Oral Ketamine for Depression: A Systematic Review

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ABSTRACT

Objective: Intravenous (IV) ketamine has rapid and robust antidepressant effects; however, poor accessibility of the IV route often limits its use. Numerous alternative routes of administration are being investigated. Oral ketamine is particularly appealing for its ease of use with the potential for high accessibility. The objective of the current systematic review, in accordance with PRISMA, is to determine the efficacy, safety, tolerability, and dose range of oral ketamine for bipolar and unipolar depression.

Data Sources: The MEDLINE/PubMed, EMBASE, and Google Scholar databases were systematically searched for relevant articles, written in English, published prior to July 2018 using relevant keywords for all variants of *ketamine*, *oral*, and *depression*.

Study Selection: All clinical studies assessing oral ketamine for bipolar or unipolar depression were included. A total of 13 published articles were identified, of which 2 were proof-of-concept, randomized controlled trials (RCTs); 1 was a prospective open-label trial; 5 were retrospective chart reviews; and 5 were case reports.

Data Extraction: Included articles were qualitatively analyzed to determine antidepressant efficacy, tolerability, safety, dose range, antisuicide effects, time to effect, and efficacy in treatment-resistant depression and study bias.

Results: Both RCTs demonstrated antidepressant efficacy with good tolerability; however, significant changes in depressive symptom severity were observed only after 2–6 weeks of treatment ($P < .05$). Both RCTs had high risk for bias, due to inadequate intent-to-treat analysis and adverse effect monitoring. Rapid antidepressant effects (ie, within 24 hours), antisuicide effects, and efficacy in treatment-resistant depression were reported only in retrospective studies. Dosages and frequency of administration were variable (ie, 0.5–7.0 mg/kg 3 times daily to once monthly), with most studies providing dosages of 1–2 mg/kg every 1–3 days. No clinically significant adverse effects were reported.

Conclusions: A small number of clinical studies assessed the antidepressant effects of oral ketamine. Initial results suggest that oral ketamine has significant antidepressant effects with good overall tolerability; however, antidepressant effects are not as rapid as those associated with IV ketamine. Antisuicide effects and efficacy in treatment-resistant depression have yet to be demonstrated. Additional well-designed RCTs are warranted.

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As the leading cause of disability worldwide, depression affects over 350 million people globally.[1] Current treatments, both pharmacologic (eg, antidepressants) and non-pharmacologic (eg, psychotherapy, brain stimulation), typically require weeks before clinically significant antidepressant effects are observed, during which time patient suffering, disability, functional impairment, and risk of suicide persist.[2] Moreover, according to the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[3] approximately half of the patients will not achieve full remission of depressive symptoms after 2 sequential adequate trials of first-line treatments. Consequently, new antidepressant treatments with greater efficacy and more rapid effects are urgently needed.

Ketamine is a dissociative anesthetic agent that has been investigated for its antidepressant effects over the past 2 decades.[4] Of note, ketamine is not currently approved for the treatment of depression; however, off-label use of ketamine for depression is increasing worldwide. Ketamine has numerous proximal and distal pharmacologic targets, with its antidepressant effects hypothesized to be primarily mediated through modulation of the glutamate system.[5] Intravenous (IV) ketamine has been shown to have robust and rapid antidepressant effects in treatment-resistant depression (TRD).[6,7] Numerous randomized controlled trials (RCTs) and meta-analyses have consistently shown large antidepressant effect sizes (Cohen *d* range, 0.9–1.2) that are observed within hours of administration of IV ketamine, with effects lasting 4–10 days after a single dose of 0.5 mg/kg IV ketamine infused over 40 minutes.[6,7] In addition to ketamine's large antidepressant effect size, there are 3 specific and clinically significant advantages that IV ketamine has compared to conventional antidepressants: (1) efficacy in TRD,[6,7] (2) rapid effects (ie, antidepressant effects observed within hours of first dose),[7] and (3) evidence for antisuicide effects.[8] Additionally, IV ketamine has been found to be generally well tolerated and safe in clinical trials for depression, with only mild, time-limited dissociative effects and increases in blood pressure commonly observed.[9]

While IV ketamine is recognized as the gold standard route of administration,[10] the use of IV

Clinical Points

- Intravenous (IV) ketamine has rapid and robust antidepressant effects; however, the antidepressant effects of oral ketamine are less known.
- Based on a small number of low-quality clinical studies, preliminary evidence suggests that oral ketamine has clinically significant antidepressant effects with good overall tolerability; however, antidepressant effects are not as rapid as those associated with IV ketamine. Antisuicide effects and efficacy in treatment-resistant depression of oral ketamine have yet to be demonstrated.

infusions has poor feasibility, accessibility, and scalability as infusion clinics are resource intensive with high costs and require patients to physically visit clinics for each treatment. Numerous investigators have assessed alternative routes of administration (eg, oral, sublingual, intranasal, intramuscular, subcutaneous).[11,12] However, comparatively fewer studies have evaluated these alternative routes.[12]

The large majority of antidepressants are orally administered, giving them the greatest potential for accessibility and scalability. Therefore, if effective and well tolerated, oral ketamine may be a preferred alternative to the IV route. Oral ketamine is commonly prescribed off-label for its analgesic effects and more recently has been prescribed for its potential antidepressant effects.[13] Due to its bitter taste, oral ketamine is typically compounded into capsules or mixed with flavored juice to make it more palatable.[14] Oral ketamine has extensive first-pass metabolism (primarily into norketamine via cytochrome P450 [CYP] 3A4) with approximately 10%–20% bioavailability.[15] Alternatively, oral ketamine may be given sublingually, in which case individuals are instructed to keep the liquid under their tongue for several minutes to allow for transmucosal absorption prior to swallowing, increasing bioavailability to approximately 30%.[16] The evidence for oral ketamine for depression was most recently reviewed by Schoevers et al,[13] who identified only low-quality evidence, with only uncontrolled, open-label studies and case report–level data and no RCTs identified.[13] Since that publication, numerous additional studies using oral ketamine for depression have been published, warranting a reanalysis of the literature.

The objective of the current systematic review is to determine the efficacy, safety, tolerability, and dose range of oral ketamine for depression. Additionally, we specifically evaluate the evidence for (1) rapid antidepressant effects (ie, within 24 hours of first treatment), (2) antisuicide effects, and (3) efficacy in TRD. These additional specific outcomes were selected as these are the effects that IV ketamine differentially provides as compared to conventional antidepressants. For this review, we examine all clinical studies (eg, case reports, chart reviews, clinical trials) using oral ketamine (including racemic ketamine, *R*-ketamine, or *S*-ketamine) for bipolar or unipolar depression. Of note, while there are other promising routes of administration for ketamine (eg, intranasal[11]), for added clarity, the focus of the current review is exclusively on oral ketamine, with a brief discussion of IV ketamine to contextualize our results.

METHODS

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, for this systematic review, the MEDLINE/PubMed, EMBASE, and Google Scholar databases were searched from inception through July 2018 for published reviews, meta-analyses, and primary clinical studies evaluating the antidepressant effects of oral/sublingual ketamine/*S*-ketamine/*R*-ketamine in individuals with bipolar or unipolar depression (ie, major depressive disorder [MDD]). The following search string was used: ((*oral* OR *sublingual* OR *PO* OR *SL* OR *transmucosal*) AND (*depression* OR *major depress** OR *MDD* OR *depressive* OR *bipolar*) AND (*ketamine* OR *esketamine* OR *s-ketamine* OR *r-ketamine*)). Reference lists from identified articles were also manually searched for additional pertinent references. Google Scholar was used to identify articles that had cited the previously identified studies to identify additional potential articles of interest. All identified articles were screened for inclusion in the current systematic review. All published human studies, written in English, assessing the antidepressant effects of oral/sublingual racemic ketamine/*S*-ketamine/*R*-ketamine were included. Of note, due to the known limited number of studies, there were no restrictions placed on study quality (ie, randomization and use of a control group; allocation concealment; or blinding of outcome assessment, study personnel, or participants). Articles reporting case studies; case series; open label, non-randomized, non-blinded clinical trials; or trials lacking a control group were also eligible for inclusion. Both retrospective and prospective studies were included. No restrictions were made on the presence or absence of comorbid disorders; studies assessing populations with depression with comorbid medical and/or psychiatric conditions were still included. Studies using primarily non-oral administration of ketamine were excluded. All preclinical studies (eg, animal studies) were excluded. A review protocol was not registered. Of note, the authors were unable to conduct a quantitative analysis (eg, meta-analysis) given the limited number of RCTs identified ($k = 2$). As such, the authors believed that meta-analyzing these studies would be inappropriate with potentially misleading results.

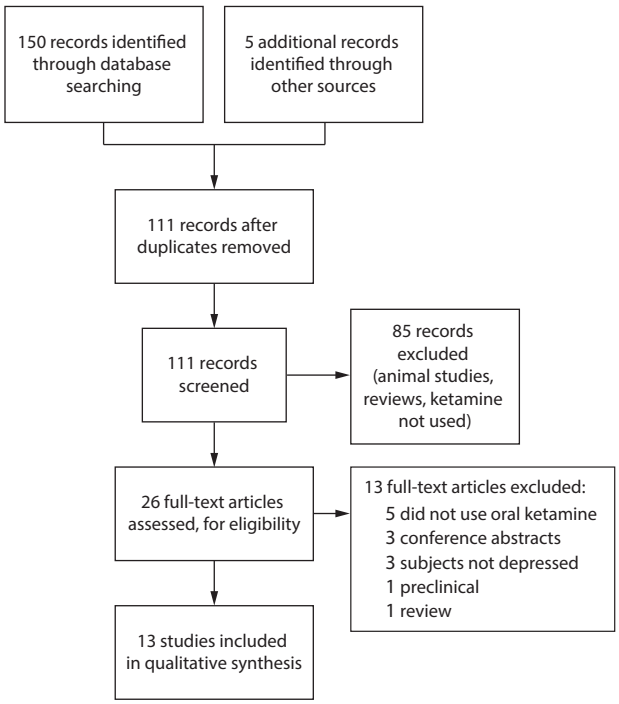
To specifically determine the evidence of oral ketamine for antisuicide effects, rapid antidepressant effects, and efficacy in TRD, all studies were systematically searched specifically for these items. Any report of decreased suicide attempts, completed suicides, suicidal ideations, or decreases in standard suicide rating scale scores was considered positive evidence for decreased suicidality. "Rapid effects" were defined a priori as statistically significant antidepressant effects within 24 hours of first dose (as seen with IV ketamine).[7] Studies reporting efficacy in samples with 2 or more failed adequate treatment trials were considered as evidence for efficacy in TRD. If the authors did not explicitly

report TRD as an inclusion criterion or number of previous treatment trials, the results were not considered to be either in support of or against a positive effect in TRD.

The risk of bias was assessed for all RCTs. As per recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*,[17] bias was assessed based on the following 6 domains: sequence generation (eg, based on description of randomization), allocation concealment, blinding of outcome assessors, intention-to-treat, for-profit bias, and adverse events bias. Risk of bias was designated to be high if described protocols were concerning for bias in a given domain. If description of the domain was omitted from the primary text, risk was labeled as "unknown." When an adequate protocol was described for a given domain, it would be labeled "low risk."

Because this was a systematic review utilizing no patient level data, research ethics board (REB) approval was not required. The REB at University Health Network in Toronto, Ontario, Canada, verified that REB approval was not required for the current study (under section 2.2.b at http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter2-chapitre2/).

Figure 1. PRISMA Flow Diagram for Study Selection



RESULTS

Search Results

After removal of duplicates, the initial search yielded 111 records (Figure 1). After screening of titles and abstracts, 26 full-text articles were evaluated for inclusion. Evaluation of full-text articles yielded 13 articles: 2 RCTs,[18,19] 1 prospective open-label trial,[20] 5 retrospective chart reviews,[21–25] and 5 case reports[14,26–29] (consisting of 1 to 4 cases per article) as summarized in Table 1 (prospective studies) and Table 2 (retrospective studies; ie, chart reviews and case reports).

Prospective Studies Assessing Oral Ketamine for Depression

Two double-blind, placebo-controlled RCTs assessing the antidepressant effects of oral ketamine were identified.[18,19] The larger RCT conducted by Arabzadeh et al[18] assessed the effects of oral ketamine 25 mg twice daily adjunctive to sertraline (starting dose of 25 mg titrated to 150 mg daily) (n = 45) compared to sertraline with adjunctive placebo (n = 45) in a sample of participants with MDD with moderate-to-severe depressive symptoms, based on a Hamilton Depression Rating Scale (HDRS) score ≥ 20. Over the course of the 6-week RCT, a significant effect in favor of adjunctive ketamine for time × treatment interaction on the HDRS scores was observed ($F_{2.19,173.01} = 5.70$, $P = .003$). Significant differences were observed in the HDRS scores at week 2 ($P < .001$), week 4 ($P = .001$), and week 6 ($P = .009$). Similarly, rates of antidepressant response (ie, proportion of participants with at least a 50% reduction in HDRS scores) were higher among participants receiving adjunctive ketamine when compared to placebo at week 2 (85.4% vs 42.5%) through week 6 (85.4% vs 57.5%). However, the remission rates (ie, proportion of participants with HDRS scores in the normal range) were not statistically significantly different between the 2 groups ($P = .42$). Notably, antidepressant effects in the first 2 weeks were not assessed; as such, it is unknown if a rapid antidepressant effect occurred with adjunctive oral ketamine. There were no reported substantial differences in adverse effects or discontinuation between the 2 groups. Interestingly, and in contrast to IV ketamine studies, there were no recorded reports of dissociative symptoms associated with ketamine treatment. In addition, the authors reported that none of the participants showed evidence of abuse of or dependence to ketamine.

In a smaller RCT, Jafarinia et al[19] assessed the antidepressant (primary outcome) and analgesic (secondary outcome) effects of monotherapy with oral ketamine 50 mg 3 times daily (n = 23) versus oral diclofenac 50 mg 3 times daily (n = 23) in participants with mild-to-moderate depression (HDRS score < 19) with comorbid chronic moderate headaches. In this 6-week trial, no significant difference in HDRS scores was observed in the first 3 weeks, and a statistically significant effect in favor of ketamine was observed only after 6 weeks of treatment with a moderate-to-large effect size (Cohen $d = 0.79$, $P = .017$). Of note, there was no significant difference in analgesic effects between groups throughout the course of the study ($P > .05$). Tolerability and safety were found to be good, with no significant differences in adverse effects or discontinuation between groups. No clinically significant dissociative effects were reported.

Irwin et al[20] conducted a prospective, single-arm, open-label trial treating depressed participants receiving hospice

Table 1. Summary of Prospective Studies, Including Double-Blind RCTs and Open-Label Studies

Study	Design	Inclusion Criteria	Intervention Groups	Antidepressant Effects	Safety and Tolerability	Limitations	Rapid	A-S	TRD
Arabzadeh et al, 2018[18]	RCT, 6 wk	Aged 18–60 y MDD, moderate-to-severe MDE (HDRS score ≥ 20), No antidepressants in past mo, no ECT in 2 mo No statement on treatment resistance	Sertraline 150 mg daily with ketamine 25 mg twice daily (n = 45) vs sertraline 150 mg with placebo twice daily (n = 45)	Significant antidepressant effect observed after 2 wk in ketamine group (response rate: 85% vs 43%) that was maintained through wk 6 (response rate: 85% vs 58%); however, no difference in remission rates ($P = .42$)	Mild, transient A/Es with no significant dissociative effects No differences in A/Es or overall discontinuation between groups	Did not report effects prior to 2 wk of treatment Unclear method for monitoring A/Es	N	N	N
Jafarinia et al, 2016[19]	RCT, 6 wk	Aged 20–55 y MDD, mild-to-moderate MDE (HDRS score < 19) with comorbid diagnosis of chronic mild-to-moderate headache No antidepressants in past mo No statement on treatment resistance	Ketamine monotherapy 50 mg 3 times daily (n = 23) vs diclofenac monotherapy 50 mg 3 times daily (n = 23)	Improvements in HDRS scores were not significantly different between treatment groups at wk 3; however, significantly different improvements in HDRS were observed between treatment groups after 6 wk (greater HDRS reduction for ketamine vs diclofenac (Cohen $d = 0.79$; $P = .017$). No significant differences in analgesic effects	Mild, transient A/Es with no significant dissociative effects No differences in A/Es or overall discontinuation between groups	Most participants had mild symptoms with likely ceiling effect for change in HDRS score Unclear method for monitoring A/Es	N	N	N
Irwin et al, 2013[20]	Single arm, open-label, 28 d	Aged over 18 y Depressive symptomatology warranting pharmacologic intervention with HADS score ≥ 15, depression subscale score ≥ 8 Life-limiting illness, receiving hospice care No statement on treatment resistance	Ketamine 0.5 mg/kg oral daily for 28 d (n = 14 starting, n = 8 completing) No control group	For participants who completed the study (8/14; 4 withdrew for nonresponse), all had significant improvement in both depressive symptoms ($P = .002$) and symptoms of anxiety ($P < .001$). Improvement in symptoms occurred by day 14 for depression (Cohen $d = 1.14$, $P = .01$) and day 3 for anxiety	Mild, transient A/Es with no significant dissociative effects Most common A/Es: diarrhea, trouble sleeping, and trouble sitting still	No control group Medically unwell population; unclear if extrapolation to general population is possible	N	N	N

Abbreviations: A/E = adverse effect, A-S = antisuicide effect reported, ECT = electroconvulsive therapy, HADS = Hospital Anxiety and Depression Scale, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, MDE = major depressive episode, N = no (in satisfying criteria), rapid = antidepressant effects reported in first 24 hours, RCT = randomized controlled trial, TRD = study used a sample with treatment-resistant depression.

care with oral ketamine 0.5 mg/kg daily for 28 days. Inclusion was based on having a terminal illness and depressive symptoms meriting pharmacologic intervention as determined by 2 separate clinicians. This study started with 14 participants; however, only 8 completed as 4 withdrew due to ineffectiveness of oral ketamine and 2 withdrew due to changes in medical status believed to be unrelated to ketamine use. Improvements in depressive symptoms, as measured using the Hospital Anxiety and Depression Scale, were observed in all 8 participants that completed the trial: significant reductions in symptoms of depression ($d = 1.14$; 95% CI, 1.09–5.9; $P = .01$) and anxiety ($d = 0.67$; 95% CI, 1.0–3.7; $P = .004$) were observed by days 14 and 3, respectively. These improvements remained significant through day 28 for both depression and anxiety ($P < .01$). Adverse effects were rare, with the most common being diarrhea, trouble sleeping, and trouble sitting still. Additionally, given that all participants had a terminal illness, it was unclear if reported "side effects" were related to ketamine use or progression of medical illness.

Notably, Irwin et al[20] did not report an intent-to-treat (ITT) analysis, but rather, reported changes in symptom severity for only the 8 participants completing the study. However, of the 6 patients (43%) who withdrew from the study, none (0%) showed an improvement on the depression subscale. As such, an ITT analysis using the last observation carried forward would yield an effect size almost half the magnitude of the reported effect sizes when including the lack of improvement in 43% of participants (ie, including the noncompleters).

Retrospective Case Series and Case Reports Assessing Oral Ketamine for Depression

Five retrospective chart reviews (with 17 to 37 cases per article) and 5 case reports (with 1 to 4 cases per article) were identified with a total of 141 patients receiving oral ketamine in these retrospective studies, as summarized in Table 2. The majority of individuals were diagnosed with treatment-resistant unipolar depression,[14,21–24,26,27] and a small number of individuals were diagnosed with bipolar depression.[22,28] Good tolerability and safety were consistently observed in all 141 cases, with no clinically significant adverse effects reported. Dissociative effects were reported in 2 chart reviews.[23,25] Antidepressant effects were inconsistent with antidepressant response rates, varying greatly from 18%[23] up to approximately

Table 2. Summary of Retrospective Studies, Including Case Series and Case Reports

Study	No. of Cases	Dose and Duration[a]	Description	Rapid	A-S	TRD
Hartberg et al, 2018[21]	37	Start at 0.5 mg/kg and titrate up by 20%–50% at each subsequent treatment During titration period, dosed twice daily at most twice per wk After titration was complete, received treatment between twice weekly and once every 2 wk Final doses ranged from 0.5 to 7.0 mg/kg for up to 3 y	Charts of patients with TRD with comorbid PTSD who received oral ketamine treatment were reviewed to compare the number and duration of psychiatric hospital admissions before and after treatment. Following treatment, inpatient hospital days were reduced by 70%, and hospital admissions were reduced by 65%. The dose of ketamine required was stable over time with no evidence of tolerance building. There were no serious adverse events and no long-term negative effects associated with ketamine reported.	N	N	Y
Iglewicz et al, 2015[25]	29	0.5 mg/kg ranging from a single dose (22/29) up to dosing 3 times daily (4/29)	Chart review of inpatients receiving hospice care who received ketamine for depression. Clinical Global Impressions scale (CGI) was used retrospectively to rate therapeutic improvement, global improvement, and side effects from ketamine over 21 d. Per the CGI, ketamine was found to be significantly therapeutically effective through the first week after ketamine dosing ($P < .05$), with 93% of subjects showing positive results for days 0–3 and 80% for days 4–7 post–ketamine dosing. Ketamine was reported to be generally well tolerated.	Y	N	N
Lara et al, 2013[22]	26	Sublingual (10 mg from a 100 mg/mL solution held under tongue for 5 min and then swallowed), repeatedly administered every 2–3 d or weekly for up to 6 mo	Chart review of outpatients with TRD (both bipolar and unipolar) who received sublingual ketamine. According to patients' reports, ketamine produced rapid (within 90 min), clear, and sustained effects, improving mood level and stability, cognition, and sleep in 20 patients (77%). No manic, psychotic or dissociative symptoms were observed, but 2 patients with bipolar depression reported agitation for a few hours. Mild light-headedness was a common but transient side effect, subsiding typically in < 30 min and more pronounced or present only after the first dose.	Y	N	Y
Al Shirawi et al, 2017[23]	22	Started at a dose of 50 mg every 3 d, titrated up by 25 mg every 3 d, according to response and tolerability Mean (SD) dose of 222 (72) mg, with a distribution as follows: 100 mg (2 patients), 150 mg (5 patients), 175 mg (1 patient), 225 mg (4 patients), 250 mg (4 patients), and 300 mg (6 patients) every 3 d for up to 2 y	Chart review of outpatients with TRD who received oral ketamine who previously failed at least 3 adequate antidepressant treatment trials and 1 adequate trial of repetitive transcranial magnetic stimulation. Over the course of treatment, 18% of the patients showed greater than 50% reduction in Beck Depression Inventory II scores and 14% reported partial improvement in mood symptoms, while 45% had no response to ketamine and 23% showed a mild worsening in their depressive symptoms. The most frequent adverse effects were acute dissociation, dizziness, blurred vision, numbness, and sedation. Neither serious adverse effects nor any cases of abuse or dependence were observed. Among responders/partial responders, documentation of continued efficacy ranged from 15 wk to 2 y from the onset of treatment.	N	N	Y
Nguyen et al, 2015[24]	17	0.5–1 mg/kg sublingual every 7–14 d for up to 18 mo	Chart review of outpatients with TRD who received sublingual ketamine. Benefit was noted in 76% of cases. The onset of response was generally noted within 24 h of taking ketamine. If patients did not respond within 24 h, they typically received no benefit from taking ketamine. No significant adverse effects were reported. The absence or presence of dissociative effects was not explicitly reported. Effects on suicidality were not reported.	Y	N	Y
Swiatek et al, 2016[27]	1	0.25 mg/kg every 8 h (dose was reduced by 50% from the recommended starting dose used in prior studies due to hepatic dysfunction from his severe malnutrition) for 10 d	A 62-year-old man was admitted to the inpatient surgical service for worsening abdominal pain. He scored 16 on Hospital Anxiety and Depression Scale-Depression (HADS-D) at baseline testing, signifying severe symptoms and emotional distress despite multidrug therapy with therapeutic doses of citalopram, mirtazapine, and lorazepam. At 48 h post-ketamine, his HADS-D score was 10 (38% change), and ketamine was continued at the same dose. Notably, the patient was taking opioids, but following the addition of ketamine, the opioid dose was reduced by 75%. No significant adverse effects were reported.	Y	N	Y

(continued)

80%[22,25] in chart reviews. Anti-suicide effects (ie, subjectively decreased suicidal ideations) were reported in only 3 cases[26,28] and 1 chart review[24] (Table 2). Dosages varied greatly from 0.5 to 7 mg/kg dosed monthly to 3 times daily for up to 3 years. The majority of cases used oral racemic ketamine, except for 1 report[29] of 4 cases using sublingual *S*-ketamine, with 2 cases having clinically significant improvement and 2 cases having no response. Only mild adverse effects were noted with sublingual *S*-ketamine in all 4 cases.

Assessment of Study Quality and Bias

The quality of the included RCTs was assessed systematically via evaluation of bias in accordance with the *Cochrane Handbook for Systematic Review of Interventions*. Included RCTs were assessed for bias in 6 domains, namely, sequence generation, allocation concealment, blinding of outcome assessors, ITT, for-profit bias, and adverse events bias, as summarized in Table 3. Systematic assessment of bias was conducted only for RCTs and was not conducted

Table 2 (continued).

Study	No. of Cases	Dose and Duration[a]	Description	RAPID	A-S	TRD
De Gioannis and De Leo, 2014[28]	2	Starting 0.5 mg/kg titrated to 1.5–3 mg/kg every 2–4 wk with unreported duration	A 44-year-old man with a history of bipolar depression and chronic suicidal ideation with comorbid severe chronic pain was treated with amitriptyline and quetiapine but remained depressed, with a scores of 36 on the Montgomery-Asberg Depression Rating Scale (MADRS) and 4/6 on the suicide item. He received ketamine ingested orally with a flavored drink every 2 wk. Starting with an initial dose of 0.5 mg/kg and gradually increasing by 0.5 mg/kg with each treatment, he achieved a sustained clinical response at around 3 mg/kg with no adverse effects. Within 24 h of his first treatment, his scores on the MADRS and suicide item decreased to 17 and 1, respectively. Repeated treatments every 2–3 wk produced sustained remission of his suicidal ideation. A 37-year-old woman with bipolar depression and suicidal ideation had undergone adequate trials of venlafaxine, mirtazapine, fluoxetine, quetiapine, and olanzapine and several courses of electroconvulsive therapy. Her current regimen included venlafaxine and quetiapine. She remained depressed, with scores on the MADRS and suicide item of 31 and 4, respectively. Oral ketamine was added. Within 24 h of her first treatment, the scores decreased to 10 on the MADRS and 2 on the suicide item. She continued to receive monthly doses of oral ketamine, and her mental state continued to improve with no suicidal ideation between treatments.	Y	Y	Y
McNulty and Hahn, 2012[14]	1	Single dose of subcutaneous ketamine 0.5 mg/kg followed by 40 mg oral ketamine daily for unknown duration (treatment ongoing)	A 44-year-old male hospice patient had severe anxiety and depression in addition to multiple near-terminal comorbid physical conditions that produce chronic pain. Prior treatments prescribed to resolve this patient's pain, anxiety, and depression had proved ineffective. However, a single low-dose (0.5 mg/kg) subcutaneous test injection of ketamine provided dramatic relief from those symptoms for 80 h. This good outcome has been sustained by daily treatment with oral ketamine as a well-tolerated and effective treatment for the triad of severe anxiety, chronic pain, and severe depression.	Y	N	Y
Irwin and Iglewicz, 2010[26]	2	Single dose of 0.5 mg/kg oral ketamine	Two cases of TRD with significant comorbid pain and terminal medical conditions are reported in which a single oral dose of ketamine provided rapid and moderately sustained symptom relief for both depression and anxiety. Suicidal ideations also greatly decreased. Significant analgesic effects were also observed. No adverse effects were noted.	Y	Y	Y
Paslakis et al, 2010[29]	4	1.25 mg/kg oral *S*-ketamine 3 times daily for 14 d	Oral *S*-ketamine was added to standard antidepressants in 4 depressed patients. Two patients with melancholic depression responded early and stayed in remission, while 2 patients with distinct somatic symptoms, chronicity or atypical features did not respond. Overall, *S*-ketamine was well-tolerated with essentially no adverse effects reported.	N	N	N
Total	141	Doses of 0.5 to 7 mg/kg given 3 times daily for 1 mo up to 3 y				

[a]Oral racemic ketamine was used unless otherwise specified.
Abbreviations: A-S = antisuicide effect reported, HDRS = Hamilton Depression Rating Scale, n = no (in satisfying criteria), PTSD = posttraumatic stress disorder, RAPID = antidepressant effects reported in first 24 hours, TRD = study used a sample of treatment-resistant depression, Y = yes (in satisfying criteria).

Table 3. Summary of Study Quality and Bias Assessment for Randomized Controlled Trials

Study	Sequence Generation	Concealment	Blinded Outcome Assessment	Intent-To-Treat Analysis	Adverse Events Bias	For-Profit Bias
Jafarinia et al, 2016[19]	Low	Low	Low	High	High	Low
Arabzadeh et al, 2018[18]	Low	Low	Low	High	High	Low

for open-label or retrospective studies as these study designs are already known to be high risk in all domains (due to, for example, lack of a control group or blinding). Both RCTs[18,19] identified were conducted by the same group using a similar protocol and had risks for bias in the same domains. Both studies described adequate randomization and blinding protocols. Risk of bias was identified in 2 domains, namely, ITT analysis and adverse events bias. In both studies, results were reported only for participants who completed the study, thus indicating failure to conduct an adequate ITT analysis. The authors reported systematic screening for adverse events; however, they did not use any validated scales to specifically rate dissociative or psychotomimetic effects, as is now standard practice in ketamine trials.[9] Additionally, they did not report changes in blood pressure, a variable that is also routinely reported in ketamine clinical trials.

DISCUSSION

The current systematic review identified 2 RCTs (with a total of 68 participants receiving oral ketamine), 1 prospective open-label trial (n = 14) and 10 retrospective studies (pooled n = 141), in total yielding results for 223 individuals receiving oral ketamine for depression. The majority of studies were

of low quality given their retrospective study design, lack of blinding, and lack of comparator control groups. As such, the evidence available to date is inadequate to reliably determine the antidepressant efficacy, safety, and tolerability of oral ketamine. Moreover, a quantitative analysis (ie, meta-analysis) was not feasible as only 2 small RCTs would be eligible for inclusion. Nevertheless, several themes emerged in our qualitative analysis of the identified studies.

The most consistent result in all prospective and retrospective studies was good tolerability with oral ketamine, having only mild and transient adverse effects, with no clinically significant tolerability or safety concerns. Intriguingly, dissociative effects, which are often reported with IV ketamine, were rarely observed. Of note, however, some studies have suggested that dissociative effects may be predictive of antidepressant effects with IV ketamine (possibly a true predictor of response or a reflection of functional unblinding),[30] while other studies have failed to demonstrate an association between dissociative and antidepressant effects.[31] Notably, the observed good tolerability profile of oral ketamine might have been secondary to (1) lower equivalent doses given its low bioavailability or (2) inadequate adverse effect monitoring and reporting, as most studies did not systematically assess for adverse effects, as is done in most studies with IV ketamine.[9] Taken together, the available literature suggests that oral ketamine is generally well tolerated; however, larger studies with more systematic evaluation of adverse effects are required.

In addition to good tolerability, the available evidence shows promise for significant antidepressant effects for oral ketamine with medium to large effect sizes, as demonstrated by prospective and retrospective studies. However, unlike IV ketamine, oral ketamine has a lag time prior to the emergence of any clinically significant antidepressant effects. Prospective studies reported a delay of 2 to 6 weeks before the emergence of any clinically significant antidepressant effects, a lag time that is comparable to that of conventional antidepressants (eg, selective serotonin reuptake inhibitors).[32] Only case report–level data provided evidence for rapid antidepressant effects (ie, within 24 hours of first dose) with oral ketamine (Table 2). Given the risk of bias associated with case reports, the generalizability of these results is unclear and the available evidence is more in favor of an absence of rapid antidepressant effects. As such, it is more likely that oral ketamine is similar to conventional antidepressants, with some patients responding rapidly after their first dose, although this effect appears to be an exception rather than the rule.[32] Alternatively, the dosages of oral ketamine required to yield rapid effects might be much higher than previously studied.

Another important difference between oral and IV ketamine is the evidence for antisuicidal effects. Of the plethora of psychotropic medications, only lithium and clozapine have definitively demonstrated antisuicide effects.[33,34] Recent evidence has demonstrated significant antisuicide effects with IV ketamine,[8] leading to increased interest in ketamine to specifically target suicidality transdiagnostically. As such, assessment of alternative routes should consider antisuicide effects specifically, as this effect is a key advantage to IV ketamine. Unfortunately, antisuicide effects were reported in only 3 individuals receiving oral ketamine (Table 2).[26,28] Notably, the majority of studies did not specifically comment on the absence or presence of antisuicide effects, such that the question of whether oral ketamine has antisuicide effects remains unanswered.

The current review has several limitations. The greatest limitation is the small number of studies identified, the majority of which were of low quality and retrospective in nature. Additionally, retrospective chart reviews and case reports are most vulnerable to publication bias, as negative case reports are very unlikely to be published. With only 2 RCTs identified, a meaningful meta-analysis could not be conducted. As such, the conclusions from our analysis are guarded, as more high quality RCTs are clearly needed and merited to more definitively determine the effects of oral ketamine. Of note, several studies evaluating oral ketamine are currently ongoing (ClinicalTrials.gov: NCT02836288, NCT02037503, NCT02992496), which may provide greater clarity in the near future.

Another notable limitation of oral ketamine is the risk of diversion and misuse. As IV ketamine is given in a clinic or hospital—a controlled setting—the risk of diversion or misuse is largely avoided. Conversely, oral ketamine lends itself to take-home doses that may easily be diverted or misused in the absence of adequate precautions.[10,35] Given these concerns, along with the lack of evidence in support of oral ketamine, prescribing oral ketamine for depression cannot be recommended until further evidence is available.[10]

CONCLUSION

Currently available evidence is insufficient to support the use of oral ketamine for depression. While a limited number of studies showed promising results for antidepressant effects and good tolerability, further research is needed to more robustly evaluate oral ketamine prior to its recommendation for clinical use. Additionally, currently available evidence suggests that oral ketamine requires 2 to 6 weeks to take effect compared to the rapid antidepressant effects observed within hours with IV ketamine. While replicated evidence has demonstrated antisuicide effects with IV ketamine, there is a paucity of evidence to support antisuicide effects with oral administration. Similarly, there is no clear evidence to demonstrate efficacy for oral ketamine in TRD samples, whereas efficacy for TRD has been repeatedly demonstrated with IV administration.[7] Dosing of oral ketamine also remains unclear, as studies used highly variable dosages. Future studies should focus on dose-response relationships, onset of action, antisuicide effects, and efficacy in TRD samples and should more rigorously evaluate safety and tolerability.

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