Maintenance ketamine treatment for depression

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Maintenance ketamine treatment for depression: a systematic review of efficacy, safety, and tolerability

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Ketamine has rapid yet often transient antidepressant effects in patients with treatment-resistant depression. Different strategies have been proposed to prolong these effects. Maintenance ketamine treatment appears promising, but little is known about its efficacy, safety, and tolerability in depression. We searched Pubmed, Embase, and the Cochrane Library and identified three randomised controlled trials, eight open-label trials, and 30 case series and reports on maintenance ketamine treatment. We found intravenous, intranasal, oral, and possibly intramuscular and subcutaneous maintenance ketamine treatment to be effective in sustaining antidepressant effect in treatment-resistant depression. Tachyphylaxis, cognitive impairment, addiction, and serious renal and urinary problems seem uncommon. Despite the methodological limitations, we conclude that from a clinical view, maintenance ketamine treatment seems to be of therapeutic potential. We recommend both controlled and naturalistic studies with long-term follow-up and sufficient power to determine the position of maintenance ketamine treatment within routine clinical practice.

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See **Online** for appendix

Introduction

Major depressive disorder is one of the leading causes of burden of disease worldwide.[1] Although it is amenable to pharmacotherapy and psychotherapy in most patients, one third of patients with depression do not achieve adequate response to current treatment options.[2] Hence, there is a pressing need to develop new treatment strategies for major depressive disorder generally, and for depression resistant to regular treatment (treatment-resistant depression) specifically.

Rapid and robust reductions in depressive symptoms have been observed following administration of the N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine, including in patients with treatment-resistant depression. However, the effects are short-lived. In most patients who respond well to a single dose of ketamine, the benefits disappear within two weeks.[3] Different strategies have been proposed to prolong these benefits, including subsequent treatment with riluzole, lithium, and repeated dosing of ketamine.[4,5] Of these, repeated dosing of ketamine has emerged as the most promising. However, even with repeated dosing, relapse rates remain high after cessation of treatment, and median time to relapse is still only two to three weeks.[3,4] Maintenance ketamine treatment might be a necessary strategy to sustain the initial antidepressant effects.

In contrast to rapidly accumulating data about short-term effects of ketamine treatment, little is known about maintenance ketamine treatment. Besides the key issue of whether maintenance treatment is indeed capable of sustaining remission of depression, questions about safety and tolerability of long-term treatment arise. Potential harmful consequences of prolonged ketamine use include ulcerative cystitis, liver injury, neurocognitive impairment, and addiction.[6–9] Therefore, with a growing interest in ketamine as a treatment for depression, as well as the increasing use of repeated dosing in both clinical and research settings, the clinical applicability of maintenance ketamine treatment must be further explored and systematically assessed. The aim of this systematic review is to present a comprehensive overview of current literature on the efficacy, safety, and tolerability of maintenance ketamine treatment in depression.

Methods

This Review was conducted and reported according to the PRISMA guidelines[10] and methods were preregistered (PROSPERO, CRD42021253253).

Search strategy and selection criteria

We searched Pubmed, Embase, and the Cochrane Library from inception to March 25, 2021. Search terms included a combination of Medical Subject Headings and text words indicative of (1) (es)ketamine, (2) depression, and (3) maintenance treatment (appendix p 1). No restrictions were set. Database search and eligibility assessment were performed independently in a standardised manner by three reviewers (SS, CE, and DT). Disagreements were resolved through consensus. A log was kept with excluded articles and reasons for exclusion. Reference lists of included articles were hand-searched to identify additional relevant publications.

Following the participants, intervention, comparison, outcomes, and study design (also known as PICOS) strategy, we included studies for which the following criteria were met: (1) participants: men and women of any age with any type of depression, including bipolar depression; (2) intervention: treatment with multiple doses of ketamine or its enantiomer esketamine, for at least four weeks beyond the initial period of acute treatment, and at any dose and in any form of administration; (3) comparison: any control intervention or no control intervention; (4) outcomes: (a) sustained antidepressant effect, as defined by: sustained depressive symptom reduction measured by validated questionnaires, clinician-observed or patient-reported sustained reduction in depressive symptoms, sustained response or remission rates, relapse or recurrence rates, time to relapse or recurrence, or

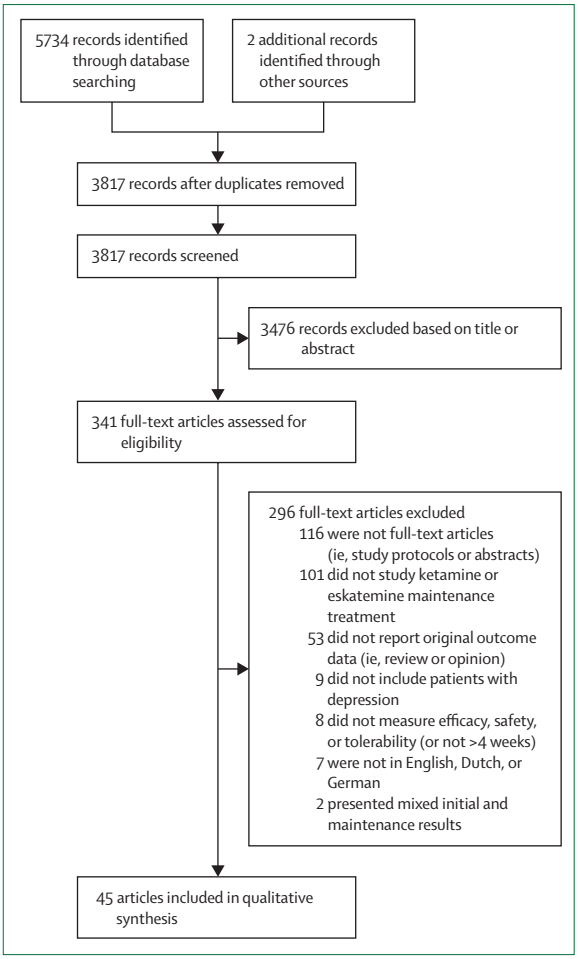

Figure: **Study selection**

functioning; or (b) safety and tolerability, as defined by: adverse events, serious adverse events, or discontinuation due to adverse events, or both (a) and (b); (5) study design: controlled and uncontrolled studies, including randomised controlled trials (RCTs), open-label trials, cohort studies, case series, and case reports. Letters or comments to editors were included if they reported on original data (eg, case series). Only papers in English, Dutch, or German were included.

Data collection and analysis

We collected information about study design, sample characteristics, ketamine intervention, comparison intervention, outcome, and source of funding. Two independent reviewers (SS and JV) assessed bias of the included studies using the Cochrane risk-of-bias tool for randomised trials, the JBI Critical Appraisal Checklist for Quasi-experimental Studies for uncontrolled studies, and the Quality Appraisal Checklists for Case Series Studies for case series and reports. Disagreements were resolved through consensus.

A meta-analysis of RCT data was initially planned but deemed inappropriate as the search revealed only three (heterogeneous) RCTs. Therefore, a qualitative systematic review of both the uncontrolled and controlled study data was undertaken. Results regarding effectiveness were subdivided into results of maintenance treatment within the first 6 months after initial response, results of maintenance treatment of 6 months to 1 year (mid-term), and results of maintenance treatment of 1 year and longer (long-term). Adverse events during these phases were merged and were reported by administration route.

Results

Overall, 5734 records were identified through database search. Two additional records were identified by the hand search of reference lists. After adjusting for duplicates, 3817 records remained. Of these, 3476 were discarded after reviewing titles and abstracts. Of the remaining 341 full-text articles, 45 met the inclusion criteria.[11–55] Eight articles included the same four (cohorts of) patients.[26,27,29,30,38,39,44,45] Nonetheless, since all articles provided complementary results, all were included in the systematic review (figure).

We included three RCTs, eight open-label trials, and 30 case series and reports, with a total of 1495 patients (table 1). Of these, 1272 were diagnosed with unipolar depression, 43 were diagnosed with bipolar depression, and one patient was diagnosed with schizoaffective disorder. In seven studies including 179 patients with unipolar, bipolar, and schizoaffective depression, no further specification was provided regarding the ratio of these diagnoses among the patients. Treatment administration was intravenous ketamine (18 studies), intranasal ketamine (three studies), intranasal esketamine (five studies), oral ketamine (ten studies), oral esketamine (one study), intramuscular ketamine (three studies), and subcutaneous esketamine (one study). Ketamine doses ranged from 0·5 mg/kg to 1·2 mg/kg for intravenous administration, from 50 mg to 200 mg for intranasal administration, from 5 mg to 300 mg and 0·5 mg/kg to 7·0 mg/kg for oral administration, and from 50 mg to 70 mg and 0·5 mg/kg to 1·0 mg/kg for intramuscular administration. Esketamine doses ranged from 28 mg to 84 mg for intranasal administration and from 0·5 mg/kg to 1·0 mg/kg for subcutaneous administration. Oral esketamine was administered in a dose of 2·0 mg/kg. The duration of the maintenance phase varied from 4 weeks to 5 years. The frequency of ketamine or esketamine administration during this phase varied from once a day to once every 12 weeks. Typically, patients continued to take their oral antidepressant medication. In at least 33 studies concomitant antidepressants were allowed or required. In one study ketamine administration was alternated with electroconvulsive therapy.[15] In most studies, maintenance treatment was only offered to people

	Design	N*	Age	Women/ men (n)	Clinical characteristics	Intervention	Dosing	Efficacy	Safety
Intravenous									
Archer et al, 2018[13]	Case series	11	51 (31–69)	10/1	Unipolar (n=8) and bipolar (n=3) treatment-resistant depression (≥5 antidepressants, psychotherapy, and electroconvulsive therapy; n=30); maintenance ketamine treatment only for initial ketamine responders (n=11)	Ketamine 0·5 mg/kg (transition to intranasal [dose not reported] in 1 patient)	Initial dose 2 times a week for 3–4 weeks; maintenance dose 2 times a week or once every 1, 2, or 3 weeks for 6–49 weeks (mean exposure 23 weeks)	Median maintenance BDI and end of treatment BDI < baseline BDI (partial sustained response) in 11 patients; median maintenance BDI and end of treatment BDI < post-acute BDI (sustained response) in 4 patients	Adverse events: feeling unsteady, blurred vision, headache, dry mouth, restlessness, abnormal body sensations, dissociation, changes in perception of stimuli, feeling drowsy, difficulties concentrating; drop-out due to an adverse event in 1 patient; no reported cognitive or urinary side effects; no reported abnormalities on laboratory studies; transient elevated heart rate and increased blood pressure
Barenboim and Lafer, 2018[14]	Open label	8	25–53	6/2	Unipolar treatment-resistant depression	Ketamine 0·5 mg/kg	Initial dose 3 times a week for 1 week; maintenance dose once every 2 weeks for 7 weeks	Mean BDI at baseline 33·75, post-acute 10·25, at end of treatment 10·75	Adverse events: some degree of dissociation in 8 patients; dissociative symptoms attenuated with repeated dosing; nausea in 2 patients; no delusions or hallucinations; no serious adverse event
Bartova et al, 2017[15]	Case report	1	45	1/0	Treatment-resistant depression (including electroconvulsive therapy and esketamine monotherapy failure)	Ketamine 75–100 mg; alternating electroconvulsive therapy	Initial dose of electroconvulsive therapy 3 times a week plus ketamine 2 or 3 times a week for 3 weeks; maintenance dose of electroconvulsive therapy plus 2 ketamine infusions once a month for 6 months	MADRS at baseline 44, post-acute 16; sustained response over the course of maintenance treatment	Adverse events: transient mild cognitive disturbances; vital parameters stable; routine blood parameters stable
Blier et al, 2012[16]	Case report	1	44	1/0	Unipolar treatment-resistant depression (including electroconvulsive therapy failure)	Ketamine 0·5 mg/kg	Single initial dose; maintenance dose 2 times a week for ~4 months	Transient response after initial treatment; sustained partial response and able to do some chores at home over the course of maintenance treatment	Adverse events: transient metallic taste and mild derealisation; MOCA 28–30/30 over the course of treatment
Bryant et al, 2019[17]	Case series	5	65–82	1/4	Unipolar and bipolar treatment-resistant depression (including electroconvulsive therapy failure; n=6); maintenance ketamine treatment only for initial ketamine responders (n=5)	Ketamine 0·5 mg/kg	Initial dose 2 times a week for 1–2 weeks; maintenance dose every 2–6 weeks for 3–15 months (mean exposure 6 months)	Sustained remission (MADRS <10) over the course of 5-month maintenance treatment in 1 patient; initial response but relapse during the maintenance phase after 3–15 months in 4 patients	Adverse events: "mild and transient"; no cognitive issues observed as measured by the MOCA; suicide attempt after relapse in 1 patient; return to alcohol misuse after years of sustained sobriety in 2 patients
Chan et al, 2018[18]	Case series	4	20–50	3/1	Bipolar treatment-resistant depression and alcohol misuse (patient 1); unipolar treatment-resistant depression (patients 2—4)	Ketamine 0·5 mg/kg	3 times a week to once every 5 weeks for 10 weeks up to 5 years	Fluctuation over the 9-months course of maintenance treatment, relatively sober from alcohol (patient 1); sustained response and able to work over the course of maintenance treatment for 5 years; mild relapse after 5 years, followed by regained response (patient 2); initial functional remission; shorter duration of effect after dosing was stretched out to monthly doses; mild relapse after 15 months (patient 3); transient effect (2–3 days) over 10-week course of treatment (patient 4)	Adverse events: dissociation, sedation, giddiness, nausea, sore throat, asymptomatic sinus bradycardia (HR 36 to 39 bpm); MOCA: 30/30 in 2 patients (data from other 2 patients are missing); no urinary symptoms; monthly urinalysis results normal

(Table 1 continues on next page)

	Design	N*	Age	Women/men (n)	Clinical characteristics	Intervention	Dosing	Efficacy	Safety
(Continued from previous page)									
Dale et al, 2020[22]	Open label	94	46 (SD 13·0; n=150)	94/56 (n=150)	Unipolar and bipolar treatment-resistant depression (including electroconvulsive therapy failure; n=150); maintenance ketamine treatment only for initial ketamine responders (n=94)	Ketamine 0·5 mg/kg	Initial dose 2 times a week for 2 weeks; maintenance dose every 2–12 weeks plus 2 or 3 additional doses if reduction in MADRS <50% for 1 year	Sustained response (reduction in MADRS >50%) over the course of maintenance treatment in 56 (59·6%) of initial 94 responders	Not reported
Kwon et al, 2018[38]	Case report	1	49	1/0	Unipolar treatment-resistant depression (including electroconvulsive therapy failure)	Ketamine 0·5 mg/kg	Every 1–2 weeks for 10 months	MADRS at baseline 45, after 1 week 25; sustained response (MADRS 20–30) over the course of maintenance treatment	Adverse events: mild visual and auditory hallucinations; no cognitive dysfunction
Medeiros da Frota Ribeiro et al, 2016[38] and 2017[39]	Case series	2	52 and 55	2/0	Unipolar treatment-resistant depression with psychotic features (patient 1); schizoaffective disorder (patient 2)	Ketamine 0·5 mg/kg	Initial dose frequency and duration not reported; maintenance dose once a month for 1 year	HDRS at baseline 19, post-acute 9; sustained remission (QIDS 6) over the course of maintenance treatment; transient relapse after cessation of ketamine; regained remission after restart (patient 1); HDRS at baseline 29, post-acute 8; sustained remission (QIDS 5) over the course of maintenance treatment (patient 2)	Adverse events: initial mild dissociative symptoms, fatigue, mild headache; no psychotic symptoms (patient 1); no psychotic symptoms (patient 2)
Medeiros da Frota Ribeiro and Riva-Posse 2017[40]	Case series	2	64 and 72	2/0	Unipolar treatment-resistant depression (5 antidepressants; patient 1); bipolar treatment-resistant depression (including electroconvulsive therapy failure; patient 2)	Ketamine 0·5 mg/kg	Initial dose 2 times a week for 2 weeks; maintenance dose once a week to once every 2 weeks for 8 weeks	QIDS at baseline 20, post-acute 6; sustained response (QIDS 6) over the course of maintenance treatment; transient relapse after cessation of ketamine; regained remission after restart (patient 1); QIDS at baseline 14, post-acute 6; sustained response (QIDS 6–7) and resumed daily activities over the course of maintenance treatment (patient 2)	Adverse events: transient psychotomimetic effects; no worsening of cognitive symptoms; no urinary or bladder problems; vital parameters stable
Messer and Haller, 2010[41]	Case report	1	46	1/0	Unipolar treatment-resistant depression (including electroconvulsive therapy failure)	Ketamine 0·5 mg/kg IBW	Initial dose every other day for 2 weeks; maintenance dose once every 3 weeks for >15 months	BDI at baseline 22, post-acute <10; sustained remission (BDI <10) over the course of maintenance treatment	No cognitive or physical impairment beyond 2 h after infusion; no tachyphylaxis or tolerance
Messer and Haller, 2017[42]	Case report	1	45	1/0	Unipolar treatment-resistant depression (5 antidepressants in current episode) and multiple sclerosis	Ketamine 0·5 mg/kg IBW	Initial dose every other day for 2 weeks; maintenance dose once a week to once every 3 weeks for 2 years	BDI at baseline 38, post-acute 19; sustained remission (BDI 5–16) over the course of maintenance treatment	No worsening of multiple sclerosis symptoms

(Table 1 continues on next page)

	Design	N*	Age	Women/men (n)	Clinical characteristics	Intervention	Dosing	Efficacy	Safety
(Continued from previous page)									
Phillips et al, 2019[44] and 2020[45]	Open label	23	42 (SD 12·0)	15/8	Unipolar treatment-resistant depression (≥2 antidepressants plus 2 augmentation strategies in current episode) and MADRS ≥25 (n=43); maintenance ketamine treatment only for initial ketamine responders (n=23)	Ketamine 0·5 mg/kg	Initial dose 3 times a week for 2 weeks; maintenance dose once a week for 4 weeks	Sustained response (reduction in MADRS ≥50%) over the course of maintenance treatment in 21 (91%) of initial 23 responders; no main effect of time on change in MADRS total score (F=0·88; p=0·49) or MADRS suicidality item (F=0·19; p=0·94) over the course of maintenance treatment	Most common adverse events: cardiorespiratory effects, numbness or tingling, dissociation, dizziness, visual disturbances; no serious adverse events; dissociative symptoms attenuated with repeated dosing (p=0·001); no reports of craving or drug-seeking behaviour
Sakurai et al, 2020[46]	Case series	44	46 (SD 19·1; n=87)	48/39 (n=87)	Unipolar and bipolar treatment-resistant depression (≥2 antidepressants; n=87); maintenance ketamine treatment only for initial (partial) responders (n=44)	Ketamine 0·5–1·2 mg/kg (transition to 50–200 mg intranasal ketamine in 3 patients)	Initial dose 2 times a week for 3 weeks; maintenance dose once every 2–6 weeks for up to 11 months (mean or median exposure not reported)	Initial response (decrease in QIDS ≥50%) or improvement (decrease in QIDS ≥35%) but relapse during the maintenance phase in 7 (16%) of initial 44 (partial) responders	No report of cognitive disturbance or urinary problems
Szymkowicz et al, 2013[50]	Case series	3	Not reported	Not reported	Unipolar treatment-resistant depression and anxiety disorder (patient 1); unipolar treatment-resistant depression (including electroconvulsive therapy failure; patient 2); bipolar treatment-resistant depression (including electroconvulsive therapy failure) and eating disorder (patient 3)	Ketamine 0·5 mg/kg IBW	Initial dose 3 times a week for 2 weeks; maintenance dose once every 2–7 weeks for 12 months	Initial remission (MADRS ≤8) within 1 day; mild relapse after 8 months; regained remission after acute ketamine series (patient 1); initial (partial) response; fluctuation over the course of maintenance treatment, including suicidal relapses (patients 2 and 3)	No adverse events (patient 1); increased cognitive difficulties (word-finding and concentration difficulties) and insomnia (patient 2); hypomanic state twice while being on mood stabilisers, overwhelming emotions, and suicide attempt (patient 3)
Vande Voort et al, 2016[51]	Open label	5	46 (SD 8; n=12)	11/1 (n=12)	Unipolar and bipolar treatment-resistant depression (≥2 antidepressants or mood stabilisers in current episode; n=12); maintenance ketamine treatment only for initial ketamine remitters (n=5)	Ketamine 0·5 mg/kg	Initial dose 3 times a week for up to 2 weeks; maintenance dose once a week for 4 weeks	Sustained remission (MADRS ≤9) over the course of maintenance treatment in 5 of initial 5 remitters	Most common adverse events in initial phase: dissociation, dizziness, numbness or tingling, sleepiness or sedation, emotionality, facial numbness; no new adverse events in maintenance phase; no hallucinations; no significant increase in YMRS scores
Wilkinson et al, 2018[54]	Case series	14	47 (SD 18·0; n=54)	33/21 (n=54)	Unipolar, bipolar, and schizoaffective treatment-resistant depression (n=54); maintenance ketamine treatment only for initial ketamine responders unable to sustain response (n=14)	Ketamine 0·5 mg/kg IBW	Initial dose 2 times a week for 2 weeks; maintenance dose every 3 or 4 weeks for 14–126 weeks (mean exposure 76 weeks; median exposure 84 weeks)	Relapse (QIDS <25% improvement from baseline) over the course of maintenance treatment in 11 (79%) of initial 14 responders; of the 11 patients who relapsed: 9 (82%) regained full response, 1 (9%) regained partial response, and in 1 (9%) tachyphylaxis	CogState battery: no correlation between number of infusions and change in cognition; no report of substance misuse or adverse events related to renal and urinary disorders; relapse resulting in suicide attempt in 2 patients

(Table 1 continues on next page)

	Design	N*	Age	Women/men (n)	Clinical characteristics	Intervention	Dosing	Efficacy	Safety
(Continued from previous page)									
Zhang et al, 2016[55]	Case series	2	30 and 60	1/1	Treatment-resistant depression (SSRI, TCA, and MAOI failure) and history of drug misuse (patient 1); treatment-resistant depression (SSRI, SNRI, TCA, and MAOI failure; patient 2)	Ketamine (dose not reported)	Once a day for 6 months (patient 1); once every 2 weeks for 3 years (patient 2)	Not reported	Adverse events: misuse and withdrawal symptoms (patient 1); urine incontinence, determined to possibly be caused by ketamine infusions (patient 2)
Intranasal									
Clark, 2014[19]	Case report	1	44	1/0	Unipolar treatment-resistant depression (including electroconvulsive therapy failure)	Ketamine 50 mg	2 times a week for 4 months	Initial response by day 3; euthymic and able to work over the course of maintenance treatment	Adverse events: brief feelings of being "high" after the first few treatment sessions; mild mood decreases on several days before the next treatment sessions
Cusin et al, 2020[21]	Case series	2	35 and 56	1/1	Treatment-resistant depression, anxiety disorder, and PTSD (patient 1); unipolar treatment-resistant depression (including electroconvulsive therapy and TMS failure; patient 2)	Ketamine 200 mg (patient 1); 60 mg (patient 2)	Every other day for 17 months (patient 1); every other day for 2 years (patient 2)	Remission for 17 months; suicide attempt without any reported trigger, followed by regained remission (patient 1); remission for 2 years, death by suicide after stressful life events (patient 2)	Adverse events: suicide attempt during maintenance treatment in both patients
Daly et al, 2018[23]	Open label	57	45 (SD 10·0; n=67)	38/29 (n=67)	Unipolar treatment-resistant depression (≥2 antidepressants), IDS ≥34, and post-RCT participation	Esketamine 28 mg, 56 mg, or 84 mg	2 times a week for 2 weeks, once a week for 3 weeks, and once every 2 weeks for 4 weeks	Mean change in MADRS score over the course of maintenance treatment −7·2 (SD 1·84); response (reduction in MADRS ≥50%) post-acute: in 38% (n=3/8) with 28 mg, in 36% (n=4/11) with 56 mg, and in 50% (n=5/10) with 84 mg; response (reduction in MADRS ≥50%) at end of maintenance treatment in 65% (n=22/34) of participants	Most common adverse events: dizziness (22 [39%]), dissociation (14 [25%]), dysgeusia (13 [23%]); elevated heart rate and increased blood pressure in most patients; dissociation attenuated with repeated dosing; no symptoms suggestive of psychosis; adverse event leading to discontinuation in 1 (2%); no adverse event leading to death
Daly et al, 2019[24]	RCT	297	46 (SD 11·1)	196/101	Unipolar treatment-resistant depression (1–5 antidepressants in current episode), IDS ≥34, and MADRS ≥28; maintenance ketamine treatment in 62 initial ketamine responders and 90 initial remitters	Esketamine 28 mg, 56 mg, or 84 mg *vs* placebo	Once a week or once every 2 weeks for up to 88 weeks (median exposure 17·7–19·4 weeks)	Relapse of responders (reduction in MADRS ≥50%) esketamine *vs* placebo: 25·8% (n=16) *vs* 57·6% (n=34; HR 0·30; 95% CI 0·16–0·55; p<0·001; NNT 4); relapse of remitters (MADRS ≤12) esketamine *vs* placebo: 26·7% (n=24) *vs* 45·3% (n=39; HR 0·49; 95% CI 0·29–0·84; p=0·003; NNT 6)	Most common adverse events in ketamine arm (n=152): dysgeusia (41 [27%]), vertigo (38 [25%]), dissociation (35 [23%]), somnolence (32 [21%]), dizziness (31 [20%]); no serious adverse event during maintenance phase; adverse event leading to discontinuation in 4 (2·6%) (worsening of depressive symptoms; transient anxiety and confusion); no adverse event leading to death; no interstitial cystitis observed

(Table 1 continues on next page)

	Design	N*	Age	Women/men (n)	Clinical characteristics	Intervention	Dosing	Efficacy	Safety
(Continued from previous page)									
Lee et al, 2019[36]	Case series	13	Not reported	Not reported	Treatment-resistant depression (including electroconvulsive therapy failure) and previous intravenous ketamine response (16 of 17; n=17); maintenance ketamine treatment only for initial ketamine responders (n=13)	Ketamine 100–150 mg	Once a week or 2 times a week for up to 1 year (mean or median exposure not reported)	Sustained response over the course of maintenance treatment in 9 (69%) of initial 13 responders	Adverse events: "minor transient side effects"; no serious adverse event; no adverse event leading to discontinuation
Starr et al, 2020[48]	Open label	23	46 (28–64)	14/9	Unipolar treatment-resistant depression; maintenance ketamine treatment only for initial ketamine responders	Esketamine 28 mg, 56 mg, or 84 mg	Once a week or once every 2 weeks for 14–35 months (mean or median exposure not reported)	Most common reported changes: improved mood (16 [69·6%]), raised daily function (14 [60·9%]), increased social activities (14 [60·9%]), improved motivation (11 [47·8%])	Most common adverse events: feeling drunk or euphoria (6 [26·1%] of 23), tiredness (2 [8·7%] of 23), bad taste (2 [8·7%] of 23)
Stultz et al, 2020[49]	Case report	1	55	1/0	Unipolar treatment-resistant depression (4 antidepressants) and anxiety disorder	Esketamine 84 mg	Initial dose frequency and duration not reported; maintenance dose bimonthly for 3 months	BDI at baseline 38, post-acute 19; sustained remission (BDI 9) over the course of maintenance treatment	Adverse events: feeling "high", slight dissociation, "wobbly legs"; vital parameters stable
Wajs et al, 2020[53]	Open label	603	52 (n=802)	505/297 (n=802)	Unipolar treatment-resistant depression (n=802); maintenance ketamine treatment only for initial ketamine responders (n=603)	Esketamine 28 mg, 56 mg, or 84 mg	Initial dose 2 times a week for 4 weeks; maintenance dose once a week (MADRS >12) or once every 2 weeks (MADRS ≤12) for 22 (n=364) or 48 (n=136) weeks (median exposure 22·9 weeks)	Mean change in MADRS score over the course of maintenance treatment 0·3 (SD 8·12); response (reduction in MADRS ≥50%) at end of maintenance treatment 76·5%; remission (MADRS ≤12) at end of maintenance treatment 58·2%	Most common adverse events during maintenance phase (n=603): dizziness (135 [22·4%]), headache (114 [18·9%]), dissociation (113 [18·7%]), somnolence (85 [14·1%]), nausea (84 [13·9%]); serious adverse event in 38 (6·3%) of 603; most common serious adverse events (n=603): suicidal ideation (4 [0·7%]), depression (3 [0·5%]), suicide attempt (2 [0·3%]), gastroenteritis (2 [0·3%]); adverse event leading to discontinuation in 23 (3·8%) of 603; most common adverse events leading to discontinuation: suicidal ideation (4 [0·7%]), depression (3 [0·5%]), increased blood pressure (2 [0·3%]), hypertension (1 [0·2%]), suicide attempt (1 [0·2%]), vertigo (1 [0·2%]); adverse event leading to death in 2 (0·3%) of 603; adverse events leading to death: acute cardiac and respiratory failure and suicide (both assessed as doubtful or unrelated to treatment); adverse event related to renal and urinary disorders during both induction and maintenance phase in 136 (17·0%) of 802 of which 6 serious but not ketamine related; no adverse cognitive effects on group level; no relevant change in laboratory and ECG parameters; no reports of drug seeking or misuse
Oral									
Al Shirawi et al, 2017[11]	Case series	7	39 (n=22)	13/9 (n=22)	Unipolar treatment-resistant depression (≥3 antidepressants plus TMS; n=22); maintenance ketamine treatment only for initial ketamine responders (n=7)	Ketamine 50–300 mg	Initial dose every 3 days for 4 weeks; maintenance dose every 3 days for 15 weeks to 2 years (mean or median exposure not reported)	Among responders (reduction in BDI >50%; n=4) and partial responders (reduction in BDI 20–50%; n=3), documentation of continued efficacy ranged from 15 weeks to 2 years	Most common adverse events (n=22): dissociation (9 [41%]), dizziness (5 [23%]), blurred vision (4 [18%]), numbness (3 [14%]); transient suicidal ideation (2 [9%]); lower urinary tract symptoms (1 [5%] determined to be unrelated to ketamine by urologist); no evidence of misuse or dependence, hepatic injury, changes in blood pressure, or memory impairment

(Table 1 continues on next page)

	Design	N*	Age	Women/ men (n)	Clinical characteristics	Intervention	Dosing	Efficacy	Safety
(Continued from previous page)									
Arabzadeh et al, 2018[12]	RCT	81	34 (SD 6·7; n=41)	31/50	Moderate or severe unipolar depression (HDRS ≥20)	Ketamine 25 mg *vs* placebo adjuvant sertraline	2 times a day for 6 weeks	Mean HDRS in ketamine arm: at baseline 24·17 (SD 2·31), at week 2 16·48 (SD 3·50), at week 4 12·73 (SD 2·97), at week 6 9·65 (SD 2·90); mean difference ketamine *vs* placebo at week 2 −3·41 (−5·07 to −1·75; p<0·001), at week 4 −2·61 (−4·11 to −1·11; p=0·001), at week 6 −1·91 (−3·34 to −0·48; p=0·009)	Adverse events in ketamine arm (n=41): tremor (4 [10%]), restlessness (3 [7%]), blurred vision (3 [7%]), dizziness (3 [7%]), nausea (3 [7%]); not significantly different from adverse events in placebo arm; no hepatic, cardiac or dissociative symptoms; no adverse event leading to discontinuation; no evidence of misuse or dependence
De Gioannis and De Leo 2014[25]	Case series	2	44 and 37	1/1	Bipolar treatment-resistant depression (including electroconvulsive therapy failure in 1 patient) and chronic suicidal ideation	Ketamine 3·0 mg/kg (patient 1); 1·5 mg/kg (patient 2)	Every 2–3 weeks, duration not reported (patient 1); every month, duration not reported (patient 2)	MADRS at baseline 36, post-acute 17 (patient 1); MADRS at baseline 31, post-acute 10 (patient 2); sustained (partial) response in both patients over the course of maintenance treatment	No adverse event; vital parameters stable
Grande 2017[28]	Case report	1	20	0/1	Bipolar depression with psychotic features and history of suicidality, alcohol misuse, and delusions	Ketamine 8–16 mg†	2 times a day plus additional rescue dose as needed for 6 months	Initial response after 1 dose of ketamine; sustained response over the course of maintenance treatment; alcohol use markedly decreased	Adverse events: mild agitation
Hartberg et al, 2018[31]	Case series	37	46 (21–84)	28/9	Unipolar treatment-resistant depression (≥2 antidepressants)	Ketamine 0·5–7·0 mg/kg	Initial dose 2 times a day up to 2 times a week; maintenance dose 2 times a week to once every 2 weeks for 6 to 36 months (median exposure 31 months)	Mean change in hospital admission over the course of maintenance treatment −70% (p<0·001); reduced number of inpatient hospital days over the course of maintenance treatment (p<0·001)	Most common adverse events: lightheadedness, sedation, dissociative symptoms; no serious adverse events; no cases of bladder toxicity; no tachyphylaxis
Jafarinia et al, 2016[32]	RCT	40	41 (SD 8·7; n=20)	30/10	Mild or moderate unipolar depression (HDRS <19) and chronic headache	Ketamine 50 mg *vs* diclofenac (control)	3 times a day for 6 weeks	Mean change in HADS score in ketamine arm at week 3 −2·10 (SD 0·72), at week 6 −2·85 (SD 1·04); mean difference ketamine *vs* diclofenac at week 3 1·05 (0·45 to 1·64; p=0·001), at week 6 0·75 (0·18 to 1·32; p=0·012)	Adverse events ketamine arm (n=20): blurred vision (1 [5%]), tremor (1 [5%]), abdominal pain (1 [5%]), loss of appetite (1 [5%]); not significantly different from adverse events in diclofenac arm; no serious adverse event; no cardiovascular events; no adverse event leading to discontinuation
Lara et al, 2013[34]	Case series	11	34 (24–79)	7/4	Unipolar and bipolar treatment-resistant depression (≥4 antidepressants; n=26); maintenance ketamine treatment for 11 of initial responders	Ketamine 5–10 mg†	Every 2–3 days or weekly for 1·5 to 6 months	Initial clinical response or remission in 23 patients; maintenance therapy >4 weeks in 11 patients; sustained clinical response over the course of maintenance treatment in 100% of initial 11 responders	Adverse events: transient lightheadedness and agitation; no manic, psychotic, or dissociative symptoms
Lascelles et al, 2021[35]	Open label	6	57 (21–70; n=12)	6/6 (n=12)	Unipolar and bipolar treatment-resistant depression (≥2 antidepressants plus psychological treatment; n=12); maintenance ketamine treatment for 6 of initial responders	Initial intravenous ketamine 0·5 mg/kg; maintenance oral ketamine at variable mg	Initial dose once a week for 3 weeks; maintenance dose 2 times a week for 2 months	Sustained clinical improvement over the course of oral maintenance treatment in 3 of initial 6 responders; initial clinical response but (partial) relapse during the oral maintenance phase in 3 of initial 6 responders	Most common adverse events (n=12): dissociation (11 [92%]), hearing unusual things (6 [50%]), blurred vision (5 [42%]), nausea (3 [25%]); adverse events (11 [92%], of which significant in 2 [18%] and minimal in 9 ([82%])
McNulty and Hahn, 2012[37]	Case report	1	44	0/1	Depression, anxiety, and advanced pulmonary, cardiac, and renal disease	Initial subcutaneus ketamine 0·5 mg/kg; maintenance oral ketamine 40 mg	Single initial dose; maintenance dose once a day for 2 months	Depression severity at baseline 8 of 10, post-acute 0 of 10; sustained remission over the course of maintenance treatment	No adverse event; no further decline in renal function

(Table 1 continues on next page)

	Design	N*	Age	Women/men (n)	Clinical characteristics	Intervention	Dosing	Efficacy	Safety
(Continued from previous page)									
Nguyen et al, 2015[43]	Case series	12	50 (28–66)	12/0	Unipolar treatment-resistant depression (≥2 antidepressants; n=17); maintenance ketamine treatment for 12 of initial responders	Transmucosal ketamine 0·5–1·0 mg/kg	Once a week, once every 10 days, or once every 2 weeks for 8 to 22 months (mean exposure ~14 months)	Ketamine refills up to time of data collection in 10 (83%) of initial 12 responders; treatment discontinued in 2 (17%) patients after 10 months and 17 months for unknown reasons	Reported adverse events (n=12): transient light headache (1 [8%]) and slight dizziness (1 [8%]); no report of serious adverse events
Veraart et al, 2021[52]	Case report	1	55	1/0	Unipolar treatment-resistant depression (including psychotherapy, electroconvulsive therapy, and DBS failure) with psychotic features and OCD	Esketamine 2·0 mg/kg	2 times a week for 18 months	HDRS at baseline 24, post-acute 6; sustained remission over the course of maintenance treatment	Adverse events: temporary dizziness; vital parameters stable
Intramuscular									
Cusin et al, 2012[29]	Case series	2	48 and 57	2/0	Bipolar treatment-resistant depression (including oral ketamine failure; patient 1); bipolar treatment-resistant depression (including oral and intranasal ketamine and electroconvulsive therapy failure; patient 2)	Ketamine 50 mg (patient 1); 50–70 mg (patient 2)	Every 3 days for 6 months (patient 1); every 4 days for 9 months (patient 2)	Initial clinical response after 1 week, partial relapse after 6 months, regained response after addition of bupropion (patient 1); initial clinical remission within days, partial relapse after 5 months, regained response after dosage increase (patient 2)	Adverse events: headache, irritability (patient 1); irritability, nightmares, dissociative feelings (patient 2)
Grott Zanicotti et al, 2012 [29] and 2013[30]	Case report	1	36	1/0	Unipolar treatment-resistant depression, disseminated cancer, and history of drug misuse	Ketamine 1·0 mg/kg	Initial dose once every 8 to 10 days for 6 weeks; maintenance dose once a week for 10 months	MADRS at baseline 24; transient remission (MADRS <10) over the course of initial treatment; sustained response (MADRS 12–13) and mostly remission (MADRS <10) over the course of maintenance treatment	Adverse events: dissociative effects and dizziness (attenuation with repeated dosing); no worsening in concentration or memory; vital parameters stable
Schwartz et al, 2021[47]	Case series	4	30–49	4/0	Unipolar (n=3) or bipolar (n=1) treatment-resistant depression and eating disorder	Initial intravenous or intramuscular ketamine 0·5 mg/kg; maintenance intramuscular ketamine 0·5–0·9 mg/kg	Single initial dose; maintenance dose once a week to once every 6 weeks for 12–18 months	Sustained response of depressive symptoms over the course of maintenance treatment in 2 patients; partial sustained response of depressive symptoms over the course of maintenance treatment in 2 patients	Adverse events: mild sedation post injection; no apparent tolerance
Subcutaneous									
Del Sant et al, 2020[26] and Delfino et al, 2021[27]	Case series	70	40 (SD 12·7)	45/25	Unipolar (56%) or bipolar (44%) treatment-resistant depression (≥2 antidepressants in current episode) and MADRS ≥25	Esketamine 0·5–1·0 mg/kg	Once a week for 6 weeks	Initial reduction of anhedonia (MADRS item 8) 24 hours after first subcutaneous administration (t=4·007; p<0·001); sustained (increased) reduction of anhedonia (MADRS item 8) over the course of treatment (F=5·827; p<0·0001)	No clinically significant adverse event; no serious adverse events; vital functions: increased SBP >30 mm Hg and increased DBP >15 mmHg in 21 (30%) of 70; SBP ≥180 mmHg or DBP ≥110 mmHg, or both, in 14 (20%) of 70; SBP and DBP returned to pre-dose levels within 2 h across all dosing days; no clinically significant cardiovascular adverse events

BDI=Beck Depression Inventory. DBP=diastolic blood pressure. DBS=deep brain stimulation. ECG=electrocardiogram. HADS=Hospital Anxiety and Depression Score. HDRS=Hamilton Depression Rating Scale. IBW=ideal body weight. IDS=Inventory of Depressive Symptomatology. MADRS=Montgomery-Åsberg Depression Rating Scale. MAOI=monoamine oxidase inhibitor. MOCA=Montreal Cognitive Assessment. OCD=obsessive-compulsive disorder. PTSD=post-traumatic stress disorder. QIDS=Quick Inventory of Depressive Symptomatology. RCT=randomised controlled trial. SBP=systolic blood pressure. SNRI=serotonin and norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant. TMS=transcranial magnetic stimulation. YMRS=Young Mania Rating Scale. *Number of patients who received maintenance treatment according to our criteria. †Sublingual.

Table 1: **Characteristics and findings of included studies**

	Design	N	Sustained response rate		
			<6 months	6 months to 1 year	≥1 year
Intravenous					
Dale et al, 2020[22]	Open label	94	..	..	60%
Sakurai et al, 2020[46]	Case series	44	84%*	..	..
Phillips et al, 2019[44] and 2020[45]	Open label	23	91%	..	..
Wilkinson et al, 2018[54]	Case series	14	..	..	21%*
Archer et al, 2018[13]	Case series	11	36%	22% (n=9)†	..
Barenboim and Lafer, 2018[14]	Open label	8	100%	..	..
Bryant et al, 2019[17]	Case series	5	40%	25% (n=4)†	0 (n=4)†
Vande Voort et al, 2016[51]	Open label	5	100%	..	..
Chan et al, 2018[18]	Case series	4	50%	50%	0
Szymkowicz et al, 2013[50]	Case series	3	33%	0	0
Medeiros da Frota Ribeiro et al, 2016[38] and 2017[39]	Case series	2	100%	100% (n=1)†	100% (n=1)†
Medeiros da Frota Ribeiro et al, 2017[40]	Case series	2	100%	..	..
Bartova et al, 2017[15]	Case report	1	100%	100%	..
Blier et al, 2012[16]	Case report	1	100%	..	..
Kwon et al, 2018[33]	Case report	1	100%	100%	..
Messer and Haller, 2010[41]	Case report	1	100%	100%	100%
Messer and Haller, 2017[42]	Case report	1	100%	100%	100%
Intranasal					
Wajs et al, 2020[53]	Open label	603	77% *	..	..
Daly et al, 2019[24]	RCT	297	73–74%*	..	..
Lee et al, 2019[36]	Case series	13	69% *	..	..
Cusin et al, 2020[21]	Case series	2	100%	100%	0
Clark, 2014[19]	Case report	1	100%	..	..
Stultz et al, 2020[49]	Case report	1	100%	..	..
Oral					
Nguyen et al, 2015[43]	Case series	12	100%	92%	80% (n=10)†
Lara et al, 2013[34]	Case series	11	100%	..	..
Lascelles et al, 2021[35]	Open label	6	50%	..	..
De Gioannis and De Leo, 2014[25]	Case series	2	100%	..	..
Grande, 2017[28]	Case report	1	100%	100%	..
McNulty and Hahn, 2012[37]	Case report	1	100%	..	..
Veraart et al, 2021[52]	Case report	1	100%	100%	100%
Intramuscular					
Schwartz et al, 2021[47]	Case series	4	50%	50%	50%
Cusin et al, 2012[20]	Case series	2	50%	0	..
Grott Zanicotti et al, 2012[29] and 2013[30]	Case report	1	100%	100%	..

RCT=randomised controlled trial. *When the duration of maintenance treatment varied between patients within one study, the exact duration per patient or the mean or median duration of the sample were chosen to categorise results in short-term, mid-term, and long-term results. When the exact or mean or medium duration of maintenance treatment was unclear, results were categorised within the term that was obtained with certainty. †Excluding responders who had not (yet) reached the mid-term or long-term results.

Table 2: **Sustained response rates, categorised according to route of administration, with studies lined up according to sample size**

whose symptoms initially responded or remitted. Definitions of response and remission varied (ie, clinical response or remission, decrease of symptom severity of 50% or more from baseline, or a cutoff score of symptom severity). All but one study[22] reported on safety or tolerability, and all but one study[55] reported on efficacy.

The overall quality of the RCTs was considered high, resulting in level 1 evidence according to the Centre for Evidence-Based Medicine. The open-label trials, case series, and case reports were evaluated low to moderate, with a high risk of bias in several domains, resulting in level 3 to 4 evidence according to the Centre of Evidence-Based-Medicine. More details are provided in the appendix (pp 2–4).

We included 18 open-label trials, case series, and case reports on maintenance intravenous ketamine treatment, including 222 patients with unipolar, bipolar, or schizoaffective treatment-resistant depression.[13–18,22,33,38–42,44–46,50,51,54,55] Duration of intravenous maintenance treatment ranged from 4 weeks to 5 years. Frequency varied from once a day to once every 12 weeks. Frequency was individually tailored in ten studies and dosing in two studies. No studies on intravenous esketamine maintenance treatment were found (table 1).

Sustained response rates within the first 6 months of maintenance treatment were reported in three open-label trials[14,44,45,51] and 12 case series and reports (table 2).[13,15–18,33,38–42,46,50] Rates ranged from 91% to 100% in the open-label trials. Of the 76 initial responders included in the case reports and case series, 55 (72%) showed sustained response. Sustained response was seen in patients with and without electroconvulsive therapy-refractory depression. No difference in effectiveness was noticed when comparing the results of studies including both patients with unipolar and those with bipolar treatment-resistant depression versus the results of studies including only patients with unipolar treatment-resistant depression, or when comparing the results of studies with different treatment frequencies or sample sizes.

Mid-term (6 months to 1 year) sustained response rates were reported in five case series[13,17,18,38,39,50] and four case reports.[15,33,41,42] Of the 29 initial responders included in these nine studies, 25 patients had reached the mid term, whereas for four patients follow-up was too short to be included as mid-term sustained responders. Of these 25 patients, ten (40%) showed sustained response after 6 months to 1 year of maintenance treatment. Sustained response was seen in both patients with unipolar and bipolar depression and in patients with and without electroconvulsive therapy-refractory depression. Numbers were too small to be able to discern any differences in response rates between populations.

Long-term (≥1 year) sustained response rates were reported in eight studies,[17,18,22,38,39,41,42,50,54] of which one was an open-label trial.[22] Of the 150 unipolar and bipolar patients whose symptoms had not responded to electroconvulsive therapy included in this open-label trial, 94 patients initially responded to intravenous ketamine. Of these, 56 (60%) had a sustained response for 1 year. Results were not stratified by diagnostic

categories (unipolar *vs* bipolar).[22] Of the 30 initial responders included in the case series and case reports, 28 patients had reached the long term, while for two patients follow-up was too short to be included. Of these 28, 21% showed sustained response beyond one year of maintenance treatment.

Adverse events were mild and transient in most patients. In the open-label trials, no serious adverse events, craving or drug-seeking behaviour, cognitive disturbance, or urinary or renal problems were reported. In the case series and reports, tachyphylaxis (n=2), urinary incontinence (n=1), ketamine addiction (n=1; history of substance misuse), persistent cognitive disturbance (n=1), and manic or hypomanic state while being on mood stabilisers (n=1) were reported. In addition, return to alcohol misuse after years of sustained abstinence was reported twice, and relapse of depressive symptoms resulting in a suicide attempt was reported four times. There were five known patients who dropped out owing to adverse events.

Maintenance treatment with intranasal ketamine or esketamine was provided in eight studies, including a total of 997 patients with unipolar treatment-resistant depression.[19,21,23,24,36,48,49,53] Duration of treatment varied from 7 weeks to 3 years and frequency from every other day to once every 2 months. One RCT, three open-label trials, and one case report reported on intranasal esketamine maintenance treatment. One case report and two case series reported on maintenance treatment with intranasal racemic ketamine (table 1).

The two trials that determined sustained efficacy rates (one placebo-controlled[24] and one uncontrolled[53], together including 900 of the 997 patients) indicated sustained response rates of 73–77% within the first 6 months of maintenance treatment (table 2). In the second uncontrolled trial, 22 (65%) of 34 participants showed response and 11 (32%) of 34 showed remission after 9 weeks of treatment.[23] However, due to the design of this trial, we could not determine the proportion of sustained responders. In the third uncontrolled trial, improvement of mood, daily functioning, social activities, and motivation were presented as the most common reported changes during maintenance ketamine treatment.[48] Finally, of the 17 patients included in the case series and reports, 13 (76%) showed sustained response within the first 6 months of maintenance treatment.[19,21,36,49] As stratification of results was mainly absent, we were not able to discern any differences in response rates.

Mid-term (6 months to 1 year) and long-term (≥1 year) intranasal efficacy data showed that response could be sustained for years.[21,24,36,53] However, as the duration of maintenance treatment varied from relative short-term to long-term within these studies and this was not taken into account when the data were analysed or presented by the authors, it was not possible to draw more exact conclusions regarding the efficacy of mid-term and long-term intranasal maintenance treatment.

Adverse events were mild and transient in most patients. Although adverse events related to renal and urinary disorders were common in one study when incidence rates of the induction and maintenance phases were combined (17%),[53] serious renal and urinary problems related to ketamine were not observed, nor were cognitive adverse effects or craving or drug-seeking behaviour. Serious adverse events were detected in two cases and in 0–6% of the participants of the controlled and uncontrolled trials. They were most often related to worsening of depressive symptoms, including suicidal ideation and suicide attempts, or to gastroenteritis. There were three serious adverse events leading to death: acute cardiac and respiratory failure in one participant,[53] and suicide in two participants.[21,53] Participants that dropped out due to adverse events occurred in 2–4% of the trial populations. Specifications of the adverse events leading participants to drop-out were often not reported, but two studies report participants dropping out due to worsening of depressive symptoms, suicidality, and transient anxiety and confusion.[24,53]

We included 11 controlled and uncontrolled trials, case series, and case reports on maintenance oral ketamine treatment, including 199 unipolar (approximately 93%) and bipolar (approximately 7%) patients with treatment-resistant depression.[11,12,25,28,31,32,34,35,37,43,52] Duration and frequency of treatment varied widely, from 6 weeks to 3 years and from 3 times a day to once a month. In some studies frequency was individually tailored, in some dosing was individually tailored, and in some both were. Details and sustained response rates can be found in tables 1 and 2.

Two controlled trials, one uncontrolled trial, and six case series and reports presented results of maintenance treatment within the first 6 months after initial response.[12,25,28,32,34,35,37,43,52] Although the RCTs were not designed to study maintenance treatment, in both studies ketamine treatment was offered for more than 4 weeks, therewith meeting our intervention criteria. In the first RCT, including 40 patients, antidepressant effects were superior for ketamine versus diclofenac after 3 weeks of treatment when measured by the Hospital Anxiety and Depression Score (HADS). These effects were preserved up to 6 weeks of treatment. However, when measured by the Hamilton Depression Rating Scale (HDRS), patients receiving ketamine achieved greater response and remission after 6 weeks of treatment, but not after 3 weeks of treatment.[32] In the second RCT, including 81 patients, antidepressant effects were superior for ketamine addition to sertraline versus placebo addition to sertraline after 2 weeks of treatment, and these effects were preserved up to 6 weeks of treatment.[12] Of the six patients included in the uncontrolled trial, 3 showed sustained response within the first 6 months of maintenance treatment.[35] Of note, in this trial, oral maintenance treatment was studied after initial intravenous treatment. Of the 6 participants

that progressed to oral ketamine treatment, four reported it to be less effective than intravenous infusions. Finally, of the 28 patients included in the six case series and reports, 100% showed sustained response.[25,28,34,37,43,52] No differences in effectiveness were found when comparing the results of studies with different treatment frequencies or sample sizes. The number of patients with bipolar depression was too small to be able to distinguish differences in effectiveness regarding diagnostic categories.

Mid-term (6 months to 1 year) and long-term (≥1 year) efficacy data were reported in three case series[11,31,43] and two case reports.[28,52] Of the 14 initial responders included in the three case studies and case reports reporting on mid-term sustained response rates, 13 (93%) showed sustained response after 6 months to 1 year of maintenance treatment.[28,43,52] Of the 13 initial responders included in the two case studies reporting on long-term sustained response rates, two patients were treated with ketamine for less than 12 months. Of the other 11 patients, nine (82%) showed sustained response after 1 year of treatment.[43,52] In the fourth case series, no sustained efficacy rates were presented, but documentation of continued efficacy ranged from 15 weeks to 2 years.[11] Finally, in a retrospective case series by Hartberg and colleagues,[31] patients were found to have reduced numbers of both hospital admissions (–65%) and inpatient hospital days (–70%) following oral ketamine therapy for up to 3 years, compared with the period before therapy.

As with intravenous and intranasal maintenance treatment, adverse events were mild and transient in most individuals. No serious adverse events, patients dropping out due to adverse events, craving, cognitive disturbance, or renal problems were reported during oral maintenance treatment. Lower urinary tract symptoms were reported once but were determined to be unrelated to ketamine. Transient suicidal ideation was reported twice.

The efficacy and safety of intramuscular maintenance treatment was the topic of three case reports and series, including three patients with bipolar and four with unipolar depression.[20,29,30,47] Duration of treatment ranged from 6 months to 18 months and frequency from once every 3 days to once every 6 weeks (table 1).

Of the seven included patients, four showed sustained response within the first 6 months of treatment (table 2). Responses were sustained in three patients in the mid-term (6 months to 1 year). Of the four patients included in the single long-term study, two still showed sustained response after 12–18 months.[47]

Adverse events were mild and transient in all patients. No serious adverse events, patients dropping out due to adverse events, craving, cognitive disturbance, urinary problems, or renal problems were reported.

We included one retrospective case series on a 6-week weekly subcutaneous treatment programme, including 70 patients with treatment-resistant depression (39 [56%] unipolar and 31 [44%] bipolar) presented in two manuscripts.[26,27] Although the programme was not designed as a maintenance treatment programme, subcutaneous esketamine treatment was offered for more than 4 weeks, therewith meeting our intervention criteria (table 1).

Depression response rates were available but not included in this Review since they concerned initial and not sustained response rates. Initial efficacy regarding anhedonia was preserved within the first 6 months of treatment.[27] There were no mid-term or long-term subcutaneous maintenance treatment data available. No serious adverse events or clinically significant adverse events were reported.[26]

Discussion

To our knowledge, this is the first systematic review of the literature on the efficacy, safety, and tolerability of maintenance ketamine treatment for depression. So far, maintenance programmes with intravenous ketamine (18 studies including 222 patients), oral ketamine or esketamine (11 studies including 199 patients), and intranasal esketamine or esketamine (eight studies including 997 patients) have been studied the most. Data on maintenance treatment with intramuscular ketamine (three studies including seven patients) and subcutaneous esketamine (one study including 70 patients) are scarce.

Whether the different routes of administration of ketamine differ in efficacy and safety is not yet clear. When discussing these different routes, differences in bioavailability of ketamine and its metabolites must be taken into consideration. The bioavailability of ketamine can be expected to be complete in intravenous administration, is slightly lower in intramuscular and subcutaneous administration (approximately 90%), and further decreases in intranasal (8–45%) and oral (8–29%) administration.[56,57] Ketamine-dosing regimens for treatment-resistant depression often focus on maximising ketamine bioavailability and limiting its first pass metabolism, based on the assumption that the ketamine parent molecule is most important for treating depression. This assumption can be challenged for several reasons, for example because ketamine metabolites seem to have important roles in ketamine's antidepressant actions.[58,59] These are interesting directions for future research to optimise ketamine treatment.

Second, it is not yet clear if there is a difference in efficacy and safety between the different formulations of ketamine. Although ketamine acts primarily as an antagonist of NMDAR, the concept of NMDAR inhibition in depression has been challenged, and various other molecular insights have been gained in the mechanistic pathways of ketamine and its component enantiomers.[60] This notion has recently renewed interest in potential safer alternatives with less affinity for the NMDAR, such

as arketamine.[61] More studies investigating its effectiveness are underway, and future direct comparisons between racemic ketamine, esketamine, and arketamine in depressed patients will be interesting.

Whether sustained responsiveness differs to a clinically significant degree in patients with bipolar depression from those with unipolar depression, or in patients with electroconvulsive therapy-refractory depression from those whose symptoms have not previously not responded to electroconvulsive therapy is also not clear. Nevertheless, even if ketamine is found to be slightly less effective for patients with bipolar treatment-resistant depression or electroconvulsive therapy-refractory depression, this difference might not be meaningful given that there are so few established options for patients with drug-resistant bipolar depression or patients with electroconvulsive therapy-resistant depression.

In summary, there is evidence for sustained therapeutic potential of intravenous, intranasal, and oral maintenance ketamine treatment within the first 6 months after initial response, and for intravenous maintenance treatment beyond 1 year after initial response. To a more limited extent, there is evidence for sustained therapeutic potential of intramuscular and subcutaneous maintenance ketamine treatment. Compared with maintenance antidepressant drug therapy with an average relapse rate of 23% in patients with non-treatment-resistant depression,[62] these results, achieved in patients with difficult-to-treat symptoms, are clearly promising.

Overall, the nature of adverse events reported was consistent with the known safety profile of initial ketamine treatment.[63] Adverse events were mild and transient in most individuals. Cognitive impairment (n=1) and addiction (n=1) were reported but seem very uncommon based upon the current data. Although adverse events related to renal and urinary disorders were common in one study, serious renal and urinary problems related to ketamine seem uncommon.

These findings contrast with previous reports that repeated use of ketamine in other populations, including animals, patients with chronic pain, and recreational users, has been linked with urological toxicity, hepatotoxicity, cognitive deficits, and dependency risks.[6–9] Possible explanations for this disparity are the relatively low dosages (both dosing and frequency) and better controlled circumstances in most treatment programmes for depression. Second, in many studies, exclusion criteria for ketamine treatment included substance use disorders and unstable medical illnesses, possibly limiting the risk of increasing or uncontrolled use with these potential side-effects. Third, current data might be too limited or follow-up time too short in general to detect infrequent but potentially severe adverse effects, including those that might require a longer time to develop. Consistent with our findings regarding the safety of maintenance treatment are the findings of Feifel and colleagues.[64] In a sample of 6630 patients receiving repeated (but not necessarily maintenance) parenteral ketamine for depression, discontinuation due to adverse effects was required in only 47 (0·7%). The most reported adverse effect that required discontinuation was psychological distress (33 [0·5%]). In three patients (0·06%) bladder dysfunction required discontinuation, in two (0·03%) hypomania, in six (0·09%) nausea, and in one (0·02%) psychotic symptoms, respiratory distress, and seizure. Adverse events that prompted discontinuation did not include addiction or cognitive deficits. A systematic review suggested that ketamine use for treatment-resistant depression is associated with cognitive improvement, probably related to a decrease in depressive symptoms.[65]

Serious adverse events were not always specified. Reported specifications were most often related to worsening of depressive symptoms, including suicidality. Relapse of depressive symptoms resulting in suicide, or a suicide attempt, was reported 14 times. These findings highlight the importance of meticulous monitoring of patients, not only during but also after cessation of treatment.

The most frequently reported reasons for discontinuation of maintenance treatment were (partial) relapse or worsening of depressive symptoms, including suicidality. Additional reported adverse events leading to discontinuation were anxiety, (transient) confusional state, manic state, cognitive impairment, ketamine addiction, increased blood pressure, vertigo, and urinary problems. However, they were not often reported in the maintenance phase. Other reasons for discontinuation were classified as other or withdrawal by patient, without any further specification.

This Review has several limitations. The overall quality of the majority of the studies was considered low to moderate, with most reports having a high risk of bias in several domains. For example, most studies were uncontrolled and underpowered, and in many studies assessment and documentation of efficacy, safety, and tolerability were inadequate. Next, publication bias might account for some of the effects we observed, especially since we included case reports, case series, and unregistered trials. Third, as a limitation of the review process, some studies were included although it is doubtful whether the intervention should be categorised as maintenance treatment. For example, repeated oral ketamine for 6 weeks could be considered as both maintenance and initial treatment. Fourth, eight patients who were included in studies that were categorised as mid term (n=4) or long term (n=4) had to be excluded from the mid-term or long-term response rate calculations, because their follow-up was too short. Finally, clinical and methodological heterogeneity between the studies was high, hindering comparison of the results. Therefore, our results should be interpreted with caution.

Conclusion

Despite the methodological limitations, we conclude that from a clinical view, there is therapeutic potential of maintenance ketamine treatment. The available data show sustained efficacy in the majority of initial responders while severe adverse events seem uncommon. Use of maintenance ketamine treatment could be considered analogous to maintenance electroconvulsive therapy, for which there are no clear clinical guidelines. Electroconvulsive therapy is currently offered in a selection of patients based on response and tolerability, and frequency of treatment is determined clinically on a case-by-case basis. Undoubtedly, there is a need for caution given the many unknowns regarding the long-term effects of ketamine treatment. However, we feel, with the current evidence, that for a select subset of patients, it is justifiable to offer maintenance ketamine treatment despite these unknowns, as there is no reasonable treatment alternative. Careful screening, management, and follow-up will be necessary, as will managing expectations about the potential of relapse and adverse events. Both controlled and uncontrolled (naturalistic) studies with long-term follow-up and sufficient power are needed to determine the position of maintenance ketamine treatment within routine clinical practice.

Contributors

SYS-A, CE and DT completed the literature search and selected the included studies. SYS-A and JKEV extracted data and assessed the quality of the included studies. SYS-A synthesised and interpreted the data and wrote the manuscript. JKEV, JS, JK, and RAS critically reviewed the manuscript for intellectual content. All authors approved the final version of the manuscript for publication.

Declaration of interests

JKEV received a speaker's fee from Janssen Pharmaceuticals, outside the submitted work. RAS received research funding for two randomised clinical trials with generic oral esketamine from the Netherlands Organisation for Health Research and Development and the National Health Care Institute, a speaker's fee and investigator initiated research grant from Janssen Pharmaceuticals, and consultancy fees from GH Research, Beckley PsyTech, and QPS, outside the submitted work. The other authors declared no competing interests.

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