally (one trial); most patients received no concomitant therapy. Response (reduction of baseline symptoms ≥50 percent) at multiple posttreatment time points occurred in more patients who received ketamine than the control condition:
    - Two hours – 51 versus 2 percent of patients
    - One day – 53 versus 7 percent

- Seven days – 31 versus 7 percent

By day 14, response was present in only 11 percent of the patients who received ketamine.

- A meta-analysis of nine trials compared a single infusion of intravenous ketamine (0.5 mg/kg infused over 40 minutes) with a control condition (typically placebo) in patients with unipolar depression (n = 208) or bipolar depression (n = 26); study drugs were typically administered as add-on therapy [38]. Response was more likely to occur in patients who received ketamine than controls, starting at 40 minutes and persisting at multiple subsequent time points; at day 7, response was three times more likely with ketamine (relative risk 3, 95% CI 2-7).

- A subsequent randomized trial compared a single dose of intravenous ketamine 0.5 mg/kg infused over 40 minutes with placebo in patients who remained depressed despite treatment with at least three successive antidepressants (n = 48) [16]. During the period of one to four days after infusion, response (reduction of baseline depression ≥50 percent) occurred in more patients who received ketamine than placebo (46 versus 13 percent).

There are no well-established clinical predictors or biomarkers of acute response to a single infusion of ketamine [50]. However, response may be more likely to occur in patients who are more severely (intensely) depressed at baseline [16]. In addition, greater dissociation during infusion [51], fewer residual depressive symptoms at day 1 [51], and a positive family history of alcohol use disorder may be associated with antidepressant efficacy [51,52].

Augmentation with ketamine may accelerate response to antidepressant treatment, which often takes 6 to 12 weeks [53]. A four-week randomized trial compared a single infusion of add-on ketamine (0.5 mg/kg) with placebo on day 1 of newly initiated treatment with escitalopram 10 mg/day [54]. The sample consisted of 27 patients with unipolar major depression, approximately half of whom were classified as treatment resistant. Study drugs were administered after a two-week washout of prior pharmacotherapy. Response occurred in more patients treated with adjunctive ketamine than placebo (92 versus 57 percent), and the mean time to response was

shorter with ketamine plus escitalopram than placebo plus escitalopram (6 versus 27 days). In addition, more than half of the patients responded within two hours of receiving intravenous ketamine, compared with none of the patients who received placebo. None of the patients discontinued treatment due to adverse effects.

In addition, a prospective observational study found that a single infusion ketamine led to a moderately large reduction of depressive symptoms in patients (n = 17) who had previously not responded to electroconvulsive therapy (ECT) [55]. However, the American Psychiatric Association Council of Research Task Force on Novel Biomarkers and Treatments concluded that ketamine is not an alternative to ECT, because following a successful course of treatment with ketamine or ECT, relapse is nearly two times greater with ketamine [4].

Treating suicidal ideation — Randomized trials in patients with suicidal ideation indicate that a single infusion of ketamine can mitigate symptoms within one hour and can be useful for short-term treatment of suicidal ideation, with benefits persisting for up to one week [48,56,57]:

- A meta-analysis of patient level data from eight randomized trials compared a single intravenous dose of ketamine (0.5 mg/kg) infused over 40 minutes with a control condition (either saline or midazolam) in 167 inpatients or outpatients with active or passive suicidal ideation at study entry [39]. Some of the trials excluded patients at high risk of suicide [58]. Most of the patients were diagnosed with unipolar major depression (77 percent); other diagnoses included bipolar disorder and posttraumatic stress disorder. Approximately 50 percent of patients were concurrently treated with psychotropic medications. After adjusting for potential confounds (eg, age, diagnosis, and use of pharmacotherapy) and concurrent changes in other depressive symptoms, the analyses showed that greater improvement with ketamine began within one day of treatment and that resolution of suicidal ideation by day 7 occurred in more patients who received ketamine than controls (60 versus 32 percent).

- A subsequent trial, lasting 24 hours, compared a single 40-minute infusion of ketamine (0.5 mg/kg) with midazolam (0.02 mg/kg) in 80 patients hospitalized with unipolar major depression, including clinically significant suicidal ideation [40]. Approximately half of the patients were receiving antidepressants.

Response (reduction of baseline suicidal ideation rating scale scores ≥50 percent) occurred in more patients who received ketamine than midazolam (55 versus 30 percent). Following the trial, patients received open-label standard pharmacotherapy, and assessments six weeks later found that the benefit of ketamine with regard to suicidal ideation persisted.

Reduction of nocturnal wakefulness may perhaps be associated with decreased suicidal ideation in patients with treatment resistant depression who receive ketamine [59]. By contrast, ketamine may be less likely to decrease suicidal ideation in patients with chronic suicidal ideation or a history of self-injury [56].

It is not known if ketamine can prevent suicide attempts or deaths [58]. Information about preventing suicidal behavior is discussed separately. (See "Suicidal ideation and behavior in adults", section on 'Management'.)

Repeated intravenous infusions — Patients not responsive to a single infusion of ketamine may improve with subsequent infusions, and improvement following a single infusion can be sustained by subsequent infusions [6,29,60]. As an example, a four-week trial randomly assigned patients with treatment resistant depression (n = 67) to one of four treatments: ketamine two times per week, placebo two times per week, ketamine three times per week, or placebo three times per week [36]. The dose of ketamine was 0.5 mg/kg, and all study drugs were infused intravenously over 40 minutes; current antidepressant drugs were continued. Response (reduction of baseline symptoms ≥50 percent) at day 15 occurred in more patients who received twice weekly ketamine than placebo (69 versus 15 percent) and more often with thrice weekly ketamine than placebo (54 versus 6 percent of patients). The effect size for the two frequencies of ketamine at day 15 was comparable, and the benefit of ketamine persisted throughout the four-week study period.

In addition, one randomized trial (n = 18) suggests that onset of antidepressant effect may perhaps be faster with repeated infusions of ketamine, compared with repeated treatments with electroconvulsive therapy [61]. A retrospective study found that repeated ketamine infusions may help patients who do not respond to ECT [62]. The benefit of repeated intravenous infusions for inducing general anesthesia in patients receiving electroconvulsive therapy is discussed separately. (See "Unipolar

major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)", section on 'Ketamine plus ECT'.)

Repeated infusions of ketamine may provide a relatively large, short-term effect compared with other treatments. A network meta-analysis of 31 randomized trials compared the efficacy of different medications, ECT, and repetitive transcranial magnetic stimulation in treatment resistant depression (sample size not reported); the study used results from direct comparisons between the treatments in head-to-head trials, as well as indirectly comparing treatments through their relative effect with a common comparator (typically placebo) [63]. The largest improvement at two weeks after onset of treatment occurred with ketamine.

Other formulations — The efficacy of intranasal and oral ketamine is as follows:

- **Single intranasal dose** – Short-term improvement of treatment resistant depression can be achieved with one dose of intranasal ketamine. A randomized crossover trial compared a single dose of add-on ketamine (50 mg) with placebo (saline) in 18 patients [28]. Patients were randomly assigned to the order in which they received each study drug (ketamine-saline or saline-ketamine). In addition, patients received each study treatment separated by at least seven days and were depressed at the time of receiving each study drug. Improvement was greater 40 minutes after administration of ketamine than placebo, and response at 24 hours occurred more often with ketamine than placebo (44 [8/18] versus 6 [1/18] percent of patients). In addition, adverse effects were mild and transient.

- **Repeated intranasal doses** – A four-week, randomized trial initially planned to compare intranasal ketamine (100 mg) with midazolam (4.5 mg) in 10 patients with treatment resistant depression [30]. However, the study was terminated early after five patients were enrolled because of poor tolerability, including elevated blood pressure, motor incoordination, and psychotomimetic effects. Absorption varied among patients.

- **Repeated oral doses** – For treatment resistant depression, repeated administration of oral ketamine can provide short-term improvement. A small, three-week randomized trial compared add-on oral ketamine 1 mg/kg with

placebo in patients receiving usual care (n = 40) [25]. Most of the patients had melancholic features and comorbid psychopathology. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received active drug than placebo (32 versus 6 percent). The number needed to treat was approximately four, meaning that for every four patients treated with ketamine and every four treated with placebo, one additional response occurred with ketamine. Follow-up assessments one week after treatment found that the benefit of ketamine persisted. In addition, adverse effects were mild and transient.

Longer-term efficacy — The benefits and safety of longer-term ketamine treatment are not known, due to the relatively short duration of treatment in high quality studies and the lack of follow-up [8,64]. Only sparse, low quality data are available for continuation and maintenance treatment in patients who respond to acute treatment with ketamine. A prospective observational study of three patients found variable responses during a 12-month course of treatment that included 16 to 34 total infusions 0.5 mg/kg per patient [65]. A second prospective observational study included 14 patients who received 12 to 45 continuation/maintenance intravenous treatments over for 14 to 126 weeks; during two years of follow-up, relapse occurred in all but three patients [66].

Concerns have been raised that tolerance or tachyphylaxis can occur, such that the antidepressant efficacy of ketamine declines over time with repeated use; this may lead to progressively larger doses and increased frequency of administration, and eventually to ketamine dependence [9,67]. The concerns include worries about causing a new drug epidemic [9,68]. (See 'Longer term' below.)

Adverse effects — Adverse effects such as psychotomimetic effects may occur more often with ketamine than esketamine [1]. However, no head-to-head trials comparing the two drugs have been published.

One review of adverse effects in patients treated for resistant depression with ketamine found that side effects occur more often with ketamine than placebo or active controls [12]. However, most side effects resolved spontaneously.

Short term — Short-term ketamine for treatment resistant depression is generally safe and well tolerated [6,29,35,66]. In a pooled analysis of three randomized trials, which called for either a single infusion of intravenous ketamine 0.5 mg/kg over 40 minutes or multiple infusions over a 12-day period, 97 patients received a total of 205 infusions [35]. During the 205 infusions, early discontinuation due to adverse effects (hypertension, anxiety, or hypotension) occurred in 2 percent.

For patients with treatment resistant depression who receive intravenous ketamine, side effects peak within two hours [3]. In short-term studies (eg, ≤30 days), transient adverse effects included:

- **Dissociation and psychotomimetic effects** – A review of 60 studies (randomized trials and observational studies with nearly 900 patients) found that dissociation and psychotomimetic effects were reported in more than 70 percent of the studies [12]. Studies of intravenous ketamine were two times more likely to report dissociation and psychotomimetic effects than non-intravenous studies.

  Randomized trials, which typically administered a single intravenous dose of ketamine, indicate that ketamine causes significant, clinically large dissociative and psychotomimetic effects at 40 to 60 minutes post infusion, which subsequently resolved within four hours [4,6,36,38,40,45]. In one trial that administered repeated infusions for up to four weeks, the intensity of dissociative symptoms appeared to diminish with repeated infusions [36]. Results from another trial suggest that dissociation occurs in a dose response manner. (See 'Intravenous' above.)

  Multiple randomized trials studying ketamine for treatment resistant depression have excluded patients with psychotic features [16,25,28,34-36,40,56].

- **Cardiovascular** – A review of 60 studies (randomized trials and observational studies) found that nearly 40 percent of the studies described cardiovascular changes [12]. In randomized trials, which typically administered a single intravenous dose of ketamine, hemodynamic effects included time-limited increases in blood pressure and heart rate:

  - Systolic blood pressure – In four randomized trials, mean increases in systolic blood pressure ranged from 8 to 19 mmHg within 40 minutes of

infusion, which normalized in four hours or less [4,16,40]. In a pooled analysis of three randomized trials that included 97 patients who received a total of 205 infusions, the transient average peak increase was 20 mmHg [35].

Diastolic blood pressure – In a pooled analysis of three randomized trials that included 97 patients who received a total of 205 infusions, the transient average peak increase in diastolic blood pressure was 13 mmHg [35]. Two subsequent randomized trials found that mean increases ranged from 8 to 13 mmHg within 40 minutes of infusion, which normalized in two hours or less [16,40].

In addition, a retrospective study included 66 patients with a mean age of 57 years who received an average of 10 ketamine infusions, 0.5 mg/kg over 40 minutes [69]. Essential hypertension controlled by pharmacotherapy was present in 36 percent. An increase in systolic pressure >30 mmHg or in diastolic pressure >15 mmHg during at least one infusion occurred in 50 percent of the patients. Nearly 80 percent of the blood pressure elevations occurred 30 to 40 minutes after onset of the infusion, and all of the elevated readings resolved within 70 minutes of onset.

- Pulse – In one randomized trial, the mean heart rate increased by 9 beats/minute within two hours of infusion, which subsequently normalized [16].

Results from randomized trials suggest that elevated blood pressure and pulse occur at higher doses in a dose response manner. (See 'Intravenous' above.)

Other cardiovascular changes that may occur include chest pain, palpitations, and/or pressure, which generally resolved within 90 minutes of receiving ketamine [12].

- **Other** – Other common, transient adverse effects of ketamine in randomized trials included [36,40,53]:
  - Anxiety

- Blurred vision
- Dizziness
- Headache
- Nausea or vomiting

The transient adverse effects of intravenous ketamine in patients with treatment resistant depression occurred at subanesthetic doses. The adverse effects of intravenous ketamine when used to induce general anesthesia (table 1) are discussed separately. (See "General anesthesia: Intravenous induction agents", section on 'Adverse effects'.)

Longer term — Longer-term, repeated use of ketamine can lead to:

- **Abuse and addiction** – Ketamine can act as a transient intoxicant/euphoriant/hallucinogenic and is liable to abuse, addiction, and diversion as an illicit recreational drug (street name “Special K”) [6,8]. Thus, multiple randomized trials studying ketamine for treatment resistant depression have excluded patients with substance related and addictive disorders [16,25,35,36,40,56]. One case report described a patient with treatment resistant major depression who received intranasal ketamine for self-administration at home and developed ketamine use disorder [11]. Another case report described ketamine use disorder in a nurse who stole intramuscular ketamine from her hospital for self-medication of major depression that had never been treated with antidepressants [70].

  The abuse potential of ketamine may be related to its structural similarity to phencyclidine and its agonist activity at opioid receptors [2,6,11,12]. (See 'Mechanism of action' above.)

- **Neurotoxicity** – Studies in ketamine abusers and rodents have found adverse effects on brain structure and function, including cognitive function [4,6,12,23].

- **Bladder toxicity** – Ketamine abuse is associated with bladder dysfunction that may require surgery [8,12,71,72].

- **Hepatoxicity** – Ketamine abuse is associated with liver injury [12].

ESKETAMINE

Administration — Information about administering intranasal esketamine is available through the US Food and Drug Administration-approved labeling [73].

Setting — In the United States, intranasal esketamine is available only through a Risk Evaluation and Mitigation Strategy program, in which the drug is sold to certified medical offices for specific patients who are enrolled in a registry [74]. Patients self-administer the drug in the office and are then monitored for at least two hours by clinicians in the office. Esketamine is kept under lock and key and is not allowed to leave the office. This program is intended to ensure safety and prevent misuse and diversion.

Route (formulation) — Esketamine is generally administered as a nasal spray.

Dose — The dose of intranasal esketamine on day 1 of treatment is 56 mg [73]. Subsequent doses are 56 mg or 84 mg, depending upon efficacy and tolerability.

Esketamine may be more potent than ketamine in treating major depression. In one randomized trial, intravenous esketamine 0.2 mg/kg was superior to placebo [17]. By contrast, two other randomized trials found that the benefit of intravenous ketamine 0.2 mg/kg and placebo was comparable [16,34].

Frequency — The recommended frequency of intranasal esketamine for treatment resistant depression is as follows [73]:

- Weeks 1 through 4 – Two times/week
- Weeks 5 through 8 – Once/week
- Thereafter – Once every one to two weeks

Concurrent treatment — Esketamine has been administered both as monotherapy and as add-on therapy with antidepressants [17,75,76].

Efficacy

Short term — For unipolar major depression, the efficacy of esketamine and ketamine appear to be comparable [1]. However, no head-to-head trials comparing the two drugs have been published.

Based upon short-term randomized trials, a single dose of intravenous or intranasal esketamine can ameliorate treatment resistant depression, including symptoms of suicidality requiring hospitalization, within two to four hours. In addition, response (reduction of baseline symptoms >50 percent) during short-term trials occurs in approximately 25 to 65 percent of patients with unipolar major depression:

- One trial assigned 30 patients to receive intravenous infusions of esketamine 0.2 mg/kg, esketamine 0.4 mg/kg, or placebo [17]. Double-blind treatment occurred during the first week, with infusions on day 1 and day 4, followed by open-label treatment with up to four infusions of esketamine over two weeks, and a subsequent follow-up assessment-only phase for another two weeks. Following the first dose of study drug, improvement with each dose of esketamine occurred within two hours, and response at 24 hours after the infusion occurred in more patients treated with esketamine 0.2 mg/kg or esketamine 0.4 mg/kg than placebo (67 and 64 versus 0 percent). The benefit of active treatment persisted for the entire five weeks of the study. The most common adverse effects of esketamine were dissociation, headache, and nausea; in two cases, esketamine 0.4 mg/kg caused severe dissociation that resolved within four hours.

- A subsequent one-week trial assigned 67 patients treated with antidepressants to add-on intranasal esketamine 28 mg, esketamine 56 mg, esketamine 84 mg, or placebo twice weekly [75]. Exclusion criteria included history of substance use disorder and psychotic disorder. Improvement of depression was greater with each dose of esketamine than placebo, the antidepressant effect began within two hours of the first dose, and larger doses of esketamine provided a greater benefit than smaller doses. Response with esketamine 28 mg, 56 mg, 84 mg, and placebo occurred in 36, 27, 42, and 3 percent of patients. The benefit of active treatment persisted during subsequent open-label treatment (total treatment = 74 days) once per week, as well as eight weeks of post-treatment follow-up. The most common adverse effects of esketamine were dizziness, headache, dissociation, and nausea. In addition, most patients treated with esketamine experienced elevations in systolic/diastolic blood pressure within 40 minutes of administering the drug, with a maximum mean

change of 19/10 mm Hg. The elevated values typically returned to baseline within two hours.

- A four-week trial compared twice weekly intranasal esketamine with placebo in 66 patients who were initially hospitalized for approximately five days due to imminent risk of suicide [76]. Inclusion criteria did not specify treatment resistant depression. Exclusion criteria included current substance use disorder and history of psychotic disorder. All patients received standard antidepressants and 24 percent received augmentation pharmacotherapy. The dose of esketamine was 56 mg or 84 mg, depending upon tolerability.

  Improvement of depression was greater with esketamine than placebo at 4 hours, 24 hours, and 48 hours after the initial dose, and the clinical effects were moderate to large. In addition, remission at day 25 with esketamine and placebo occurred in 60 and 42 percent of patients; although a statistical test was not reported, a difference of this magnitude, if real, would be clinically meaningful. The number needed to treat was six, meaning that one additional remission occurred with esketamine for every six patients treated with esketamine and every six treated with placebo.

  Improvement of suicidal ideation was greater with esketamine than placebo four hours after the initial dose and the clinical effect was moderate to large. Also, resolution of suicidal risk at 24 hours after the initial dose occurred in six times as many patients who received esketamine than placebo (40.0 versus 6.5 percent).

  Discontinuation of treatment due to adverse effects occurred nearly five times more often with active drug than placebo (14 and 3 percent of patients [5/35 and 1/31]). Adverse effects that occurred in at least twice as many patients who received esketamine than placebo included anxiety, dissociation, dizziness, nausea, vomiting, paresthesia, and sedation. Dissociation resolved within two hours of onset and was less severe with repeated doses. In addition, elevations in blood pressure occurred each day that study drugs were administered and generally resolved within two hours; the maximum mean increases of systolic/diastolic pressures with esketamine and placebo were 17/12 and 9/8 mmHg.

Longer term — One randomized trial enrolled depressed patients (n = 176) who remitted after acute treatment with intranasal esketamine plus an antidepressant, and randomly assigned them to maintenance treatment with esketamine (56 or 84 mg) plus antidepressant or placebo plus antidepressant [73]. Maintenance treatment lasted for up to 80 weeks, during which adjunctive esketamine or placebo were administered once every week or every other week. Time to relapse was longer with esketamine than placebo (hazard ratio 0.5, 95% CI 0.3-0.8).

Adverse effects — Adverse effects such as psychotomimetic effects may occur less often with esketamine than ketamine [1]. However, no head-to-head trials comparing the two drugs have been published.

Randomized trials compared intranasal esketamine plus antidepressant with placebo plus antidepressant in a total of 568 patients with treatment resistant depression [73]. The frequency of adverse effects with adjunctive esketamine versus placebo included the following:

- Anxiety – 13 versus 6 percent of patients
- Increased blood pressure – 10 versus 3 percent
- Dissociation – 41 versus 9 percent
- Dizziness – 29 versus 8 percent
- Hypoesthesia – 18 versus 2 percent
- Lethargy (fatigue) – 11 versus 5 percent
- Nausea – 28 versus 9 percent
- Vomiting – 9 versus 2 percent
- Sedation (somnolence) – 23 versus 9 percent
- Vertigo – 23 versus 3 percent
- Feeling drunk – 5 versus 1 percent

We presume that longer term, repeated use of esketamine can potentially lead to adverse effects that are seen with longer-term, repeated use of ketamine. (See 'Longer term' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- Ketamine is a racemic mixture of two enantiomers, S-ketamine (esketamine) and R-ketamine. Ketamine and esketamine can each rapidly and transiently alleviate treatment resistant unipolar major depression, including suicidal ideation. (See 'Introduction' above and 'Chemical structure' above.)
- Ketamine or esketamine may be indicated for treatment resistant, severe unipolar major depression without psychotic features, if patients have failed or declined other indicated treatments for resistant depression. Patients receiving ketamine or esketamine should be under the care of a psychiatrist who can determine whether other treatments have been appropriately administered and can monitor the outcome of the ketamine/esketamine trial.(See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- Although the mechanism of action for the rapid antidepressant effects of ketamine or esketamine is not known, several studies indicate that ketamine has an affinity for multiple receptors. (See 'Mechanism of action' above.)
- If ketamine is used for treatment resistant depression, clinicians need to determine different aspects of administration, including setting, route of administration, dose, frequency, and use of concomitant medications. (See 'Administration' above.)

- Randomized trials have demonstrated that intravenous ketamine and intranasal esketamine can each rapidly improve treatment resistant depression, including symptoms of suicidal ideation. (See 'Short-term efficacy' above and 'Short term' above.)

- In patients treated for resistant depression with ketamine, side effects occur more often with ketamine than placebo or active controls. Short-term adverse effects include dissociation, psychotomimetic effects, and cardiovascular changes such as increased systolic and diastolic blood pressure and increased pulse; most of these side effects resolve quickly. However, ketamine can act as a transient intoxicant and is liable to abuse, addiction, and diversion as an illicit recreational drug. Ketamine abuse is also associated with neurotoxicity and bladder dysfunction. (See 'Adverse effects' above.)

- Adverse effects that occur at least twice as often with intranasal esketamine plus antidepressant, compared with placebo plus antidepressant, include anxiety, increased blood pressure, dissociation, dizziness, nausea, sedation, and vertigo. We presume that longer-term, repeated use of esketamine can potentially lead to adverse effects that are seen with longer-term, repeated use of ketamine. (See 'Adverse effects' above and 'Longer term' above.)

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Topic 119992 Version 5.0

GRAPHICS

Intravenous anesthetic induction agents

Drug	Uses	Suggested induction dose	Advantages	Potential adverse effects
Propofol	Induction agent of choice for most patients	▪ 1 to 2.5 mg/kg ▪ Older age: 1 to 1.5 mg/kg ▪ Hypovolemia or hemodynamic compromise: ≤1 mg/kg	▪ Rapid onset and offset ▪ Antiemetic properties ▪ Antipruritic properties ▪ Bronchodilation ▪ Anticonvulsant properties ▪ Decreases $CMRO_2$, CBF, and ICP	▪ Dose-dependent hypotension ▪ Dose-dependent respiratory depression ▪ Pain during injection ▪ Microbial contamination risk ▪ Rare anaphylaxis in patients with allergy to its soybean oil emulsion with egg phosphatide
Etomidate	May be selected in patients with hemodynamic instability due to any cause	▪ 0.15 to 0.3 mg/kg ▪ Presence of profound hypotension: 0.1 to 0.15 mg/kg	▪ Rapid onset and offset ▪ Hemodynamic stability with no changes in BP, HR, or CO ▪ Anticonvulsant properties ▪ Decreases $CMRO_2$, CBF, and ICP	▪ High incidence of PONV ▪ Pain during injection ▪ Involuntary myoclonic movements ▪ Absence of analgesic effects ▪ Transient acute adrenocortical suppression
Ketamine	May be selected in hypotensive patients or those likely to develop hypotension (eg, hypovolemia, hemorrhage, sepsis, severe cardiovascular compromise)	▪ 1 to 2 mg/kg ▪ Chronic use of tricyclic antidepressants: 1 mg/kg ▪ Presence of profound hypotension: 0.5 to 1 mg/kg ▪ Intramuscular dose: 4 to 6 mg/kg	▪ Rapid onset ▪ Increases BP, HR, and CO in most patients ▪ Profound analgesic properties ▪ Bronchodilation ▪ Maintains airway reflexes and respiratory drive ▪ Intramuscular route available if IV access lost	**Cardiovascular effects** ▪ Increases myocardial oxygen demand due to increases in HR, BP, and CO ▪ Increases pulmonary arterial pressure (PAP) ▪ Potentiates cardiovascular toxicity of cocaine or tricyclic antidepressants ▪ Exacerbates hypertension, tachycardia, and arrhythmias in pheochromocytoma ▪ Direct mild myocardial depressant effects **Neurologic effects**

				▪ Psychotomimetic effects (hallucinations, nightmares, vivid dreams) ▪ Increases CBF and ICP; may increase $CMRO_2$ ▪ Unique EEG effects may result in misinterpretation of BIS and other processed EEG values **Other effects** ▪ Increases salivation
Methohexital	Induction for electroconvulsive therapy (ECT) because it activates seizure foci	▪ 1.5 mg/kg	▪ Lowers seizure threshold, facilitating ECT ▪ Decreases $CMRO_2$, CBF, and ICP	▪ Limited availability ▪ Dose-dependent hypotension ▪ Dose-dependent respiratory depression ▪ Involuntary myoclonic movements ▪ Pain during injection ▪ Contraindicated in patients with porphyria

$CMRO_2$: cerebral metabolic oxygen requirement; CBF: cerebral blood flow; ICP: intracranial pressure; BP: blood pressure; HR: heart rate; CO: cardiac output; PONV: postoperative nausea and vomiting; EEG:electroencephalographic; ECT: electroconvulsive therapy.

Graphic 102350 Version 11.0

Contributor Disclosures

Michael Thase, MD Grant/Research Support: Acadia [Depression]; Alkermes [Depression]; Allergan (Forest, Naurex) [Depression]; AssureRx Health [Depression]; Avanir [Depression; Axsome [Depression]; BioHaven [Depression]; Intracellular [Depression]; Johnson & Johnson; Janssen, Ortho-McNeil [Depression (Risperidone, Esketamine)]; National Institute of Mental Health [Depression]; NeoSync [Depression (transcranial magnetic stimulation)]; Otsuka [Depression (Aripiprazole, Brexpiprazole)]; Patient-Centered Outcomes Research Institute [Depression]; Takeda [Depression]. Consultant/Advisory Boards: Acadia [Depression]; Akili [Depression]; Alkermes [Depression]; Allergan (Forest, Naurex) [Depression (Botulinum Toxin A)]; Fabre-Kramer Pharmaceuticals [Depression]; Gerson Lehrman Group [Depression]; Guidepoint Global [Depression]; Johnson & Johnson (Janssen, Ortho-McNeil) [Depression (Risperidone, Esketamine]; H Lundbeck [Depression (Vortioxetine)]; Neuralstrim [Depression]; Novartis [Depression]; Otsuka [Depression (Aripiprazole, Brexpiprazole)]; Pfizer [Depression (Venlafaxine, Desvenlafaxine, Ziprasidone)]; Sunovion [Depression (Lurasidone)]. Employment (Spouse): Peloton Advantage. Other Financial Interest: American Psychiatric Foundation (royalties); Guilford Publications (royalties); Herald House (royalties); WW Norton & Company (royalties). **K Ryan Connolly, MD, MS** Nothing to disclose **Peter P Roy-Byrne, MD** Employment: Mass Medical Society (journal Watch); Wiley Lliss (Depression and Anxiety) [Editor in Chief]. Stock Options: Valant Medical Solutions [behavioral health (EMR)]. **David Solomon, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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