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Ketamine as a new treatment for depression: A review of its efficacy and adverse effects

Natalie Katalinic[1], Rosalyn Lai[1], Andrew Somogyi[2], Philip B Mitchell[1,3,4], Paul Glue[5] and Colleen K Loo[1,3,6,7]

Abstract

Objective: Narrative review of the literature on the efficacy and safety of subanaesthetic doses of ketamine for the treatment of depression.

Method: Medline and PubMed databases were searched up to October 2012 using appropriate keywords.

Results: The studies consistently report substantial efficacy with high response and remission rates from 4 to 72 hours (averages 77% and 43%, respectively) from single doses, though not all patients respond to ketamine. Early relapse is common. While the usual procedure involves the administration of intravenous ketamine at a dose of 0.5 mg/kg over 40 minutes, some preliminary evidence suggests other dosing regimens and routes of administration may be useful or even better. Repeated doses and maintenance pharmacological treatments have been investigated in order to prolong the antidepressant effects, with only modest success.

Conclusions: Current research on the antidepressant effects of ketamine has consistently shown rapid and substantial improvement in mood in the majority of patients. However, these effects have often been found to be short-lived. Future research should focus on identifying predictors of response (e.g. clinical, genetic, pharmacokinetic, environmental), examining different dosing regimens and routes of administration, and strategies to maintain the antidepressant response.

Keywords

Adverse effects, antidepressive agents, depressive disorder, ketamine, treatment outcome

Introduction

Depression is an increasingly common debilitating illness, currently projected to affect 121 million people worldwide (World Health Organization, 2012). Despite its high prevalence and disability, treatment response and remission rates remain frustratingly low. This was exemplified in a large effectiveness study in which a third of depressed patients did not achieve remission even after up to four trials of different antidepressant medications (STAR*D; Warden et al., 2007). Presently, electroconvulsive therapy (ECT) is considered the most effective management of treatment-resistant depression, with a rapid onset of response and high remission rate (UK ECT Review, 2003). However, its use is restricted by the risk of memory and cognitive impairment (UK ECT Review, 2003). Therefore, there is interest in developing alternative treatment options for depression which have both a faster onset of response and a higher success rate than current pharmacological and other physical treatment options.

[1]School of Psychiatry, University of New South Wales, Sydney, Australia
[2]Discipline of Pharmacology, University of Adelaide, Adelaide, Australia
[3]Black Dog Institute, Sydney, Australia
[4]Brain Sciences, University of New South Wales, Sydney, Australia
[5]Psychological Medicine, Dunedin School of Medicine, Otago, New Zealand
[6]St George Hospital, Sydney, Australia
[7]Wesley Hospital Kogarah, Sydney, Australia

Corresponding author:
Colleen K Loo, Level 2, James Laws House, St George Hospital, Gray Street, Kogarah NSW 2217, Sydney, Australia.
Email: colleen.loo@unsw.edu.au

Since the first placebo-controlled trial investigating the antidepressant effects of subanaesthetic ketamine doses in 2000 (Berman et al., 2000) which found rapid and large effects, interest has risen quickly and many research studies have followed. The aim of this review is to collate the current evidence for ketamine as a potential new treatment for depression and to address factors that pose a barrier to its becoming a useful clinical treatment.

Materials and methods

Medline and PubMed databases were searched up to October 2012 using combinations of the keywords "ketamine", "NMDA", "depression", "major depressive disorder", and "bipolar depression". Once identified, all papers were reviewed by author NK providing that the studies fulfilled inclusion criteria of: being written in the English language; including depressed patients receiving ketamine; assessing mood outcomes; and publication in a peer-reviewed journal. As the dose range for ketamine as an anaesthetic is 1–4.5 mg/kg by intravenous administration (Knox et al., 1970; MIMS, 2010), only research using doses ≤1 mg/kg, given intravenously or by other routes, was included in this review. Due to the large methodological variations between studies and questions over the adequacy of blinding in many trials when saline was used as a placebo, we decided to undertake a qualitative and narrative review rather than a systematic meta-analysis. Thus, no additional inclusion or exclusion criteria were imposed. We considered all types of studies (e.g. double-blind/single-blind randomized controlled trials; open-label uncontrolled studies; intraindividual crossover or parallel group trials; naturalistic observations; case reports; case series) and formats (research reports, brief reports, letters to the editor, correspondence, editorials). References from these publications were checked to identify any further relevant publications to ensure that the review was thorough and that there was no duplication of clinical data from multiple reports emanating from the same author(s). The studies reviewed and their details are summarized in Table 1.

Review

Evidence for efficacy of ketamine as an antidepressant treatment

Open-label studies. Research investigating the antidepressant effects of ketamine has consistently reported rapid and robust improvement using mostly intravenous infusions of 0.5 mg/kg ketamine over 40 minutes. Most open-label studies analysing the effect of a single ketamine infusion on Montgomery-Asberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HDRS) scores have found high response (≤50% baseline MADRS/HDRS score) rates within 230 minutes, ranging from an average of 33% in a series of three separate studies by the same group (Salvadore et al., 2009, 2010, 2011) to 43% (Phelps et al., 2009) and 44% (Machado-Vieira et al., 2009; estimate based on graphs presented). Furthermore, other similarly designed studies have found response rates of 50% and 46% earlier than 230 min (110 minutes, Thakurta et al., 2012b; 120 minutes, Mathew et al., 2010). In Mathew et al., (2010), 65% of patients responded by 72 hours and 50% of the sample maintained remission (MADRS score <10) from 24 hours post injection through to 72 hours. However, while the response rate for the sample in Thakurta et al., (2012b) initially increased to 77% by day 1 after treatment, this decreased to 13% by day 7 and 5% by day 14.

Three open-label studies (Price et al., 2009; Larkin and Beautrais, 2011, Thakurta et al., 2012a) have suggested that ketamine may be an appropriate treatment to rapidly reduce acute suicide risk in depressed patients. Larkin and Beautrais (2011) found a significant reduction in the Suicide Ideation item on the MADRS from the baseline score of 3.9 (SEM 0.4) at 40 minutes (0.6, SEM 0.2), 80 minutes (0.6, SEM 0.2), 120 minutes (0.7, SEM 0.2), and 240 minutes (0.6, SEM 0.1). In Price et al., (2009), 24 hours after infusion of ketamine, 81% of patients achieved a score of 1 or 0 (median score 0) out of a possible 6 on the Suicidal Thoughts item of the MADRS – a significant decrease from the pretreatment median score of 3.5. In addition, the patients' previous association between the words "Escape" and "Me" on the Implicit Association Test (an item that correlates highly with explicit suicide ideation) were significantly reduced at 24 hours. Effect sizes for reduction in both implicit and explicit suicide ideation were large, ranging from 1.36–1.67. Using the same dosing regimen, Thakurta et al., (2012a) found that scores on the Scale for Suicide Ideation and the HDRS-suicidality item were significantly decreased from 40 minutes through to 230 minutes post ketamine. The biggest change from baseline was noted at 40 minutes, with 80% reduction in the mean score. However, scores returned to baseline the day after the infusion.

Investigating whether 0.5 mg/kg ketamine could be an appropriate treatment where treatment with ECT had failed, Ibrahim et al., (2011) reported significant decreases in MADRS scores by 230 minutes in both ECT-naïve (n=23) and ECT-resistant (n=17) depressed patients. Despite both groups improving and there being no significant differences between groups in the proportion of responders, the effect size was halved in the ECT-resistant sample (Cohen's D 0.50).

In addition, there have also been several reports of ketamine at both full anaesthetic and subanaesthetic doses possibly enhancing the antidepressant effects of ECT at times resulting in greater reductions in depression scores and fewer ECT treatments required (Ostroff et al., 2005;

Table 1. Details of ketamine for depression studies, including design and sample size, treatment details, outcome measures used, and antidepressant outcomes.

Study	Design and sample	Treatment details	Outcome measures	Baseline depression score[a]	Antidepressant outcomes[b]
Berman et al., 2000	RCT, intraindividual crossover, *n*=8, MDD	0.5 mg/kg i.v. ketamine or saline placebo over 40 min, separated by a week	HDRS and BDI, measured at baseline, 80, 230 min, 24, 48, 72 h after beginning of infusion	HDRS: ketamine: 33.0±6.7; placebo: 26.9±5.8	Ketamine > saline placebo: mean HDRS at 230 min (26 vs. 24.9)[c], 24 h (22 vs. 28.9)[c], 48 h (20.5 vs. 27.9)[c], and 72 h (20 vs. 26.4) [c] Difference is also significant for BDI at 230 min, 24 h, 48 h, and 72 h Response[d] at 72 h (HDRS): ketamine 4/8, Saline placebo 1/8 Ketamine-induced antidepressant effects returned to baseline after 1–2 weeks, except in one participant
Kudoh et al., 2002	RCT, parallel group, *n*=95, undergoing orthopaedic surgery (70 depressed, 25 healthy)	Group A (depressed): 1 mg/kg ketamine, 1.5 mg/kg propofol, 2 μg/kg fentanyl Group B (depressed): 1.5 mg/kg propofol, 2 μg/kg fentanyl Group C (not depressed): 1 mg/kg ketamine, 1.5 mg/kg propofol, 2 μg/kg fentanyl	HDRS, measured at baseline, 1 day (day 1) and 3 days (day 3) after the operation	HDRS: group A: 12.7±5.4; group B: 12.3±6.0	Group A > group B at day 1: mean HDRS 9.9±4.1 vs. 14.4±3.0
Zarate et al., 2006	RCT, intraindividual crossover, *n*=18, TRD	0.5 mg/kg i.v. ketamine over 40 min, or saline placebo, separated by a week	HDRS and BDI, measured 60 min prior to and 40, 80, 110, 230 min and days 1, 2, 3, 7 after the beginning of infusion	HDRS: ketamine: 24.7±6.9; placebo: 21.1±6.9	Ketamine > saline placebo: mean HDRS at 110 min (15 vs. 19)[c], 230 min (15 vs. 20)[c], day 1 (12.5 vs. 22)[c], day 2 (14 vs. 23)[c], day 3 (15 vs. 23)[c] and day 7 (20 vs. 25)[c] Ketamine showed improvement in BDI from 40 min through to day 7 compared to baseline Note: evidence of carryover effects for those who begun on ketamine HDRS: response at day 1: ketamine 12/17, saline placebo 0/14; remission at day 1: ketamine 5/17, 0/14 saline placebo

(Continued)

Table 1. (Continued)

Study	Design and sample	Treatment details	Outcome measures	Baseline depression score[a]	Antidepressant outcomes[b]
Machado-Vieira et al., 2009	Open label, *n*=23, TRD	0.5 mg/kg i.v. ketamine over 40 min	MADRS, measured 60 min prior to and 40, 80, 120, 230 min after the beginning of the infusion.	MADRS: 33.5±4.3	MADRS: ketamine decreased mean scores at all post-infusion time points compared to baseline: 80 min (18)[c], 120 min (21.25)[c], 230 min (19)[c]
Phelps et al., 2009	Open label, *n*=26, TRD, with family history of alcohol dependence (FHP) or without (FNP)	0.5 mg/kg i.v. ketamine over 40 min	MADRS, HDRS, and BDI, measured 60 min prior to and 40, 80, 120, 230 min after the beginning of infusion	MADRS: 33[c]	FHP > FNP: MADRS scores at 120 min (22.5)[c] after infusion, difference continuing at trend level at other time points Results were similar with BDI and HDRS Overall MADRS response: 43% at 230 min (FHP: 67%, FNP: 18%) Overall MADRS remission: 26% (FHP: 42%; FNP: 9%)
Price et al., 2009	Open label, *n*=26, TRD	0.5 mg/kg i.v. ketamine over 40 min	MADRS item 10 and IAT (*n*=10), measured 150 min before and 24 h after infusion	MADRS item 10 score: 2.85±1.64	MADRS item 10: at 24 h, 81% of patients achieved a score of 0 or 1 on this item (mean 0.77)[c] IAT: reduction in Escape=Me associations at 24 h (which correlates highly with explicit suicide ideation)
Price et al., 2009 (continuation phase)	Open label, *n*=10, responders at 24 h	0.5 mg/kg i.v. ketamine over 40 min infusion on days 1, 3, 5, 8, 10, and 12	MADRS item 10, measured 150 min before and 24 h after infusion	Mean MADRS item 10 score: 3±1.63	MADRS item 10: at 24 h, 90% of patients achieved a score of 0 after the first infusion (mean 0.1)[c] No patient scored >2 on MADRS item 10 at any post-baseline assessment
Salvadore et al., 2009	Open label, *n*=11, MDD	0.5 mg/kg i.v. ketamine over 40 min infusion	MADRS and HARS, measured before ketamine infusion and 230 min after beginning of infusion	MADRS: 31.9±3.3	MADRS: improvement from baseline at 230 min (mean 20.4) HARS at 230 min: improvement from baseline

(Continued)

Table 1. (Continued)

Study	Design and sample	Treatment details	Outcome measures	Baseline depression score[a]	Antidepressant outcomes[b]
aan het Rot et al., 2010	Repeated dose, open label, *n*=10, TRD	0.5 mg/kg i.v. ketamine over 40 min; 6 infusions over 12 days	MADRS, QIDS-SR, and CADSS, measured at baseline, 2 h, 4 h, and 24 h after each infusion; after final infusion measured for at least 4 weeks or until relapse	MADRS: 32.7±6.4	MADRS response at 24 h after 1st infusion: 9/10 [Mean MADRS at 2 h (16.8), 4 h (11.4), and 24 h (6.9)] QIDS response at 24 h after 1st infusion: 8/9 4 h after 6th infusion: response: 9/9, remission 8/9 8/9 relapsed after an average of 30 days from the first infusion
Diazgranados et al., 2010	RCT, intraindividual crossover, *n*=18, BPAD	0.5 mg/kg i.v. ketamine over 40 min;or saline placebo, separated by 2 weeks Maintained on lithium and sodium valproate during trial	MADRS, HDRS-17, and HARS, measured 60 min prior to and 40, 80, 110, 230 min and 1, 2, 3, 7, 10, 14 days post infusion	MADRS: ketamine: 32.1±4.1; placebo: 31.7±6.5	ITT Ketamine > saline placebo: MADRS at 40 min (18 vs. 28)[c], 80 min (19.5 vs. 28)[c], 110 min (18 vs. 29)[c], 230 min (19 vs. 28)[c], day 1 (19 vs. 30)[c], day 2 (17 vs. 31)[c], and day 3 (20 vs. 29)[c] HDRS from 40 min through to day 3 HARS from 230 min through to day 3 At day 1 (MADRS): response: ketamine 7/16, saline placebo 0/16; remission: ketamine 5/16, saline placebo 0/16 Completers Ketamine > saline placebo MADRS from 40 min through to 7 days
Mathew et al., 2010	RCT of lamotrigine or placebo added to ketamine, *n*=26, TRD	0.5 mg/kg i.v. ketamine over 40 min. Two h pre-infusion, randomized to either 300 mg oral lamotrigine or saline placebo	MADRS and QIDS-SR, measured at baseline and 40, 80, 120, 240 min, and 24, 48, 72 h post infusion	MADRS: 36.9±5.4	Response (MADRS and QIDS-SR consistent): 12/26 at 120 min; 16/26 at 240 min; 17/26 at 24 h (mean MADRS 15.9); 17/26 at 48 h and 72 h Remission (MADRS and QIDS-SR consistent): 13/26 at 24 h, 13/26 at 48 h and 72 h

(Continued)

Table 1. (Continued)

Study	Design and sample	Treatment details	Outcome measures	Baseline depression score[a]	Antidepressant outcomes[b]
					No differences between lamotrigine and saline placebo pretreatment in efficacy at any time point
Salvadore et al., 2010	Open label, *n*=15, MDD	0.5 mg/kg i.v. ketamine over 40 min	MADRS and HARS, measured at baseline and 230 min after beginning of infusion	MADRS: 33.5±4.8	MADRS: improvement from baseline at 230 min (mean 21.0) HARS: improvement from baseline at 230 min
Ibrahim et al., 2011	Open label, *n*=40, MDD (17 failed ECT, 23 ECT naïve)	0.5 mg/kg i.v. ketamine over 40 min	MADRS, measured 60 min prior; and 40, 80, 120, 230 min after beginning of infusion	MADRS: Failed ECT: 34.1±5.6; ECT-naïve: 32.0±4.3	MADRS: Failed-ECT sample had decreased scores compared to baseline at 230 min (mean 25)[c] ECT-naïve sample had decreased scores compared to baseline at 230 min (mean 17)[c]
Larkin and Beautrais, 2011	Open label, *n*=14, MDD with suicide ideation	0.2 mg/kg i.v. bolus ketamine over 1–2 min	MADRS and SSI, measured at baseline, 40, 80, 120, 240 min, and 1–10 days post administration (note: 1 patient only followed to day 7)	MADRS: 42 (IQR 38–47)	Significant decrease in mean MADRS score from baseline at 240 min (14)[c], day 1 (10)[c], day 4 (8)[c], day 7 (10)[c], and day 10 (8)[c] 12/13 maintained response criteria at day 10 SSI: Suicide ideation significantly decreased from baseline at 40 min and sustained till day 10
Salvadore et al., 2011	Open label, *n*=14, MDD	0.5 mg/kg i.v. ketamine over 40 min	MADRS and HARS, measured at baseline and 230 min after infusion	MADRS: 33.4±5.9	MADRS: improvement from baseline at 230 min (mean 25.1) HARS: improvement from baseline at 230 min
Valentine et al., 2011	Intraindividual crossover (fixed), *n*=10, MDD	i.v. saline placebo infusion over 40 min, followed by ketamine 0.5 mg/kg over 40 min 1 week later	HDRS and BDI, measured at baseline and 60, 180 min, 24, 48, 72 h, and days 5 and 7 after each infusion	HDRS: ketamine: 26.8±4.2; placebo: 28.4±2.4	Ketamine > saline placebo: mean HDRS at 60 min (25 vs. 30)[c], 24 h (20 vs. 27)[c], 48 h (20 vs. 30)[c], 72 h (20 vs. 26)[c], and day 7 (24 vs. 29)[c] Significant decrease in BDI scores after ketamine at 60 min, 210 min, 24 h, 48 h and 72 h

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Table 1. (Continued)

Study	Design and sample	Treatment details	Outcome measures	Baseline depression score[a]	Antidepressant outcomes[b]
Ibrahim et al., 2012	RCT of riluzole or placebo added to ketamine, *n*=42, TRD	0.5 mg/kg i.v. ketamine over 40 min infusion; with riluzole 100mg or saline placebo given 4–6 h after	MADRS, HDRS, BDI, and VAS-D, measured 60 min prior to and 40, 80, 110, 230 min, and daily for 28 days post infusion	MADRS: 32.7±5.7 HDRS: 20.8±4.5	Mean MADRS scores were significantly lower than baseline from days 1 (14)[c] to 28 (16)[c] Response (MADRS): 62% responded overall 27% of these participants did not relapse in the 4-week study; 38% did not relapse after 2 weeks, and 58% did not relapse after 1 week 33% of the ketamine-riluzole group and 21% of the ketamine-placebo group did not relapse before day 28
Thakurta et al., 2012a	Open label, *n*=27, MDD-TR	0.5 mg/kg i.v. ketamine over 40 min infusion	HDRS, HDRS-SI, and SSI, measured 60 min prior to and 40, 80, 110, 230 min and days 1 and 2 post infusion	SSI: 4.85±5.4 HDRS-SI: 1.37±1.3 HDRS: 22.96±1.2	Significant improvement from baseline on HDRS-SI and SSI scores: mean HDRS-SI: 40 min (0.41), 230 min (1.37); SSI: 40 min (0.78), 230 min (0.78) Biggest change in SSI occurred at 40 min (80% decrease) Significant improvement from baseline on mean HDRS: 80 min (17.5), 230 min (12.41) day 2 (15.6) Biggest change in HDRS was at 230 min (45% decrease)
Thakurta et al., 2012b	Open label, *n*=22, MDD-TR	0.5 mg/kg i.v. ketamine over 40 min infusion	HDRS, measured 60 min prior, and 40, 80, 110, 230 min and days 1, 2, 3, 4, 7, 14 post infusion	HDRS: 22.55±5.2	Mean HDRS scores decreased from 22.55 to 15.23 at 80 min, and this remained significant until day 3 The maximum change occurred at 230 min (10.77) Response (HDRS): 50% of participants at 110 min, 77% of participants at day 1, 13% of participants at day 7, 5% of participants at day 14 Remission (HDRS): 0% at any time point

(Continued)

Table 1. (Continued)

Study	Design and sample	Treatment details	Outcome measures	Baseline depression score[a]	Antidepressant outcomes[b]
Zarate et al., 2012	RCT, intraindividual crossover, *n*=15, BPAD I or BPAD II	0.5 mg/kg i.v. ketamine over 40 min infusion; or saline placebo	MADRS, HDRS, BDI, and VAS-D, 60 min prior to and 40, 80, 110, 230 min and days 1, 2, 3, 7, 10, 14 post infusion	MADRS: i.v. ketamine: 32.45 (SE: 2.3); placebo: 34.65 (SE: 1.95)	MADRS: ITT sample: ketamine > saline placebo from at 40 min (mean 17 vs. 32)[c], 80 min (17 vs. 31)[c], 110 min (17 vs. 31)[c], 230 min (19 vs. 30)[c], day 1 (20 vs. 32)[c], day 2(23 vs. 34)[c],and day 3 (25 vs. 31)[c] The biggest effect size was observed at 40 min Completers Ketamine > saline placebo from 40 min to day 3 Response: altogether, 79% responded to ketamine at some point. 0% responded to saline placebo; 64% ketamine responded at 40 min; 50% ketamine responded at 230 min; 43% responded at day 1; 2/22 maintained response until at least day 7; 1/22 until day 10, and 1/22 until day 14 Remission: 7% ketamine remitted at 40 min, 36% ketamine remitted at 230 min, 29% ketamine remitted at day 1; median time to relapse was until day 2 HRDS: ketamine > saline placebo from 40 min through to day 2 BDI and VAS-D: ketamine > saline placebo from 40 min to day 14.

[a]Only shown for primary measure outcome. Values are mean±SD unless otherwise stated.
[b]A > B: A had significantly better outcomes than B. This may be lower depression scores, lower adverse effects, greater response, etc. It does not reflect the specifics of the measure used.
[c]Response defined as at least 50% reduction in depression score.
[d]Estimated from graph.
BDI, Beck Depression Inventory; BPAD, bipolar affective disorder; CADSS, Clinician Administered Dissociative Symptoms Scale; ECT, electroconvulsive therapy; HARS – Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; HDRS-17, Hamilton Depression Rating Scale 17-item; HDRS-21, Hamilton Depression Rating Scale 21-item; HDRS-SI, Hamilton Depression Rating Scale – Suicidality Item; IAT, Implicit Association Test; IQR, interquartile range; ITT, intention to treat; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; QIDS-SR, Quick Inventory of Depressive Symptomatology – Self Rated; RCT, randomized controlled trial; SE, standard error; SSI, Scale for Suicide Ideation; TRD, treatment-resistant depression; VAS-D, Visual Analogue Scale – Depression.

Goforth and Holsinger, 2007; Okamoto et al., 2010; Abdallah et al., 2012; Loo et al., 2012; Wang et al., 2012).

However, open-label studies carry an important methodological limitation – specifically, the presence of expectation effects and potential placebo effects. With the growing interest over ketamine as a new treatment for depression, it is imperative to control for these effects by using a blinded, randomized controlled trial design.

Case reports and case series. The impact of ketamine on depression has also been reported in several case reports (often in a single patient), administering ketamine by the intravenous, oral, or intra musculararroutes, and some assessing the use of S-ketamine, the enantiomer that has been reported to have fewer dissociative effects (Paul et al., 2009) (see Supplementary Table). When examining intravenous ketamine at 0.5 mg/kg, case series have found similar results to open-label studies, with apparent response dissipating after 3 or 4 days (Kollmar et al., 2008; Paul et al., 2009). S-ketamine has been found to be similarly efficacious, although the time to relapse may be similar (Paul et al., 2009; Denk et al., 2011; Zanicotti et al., 2012b). Finally, two case series found that the patients who responded to oral racemic ketamine (Irwin and Iglewicz, 2010) and oral S-ketamine (Paslakis et al., 2010) remained in remission or near remission for 1–2 weeks. It is noteworthy, though, that in the Paslakis et al., (2010) study, only two of four patients responded. The authors noted that their responders had melancholic features, whereas the two who did not respond had atypical depression and some additional comorbidities. If replicated, these clinical features may be important predictors of response.

Intraindividual crossover trials. In an attempt to more confidently ascertain and quantify the antidepressant effects of ketamine, several studies have used an intraindividual crossover design to compare the effects of ketamine with saline placebo. In these studies, participants were generally randomly assigned to receive ketamine or placebo first, with the other treatment given a week later. Ketamine was usually infused over 40 minutes at 0.5 mg/kg. In the Zarate et al., (2006), Valentine et al., (2011), and Berman et al., (2000) studies focusing on patients with major depressive disorder (MDD), the ketamine group had significantly lower HDRS scores as early as 60 minutes post infusion, persisting through to the final time point of follow up (3 days for the Berman study; 7 days for the Zarate and Valentine studies). The ketamine condition in the Zarate et al., (2006) study showed response rates of 12/17 (compared to 0/14 in the placebo group) and remission rates of 5/17 (compared to 0/14) 1 day after the infusion. In the Berman et al., (2000) study, response rates were 4/8 in the ketamine and 1/8 in the placebo groups 3 days after the infusions.

The Zarate group conducted a further study in 18 patients with bipolar affective disorder, using the same treatment protocol. Ketamine showed significantly superior efficacy in MADRS scores and HDRS scores from the end of the infusion to 3 days in an intention-to-treat sample (Diazgranados et al., 2010). Moreover, when receiving ketamine, 7/16 of this sample responded and 5/16 remitted, in comparison with 0/16 for both outcomes with placebo. When only completers (i.e. those who completed both treatment conditions) were analysed, ketamine was found to be significantly superior to placebo from 40 minutes after the infusion to a week later. A recent replication study in a sample of 15 patients with bipolar depression was performed by this group; they found that there was a 79% response to ketamine at some time point for the sample (Zarate et al., 2012). Similar rates of relapse to the 2010 study were also observed (median time to relapse: 2 days).

There are two major methodological concerns with these crossover design trials. First, Zarate et al., (2006) discovered order effects in their study, such that those who received the ketamine dose first had lower pretreatment scores a week later when they were treated with placebo. These carryover effects were not found (Diazgranados et al., 2010) or examined (Berman et al., 2000) in other studies. Moreover, in the Valentine et al., (2011) study, the placebo session was always given first to avoid such carryover effects. An even greater methodological concern is that ketamine induces marked psychotomimetic effects (e.g. dissociative symptoms), which would have been clearly evident to participants and investigators, whereas saline does not induce any such sensations. Thus, it is questionable if blinding was adequate in the saline-controlled, crossover trials.

Parallel group design trials. Only one randomized controlled trial used a parallel-group design in which participants were assigned to receive either ketamine or placebo, without crossing over to the other treatment condition. Such methodology avoids the potential confound of carryover effects and limits blinding due to the subjective effects of ketamine. Kudoh et al., (2002) investigated ketamine's antidepressant effects in a sample of 95 patients undergoing orthopaedic surgery, 70 of whom were depressed based on diagnoses made by their treating psychiatrists. Ketamine 1 mg/kg was given during anaesthesia to 35 of the 70 depressed patients. They found that the HDRS scores the day after surgery were significantly lower in the depressed patients who received ketamine than in the depressed patients who did not receive ketamine [mean HDRS 9.9 (SEM 4.1) vs. 14.4 (3.8), 22% decrease in HDRS scores from baseline vs. 17% increase, respectively], but these differences were no longer significant at 3 days post surgery. The patients who were not depressed did not experience significant changes in mood at any of the assessment time points.

Optimal dose and mode of administration

Pharmacology of ketamine. Ketamine is a non-competitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor (ionotropic glutamate) Ca^{2+} channel pore, with additional binding to the PCP binding site, to cause inhibition of NMDA receptor activity (Hirota and Lambert, 1996). It also interacts with opioid receptors, muscarinic receptors, adrenergic receptors, and voltage-gated Ca^{2+} channels (Quibell et al., 2011), but whether these interactions occur at clinically relevant doses/concentrations is unlikely. Ketamine has a chiral carbon atom and is marketed in most countries (including Australia) as a racemate – an equal mixture of S- and R-enantiomers. The affinity (Ki) at the PCP binding site of S-ketamine is about 5-times that of R-ketamine (Ebert et al., 1997) and S-ketamine is regarded as "… having twice the analgesic potency and fewer psychotomimetic effects" (Quibell et al., 2011). In addition, a metabolite S-norketamine has a Ki one-sixth that of S-ketamine (Ebert et al., 1997), but is reported to be equipotent as an analgesic and achieves higher plasma concentrations than ketamine after parenteral administration (Domino et al., 1965). Ketamine is extensively metabolized by the hepatic CYP450 enzyme system (Yanagihara et al., 2001). The primary and active metabolite is norketamine by the enzymes CYP2B6 (major) and CYP3A4. Ketamine has a high systemic clearance (about 1L/min), a short half life of about 3 hours, and, due to a high hepatic first pass, oral bioavailability is about 20%. Preliminary research suggests that there may be a complex relationship between ketamine, its metabolites, and antidepressant effects (Zarate et al., 2012).

Alternative doses and administration routes. While the presence of a significant antidepressant effect with ketamine has been investigated quite thoroughly, there is little information on the dose–response relationship, or the optimal mode of drug administration – crucial elements if ketamine is to gain clinical acceptance and regulatory approval. As noted above, most studies tested ketamine's antidepressant effects using 0.5 mg/kg infused intravenously over 40–60 minutes and reported high response and remission rates, though for most participants the improvement only lasted a few days (Berman et al., 2000; Zarate et al., 2006, 2012; Machado-Vieira et al., 2009; Phelps et al., 2009; Price et al., 2009; Salvadore et al., 2009, 2010, 2011; Thakurta et al., 2012b). This is the dosing approach used in the initial pilot trial of ketamine (Berman et al., 2000).

Only two studies have investigated intravenous ketamine at a different dose, both involving rapid bolus injections – Kudoh et al., (2002) gave 1 mg/kg ketamine during general anaesthesia and Larkin and Beautrais (2011) gave a 0.2 mg/kg bolus over 1–2 minutes to suicidal patients in the emergency department. Larkin and Beautrais (2011) found a significant antidepressant response 240 min post injection [mean MADRS changed from 40.4 (SEM 1.8) pretreatment to 11.5 (SEM 2.2) at 240 min]. Improvement was maintained at 7 days [mean MADRS 8.4 (SEM 1.6)] and 10 days [mean MADRS 9.2 (SEM 1.7)] in all 13 patients. By day 10, 12/13 participants continued to meet the criterion for response. The results of Larkin and Beautrais (2011) are remarkable in that antidepressant effects were largely sustained over the 10-day follow-up period, in contrast to all other studies. The reasons for this difference are unclear, but could arise from the open-label use of ketamine and the particular clinical setting (patients presenting to the emergency department in crisis) or the mode of administration used (bolus injection rather than slow infusion). It is also possible that the dose–response curve for antidepressant effects of ketamine may not be linear and that 0.2 mg/kg as a bolus may be a more optimal dose for antidepressant effects. For example, previous animal studies indicate that ketamine's effects on glutamate transmission may show a complex inverted U-shape dose–response relationship (Li et al., 2010; Autry et al., 2011). These observations highlight the need for dose–response and pharmacokinetic studies, which examine the relationship between ketamine dose, speed (and route) of administration, plasma ketamine concentrations, therapeutic antidepressant response, and adverse effects.

The only report of the dose–antidepressant response relationship to date is that of Glue et al., (2011), who also gave ketamine by an alternative route (intramuscular injection) and tested a range of doses (0.5, 0.7, and 1.0 mg/kg) in two patients with refractory depression. A clear dose–response relationship was evident, with higher doses leading to greater antidepressant response (average improvement in scores from 15% to 44% to 70%).

The oral route of administration has also been trialled. Irwin et al., (2010) gave a single dose of oral ketamine (0.5 mg/kg) to two depressed patients in hospice care and reported acute results similar to those reported for intravenous ketamine – both patients experienced a substantial improvement (45% and 37%) in mood by 60 minutes after the dose. Both patients also had a marked improvement in anxiety symptoms. Of interest, improvement was maintained for the duration of follow up (15 and 8 days respectively), in contrast to the results of most intravenous studies. These results are very promising, though the reliability of antidepressant results with the oral route of administration needs to be tested in larger samples, given the likelihood of variable plasma concentrations because of extensive first-pass hepatic metabolism of ketamine. Another consideration is that the relative plasma concentrations of ketamine and its major metabolite, norketamine, differ between the oral (1:15) and intravenous routes (1:1) (Yanagihara et al., 2003; Peltoniemi et al., 2011). The contribution of norketamine to antidepressant effects is unknown.

A recent case series by Cusin et al., (2012) described two patients with treatment-resistant bipolar depression

and attention deficit hyperactivity disorder who were successfully treated with intramuscular ketamine. The first patient had only attained a short-term response from intravenous ketamine (0.5 mg/kg over 40 minute infusion), and had subsequently not responded to a 3-week course of either oral ketamine (210 mg capsules, taken three times a week) or intranasal ketamine (200 mg/ml, "three sprays", three times a week). However, complete remission after one administration of 32 mg of intramuscular ketamine was achieved, and with continued administrations (increased to 50 mg) every 4 days, stayed well for 5 months before a partial relapse. The second patient received intramuscular 50 mg ketamine, administered every 3 days, leading to improvement after 1 week. This schedule was continued for 6 months before a partial relapse occurred. The success of intramuscular administration after short-term response and failed trials of intravenous, oral, and intranasal administrations is promising. The authors note that the reasons for this success are most likely to do with differences in the bioavailability of ketamine across administrations (93% intramuscular vs. 17–20% oral) (Cusin et al., 2012). It is noteworthy, though, that both patients experienced adverse effects – namely irritability, nightmares, dissociative feelings, and headaches.

Given the sparse data to date, it is not clear how route of administration, the drug itself (racemic vs. S-ketamine), and dosage, affect the antidepressant response of ketamine. Promising results have been reported with the intramuscular and oral routes, but in small numbers of patients and open-label treatment settings. It remains to be seen if these results are replicated in double-blind, placebo-controlled trials.

Adverse effects

Given the increasing interest in ketamine as an antidepressant, it is of great importance to also evaluate related adverse effects associated with its use. While expected to be transient, these effects can be nonetheless distressing for patients (Table 2).

Psychotomimetic and neuropsychological adverse effects. Most of the research conducted using subanaesthetic doses of ketamine has shown increases in several adverse effects: general psychiatric symptoms (n=154) (Krystal et al., 1994, 1998, 2000; Malhotra et al., 1996; Adler et al., 1998; Anand et al., 2000; Berman et al., 2000; Hetem et al., 2000; Umbricht et al., 2000; Abel et al., 2003; Honey et al., 2003, 2005, 2006; Morgan et al., 2004a,b; Parwani et al., 2005; Rowland et al., 2005; ; Zarate et al., 2006, 2012; Stefanczyk-Sapieha et al., 2008; Diazgranados et al., 2010; Coull et al., 2011; Thakurta et al., 2012b); positive symptoms of schizophrenia (n=273) (Ghoneim et al., 1985; Krystal et al., 1994, 1998, 2000; Adler et al., 1998; Anand et al., 2000; Hetem et al., 2000; Honey et al., 2003, 2005, 2006; Morgan et al., 2004a,b; ; Zarate et al., 2006; Stefanczyk-Sapieha et al., 2008; Diazgranados et al., 2010; Thakurta et al., 2012b); negative symptoms of schizophrenia (n=107) (Krystal et al., 1994, 1998, 2000; Hetem et al., 2000; Rowland et al., 2005); dissociative symptoms (n=290) (Krystal et al., 1998, 2000; Anand et al., 2000; Abel et al., 2003; Morgan et al., 2004a,b; Parwani et al., 2005; Rowland et al., 2005; Liebrenz et al., 2007, 2009; aan het Rot et al., 2010; Diazgranados et al., 2010; Coull et al., 2011; Ibrahim et al., 2011; Larkin and Beautrais, 2011; Valentine et al., 2011; Zarate et al., 2012; Zanicotti et al., 2012b); and manic symptoms (n=129) (Harborne et al., 1996; Newcomer et al., 1999; Anand et al., 2000; Pfenninger et al., 2002; Zarate et al., 2006; Diazgranados et al., 2010; Mathew et al., 2010). Fortunately, these effects have mostly been restricted to the time of administration, disappearing completely by 60 minutes afterwards.

Other adverse effects experienced by patients include feelings of intoxication and lowered inhibitions (Pfenninger et al., 2002; Honey et al., 2003, 2005, 2006; Messer et al., 2010); confusion (Newcomer et al., 1999; Morgan et al., 2004a,b); decreased concentration (Harborne et al., 1996; Pfenninger et al., 2002; Honey et al., 2003, 2005, 2006; Lofwall et al., 2006; Mathew et al., 2010); and perceptual disturbances (Newcomer et al., 1999; Honey et al., 2003, 2005, 2006; Morgan et al., 2004a,b; Mathew et al., 2010; Messer et al., 2010; Zanicotti et al., 2012b; Zarate et al., 2012). Finally, an extensive review (Morgan and Curran, 2006) has shown that non-chronic usage of ketamine acutely impairs several memory systems, including encoding of information into episodic memory, the manipulation of information in working memory, and some components of semantic memory. Once again, though, most of these impairments were only apparent during the infusions, and none persisted longer than 2 hours after the beginning of the infusions.

Using S-ketamine, which is considered to have a lower incidence of psychotomimetic effects, studies have found the same effects with general psychiatric symptoms (Passie et al., 2005) and dissociative symptoms (Denk et al., 2011), but not for perceptual disturbances (Paul et al., 2009). One study comparing S-ketamine, R-ketamine, and racemic ketamine found that S-ketamine caused less drowsiness and impaired concentration than racemic ketamine (Pfenninger et al., 2002). In addition, one case report observed no psychotomimetic effects at all with S-ketamine (Paslakis et al., 2010). However, S-ketamine – like racemic ketamine – has been found to cause confusion and decreased inhibition (Paul et al., 2009) but its use may increase sufficiently the therapeutic index of ketamine.

Nonetheless, while ketamine consistently produces psychotomimetic and psychiatric adverse effects, these have been restricted to either the time of administration or immediately thereafter. Additionally, severity of these effects has not been found to be substantially different

Table 2. Summary of adverse effects found in studies using ketamine, including combined sample size and additional comments.

Adverse effect	Studies where increases were reported	Total	Comments
General psychiatric symptoms (Brief Psychiatry Rating Scale (including factors for thought disorder, withdrawal-retardation, anxiety-depression, and hostility-suspiciousness); Present State Examination, and Visual Analogue Scales for anger, sadness, irritability, and anxiety)	Krystal et al., 1994, 1998; Malhotra et al., 1996; Adler et al., 1998, Anand et al., 2000; Berman et al., 2000; Hetem et al., 2000; Umbricht et al., 2000; Abel et al., 2003; Honey et al., 2003, 2005, 2006; Parwani et al., 2005; Rowland et al., 2005; Coull et al., 2011	154	These adverse effects were restricted to the time of administration, disappearing completely by 60 minutes after the end of administration
Positive symptoms of schizophrenia	Ghoneim et al., 1985; Krystal et al., 1994, 1998, 2000; Adler et al., 1998; Hetem et al., 2000; Anand et al., 2000; Honey et al., 2003, 2005, 2006; Morgan et al., 2004a,b; Zarate et al., 2006; Stefanczyk-Sapieha et al., 2008; Diazgranados et al., 2010; Thakurta et al., 2012b	273	
Negative symptoms of schizophrenia	Krystal et al., 1994, 1998, 2000; Rowland et al., 2005	107	
Dissociative symptoms	Krystal et al., 1998, 2000; Anand et al., 2000; Hetem et al., 2000; Abel et al., 2003; Morgan et al., 2004a,b; Parwani et al., 2005; Rowland et al., 2005; Liebrenz et al., 2007, 2009; aan het Rot et al., 2010; Diazgranados et al., 2010; Coull et al., 2011; Ibrahim et al., 2011; Larkin and Beautrais, 2011; Valentine et al., 2011; Zanicoti et al., 2012b; Zarate et al., 2012	290	
Manic symptoms	Harborne et al., 1996; Newcomer et al., 1999; Anand et al., 2000; Pfenninger et al., 2002; Zarate et al., 2006; Diazgranados et al., 2010; Mathew et al., 2010	129	
Feelings of intoxication and lowered inhibitions	Pfenninger et al., 2002; Honey et al., 2003, 2005, 2006; Messer et al., 2010	49	These adverse effects were restricted to the time of administration, disappearing completely by 2 h after the beginning of infusions
Confusion	Newcomer et al., 1999; Morgan et al., 2004a,b	69	
Decreased concentration	Harborne et al., 1996; Pfenninger et al., 2002; Honey et al., 2003, 2005, 2006; Lofwall et al., 2006; Mathew et al., 2010	80	
Perceptual disturbances	Newcomer et al., 1999; Honey et al., 2003, 2005, 2006; Morgan et al., 2004a,b; Mathew et al., 2010; Messer et al., 2010; Zanicotti et al., 2012b; Zarate et al., 2012	166	
Acute cognitive impairment	Curran and Morgan, 2000	54	Systems affected from the day of ingestion of ketamine to 3 days later included: encoding of information into episodic memory; manipulation of information in working memory; some parts of semantic memory

Adverse effect	Studies where increases were reported	Total	Comments
Transient physical adverse effects: light-headedness; headache; nausea; diplopia; drowsiness; dizziness	Ghoneim et al., 1985; Krystal et al., 1994; Newcomer et al., 1999; Hetem et al., 2000; Pfenninger et al., 2002; Honey et al., 2003, 2005, 2006; Morgan et al., 2004a,b; Curran and Morgan, 2000; Liebrenz et al., 2007, 2009; Mathew et al., 2010; Zanicotti et al., 2012b; Zarate et al., 2012	289	These adverse effects tended to be dose-dependent, benign, and limited mainly to infusion or for a short time following
Elevation in heart rate and blood pressure	Zarate et al., 2006; aan het Rot et al., 2010; Mathew et al., 2010; Messer et al., 2010; Diazgranados et al., 2010; Valentine et al., 2011; Ibrahim et al., 2012; Thakurta et al., 2012b	148	Adverse effects occurred during the period of infusion and for up to 80 minutes after dosing
Reduced oxygen saturation	aan het Rot et al., 2010	10	Adverse effect observed during the period of ketamine infusion
Urinary tract complications	Shahani et al., 2007; Chu et al., 2008; Cottrell and Gillatt, 2008; Gregoire et al., 2008; Oxley et al., 2009; Storr and Quibell, 2009; Tsai et al., 2009; Ho et al., 2010; Mason et al., 2010; Persson, 2010;	125	Most of these cases were reported in the context of recreational ketamine abuse, but five cases arose in the context of medically prescribe ketamine for analgesia. However, doses tended to be higher than those employed in depression trials (>6 mg/kg/day), and for longer periods of time (daily for 5 months to 1 year, except for once case for whom it was daily for 9 days)
Liver toxicity	Dundee et al., 1980; Kiefer et al., 2008	138	Moderate elevations were noted at anaesthetic doses
S-Ketamine			
General psychiatric symptoms	Passie et al., 2005	12	
Dissociative symptoms	Denk et al., 2011	1	
Confusion	Paul et al., 2009	2	
Decreased inhibition	Paul et al., 2009	2	

between doses or modes of administration. Therefore, outside recreational usage, there have been no reports of persistent adverse effects with subanaesthetic uses of ketamine.

Physical adverse effects. There have been no significant adverse effects reported in studies of low-dose ketamine and S-ketamine in antidepressant trials to date. Many have reported on a variety of transient physical effects such as light-headedness, headache, nausea, diplopia, drowsiness, and dizziness (Morgan et al., 2004b; Honey et al., 2005; Liebrenz et al., 2007; Mathew et al., 2010; Zanicotti et al., 2012b; Zarate et al., 2012; also see recent reviews by Ghoneim et al., 1985; Krystal et al., 1994; Newcomer et al., 1999; Curran and Morgan, 2000; Hetem et al., 2000; Pfenninger et al., 2002; Honey et al., 2003, 2006; Morgan et al., 2004a; Liebrenz et al., 2009; aan het Rot et al., 2012). These symptoms tend to be dose-dependent, benign, and limited mainly to the period of the infusion or for a short time following.

Depression trials investigating subanaesthetic doses of ketamine consistently report on transient elevations in blood pressure and heart rate during the period of infusion and for up to 80 minutes after dosing (Zarate et al., 2006; aan het Rot et al., 2010; Diazgranados et al., 2010; Mathew et al., 2010; Messer et al., 2010; Valentine et al., 2011; Ibrahim et al., 2012; Thakurta et al., 2012b). Most studies have observed no changes in oxygen saturation (Diazgranados et al., 2010; Mathew et al., 2010; Ibrahim et al., 2012), though one found reduced

saturation during the period of ketamine infusion (aan het Rot et al., 2010).

There have been a number of case reports that have linked repeated ketamine use to urinary tract problems (Chu et al., 2008; Cottrell and Gillatt, 2008; Oxley et al., 2009; Tsai et al., 2009; Shahani et al., 2007; Ho et al., 2010; Mason et al., 2010). Almost 200 cases of ketamine-associated uropathy have been described in the literature. These reports have arisen from ketamine use either in chronic abuse contexts or in analgesia; however, it is important to be aware of these effects given that repeated ketamine administrations are being considered for the treatment of depression. Whilst these cases have mainly been reported in the context of recreational ketamine abuse (where use is chronic, doses are high, and comorbidity with other substance use is common), there have nonetheless been five reported cases of uropathy arising in the context of medically prescribed ketamine for analgesia (Gregoire et al., 2008; Storr and Quibell, 2009; Persson, 2010). In these reports, there appears to be a strong link between dose and symptoms, and doses used have tended to be higher than those being employed in ketamine depression trials (>6 mg/kg/day compared with 0.5 mg/kg). Ketamine had been administered daily from 5 months to 1 year prior to the appearance of urinary symptoms in all but one case study (Gregoire et al., 2008), in which the 16-year-old female patient experienced symptoms after receiving ketamine for 9 days at 8 mg/kg/day.

Ketamine-induced hepatotoxicity with modest temporary elevations of liver enzymes has been noted at anaesthetic doses (≥1 mg/kg) of ketamine (Dundee et al., 1980; Kiefer et al., 2008) and in patients receiving low-dose continuous infusions (i.e. 100 hour continuous infusions at rates of 10–20 mg/hour) (Sigtermans et al., 2009; Noppers et al., 2011). When investigated in trials using single doses of ketamine <1 mg/kg, there have been no significant changes noted in liver function tests (Mathew et al., 2010; Ibrahim et al., 2012).

Finally, there are concerns about the potential for dependence through long-term or repetitive ketamine use. Certainly, studies of the recreational drug-using population have found that ketamine users develop cravings for the drug, physiological tolerance, and possibly a withdrawal syndrome on cessation of ketamine (Morgan and Curran, 2012). The development of physiological tolerance is suggested for individuals who have undergone repeated anaesthesia with ketamine (Collier, 1981; MacLennan, 1982). However, this is less clear for ketamine use in analgesia (Hocking and Cousins, 2003), suggesting that low-dose usage in a medical setting is less likely to produce tolerance. Perry et al., (2007) followed up healthy subjects who had been involved in controlled trials using subanaesthetic doses of ketamine and found that, for up to 6 months following exposure, there was no evidence of cravings for ketamine or use of ketamine outside of the research study.

Persistence of antidepressant effect with ketamine

The research reviewed on ketamine as an antidepressant has found that its therapeutic effects persist well beyond its half-life of 2.5–3 hours (Kohrs and Durieux, 1998). Nevertheless, while most studies found high antidepressant efficacy with ketamine, these effects had often waned by the end of the follow-up period (up to 10 days) (Berman et al., 2000; Zarate et al., 2006; Price et al., 2009; Larkin and Beautrais, 2011; Valentine et al., 2011). Typically, antidepressant effects did not persist beyond 1–2 weeks after a single dose (Berman et al., 2000; Diazgranados et al., 2010).

In light of these results – rapid and profound but short-lived improvement – others have investigated means to prolong the antidepressant response. Mathew et al., (2010) studied the synergistic effects of pretreatment with lamotrigine (a glutamate release inhibitor) prior to ketamine treatment, on the basis that previous research had found it attenuated the acute psychotomimetic and cognitive adverse effects of ketamine while increasing its mood-elevating effects. In a sample of 26 participants with treatment-resistant depression, no differences were found between placebo and lamotrigine pretreatment with regards to efficacy of ketamine at any time point. Moreover, responders who consented (n=14) were randomized to riluzole or placebo continuation to investigate if riluzole may prevent relapse. Riluzole was chosen due to its blockade of NMDA receptor activation (Pittenger et al., 2008), as well as its previous success as monotherapy for depression. However, Mathew et al., (2010) found no differences in relapse rates, with the riluzole group relapsing an average of 24 days after ketamine treatment compared with 22 days in the placebo group. These results are supported by a similar study by Ibrahim et al., (2012); this was a randomized controlled trial of riluzole, which also found no significant difference between rates of relapse in the ketamine-riluzole group (33%) and the ketamine-placebo group (21%) in a 4-week trial. In contrast to lamotrigine and riluzole, one case study found positive results with memantine (another drug acting on the glutamatergic system) (Kollmar et al., 2008). In this case study, after failing to maintain an adequate response with two ketamine infusions, the treatment-resistant MDD patient remained well for 6 months (the final point of follow up) after commencing oral memantine 5 mg per day, titrated to 15 mg/day over 4 weeks, and remaining on this dose in addition to duloxetine, olanzapine, lorazepam, venlafaxine, mirtazapine, and lamotrigine.

In several case reports, a second dose of ketamine was administered after participants relapsed following either a modest (Stefanczyk-Sapieha et al., 2008) or a good (Liebrenz et al., 2007, 2009; Kollmar et al., 2008) first dose response. The time interval between doses ranged from 10 days through to 6 weeks. In two cases, the response to the second dose was somewhat less marked than the first dose

(Liebrenz et al., 2007, 2009; Kollmar et al., 2008), while in the third it was slightly better (Stefanczyk-Sapieha et al., 2008). Nevertheless, relapse still occurred either earlier (Kollmar et al., 2008; Stefanczyk-Sapieha et al., 2008) or at about the same time (Liebrenz et al., 2007, 2009) as with the first dose.

Zanicotti et al., (2012b) reported almost 80% improvement in MADRS score when using 1 mg/kg intramuscular ketamine on a depressed female patient with ovarian cancer. The patient was taking venlafaxine, quetiapine, and methadone during treatment, doses of which had been stable for at least 4 weeks. However, due to relapse 1 week later, they administered five additional ketamine treatments using the same dose and administration, spaced 7–8 days apart. They found identical responses in terms of magnitude and time to relapse after each dose. After completing 7 months of weekly ketamine dosing, with sustained improvement in depression ratings, the patient remained free of depression for at least 6 months (Zanicotti et al., 2012a). While this may suggest that repeated ketamine dosing over several months may be able to sustain an antidepressant response, outcomes in this case are confounded by the co-administration of methadone, which has been found to also block the NMDA receptor, demonstrating an affinity equal to ketamine for the MK-801 binding site (Ebert et al., 1998).

Other studies have investigated the use of multiple doses, in a model akin to that of a course of ECT treatments. Murrough et al., (2011) administered 0.5 mg/kg ketamine three times a week over 2 weeks to a patient with treatment-resistant depression. Twenty-four hours after the first treatment, a substantial antidepressant effect was observed (the MADRS score had dropped from 44 to 5), and they reported that remission was maintained for 3 months as measured by the Quick Inventory of Depressive Symptomatology. Messer et al., (2010) presented a case series where two patients with major depression were randomized to either receive six sessions of 0.5 mg/kg ketamine on alternate days over 12 days, or ketamine on day 1 and 7, with placebo sessions at other "treatment" time points. Both patients showed significant decreases in their Beck Depression Inventory scores after only a couple of days. However, the patient who only received two ketamine sessions relapsed by day 25, compared to the other case who relapsed on day 40.

In the Price et al., (2009) study, the 9/10 participants who responded to a single dose of ketamine (measured at 24 hours) continued in the study to receive five additional infusions on alternate days, totalling a 2-week course. This sample was only followed up to the final ketamine treatment and was found to be significantly improved at this time point, with an impressive effect size of d=5.98. However, given that they were not followed up past this point, it is unknown whether repeated infusions prevented relapse in this study. Perhaps the most seminal study to date in this regard is that of aan het Rot et al., (2010), who followed an identical dosing schedule in their open-label study. In line with single-dose studies, they found substantial response rates 4 hours after the sixth and final infusion (9/9 participants). However, 8/9 of their MDD sample relapsed at an average of 30 days after their first infusion, suggesting that antidepressant effects of repeated ketamine only lasted for about 2 weeks after ceasing the course.

Conclusions and future directions

Overall, while almost all studies have found significant antidepressant effects with ketamine administration, it is clear that not all patients respond. With the increasing number of studies finding rapid and substantial effects in a proportion of their patients, research should begin to focus on identifying predictors of response. Moreover, maintenance of these effects continues to be a major limitation. Of the studies that followed participants until relapse, about one-third reported relapse within 3 days, one-third reported relapse in about a week, and one-third reported relapse between 20 and 40 days. Generally, it appears that frequent, repeated infusions (in a model similar to an ECT course) may prolong the period of remission. While pretreatment with lamotrigine and riluzole were found to be unsuccessful in significantly prolonging remission, one case study found positive results with memantine. However, use of this method and its subsequent success are limited to one case.

Use of subanaesthetic ketamine can produce a variety of psychotomimetic, cognitive, or physical adverse effects; however, these are restricted to the time of administration or immediately following it, and have not been found to persist longer than 1–2 hours after treatment.

Future research should examine the efficacy of different doses and routes of administration. With regards to dosing, the relationship between ketamine dose and antidepressant efficacy may be more complex than a simple linear relationship. Investigating different routes of administration is important as it may show stronger efficacy, lower incidence and severity of adverse effects, or equivalent outcomes but within a more practical administration method. Currently, data in this field is sparse. Examining the pharmacokinetic and pharmacodynamic determinants of treatments response would also be extremely beneficial. Future research should further investigate the use of S-ketamine as an alternative to racemic ketamine for antidepressant treatment, as preliminary evidence has suggested that it is similarly efficacious but with less adverse effects (Paul et al., 2009).

Finally, future research examining ketamine's antidepressant effects should be undertaken in controlled trials, with an appropriate active control. Open-label studies lead to ambiguous results confounded by expectation effects. Moreover, placebo-controlled trials completed to date have used saline placebo as a comparator, which is insufficient for blinding purposes. Currently, several clinical trials of ketamine in the treatment of obsessive-compulsive

disorder, MDD, post-traumatic stress disorder, and suicidal ideation are using midazolam as the placebo comparator, due to its similar adverse-effect profile to ketamine (www.clinicaltrials.gov).

Overall, the studies reviewed in this paper suggest that response to ketamine is variable and may be influenced by many factors. Further research is needed to investigate the optimal method of eliciting and subsequently maintaining ketamine's strong antidepressant effects. In addition, future research should identify predictors (e.g. biomarkers, clinical phenotype) of antidepressant response with ketamine.

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Declaration of interest

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