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REVIEW

Ketamine and depression: a narrative review

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Abstract: Depression is the third leading cause of disability in the world. Depressive symptoms may be reduced within several weeks after the start of conventional antidepressants, but treatment resistance concerns one-third of patients who fail to achieve recovery. Over the last 20 years, ketamine, an antagonist of the N-methyl-D-aspartate receptor, has been described to have antidepressant properties. A literature review was conducted through an exhaustive electronic search. It was restricted to Cochrane reviews, meta-analyses, and randomized controlled trials (RCTs) of ketamine for major depressive disorder and/or bipolar disorder. This review included two Cochrane reviews, 14 meta-analyses and 15 trials. Ketamine was studied versus placebo, versus other comparators and as an anesthetic adjuvant before electroconvulsive therapy. In 14 publications, ketamine provided a rapid antidepressant effect with a maximum efficacy reached at 24 hrs. Its effect lasted for 1–2 weeks after infusion, but a longer-term effect is little reported. Ketamine does not seem to improve depressive symptoms at the end of electroconvulsive sessions. Safety and tolerability profiles with ketamine at low single dose are generally good in depressed patients. However, there is a lack of data concerning ketamine with repeated administration at higher doses. The clinical use of ketamine is increasing. Intranasal (S)-ketamine has recently been approved for depression by the Food and Drug Administration. It could be a promising treatment in depressed patients with suicidal ideation. Collectively, the level of proof of efficacy remains low and more RCTs are needed to explore efficacy and safety issues of ketamine in depression.

Keywords: ketamine, depression, major depressive disorder, bipolar depression, suicide, efficacy

Introduction

Depression, a major public health problem, is the third leading cause of disability in the world. Depression is different from usual mood fluctuations and common depressive episodes.[1] It affects approximately 350 million individuals worldwide[2] and results in personal suffering and economic loss.[3] Low mood, sadness, feelings of guilt, lack of motivation, anxiety, and suicidal thoughts are common symptoms shown in depression. A distinction can be made between depression in people who have or do not have a history of manic episodes. Both types of depression can be chronic with relapses, especially if they go untreated.[1]

Major depressive disorder (MDD), also known as unipolar depression, is estimated to 28.2% over a lifetime in the general population.[4] Bipolar disorder of type I (with mania) and type II (with hypomania) is considered as an episodic and debilitating condition, with a lifetime prevalence of 2.4%.[5] Depressive symptoms (bipolar depression or BD) predominate over manic/hypomanic symptoms during the longitudinal course of both bipolar I and II disorder.[6,7]

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A reduction in depressive symptoms is observed within several weeks after the start of treatment after conventional antidepressants but remission with this therapy remains insufficient after several weeks and one-third of patients fail to achieve functional recovery despite multimodality treatment interventions.[8] The pathophysiology of depression relies mainly on monoamine deficiency,[9] but an increase of glutamate has also been suggested in animals[10] and humans,[11,12] N-methyl-D-aspartate receptors (NMDAR) are hence at the heart of the pathophysiology of depression. In that context, the non-competitive voltage-dependent NMDAR antagonist ketamine is very interesting with its specific and rapid action on the NMDAR and on a myriad of other receptors.

In patients with MDD or BD, abnormalities in neurotransmission and neuronal plasticity may lead to aberrant functional connectivity patterns within large brain networks.[13] Network dysfunction in association with altered brain levels of glutamate and gamma-aminobutyric acid (GABA) have been identified in both animal and human studies of depression.[13,14]

Increased synaptic glutamate concentration has been described in MDD,[15–17] a phenomenon linked to complex molecular changes such as lower expression α-amino-3-hydroxy-5-méthylisoazol-4-propionate receptor (AMPAR), impaired mechanistic target of rapamycin (mTOR) complex signaling pathway, and lower level of brain-derived neurotrophic factor (BDNF)[18] that may lead to neuronal atrophy (dendritic retraction, decrease in dendritic tree structure and number of synapses).[19]

Ketamine has been shown to have an antidepressant effect in animal models with increases of AMPAR activity, levels of phosphorylated mTOR, and expression of BDNF.[18] Over the last 20 years, ketamine has received great attention for its rapid antidepressant property after a single sub-anesthetic dose in individuals with (treatment-resistant) MDD or BD.[20–23] This narrative review aims to explore in the literature the efficacy of ketamine when used in MDD and BD.

Methods

A literature review was conducted through an exhaustive electronic search of Medline, PubMed, Google Scholar, and Cochrane databases. Key words such as "ketamine depression", "major depressive disorder", or "bipolar disorder" were used without limitation in language or date of publication. The last search was conducted in May 2019. It was restricted to meta-analyses, Cochrane reviews, parallel-group and cross-over randomized controlled trials (RCTs), comparing ketamine versus placebo (saline infusion) or active control for MDD and/or BD. This search included studies concerning ketamine as a pharmacological drug to treat depression and as an anesthetic adjuvant before electroconvulsive therapy (ECT). Inclusion criteria were established prior to article review:

- Design: Cochrane reviews, meta-analyses, double- or single-blind, cross-over or parallel, versus placebo or active control RCTs;
- Etiology: (treatment-resistant) MDD and BD;
- Outcomes (primary or secondary): ketamine efficacy defined by a significant change in depression severity score before and after treatment, assessed by validated depression rating scales (Montgomery–Asberg Depression Rating Scale (MADRS);[24] Hamilton Depression Rating Scale (HDRS);[25,26] Beck Depression Inventory (BDI));[27] response rate generally defined by a reduction of at least 50% compared to baseline on the validated scales (MADRS, HDRS, or BDI); remission rate defined, according to studies, by a score of <7 on the HDRS-17,[28] or <8 for all the other longer versions of the HDRS, or <11 on the MADRS;[29] suicidal ideation assessed by validated scales (MADRS-suicidal ideation scores, Quick Inventory of Depressive Symptomatology – Self-Report suicidality item, Beck Scale for suicidal ideation).

Results

A total of 2861 items were identified after database research and 417 were eligible for this review. After having discarded duplicates, screened abstracts, and removed excluded publications (Figure 1), 31 articles were included in this review: 2 Cochrane reviews, 14 meta-analyses, and 15 RCTs that had not been included in the Cochrane reviews and meta-analyses. Studies included in Cochrane reviews or in meta-analyses were not analyzed separately. In the selected literature, ketamine was used:

1. Alone as a pharmacological drug versus placebo, or in combination (one study) with escitalopram to treat MDD and BD versus placebo,
2. Alone as a pharmacological drug to treat MDD and BD versus other comparators,
3. As a pre-ECT anesthetic adjuvant alone or in combination with thiopental or propofol versus placebo or active control.

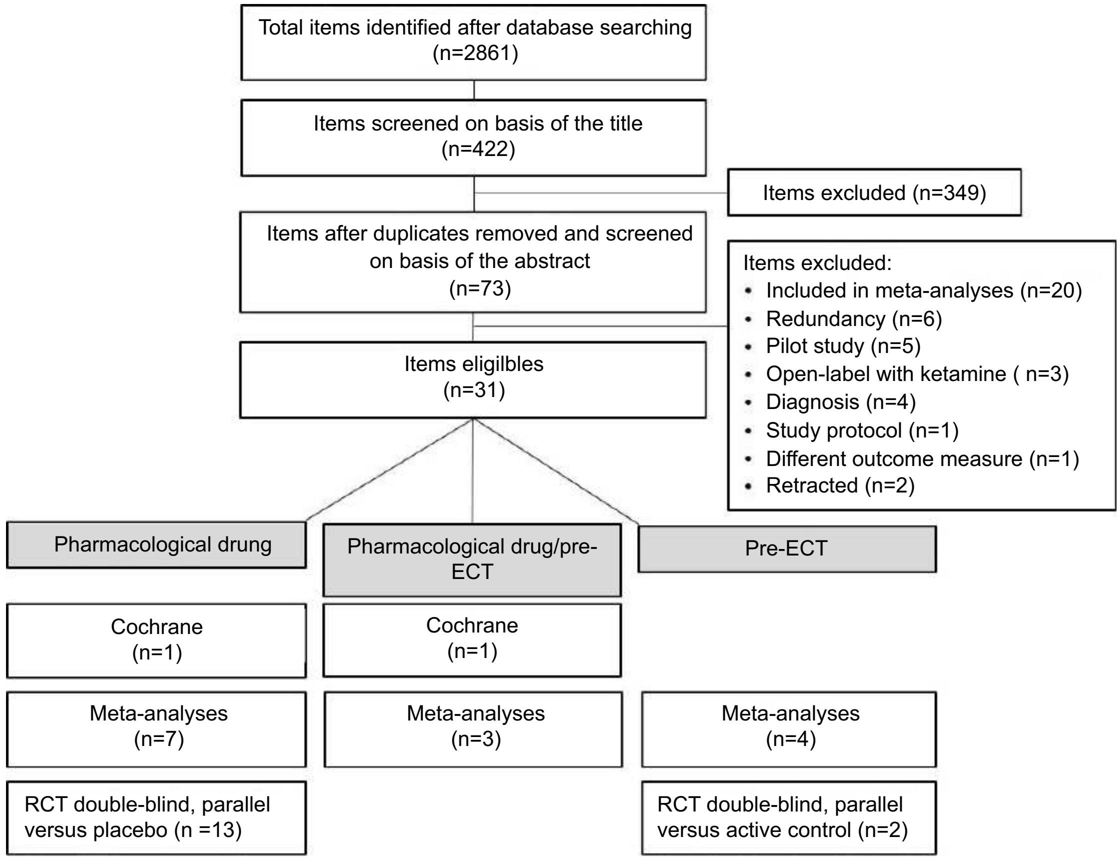

Figure 1 Flowchart of the literature review process.
Abbreviations: ECT, electroconvulsive therapy; RCT, randomized controlled trial.

Two Cochrane reviews have been published, McCloud et al, 2015 in BD[30] and Caddy et al, 2015 in MDD and BD.[31] A total of 14 meta-analyses (1–16 studies per meta-analysis, n=35–928) in MDD and BD were included in this review.[32–45] Among RCTs included in these meta-analyses, 7 RCTs were also included in the Cochrane reviews. All the articles included in the Cochrane reviews and in the meta-analyses are listed in Table 1. An additional number of 15 double-blind parallel RCTs versus placebo[46–56] or versus active control[57,58] in MDD patients have been published since the publication of the Cochrane reviews and the meta-analyses (Table 2).

Ketamine efficacy, response, and remission

Ketamine versus placebo

Ketamine efficacy, defined by a significant difference in depression severity score before and after treatment, assessed by validated depression rating scales, was shown in favor of ketamine over placebo at 40 mins,[51,53,55] 60–80 mins,[34,53] 2 hrs,[53,54,56] 4 hrs,[49,51,52,54,56] 1 day,[30,33,49,50,52–54] 2 days,[33,50,53,56] 3 days,[30,33,51,53,54,56] 4 days,[33,53] 5 days,[53] 6 days,[53] 1 week,[33,50,51,53,54] 2 weeks,[32,48,50,51,53,54] 3 weeks,[51] 4 weeks,[47,48,53] and 6 weeks.[48] However, some studies did not find a difference at 40 mins,[52] 60–80 mins,[52,54,55] 2 hrs,[52,55] 4 hrs,[34,55] 1 day,[47] 1 week,[30,46,47] 2 weeks,[30,33,34,46,47] 3 weeks,[46,47,54] and 4 weeks.[49,54] There were more responders (defined by a reduction of at least 50% compared to baseline on the validated scales) with ketamine versus placebo at 40 mins,[55] 80 mins,[55] 4 hrs,[52] 1 day,[30,52,53,56] 3 days,[30] 4 days,[53] 2 weeks,[32] 3 weeks,[51] and 6 weeks.[48] There was no difference at 2 hrs,[55] 4 hrs,[55] 1 day,[47] 1 week,[30] 2 weeks,[30] 3 weeks,[46] 4 weeks,[47] and 3 months.[46] There was no available data for ketamine efficacy at 4, 6, and 8 weeks in a meta-analysis.[32] Concerning remitters rate, only one study showed a significant difference in favor of ketamine at 3 weeks of treatment,[51] otherwise there was no evidence at any time point for this endpoint.[30,46,48]

A RCT observed that ketamine combined with escitalopram brought a significant difference in depression severity score at 2 hrs, 4 hrs, 1 day, 3 days, 1 week, and

Table 1 Synthesis of Cochrane review and meta-analyses which have included RCT studies in their analyses, concerning ketamine efficacy

Authors	Etiology	Review type [articles included]	n studies (n K studies)	n subjects (n K subjects)	Design	Ketamine efficacy
Ketamine versus placebo						
Papadimitropoulou et al, 2017[32]	TR MDD	MA[63]	31 (1) no ECT	5515 (35)	DB, P, vs PBO	Efficacy at week 2. No data at week 4, 6, and 8
McCloud et al, 2015[30]	BD	Cochrane[102,108]	5 (2) no ECT	329 (33)	DB, CO, vs PBO	Efficacy at day 1 and 3. No efficacy at week 1 and 2.
Romeo et al, 2015[33]	MDD, BD	MA[68,102,108–111]	6 (6) no ECT	103 (103)	DB, CO, vs PBO	Efficacy at day 1, 2, 3–4 and week 1. No efficacy at week 2.
Caddy et al, 2014[34]	MDD, BD	MA[102,108,110–112]	5 (5) no ECT	66 (66)	DB, CO, vs PBO except [101]: OL, P	Efficacy at 60–80 mins. No efficacy at 4 hrs, week 2.
Ketamine versus other comparators						
Kishimoto et al, 2016[35]	MDD, BD	MA[63,102,108–111,113,114] Lai et al, 2014 (case report)	14 (9) no ECT	588 (234)	DB, CO, P, vs PBO or active PBO	Efficacy at 40–60 mins, day 1, 5–8. No efficacy at week 2.
Xu et al, 2016[36]	TR MDD, BD	MA[68,102,108–111,113,114] Loo unpublished data	9 (9) no ECT	201 (201)	DB, CO, P, vs PBO or active PBO	Efficacy at day 1 and 3. No efficacy at week 1.
Lee et al, 2015[37]	TR MDD, BD	MA[102,108–111,113]	5 (5) no ECT	125 (125)	DB, CO, P vs PBO or active PBO	Efficacy at day 1 and week 1.
McGirr et al, 2015[38]	MDD, BD	MA[68,102,108–111,113]	7 (7) no ECT	183 (183)	DB, CO, P vs PBO or active PBO	Efficacy at day 1.
Ketamine as pre-ECT anesthetic adjuvant versus placebo or active placebo						
Ren et al, 2018[39]	MDD, BD	MA[115–130]	16 (16) ECT	928 (928)	DB, OL, P, vs PBO or active PBO pre-ECT	Efficacy after the 1st, 3rd, 4th, 5th, 6th ECT. No efficacy after the 2nd, 8th, 10th, 12th ECT and at the end of ECT sessions.
McGirr et al, 2017[40]	MDD, BD	MA[115–118,120,122–125,131]	10 (10) ECT	602 (602)	DB, P, vs PBO or active PBO pre-ECT	No efficacy at the end of ECT sessions.
Fond et al, 2016[41]	MDD, BD	MA[115–119]	14 (5) ECT	610 (84)	DB, P, vs active PBO pre-ECT	No efficacy after the 6th ECT.
McGirr et al, 2015[42]	MDD, BD	MA[115–119]	5 (5) ECT	182 (182)	DB, P, vs active PBO pre-ECT	No efficacy at the end of ECT sessions.

(*Continued*)

Table 1 (Continued).

Authors	Etiology	Review type [articles included]	n studies (n K studies)	n subjects (n K subjects)	Design	Ketamine efficacy
Ketamine alone and as pre-ECT anesthetic adjuvant versus placebo or active placebo						
Caddy et al, 2015[31]	MDD, BD	Cochrane -113 -116 -109,110,111,115,117 -64	25: - 1 no ECT - 1 ECT - 5 no ECT+ECT - 1 no ECT	1242: - 73 no ECT - 29 ECT - 130 no ECT + ECT - 18 no ECT	DB - P, vs midazolam (no ECT) - P, vs thiopental (pre-ECT) - CO (no ECT), P (pre-ECT), vs PBO - SB, P, vs ECT	No and pre-ECT: efficacy at day 1 (vs PBO, midazolam, ECT), day 3 (vs PBO, thiopental, ECT), week 1 (vs PBO, ECT). No efficacy at day 3 (vs midazolam), week 1 (vs midazolam), week 2 (vs PBO, thiopental, ECT), week 4 (vs thiopental).
Coyle and Laws, 2015[43]	MDD, BD	MA[59,68,102,108–110,113,117,118,120,132–141]	21 (21) no ECT and ECT	437 (437)	RCT, no RCT, DB, OL, no ECT, pre-ECT	No and pre-ECT: efficacy at 4 hrs, day 1, week 1 and 2.
Newport et al, 2015[44]	MDD, BD	MA -68,102,108–111,113–119	12: - 7 no ECT - 5 ECT	236: - 147 no ECT - 89 ECT	DB, CO, P vs PBO or active PBO	No ECT: efficacy at day 1 and week 1. Pre-ECT: efficacy after the 1st ECT; no efficacy at the end of ECT sessions.
Fond et al, 2014[45]	MDD, BD	MA -64,90,108–113,142 -115,117–119	12: - 9 no ECT - 4 ECT	310: - 192 no ECT - 118 ECT	DB, CO, P - vs PBO or active PBO or vs ECT - vs PBO or active PBO pre-ECT	No ECT: efficacy at day 1. Pre-ECT: efficacy at day 1.

Abbreviations: RCT, randomized controlled trial; TR, treatment-resistant; MDD, major depressive disorder; BD, bipolar depression; MA, meta-analysis; ECT, electroconvulsive therapy; K, ketamine; PBO, placebo; DB, double-blind; SB, single-blind; OL, open-label; P, parallel; CO, cross-over.

Table 2 Synthesis of additional RCT not including in the Cochrane reviews and the meta-analyses, concerning ketamine efficacy

Authors	Etiology	n subjects	Design	Rating scale	Ketamine efficacy
Ketamine versus placebo					
Ionescu et al, 2019[46] Single center	TR MDD	26	(a) K: 6 IV infusions 0.5 mg/kg over 45 mins, twice weekly for 3 weeks (n=13) (b) PBO (n=13)	HDRS	No efficacy across infusions at week 1, 2, and 3.
Popova et al, 2019[47] Multicenter	TR MDD	223	(a) Intranasal (S)-K, 56 or 84 mg twice weekly+AD for 4 weeks (n=114) (b) PBO+AD for 4 weeks (n=109)	MADRS	Efficacy at week 4. No efficacy at day 1, week 1, 2, and 3.
Arabzadeh et al, 2018[48] Single center	MDD	90	(a) Oral K, 25 mg twice daily for 6 weeks (n=45) (b) PBO (n=45)	HDRS-17	Efficacy at week 2, 4, and 6.
Canusco et al, 2018[49] Multicenter	TR MDD	66	(a) Intranasal (S)-K, 84 mg twice weekly for 4 weeks (n=35) (b) PBO (n=31)	MADRS	Efficacy at 4 hrs and day 1. No efficacy at day 25.
Daly et al, 2018[50] Multicenter	TR MDD	67	(a) Intranasal (S)-K, 28 (n=11), 56 (n=11) or 84 mg (n=12) administered twice weekly for 2 weeks (double-blind period) (b) PBO (n=33)	MADRS	Efficacy at day 1 and 2, week 1 and 2.
Domany et al, 2018[51] Single center	MDD	41	(a) K (n=22): 1 mg/kg thrice weekly for 21 days by oral route (b) PBO (n=19)	MADRS	Efficacy at 40 mins, 4 hrs, day 3, week 1, 2, and 3.
Chen et al, 2018[52] Single center	TR MDD	24	(a) Ketamine (n=8): 1 IV infusion 0.5 mg/kg over 40 mins (b) Ketamine 0.2 mg/kg (n=8): 1 IV infusion 0.2 mg/kg over 40 mins (c) PBO (n=8)	HDRS-17	Efficacy (0.5 mg/kg) at 4 hrs and day 1. No efficacy at 40 mins, 80 mins and 2 hrs.
Su et al, 2017[53] Single center	TR MDD	71	(a) K (n=24): 1 IV infusion 0.5 mg/kg over 40 mins (b) K (n=23): 1 IV infusion 0.2 mg/kg over 40 mins (c) PBO (n=24)	HDRS-17	Efficacy (0.5 mg/kg) from 40 mins to 4 weeks post-infusion.
Hu et al, 2016[54] Single center	TR MDD	23	(a) K: 1 IV infusion 0.5 mg/kg over 40 mins+escitalopram: 10 mg/day for 4 weeks (n=13) (b) PBO+escitalopram (n=14)	MADRS	Efficacy at 2 hrs, 4 hrs, day 1, 3, week 1 and 2. No efficacy at 60 mins, weeks 3 and 4.
Li et al, 2016[55] Single center	TR MDD	48	(a) K (n=16): 1 IV infusion 0.5 mg/kg over 40 mins (b) K (n=16): 1 IV infusion 0.2 mg/kg over 40 mins (c) PBO (n=16)	HDRS-17	Efficacy (both groups) at 40 mins. No efficacy at 80 mins, 2and 4 hrs.
Singh et al, (a) 2016[56] Multicenter	TR MDD	30	(a) (S)-K (n=11): 1 IV infusion 0.4 mg/kg over 40 mins (b) (S)-K (n=9): 1 IV infusion 0.2 mg/kg over 40 mins (c) PBO (n=10)	HDRS-17	Efficacy (both groups) at 2 hrs, 4 hrs, days 2 and 3.

(*Continued*)

Table 2 (Continued).

Authors	Etiology	n subjects	Design	Rating scale	Ketamine efficacy
Ketamine as pre-ECT anesthetic adjuvant versus active placebo					
Carspecken et al, 2018[57] Single center	TR MDD	50	(a) K (n=23): 1–2 mg/kg (b) Methohexital (n=27): 1–2 mg/kg ECT: 3 consecutive sessions/week (right unilateral)	HDRS-21	No efficacy post-ECT (with a total of 3 ECT sessions).
Gamble et al, 2018[58] Single center	TR MDD	27	(a) K (n=14): IV infusion 0.75 mg/kg (b) Propofol (n=13): 1 mg/kg 4–8 ECT (uni or bilateral): 2 or 3 sessions/week	MADRS	Faster improvement of depressive symptoms with ketamine.

Abbreviations: RCT, randomized controlled trial; TR, treatment-resistant; MDD, major depressive disorder; BD, bipolar depression; MA, meta-analysis; ECT, electroconvulsive therapy; K, ketamine; PBO, placebo; DB, double-blind; SB, single-blind; OL, open-label; P, parallel; CO, cross-over; MADRS, Montgomery–Asberg Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; IV, intravenous; AD, antidepressant.

2 weeks with no difference at 60 mins, 3 weeks, and 4 weeks versus placebo combined with escitalopram.[54] Responders and remitters rates were significantly higher with ketamine at 4 weeks only (Figure 2A).[54]

Ketamine versus other comparators

Versus both placebo and active placebo

Meta-analyses found that ketamine efficacy was better than placebo and active placebo at 40/60 mins,[35] 1 day,[35–38,44,45] 3 days,[36] 5 days,[35] and 1 week.[35,37,44] A few meta-analyses have found no efficacy at 1 week[36] and 2 weeks.[35] Ketamine showed a higher response rate at 4 hrs,[35,44] 1 day,[36,38,44] 2–3 days,[36,38,44] 1 week,[36,38] and 2 weeks[44] compared with the control group. Remission symptoms with ketamine were observed at 80 mins,[35,44] 1 day,[35,36,38,44] 3–5 days,[35,36,38,44] and at 1 week[36,38] but no longer at 2 weeks.[44]

Versus midazolam

A Cochrane review by Caddy et al showed that ketamine was more effective than midazolam at 1 day but no longer at 3 days or at 1 week.[31] Ketamine was better than midazolam in response rate at 1 day, 3 days, and 1 week.[31] A significant difference in remission in favor of ketamine was found at 1 day. There was no difference at 3 days and at 1 week.[31]

Versus ECT

A Cochrane review[31] compared ketamine, as a pharmacological agent, versus ECT in MDD patients. Ketamine was more effective than ECT at 1 day, 3 days, and 1 week but no longer at 2 weeks.[31] Response rate was more important with ketamine than ECT at 1 day and 3 days but no longer at 1 and 2 weeks.[31] There was no difference in remission at any time point (Figure 2A).[31]

Ketamine as pre-ECT anesthetic adjuvant

Ketamine effect has been studied as pre-ECT anesthetic adjuvant alone or in combination with either thiopental, propofol, or methohexital (Figure 2B).

Ketamine as an anesthetic adjuvant alone versus active placebo pre-ECT

Versus thiopental. Ketamine was more effective than thiopental at 3 days but no longer at 2 weeks or at 4 weeks.[31] There was no difference between the two groups in term of response at any time points and there was no remitter at any time point in each group.[31]

Versus methohexital. In one parallel RCT versus methohexital, ketamine was administered before three

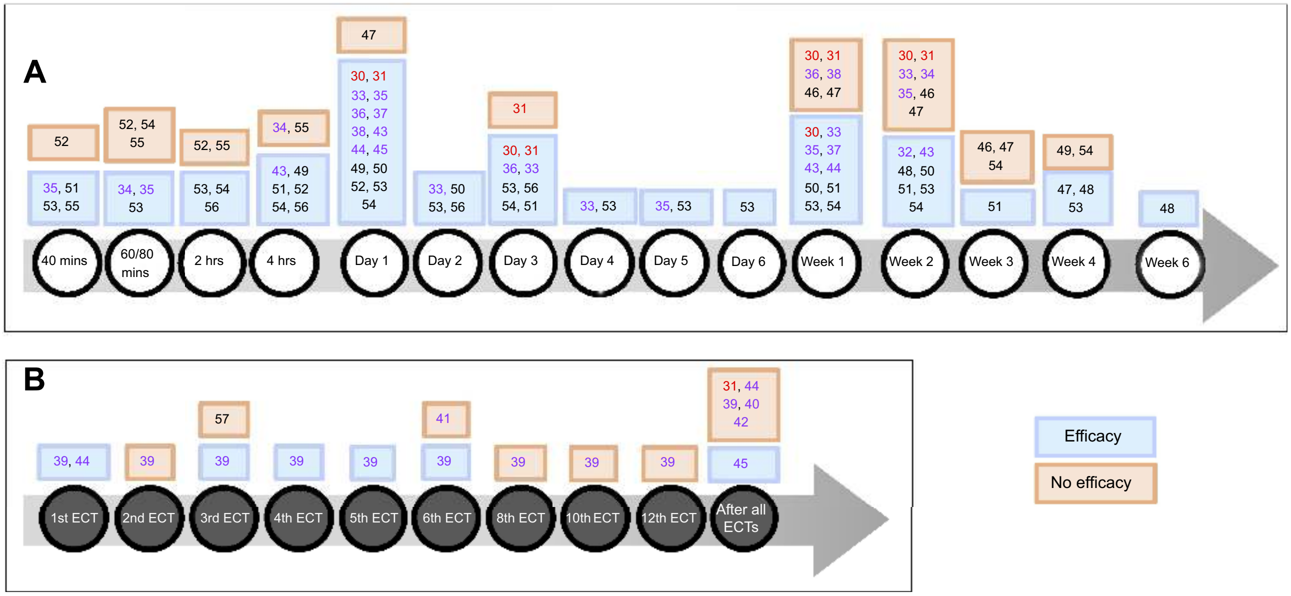

Figure 2 (**A**) Ketamine efficacy with time (versus placebo or other comparators). (**B**) Ketamine efficacy with the number of electroconvulsive therapies (ECT) (ketamine given as an anesthetic adjuvant pre-ECT).
Notes: Numbers represent references. Bold red: Cochrane review; bold purple: meta-analyses; others: randomized controlled trials.

consecutive ECT sessions.[57] Even though depression scores improved after ECT sessions, there was no significant difference in ketamine efficacy between the groups. There was no data for response and remission.[57]

Versus propofol. In another parallel RCT versus propofol, ketamine was administrated with a frequency of two or three sessions per week, before each ECT sessions.[58] This study showed faster improvement of depressive symptoms with ketamine (response rate was attained after two ECT with ketamine versus four ECT with propofol), and fewer treatments to achieve remission (four ECT in the ketamine arm versus seven ECT in the propofol arm).[58]

Ketamine as an anesthetic adjuvant alone and/or in combination with another pre-ECT anesthetic drug versus placebo or active placebo

Meta-analyses showed that ketamine efficacy was observed at day 1[45] or after the 1st,[39,44] 3rd,[39] 4th,[39] 5th,[39] and 6th ECT sessions,[39] but with no difference after the 2nd,[39] 3rd,[57] 6th,[41] 8th,[39] 10th,[39] and 12th ECT[39] or at the end of the complete course of ECT sessions.[39,40,42,44] There was no difference in terms of response[39–42,44] and remission.[39,40,42,44]

Ketamine administration

Ketamine efficacy was observed after only one intravenous (IV) infusion of 0.5 mg/kg over 40 mins versus placebo[30,31] or midazolam.[31] A single IV infusion of either 0.2 mg/kg or 0.5 mg/kg of ketamine compared with placebo was used in three RCTs and ketamine efficacy was observed with a dose of 0.5 mg/kg[52,53] but not with the 0.2 mg/kg dose.[53] Another study showed that both ketamine dosages showed higher efficacy than placebo.[55] One study used a single IV infusion of (S)-ketamine with two doses of 0.2 and 0.4 mg/kg in each group. An improvement in both (S)-ketamine groups was observed.[56] One study performed a single IV infusion of 0.5 mg/kg of ketamine in combination with escitalopram (10 mg per day for 4 weeks) versus placebo and escitalopram and ketamine efficacy was observed until 2 weeks.[54]

Ketamine was administered in repeated doses by IV route in one study with a total of six infusions of 0.5 mg/kg twice weekly for 3 weeks but with no significant difference in favor of ketamine versus placebo across infusions.[46] In a Cochrane review,[31] ketamine was administered by three IV infusions of 0.5 mg/kg over 45 mins every 48 hrs and compared with three ECT sessions every 48 hrs (with 2–3 mg/kg of thiopental pre-ECT) and efficacy was observed until 1 week.

Repeated oral racemic ketamine administration brought efficacy in two studies, with a dose of 25 mg twice daily for 6 weeks[48] or 1 mg/kg thrice weekly for 3 weeks[51] versus placebo.

Intranasal (S)-ketamine was used in three recent RCT with a dose of 84 mg twice weekly for 4 weeks in addition to comprehensive standard-of-care treatment[49] or with an oral antidepressant[47] and from 28 to 84 mg administered twice weekly for 2 weeks.[50]

Caddy et al[31] compared ketamine (1–2 mg/kg) versus thiopental (2–3 mg/kg) in MDD patients, for pre-ECT anesthesia. A total of six ECT sessions were performed in each group, with three sessions per week and ketamine was more efficient than thiopental up to 3 days after ECT sessions. In meta-analyses, ketamine was reported with a dose between 0.3 and 1–2 mg/kg pre-ECT as an anesthetic agent alone or associated with another anesthetic agent (thiopental, propofol) with limited evidence in favor of ketamine. In one RCT, ketamine was administered with a dose of 1–2 mg/kg versus 1–2 mg of methohexital, before three consecutive ECT sessions[57] with no difference between both groups. Another study used a dose of 0.75 mg/kg of ketamine versus 1 mg/kg of propofol before ECT sessions with a frequency of two or three sessions per week,[58] with a faster improvement of depressive symptoms with ketamine. Overall, depression was not improved significantly when ketamine was associated with ECT.

Ketamine and suicide

Several RCTs have assessed suicidal ideation in depressed patients.[46,49,54,59–61] In treatment-resistant MDD or BD patients, ketamine provided a reduction in MADRS-suicidal ideation scores[59] versus placebo and a reduction in explicit suicidal cognition versus midazolam[60] 1 day after a single infusion of 0.5 mg/kg over 40 mins. A single dose of ketamine combined with escitalopram significantly reduced Quick Inventory of Depressive Symptomatology – Self-Report suicidality item versus placebo until 3 days post-infusion.[54] Significantly greater improvement was also observed with intranasal S-ketamine on the MADRS-suicidal thoughts item score at 4 hrs, but not at 24 hrs or at day 25.[49]

However, one RCT did not find a difference 1 day following treatment in Beck Scale for suicidal ideation score between ketamine 0.5 mg/kg and midazolam, even though a significant difference emerged at 2 days.[61] In this study, the MADRS-suicidal ideation score was lower in ketamine compared to midazolam at day 1.[61] In a recent study, ketamine did not have significantly better effect on suicidal ideation than placebo after six ketamine infusions (0.5 mg/kg over 45 mins) over 3 weeks.[46]

Discussion

Ketamine as a pharmacological drug

This review shows that ketamine provides a rapid and robust antidepressant effect with an onset of 40 mins after a single IV infusion in MDD and BD with a maximum efficacy at 24-hr post-infusion in 14 publications.[30,31,33,35–38,44,45,49,50,52–54] This effect on depression is however transient and disappears 1–2 weeks post-infusion. There is limited evidence for ketamine efficacy in depressive patients (over placebo) after 1 week and even less after 2 weeks.[31] This limited evidence in favor of ketamine could be explained by differences in the etiology and subtype of patients, ketamine dosage, mode of administration, and pharmacokinetics.

Ketamine short-term efficacy variability

Subtypes of patients

Ketamine could act differently according to specific subtypes of patients. Ketamine effects were modulated by depression severity at baseline and were not effective in patients with mild depression. In patients with greater depression severity at baseline, the 0.5 mg/kg dose increasingly separates from placebo and 0.2 mg/kg dose.[53] The antidepressant effect of ketamine may also vary according to the etiology. A meta-analysis showed that treatment effect is moderately attenuated for patients with MDD at 7 days. In both trials with BD, treatment effect dissipated by days 4–7.[36] Moreover, there are preliminary results to indicate that ketamine may have superior antidepressant properties among treatment-resistant patients with an anxious form of BD as opposed to non-anxious BD. In this study, the anxious depressed group did not show a clear antidepressant response disadvantage over the non-anxious group.[62]

Ketamine administration

Most studies used IV route and a single dose of ketamine (mostly at 0.5 mg/kg over 40–45 mins) was enough to improve depression state when ketamine was used alone or in combination with thiopental or propofol. A dose-related antidepressant effect was suggested as 0.2 mg/kg but was not efficacious.[53] Ketamine antidepressant efficacy could also vary with the number of IV infusion or mode of administration. Several studies have examined whether repeated doses of 0.5 mg/kg by IV route could have a better antidepressant effect and might extend the duration of antidepressant effect compared to a single dose.

Overall, the effect stopped after discontinuation of the treatment (or was not assessed). One study did not show a significant difference between ketamine and placebo groups with depression rating scale score across infusions (or with response or remission rates).[46] Another study showed significant difference in MADRS scores at day 15 and day 29.[63] The last study included in this review showed benefice 72-hr post-infusion but no longer at one-week post-treatment.[64]

Ketamine bioavailability by oral route varies from 17% with 0.5 mg/kg[65,66] to 30% with 50 mg[67] of racemic ketamine, because of an extensive first-pass metabolism. Repeated administration of ketamine by oral route was used in three studies and provide efficacy during all the treatment intake (3 weeks[51] and 6 weeks).[48] However, no assessment was done after discontinuation of oral ketamine.

Racemic ketamine bioavailability by intranasal route is higher than oral route and reaches 45% with a dose of 25 mg.[67] Several RCTs were focused on the intranasal route and one study[68] was included in five meta-analyses.[33,36,38,43,45] These RCTs provide the first controlled evidence for the rapid antidepressant effects of intranasal ketamine,[47,49,50,68] including suicidal ideation improvement.[50] (S)-ketamine efficacy was observed during the 2 weeks of treatment with adjunctive oral antidepressant.[50] This effect was perceived over the 8-week follow-up phase (without additional (S)-ketamine doses) in participants who remained in the study.[50] Overall these results are rewarding, especially for suicidal ideation. In March 2019, the US Food and Drug Administration has approved the use of nasal S-ketamine in the first days of treatment-resistant depression, in conjunction with an oral antidepressant.

Ketamine pharmacokinetics – pharmacodynamics

Concerning ketamine kinetics, once absorbed it is rapidly distributed in the brain and highly perfused tissues, the distribution half-life is short in the range of 2–4 mins, and the elimination half-life 2–4 hrs.[66,69] Ketamine's pharmacokinetics could partly explain ketamine short-term efficacy that may be linked to the immediate effect on NMDAR to offset the dysfunction in glutamatergic neurotransmission. Indeed, postmortem studies have highlighted increased level of glutamate in the frontal cortex from MDD and BD patients,[70] that could be due to a reduction in the expression of genes for glutamate transporters (such as EAAT-1 and EAAT-2) in the anterior cingulate cortex and dorsolateral prefrontal cortex or of enzymes (L-glutamate-ammonia ligase) that converts glutamate to glutamine in depressed patients.[71] This glutamate surge which results in synaptogenesis and synaptic potentiation,[72,73] modulated by AMPAR activation and mTORC1 subsequent involvement has been suggested.[14]

Moreover, preclinical evidence has shown that ketamine displays other mechanisms of action that include $5HT_{1B}$ receptor,[74] 5HT transporter,[75] increase of 5HT brain level,[76,77] $GABA_A$ receptor,[78] nicotinic acetylcholine receptors,[79] sigma receptors, especially the subunits σ1R and σ2R[80] and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, in particular the HCN1 channel.[81] All these actors may play a role in ketamine's rapid and potentially long-term antidepressant effect, but more evidence are needed. Possible ketamine interactions with the opioid system have also been suggested. Pretreatment with naltrexone, an opioid receptor antagonist, diminished ketamine antidepressant effect in MDD patients, suggesting that opioid receptor activation is required for ketamine antidepressant action.[82] But the sample size was very small (n=7) and this finding was not observed in rodent model of depression[83] or in another pilot study.[84] Other results suggest that combined ketamine with naltrexone might enhance the treatment of comorbid alcohol use disorder.[84]

Ketamine enantiomers and metabolites

Ketamine enantiomers may also play a role. Due to an asymmetric carbon atom in position C2, ketamine has a chiral structure composed of two enantiomers: (S)-ketamine and (R)-ketamine. The enantiomer (S)-ketamine is twice as potent as the racemic mixture and four times more potent than the (R)-ketamine enantiomer at NMDAR.[85] One study compared (S)-ketamine at doses of 0.2 or 0.4 mg/kg versus placebo and (S)-ketamine had a rapid onset of robust antidepressant effect in patients with treatment-resistant MDD after a 40-min IV infusion.[56] The authors suggested that a lower dose may allow for better tolerability than the racemic mixture while maintaining efficacy.

However, although (S)-ketamine has long been considered as an active substance for the action of ketamine, (R)-ketamine has been reported to exhibit longer-lasting and more potent antidepressant effects than (S)-ketamine in rodent models.[72,86–88] Administration of equal doses of (R)-ketamine and (S)-ketamine did not yield different levels of these enantiomers in the brain in rodents, indicating that increased antidepressant effect of (R)-ketamine is not due to greater brain drug levels.[78,87] A preclinical study demonstrated that both (R)-ketamine and (S)-ketamine exhibited antidepressant effects at 30 mins and 1 day after administration. At 2 days after administration, (R)-ketamine still exerted a significant antidepressant effect, whereas the effect of (S)-ketamine was no longer observed.[87] These results suggest that ketamine exerts its antidepressant action not solely via antagonism of NMDAR. BDNF reduction and a decreased phosphorylation of TrkB were observed in the prefrontal cortex and hippocampus (dentate gyrus, CA3) of depressed mice after social defeat stress, phenomenon attenuated with both ketamine enantiomers.[88] However, (R)-ketamine induced a more potent beneficial effect on decreased dendritic spine density, BDNF–TrkB signaling and synaptogenesis in those cerebral regions compared with (S)-ketamine.[88]

Zanos et al[78] have reported that not only (R)-ketamine has more potent antidepressant effects than (S)-ketamine, but also ketamine metabolite (2S,6S; 2R,6R)-hydroxy-norketamine (HNK) is essential and sufficient to exert the antidepressant effects of ketamine, finding also supported by others researches,[89] even if more studies are needed to confirm this mechanism. In 2019, Phase I clinical studies will study the antidepressant action of (R)-ketamine and (2R,6R)-HNK.[89]

Ketamine, a long-term efficacy?

It should be noted that although ketamine has an effect limited to 1–2 weeks, its antidepressant action can persist for over 2 weeks in some patients,[43] although plasma levels of ketamine are no longer detectable 1 day after a 0.5 mg/kg infusion of ketamine.[90] This may be linked to other active compounds as ketamine is highly metabolized by hepatic cytochromes P450.[91] The major metabolic pathway concerns the N-demethylation of ketamine to norketamine, an active metabolite in humans.[92,93] Norketamine is then metabolized to HNK and dehydronorketamine (DHNK).[94] HNK metabolites are formed by hydroxylation of the cyclohexyl ring of norketamine at several locations, with (2R,6R; 2S,6S)-HNK and (2S,6R; 2R,6S)-HNK being the predominant forms in plasma.[95,96] The metabolites DHNK and (2R,6R; 2S,6S)-HNK are still detectable 3 days after infusion,[90] and previous report suggests that metabolites had antidepressant action in animal model.[72]

A case report has suggested that repeated low doses of ketamine can extend its acute efficacy for few months.[97] But effective methods to prolong initial antidepressant response of ketamine, by targeting glutamatergic system and with lower adverse effect to avoid ketamine abuse and dependence, are still needed. For example, a clinical study (NCT01602185) has assessed dextromethorphan, another NMDAR antagonist, as a ketamine relay to maintain ketamine pain relief in neuropathic pain patients.[98]

Ketamine as pre-ECT anesthetic adjuvant

Concerning ketamine as an anesthetic adjuvant alone or in combination to augment benefit of ECT, no real improvement was found in term of depressive symptoms or in response and remission rates. Even if ECT itself is an effective treatment for depression with a response rate of 80% when patients received enough ECT sessions,[99] repeated ketamine administration, as a monotherapy, has been demonstrated to result in greater improvement than ECT sessions.[64]

Possible reasons that may explain the lack of ketamine efficacy in addition to ECT are that the potential benefit of ketamine has been canceled by ECT even if a meta-analysis showed an enhanced antidepressive effect of ECT in the initial course of treatment.[39] However, an accelerated effect was found in this meta-analysis[39] when ketamine was used as an add-on anesthetic with sub-anesthetic doses. The optimal dosing of ketamine for its antidepressant effect is still under investigation, but it is then possible to think that ketamine at anesthetic dose (1–2 mg/kg) could not have antidepressant effect. Moreover, some studies used barbituric agents (thiopental, propofol) and these molecules do potentiate GABAergic neurons and inhibition of AMPAR. Barbiturics may counteract ketamine inhibition on GABAergic neurons and activation of AMPAR, mechanisms involved in ketamine's antidepressant action.[72]

Ketamine and suicide

Patients with MDD or BD frequently present hopelessness and can experience suicidal thoughts during a current depressive episode. About 20–25% of BD patients have reported a history of suicide attempts.[5] Existing treatment options for these patients include conventional antidepressants, ECT, psychotherapy, lithium, or valproate but some patients are resistant and these treatments have relative sluggishness of therapeutic onset, and hence, the suicidal act may occur during this period.[100] Ketamine has been shown to have rapid effect on suicidal ideation within 2 hrs of administration in patients with treatment-resistant MDD[59,101] or in BD,[102] making it as an attractive therapy for depressed patients with imminent risk of suicide. But some recent studies have found no benefice in the improvement of suicide ideation.[46,61] A study has shown that ketamine had greater effects in patients with higher level of basal suicidal cognition or with a previous history of suicide attempt.[60] Ketamine may work most efficaciously in patients at the highest risk of suicide, and this hypothesis could be linked with its efficacy relative to the level of depression because this molecule was not effective in patients with relatively mild depression.[53] The authors have suggested that ketamine's antidepressant and antisuicidal effects could be the same property because the main antisuicidal effect was reduction in overall (non-suicide related) depressive symptoms.[60] However, this antisuicidal property has not been assessed in non-depressed patients experiencing suicidal thoughts. Moreover, one study collected patient-level data from four independent, previously published clinical trials and they showed that ketamine exerted an effect on suicidal ideation that was independent of depression and anxiety.[103]

A previous report indicated an increase of quinolinic acid, an NMDAR agonist, in the cerebrospinal fluid (CSF) of suicide attempters. Level of this agonist was correlated with the total scores on Suicide Intent Scale and was associated with higher levels of CSF interleukin-6.[104] Changes in glutamatergic neurotransmission could be specifically linked to suicidality and might explain the observed remedial effects of ketamine through NMDAR.

Ketamine safety and toxicity

Concerning safety and toxicity, only one Cochrane review demonstrated a difference in favor of placebo over ketamine about confusion and emotional blunting in patients with MDD or BD.[31] However, no conclusive evidence about adverse event was found when ketamine was compared to placebo in BD.[30] Studies have shown that safety and tolerability profiles are generally good at low doses and with short-term treatment in depressed patients. The adverse events associated with ketamine usually occur with very high doses that are administered for prolonged periods of time and can be relieved by cessation according to Zhu et al.[105] A recent review has listed all the studies to assess side effects induced by ketamine as a pharmacological drug or pre-ECT in depressive patients. Acute ketamine psychiatric side effects were described in 38% of studies, whereas psychotomimetic or dissociative side effects were described in 72% of studies.[106] An isolated case of a suicide attempt was reported in one study.[63] No long-term psychotomimetic side effects were reported.[106]

Concerning intranasal (S)-ketamine administration, most adverse events were of mild or moderate severity (dizziness, dissociation, dysgeusia, vertigo, and nausea), were transient and well tolerated.[47,49,68] A minority of patients with (S)-ketamine experienced adverse events leading to discontinuation of the study drug: 3/56 during the double-blind phase (compared with none receiving placebo) (syncope, headache, dissociative syndrome, and ectopic pregnancy);[50] 8/114 (single events of anxiety, depression, depressive symptoms, panic attack, drug intolerance, feeling drunk, dizziness, headache, vertigo, nausea, road traffic accident, and multiple injuries); 1/109 in the antidepressant plus placebo arm (generalized rash);[47] 5/35 (agitation, aggression, unpleasant taste, and ventricular extrasystoles in one participant each, and dizziness, dyspnea, and nausea in one participant); and 1/31 in the placebo group (dissociative disorder and panic attack).[49]

However, there is a lack of data concerning ketamine repeated administration at higher dose in depression. More studies should focus on the risk of serious liver damage, uro-nephrogenic damage or dependence, adverse event previously observed with recreational users.[107]

Conclusion

Ketamine may provide a rapid, robust, but transient antidepressant effect in MDD and BD. It appears particularly interesting in patients experiencing suicidal thoughts with its rapid effect in suicidal ideation. The benefits of ketamine are transient, up to 1–2 weeks after infusion and its long-term effect is less reported. Acute side effects associated with single-dose use in depression are common, although generally transient and resolve spontaneously. However, acute and long-term efficacy and safety issues must be further explored, and adverse event should be systematically assessed. Further studies are needed to explore the best dose and mode of administration to optimize ketamine antidepressant effect and to clarify its mechanism of action.

Abbreviations

AMPAR, α-amino-3-hydroxy-5-méthylisoazol-4-propionate receptor; BDI, Beck Depression Inventory; BD, bipolar depression; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; DHNK, dehydronorketamine;

ECT, therapy; GABA, gamma-aminobutyric acid; HDRS, Hamilton Depression Rating Scale; HNK, hydroxy-norketamine; HCN, hyperpolarization-activated cyclic nucleotide-gated; IV, intravenous; MDD, major depressive disorder; mTOR, mechanistic target of rapamycin; MADRS, Montgomery–Asberg Depression Rating Scale; NMDAR, N-methyl-D-aspartate receptor; RCT, randomized controlled trial.

Disclosure

The authors declare that there are no competing financial or non-financial interests in this work.

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