Journal of Psychiatric Research 151 (2022) 693–709

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis

Yazen Alnefeesi [a], David Chen-Li [a], Ella Krane [a], Muhammad Youshay Jawad [a], Nelson B. Rodrigues [a], Felicia Ceban [a,d], Joshua D. Di Vincenzo [a], Shakila Meshkat [a], Roger C.M. Ho [e,f], Hartej Gill [a], Kayla M. Teopiz [a], Bing Cao [a,g], Yena Lee [a], Roger S. McIntyre [a,b,c,d], Joshua D. Rosenblat [a,b,*]

[a] Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada
[b] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[c] Department of Pharmacology, University of Toronto, Toronto, ON, Canada
[d] Brain and Cognition Discovery Foundation, Toronto, ON, Canada
[e] Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[f] Institute of Health Innovation and Technology (iHealthtech), National University of Singapore, Singapore
[g] Key Laboratory of Cognition and Personality, Faculty of Psychology, Ministry of Education, Southwest University, Chongqing, 400715, PR China

ARTICLE INFO

Keywords:
Ketamine
Esketamine
Treatment resistant depression
Depression
Bipolar disorder
Suicide

ABSTRACT

Ketamine is a promising therapeutic option in treatment-resistant depression (TRD). The acute efficacy of ketamine in TRD has been demonstrated in replicated randomised-controlled trials (RCTs), but the generalizability of RCT data to real-world practice is limited. To this end, we conducted a systematic review (Search date: 25/12/2021; 1482 records identified) and meta-analysis of studies evaluating the real-world clinical effectiveness of ketamine in TRD patients. Four overlapping syntheses (Total n = 2665 patients; k = 79 studies) and 32 meta-regressions (Total n = 2050; k = 37) were conducted. All results suggest that the mean antidepressant effect is substantial (mean ± 95% CI, % responded = 45 ± 10%; $p < 0.0001$, % remitted = 30 ± 5.9%; $p < 0.0001$, Hedges g of symptomatological improvement = 1.44 ± 0.609; $p < 0.0001$), but the effect varies considerably among patients. The more treatment-resistant cases were found to remit less often ($p < 0.01$), but no such effect on response was evident ($p > 0.05$). Meta-regressions also confirmed that the therapeutic effect does not significantly decline with repeated treatments ($p > 0.05$). These results demonstrate that even the most treatment-resistant patients may benefit from ketamine, and that mid-to-long term treatment is effective in many patients.

1. Introduction

Ketamine is an N-methyl-D-aspartate receptor (NMDAR) antagonist and a rapid-acting antidepressant with proven efficacy. Brain derived neurotrophic factor (BDNF) and its cognate receptor tropomyosin receptor kinase B (TrkB) are thought to be necessary for a prolonged effect of the drug (Duman and Voleti, 2012; Zanos and Gould, 2018). The induction of BDNF is among the most common effects of antidepressants (Björkholm and Monteggia, 2016; Brunoni et al., 2008), and the lasting therapeutic effects of these medications are known to involve circuit remodeling (Alnefeesi et al., 2021; Carhart-Harris et al., 2017; de Pins et al., 2019). Clinical studies have shown that the Val allele in Val66Met-BDNF is associated with increased antisuicidal and antidepressant effects of ketamine (Chen et al., 2021; Hashimoto, 2012; Laje et al., 2012). Polymorphisms in TrkB and NMDAR encoding genes also moderate ketamine's rapid antidepressant impact (Chen et al., 2021; Guo et al., 2018). In line with these insights, it has been hypothesized that ketamine's rapid antidepressant effect is largely mediated by blockade of NMDARs on γ-aminobutyric acid (GABAergic) interneurons. This is commonly thought to be the most consequential contributor to the observed increases in BDNF and synaptogenesis (Kavalali and Monteggia, 2012; Zanos et al., 2018). However, the NMDAR antagonism of ketamine may not account for all the effects of its administration.

Ketamine is hepatically metabolized by cytochrome P450 enzymes

* Corresponding author. University Health Network, 99 Bathurst Street, MP 9–325, Toronto, ON, M5T 2S8, Canada
E-mail address: joshua.rosenblat@uhn.ca (J.D. Rosenblat).

https://doi.org/10.1016/j.jpsychires.2022.04.037
Received 12 January 2022; Received in revised form 10 April 2022; Accepted 26 April 2022
Available online 25 May 2022

which yield pharmacodynamically distinct metabolites of the drug. (2,6)-hydroxynorketamine (HNK) is one of the major ketamine metabolites (Farmer et al., 2020; Grunebaum et al., 2019; Zarate et al., 2012), and its 2R,6R stereoisomer is known to elicit antidepressant-like effects in preclinical models (Fukumoto et al., 2019; Herzog, 2021); the antidepressant potential of (2R,6R)-HNK is the subject of an ongoing clinical trial (National Institute of Mental Health (NIMH), 2022). Importantly, what happens between the drug or metabolite traversing the blood brain barrier and the increased expression of BDNF is the subject of ongoing speculation. The underwhelming antidepressant effects of other NMDAR antagonists also casts some doubt on the importance of the receptor (Abdallah, 2017; Zanos et al., 2016, 2018). It is widely accepted, however, that NMDAR antagonism mediates the dissociative effects of ketamine (Zanos et al., 2018). In the context of mood disorders, the derealization component of the dissociation seems to correlate with the antidepressant response (Niciu et al., 2013). Such findings suggest that the NMDA receptor is relevant, but the nature and extent of its relevance is debatable (Zanos et al., 2016; Zanos and Gould, 2018). Notwithstanding the pharmacodynamics, the antidepressant efficacy of the drug is now well established.

Multiple randomized-controlled trials (RCTs) have demonstrated the therapeutic effects of ketamine in treatment-resistant depression (TRD) (McGirr et al., 2015; McIntyre et al., 2020). Such studies have established that the main clinical role of ketamine in depression is to treat cases wherein the common monoaminergic drugs and their adjuncts fail. The antisuicidal effect of ketamine also implies potential utility with suicide attempters in the emergency room (Sathyanarayana Rao and Andrade, 2017). However, since the publication of these promising studies (see McIntyre et al., 2020 and McGirr et al., 2015 for representative meta-analyses), off-label ketamine has been increasingly available for TRD patients, revealing unexpected effects such as affective switch (Banwari G. et al., 2015; Wilkowska A. et al., 2020), worsening of depression (Zhuo C. et al., 2020), and underwhelming response rates (Gosek P. et al., 2014; McIntyre R.S. et al., 2020). Importantly, the enrollment criteria applied in RCTs, such as the exclusion of bipolar or suicidal patients (Farmer et al., 2020; Lapidus et al., 2014), do not adequately represent the heterogeneous patient populations encountered in clinical practice. Discrepancies between the impacts of treatments in the idealized conditions of RCTs and those observed in the clinic are a testament to the difference between statistical and clinical significance; such differences have been formalized as the distinction between 'efficacy' and 'effectiveness'.

Whereas the purpose of efficacy studies is to determine whether therapeutic effects are real, effectiveness studies aim to investigate when and whether these effects are strong enough to overcome the confounds encountered in clinical practice. Accordingly, the roles of efficacy and effectiveness studies are both crucial and complementary. Evidence from RCTs is indispensable, but real-world evidence is equally necessary to inform predictions of therapeutic outcomes, tolerability, and safety, that position the drug in the hierarchy of candidate treatments. To our knowledge, there has not yet been a representative synthesis of studies on the real-world effectiveness of ketamine in TRD. Such a synthesis could address important questions: Is ketamine an effective treatment for TRD? To what extent does the effectiveness of ketamine vary among patients? What moderates the therapeutic effects of ketamine? As the number of viable treatments for TRD grows, the answers to these questions become increasingly relevant in clinical decision making, especially with respect to comparisons with emerging augmentation options (Bartoli et al., 2021; Nuñez et al., 2022). Concretely, the present study evaluates the antidepressant effectiveness of ketamine in a heterogeneous and treatment-resistant clinical sample of patients with unipolar or bipolar depression.

2. Methods

The present review was registered on PROSPERO (CRD42020200634) prior to data extraction. This review adheres to the recommendations of the PRISMA statement (Moher et al., 2009; Page et al., 2021).

2.1. Eligibility criteria & literature search

In order to capture the full range of naturalistic clinical conditions, the search strategy was designed to be exhaustive. Peer-reviewed studies reporting on the effectiveness of ketamine in the treatment of depression were sought by a large scale search on the OVID platform and supplemental searches on Google Scholar and CINAHL. The OVID search employed filters which required articles to have been written in English and conducted in humans aged ≥18 years. Additional filters omitted publications within the following OVID-defined categories: clinical trials, experimental replication, prospective study, focus group, mathematical model, and scientific simulation. The OVID databases searched were APA Psycinfo, MEDLINE/PubMed, EMBASE, and HAPI.

The permitted study designs were any that captured the effectiveness of ketamine in depression, as opposed to the efficacy thereof (see **Supplementary Methods** for full disclosure of eligibility criteria). Letters/commentaries/correspondences were omitted because they tended to recapitulate data reported in associated research articles. Abstract-only documents (i.e., poster sessions or conferences) were only included if the constituent data were not reported in full-length publications. Table 1 shows the full search query and each constituent of the three concepts was sought in all searchable fields. We also replicated this query in an additional search of CINAHL through the EbscoHost platform. The first five pages of results from a Google Scholar search were also downloaded (see Table 1 for the search query). All publications were imported into the Covidence platform for systematic review management (covidence.org) to remove remaining duplicates and facilitate screening.

2.2. Data extraction

Literature screening and initial data extraction were the joint effort of three reviewers: YA, DC, and EK. Titles and abstracts were screened for general relevance to the effectiveness of ketamine, and the resulting collection of full texts was further vetted for its representativeness of real-world conditions. The eligible full texts were then included in respective quantitative syntheses if they reported main outcome data: response rate, remission rate, or mean pre- and post-treatment depressive symptomatology scores with associated standard deviations (SDs).

Table 1
Search queries applied in the literature search of the present study.

Search Platforms	Databases
OVID, CINAHL	APA Psycinfo, MEDLINE/PubMed, EMBASE, HAPI, CINAHL
Search Query	
1)	Ketamine OR esketamine OR s-ketamine OR arketamine OR r-ketamine OR Spravato OR NMDA-receptor antagonist OR NMDA receptor antagonist OR NMDA antagonist OR NMDAR antagonist OR racemic-ketamine
2)	Retrospective OR open label OR case report OR case series OR case study OR effectiveness OR chart review OR real world OR naturalistic
3)	depress* OR TRD OR treatment resistant depression OR MDD OR depression OR major depressive disorder OR mood disorder OR depressive OR bipolar disorder OR bipolar depression OR bipolar depressive OR major depressive episode OR manic-depression OR manic depression OR dysthymia OR dysthymic disorder OR cyclothymia OR cyclothymic disorder OR MDE OR major depressive episode
4)	1 AND 2 AND 3 (search lines 1–3 are applied to all fields)
5)	Limit to human studies in English
6)	Limit to peer reviewed journals, participants aged ≥18 years, remove studies with the following methodologies, as indexed in Ovid: clinical trials, experimental replication, prospective study, focus group, mathematical model, scientific simulation
7)	Omit duplicates by abstract comparison
Google Scholar Search:	ketamine depression effectiveness OR retrospective OR "chart review" -intitle: anesthetic –OR -anesthesia –OR -electroconvulsive

Calculation of the SDs from related statistics was necessary at times, but studies were omitted from the meta-analysis of symptomatologic improvement scores if they did not clearly specify the reported measure of spread (i.e., standard error (SE), SD, or 95% confidence intervals). When the relevant data were only presented in graphs, we used screenshots and graphreader.com to extract the needed values. Relevant secondary literature was included at the title and abstract screening stage in order to identify additional primary studies in reference lists.

The present study sought to quantify the effectiveness of ketamine for both the short and long term, and the purpose of this was twofold: 1) To quantify the drug's overall utility in summary statistics, and 2) to discover, by regression, whether ketamine's effectiveness diminishes with repeated treatments or time. However, almost all studies reported outcomes within a few hours or days of treatment, and few studies reported outcomes over the mid-to-long term. Crucially, the later the endpoint, the fewer the data due to participant discontinuation. Therefore, if the analyses only included the latest endpoints, then short-term studies would unduly dominate. On the other hand, if all time points were included, then the biases of studies that reported multiple time-points would be amplified. As such, there was a need to extract one time point per study in each analysis. This required optimization for the greatest sample sizes and the latest endpoints because the two variables were anticorrelated.

To our knowledge, there are no standard methods or reliable formulae to optimize as needed, and if there were such methods, choosing one would be arbitrary. Consequently, we prioritized the extraction of later endpoints with some sensitivity for depleting sample sizes to capture the overall trend across as long a time period as was possible. Outcome data were extracted when they represented the longest baseline-to-endpoint period for the greatest number of patients with the goal of maintaining sample sizes and investigating the antidepressant effect longitudinally. For instance, if the outcomes for only seven of 30 patients were reported at six months post-treatment, data from 21 patients were available at one month, and data from all 30 were available at one week, then the outcomes at one month were included for meta-analysis. While these decisions were arbitrary, they allowed for a more realistic appraisal of ketamine's mid-to-long term effectiveness by enabling regressions that had more balanced sample sizes. See **Supplementary Material: Methods & All Data** for details on screening and data extraction.

2.3. Statistical analyses

In the interest of brevity, this section was made dense with specialized meta-analytic terms. If these concepts are unfamiliar, we strongly recommend reading Supplementary Methods, consulting the cited publications, and searching the terms online. It takes some endurance to understand these concepts, but the methods are simpler than they appear. Random-effects meta-analyses were conducted on logit-transformed response and remission rates, and the variance between true effects τ^2 was estimated by the DerSimonian-Laird method in all analyses (DerSimonian and Laird, 1986); this variance is used to weight the studies in meta-analysis. A third meta-analysis of Hedges *g* values for change from baseline depressive symptomatology only included studies for which the SDs of both baseline and endpoint scores were available; this was to avoid the pitfalls of imputing inaccurate pre-post correlations. Effect sizes were computed such that positive values indicate improvement and negative values indicate worsening; all subsequent reporting follows this directionality. Furthermore, all studies with $n < 5$ patients were excluded from all meta-analyses to limit small study bias. To capture the estimated variation of effect sizes (i.e., "heterogeneity"), 95% prediction intervals were reported alongside the usual statistics (Borenstein et al., 2010, 2017; IntHout et al., 2016). The 95% prediction interval represents 95% of the estimated distribution of true effects. The interval consists of 2τ above and 2τ below the random-effects mean (Borenstein et al., 2017), wherein τ is the estimated standard deviation of true effects (DerSimonian and Laird, 1986). Furthermore, a correction for the increased risk of false positives due to multiple comparisons was necessary because a large number of meta-regressions were conducted in this study. To this end, a simplified false discovery rate (FDR)-based method was applied.

2.4. Quality assessments & testing for bias

Quality assessments were conducted using a modified risk of bias tool originally designed for case series (Murad et al., 2018) that was applied as previously described (Alnefeesi et al., 2021); this simplified checklist is shown in Table 2. The tool was applied to all included studies, irrespective of study design, as the modified checklist was sufficiently generic to capture all possible methodological limitations. Both Egger's regression and rank-correlation methods were conducted to test for small-study bias (Lin and Chu, 2018; Macaskill et al., 2001). The Vevea-Hedges weight function, which tests for bias towards large effects (Vevea and Hedges, 1995), could not provide meaningful results for the dichotomous outcomes because the logit-transformed values necessarily surround zero and the untransformed values have unstable variances (see Supplementary Methods for explanations of the logit transformation and variance instability). This weight function requires specification of the expected direction of the effect sizes, and this directionality is only defined with respect to zero (a value which represents a 50% event rate on the log-scale). Because of this ambiguity, the function was only applied to the meta-analysis of mean change from baseline using Jefferey's Amazing Statistics Program (JASP) (JASP Team, 2021).

3. Results

3.1. Search results & syntheses

The systematic search was first applied on 22/07/2020 and all syntheses herein are based on those search results. On 25/12/2021, the systematic review was replicated to test whether the addition of newer studies would significantly alter the main results. These additions did not alter the main results and the original numbers were thus retained for reasons explained in **section 3.5**. As of 22/07/2020 the systematic search results consisted of 1152 publications, 3 of which were found from other sources (see Fig. 1 for a PRISMA flow chart of stage-wise tallies and reasons for exclusion). Seventy-nine studies from this collection met general criteria for inclusion. Of these studies, 34, 23, and 14 studies were included in the meta-analyses of response rates, remission rates, and symptomatologic change scores, respectively. Forty-two studies only provided piecemeal data that could not be included in any of the meta-analyses. This necessitated the crude synthesis of outcomes shown in Fig. 2. (see **Supplementary Methods** for details); studies with $n < 5$ were included in the crude analysis. Summaries of basic data from all 79 studies are provided as **Supplementary Material: All Data: All Studies**. To provide a snapshot of the included literature, an arbitrarily selected set of 19 studies were summarized in greater depth and reported in Table 3. (see **Supplementary Material:**

Table 2
Modified quality assessment checklist applied in the present study.

Selection	Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
Ascertainment	Was the exposure adequately ascertained? Was the outcome adequately ascertained
Causality	Were other alternative causes that may explain the observation ruled out?
Reporting	Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?

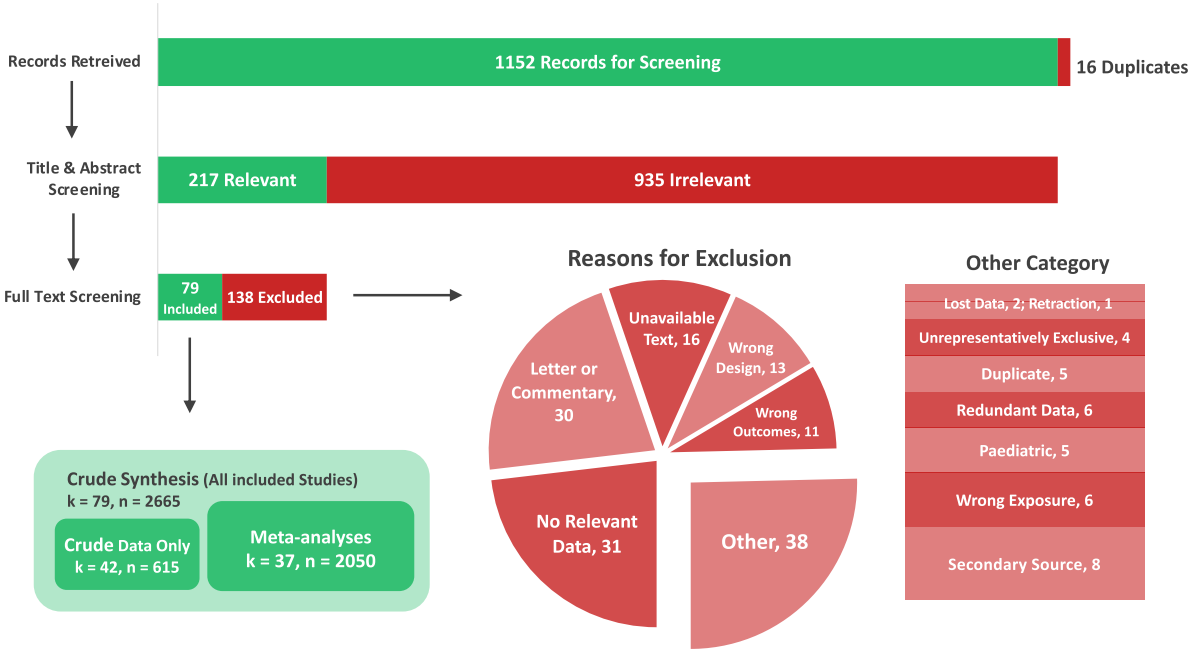

Fig. 1. PRISMA flow diagram for the systematic review showing the number of studies **included (green)** and **excluded (red)** at each stage of the present study, wherein ***k*** denotes the **number of studies**, ***n*** denotes the corresponding **pooled sample size,** and **red charts** disclose the **reasons for exclusion**.

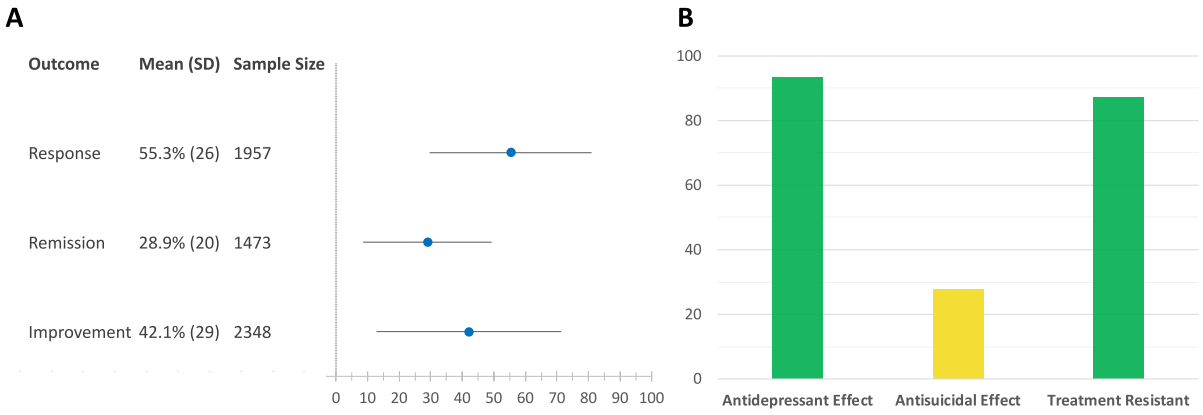

Fig. 2. Depressive outcome data summary for all studies included in the systematic review, representing data from **k = 79 studies** with a pooled sample size of **n = 2665 patients**; wherein **(A)** shows **weighted means** of respective outcomes as **mean event rates** expressed as percentages **(response** and **remission)** or **mean percent symptomatologic improvement (change)** with **error bars** covering one **SD** above and one below the respective mean, and **(B)** depicts a **weighted count (%)** of all studies that reported the respective **effect/condition** to represent their samples/results. All these outcomes were **weighted by sample size**, and the **SDs** only capture the **spread of study-level means**.

Synthesis Workbook & All Data for more detailed summaries of selected studies and data summaries of all studies, respectively). While the choice of these 19 studies was arbitrary, the goals were to: 1) adequately represent the synthesized literature (i.e., heavily weighted studies), and 2) relay the most clinically relevant findings.

3.2. Risk of bias assessments

The methodological quality of this collection (k = 79 studies) was appraised by two reviewers, and the consensus judgements are summarized in Fig. 3. (see **Supplementary Material: ROB Assessments** for all study-specific judgements). Quality assessments of the studies included in meta-analyses are summarized in Fig. 4. As indicated in these figures, the most common methodological issue was a failure to limit the influence of confounds (i.e., high risk of bias in the 'Causality' domain; all domains are defined in Table 2.). Most of these judgments pertained to studies wherein the researchers did not ensure the stable dosing of concomitants.

3.3. Overall results of meta-analyses

The prediction intervals in all syntheses demonstrate appreciable heterogeneity in the effect sizes of the included studies, but the means favored the effectiveness of ketamine nevertheless. This variability was not caused by small-study bias as both Egger's regression and the rank-correlation tests were negative in all three meta-analyses ($p > 0.1$), and no bias towards large effects was detected by the weight function ($p > 0.05$; one-sided p-value cutoff set to 0.025) (see **Supplementary Material: JASP Outputs**). The meta-analysis of response rates produced an estimated mean effect size ±95% CI of 45 ± 10% ($p < 0.0001$), and the

Table 3
Summaries of arbitrarily selected studies reporting clinically relevant findings.

Study	Details	Description	%Rs	% Rm	%Δ	AS	TRD
Al Shirawi et al., 2017	Design: Case Series Location: Canada Sample (N): 22 Sex (Female): n = 13, 59% Mean Age (years): 39 Dose (mg/kg): #Doses/patient (avg.): 4.44 Isomer(s): Racemic Depression Scale(s) (MCID): Beck Depression Inventory 2 Suicidality Scale(s): Comorbidities: generalized anxiety disorder Concomitants: SSRI, SSNRI, TCA, bupropion, trazodone, SGA	**Main Outcomes:** Symptomatologic improvements occurred in 32% of the cohort, 45% had no response to the ketamine, and 23% experienced a mild worsening in depression. **Most frequent TEAEs:** dissociation, dizziness, blurred vision, numbness, and sedation. None of these were considered serious.	18.0	–	15.7	–	Y
Basso et al. (2020)	Design: Open-label Study Location: Berlin, germany Sample (N): 24 Sex (Female): n = 15, 60% Mean Age (years): 49.08 Dose (mg/kg): 0.5 #Doses/patient (avg.): 6 Isomer(s): R-ketamine Depression Scale(s) (MCID): German MADRS (1.9) Suicidality Scale(s): Other Morbidities (n): BD (2), Comorbidities (n): Personality Disorders (4), Anxiety Disorders (3), Drug Dependence/Abuse (3) Concomitants: Several unspecified ADs, antipsychotics, benzodiazepines, and mood stabilizers	**Main Outcomes:** Both ECT and R-ketamine had comparable effectiveness in treating depressive symptoms but R-Ketamine affected symptoms faster than ECT. **Secondary Outcomes:** R-ketamine enhanced attention and executive function; an opposite and mild effect was observed in the ECT cohort.	–	–	49.2	–	Y
Bloch et al., (2011), 2012	Design: Open label study Location: Connecticut, USA Sample (N): 16 Sex (Female): unknown Mean Age (years): unknown Dose (mg/kg): 0.5 #Doses/patient (avg.): 1 Isomer(s): Racemic Scale(s): HDRS, Y-BOCS Suicidality Scale(s): Other Morbidities: OCD, social phobia, PTSD, Eating disorder, NOS, trichotillomania, past tic disorder Concomitants: SRIs, antipsychotic medications, glutamate-modulating agents (both N-acetylcysteine and riluzole)	**Main Outcomes (2 Studies):** Single infusion induced response in both OCD and depressive symptoms; peak response in depressive symptoms occurred 2 days after infusion, and that of OCD symptoms occurred on day 1 post-infusion. **TEAEs:** dissociation, gaps in memory, sensory distortions, perturbed temporal perception, and derealization; these effects were well tolerated.	53.8	–	–	–	–
Bryant et al. (2019)	Design: Case Series Location: Cleveland, Ohio, USA Sample (N): 6 Sex (Female): n = 2, 33.3% Mean Age (years): 70 Dose (mg/kg): 0.5 #Doses/patient (avg.): 15.5 Isomer(s): Racemic Depression Scale(s) (MCID): MADRS (1.9) Suicidality Scale(s): Comorbidities: GAD, Substance abuse (in remission), numerous non-psychological morbidities. Concomitants: Unstated	**Main Outcomes:** 5 geriatric patients responded (1 remitted briefly) within the acute phase of infusions, none retained their responder status by endpoint.	0.0	0.0	–	N	Y
Cornwell et al. (2012)	Design: Open-label Study Location: Maryland, USA Sample (N): 20 Sex (Female): n = 3, 15% Mean Age (years): unknown Dose (mg/kg): 0.5 #Doses/patient (avg.): 1 Isomer(s): Racemic	**Main Outcomes:** Greater blood [norketamine] and somatosensory cortical excitation in short-term responders vs. non-responders.	45.0	–	40.9	–	Y

(*continued on next page*)

Table 3 (*continued*)

Study	Details	Description	%Rs	% Rm	%Δ	AS	TRD
	Depression Scale(s) (MCID): MADRS (1.9) Suicidality Scale(s): Other Morbidities: unknown Concomitants: none						
Cusin et al. (2013)	Design: Open-label Study Location: Boston, Massachusetts, USA Sample (N): 12 Sex (Female): n = 10, 83.3% Mean Age (years): 51.1 Dose (mg/kg): 0.5-0.75 #Doses/patient (avg.): 6 Isomer(s): Racemic Depression Scale(s) (MCID): HAM-D-28, Other Scales: CADSS Suicidality Scale(s): Other Morbidities: Unstated Concomitants: Unspecified	**Main Outcomes:** Patients who sustained response for four weeks exhibited insignificant but heightened EEG power in the gamma range; the same was seen in the delta range in unresponsive patients. **Note:** Lack of statistical significance was attributed to small n.	33.0	17.0	–	Y	Y
Feifel et al. (2017)	Design: Retrospective Chart Review (Longitudinal) Location: UCSD, California, USA Sample (N): 7 (BDI-II) + 7 (PHQ-9) Sex (Female): n = 9, 64% Mean Age (years): 48.3 Dose (mg/kg): 0.25–1.0 #Doses/patient (avg.): Isomer(s): Racemic Depression Scale(s) (MCID): BDI-II (5), PHQ-9 (3) Suicidality Scale(s): Comorbidities: Concomitants:	**Main Outcome:** Average 60% change from baseline at 12 months, and 78% at 6 months as measured by BDI-II in n = 7. **TEAEs:** 3 episodes of dissociation-induced panic in 2 patients, and 2 episodes of vomiting in 2 others.	–	–	37.0	–	Y
Henderson (2016)	Design: Retrospective Chart Review Location: Sample (N): 100 Sex (Female): n = 51, 51% Mean Age (years): 41.2 Dose (mg/kg): 0.5 #Doses/patient (avg.): 4.3 Isomer(s): Racemic Depression Scale(s) (MCID): QIDS-SR-16 (28.5%) Suicidality Scale(s): Item 12 of QIDS-SR-16 Other Morbidities (n): BD (20) Concomitants (n): Benzodiazepines (29), cannabis (19), midazolam, and others.	**Main Outcomes:** more than 70% of patients had a score of 2 or 3 on the suicidality item, and these scores were reduced to 1 or 0 for most patients (including non-responders). **Followup:** Most remained on oral ADs which were effectively controlling symptoms at 2–3 months. **Note:** 1 mg midazolam was often given to patients prior to infusions, and the AD response does not seem hindered by it.	80.0	–	49.4	Y	Y
Ionescu et al. (2014)	Design: Open-label Study Location: Maryland, USA Sample (N): 26 Sex (Female): n = 9, 34.6% Mean Age (years): 49.4 Dose (mg/kg): 0.5 #Doses/patient (avg.): 1 Isomer(s): Racemic Depression Scale(s) (MCID): MADRS (1.9), HDRS Suicidality Scale(s): Other Morbidities: unknown Concomitants: none	**Main Outcome:** Greater responsiveness in anxious TRD as compared to non-anxious TRD.	69.0	0.0	25.1	–	Y
Liu et al. (2020)	Design: Open-label Study Location: Guangzhou, China Sample (N): 103 Sex (Female): 49.24% Mean Age (years): 34.72 Dose (mg/kg): 0.5 #Doses/patient (avg.): 6 Isomer(s): Racemic Depression Scale(s) (MCID): MADRS (1.9) Suicidality Scale(s): Other Morbidities: BD Concomitants: unspecified but stable dosages	**Main Outcome:** High insomnia scores on the MADRS predicted a faster and greater response to ketamine than low insomnia scores.	50.8	36.4	44.3	–	Y
Machado-Vieira et al. (2009)	Design: Open-label study Location: USA	**Main Outcomes:** Significant improvement in symptoms but no changes in serum BDNF levels at 230min post-infusion.	47.8	–	–	–	Y

(*continued on next page*)

Table 3 (*continued*)

Study	Details	Description	%Rs	% Rm	%Δ	AS	TRD
	Sample (N): 23 Sex (Female): n = 9, 39% Mean Age (years): 43.9 Dose (mg/kg): 0.5 #Doses/patient (avg.): 1 Isomer(s): Racemic Depression Scale(s) (MCID): MADRS, BDI, HRDS-17 Suicidality Scale(s): Other Morbidities: Concomitants:	**Secondary Outcome:** No significant differences between responders and non-responders in BDNF levels.					
McIntyre et al. (2020)	Design: Retrospective Chart Review Location: Mississauga, Ontario, Canada Sample (N): 207 Sex (Female): n = 118, 55.4% Mean Age (years): 45 Dose (mg/kg): 0.5-0.75 #Doses/patient (avg.): 4 Isomer(s): Racemic Depression Scale(s) (MCID): QIDS-SR-16 (28.5%), Other Scales: GAD-7, SDS, CADSS Suicidality Scale(s): QIDS-SR-Item Morbidities: MDD (183), BD (30) Comorbidities: PTSD (16), OCD (9), SAD (9), GAD (33), Personality Disorder (11) Concomitants: Unstated	**Main Outcomes:** Four infusions given; mean suicidality item score was 1.9 at BL and 1.2 at last follow-up. **TEAEs:** typical and well-tolerated presentations (dissociation, nausea etc.).	23.0	13.0	31.4	Y	Y
McIntyre et al. (2020)	Design: Retrospective Chart Review Location: Mississauga, Canada Sample (N): 201 Sex (Female): n = 112, 55.7% Mean Age (years): 45.2 Dose (mg/kg): 0.5-0.75 #Doses/patient (avg.): 4 Isomer(s): Racemic Depression Scale(s) (MCID): QIDS-SR16 (28.5%), Other Scales: GAD-7 Suicidality Scale(s): QIDS-SR16 item Other Morbidities: BD (24), PTSD (6), OCD (3) Concomitants: unknown	**Main Outcomes:** Anxious TRD patients were more responsive than non-anxious counterparts; favourable effects in both. **Secondary Outcomes:** Significant post-acute anti-suicidal and anxiolytic effects.	–	–	35.8	Y	Y
Rasmussen et al. (2013)	Design: Open-label Study Location: Mayo Clinic, Rochester, MN, USA Sample (N): 10 Sex (Female): n = 6, 60% Mean Age (years): 47.2 Dose (mg/kg): 0.5 #Doses/patient (avg.): 3.1 Isomer(s): Racemic Depression Scale(s) (MCID): MADRS (1.9), Other (s): YMRS, BPRS, CGI Suicidality Scale(s): SSI, SSF Other Morbidities: Bipolar II Concomitants: Bupropion, duloxetine, citalopram, venlafaxine, nortriptyline, lithium, lamotrigine, ECT	**Main Outcome:** Average of 3.1 infusions over two weeks produced highly statistically significant reductions of suicidality in responders only. **TEAEs:** 70% experienced dizziness, diplopia, drowsiness; of those 7, 1 had visual hallucinations, and another had dysmegalopsia and anxiety.	80.0	50.0	49.8	Y	Y
Sakurai et al. (2020)	Design: Retrospective Chart Review Location: Boston, Massachusetts, USA Sample (N): 85 Sex (Female): n = 48, 55.2% Mean Age (years): 46 Dose (mg/kg): 0.5 #Doses/patient (avg.): 3 Isomer(s): Racemic Depression Scale(s) (MCID): QIDS-SR-16 (28.5%) Suicidality Scale(s): Item 12 of QIDS-SR-16 Morbidities (n): Bipolar (9), Comorbidities (n): GAD (32), PTSD (12), OCD (6), ADHD (17), other (22). Concomitants: lorazepam, ondansetron, prochlorperazine, labetalol, unspecified ADs and antipsychotics	**Main Outcomes:** 3 weekly infusions;; 29 patients improved by 35% or more (QIDS score); this latter group does not include 15 true responders. **Secondary Outcome:** Suicidality became completely absent in 12 patients who had scored >0 on Item 12, and was reduced by at least 1 point in 25 others. **Discontinuations**: 11 due to lack of response.	17.6	–	–	Y	Y

(*continued on next page*)

Table 3 (*continued*)

Study	Details	Description	%Rs	% Rm	%Δ	AS	TRD
Wajs et al. (2020)	Design: Open-label Study (Longitudinal) Location: n/a Sample (N): 756 Sex (Female): n = 502/802, 62.6% Mean Age (years): 52.2 Dose (mg): 28 or 56 or 84 #Doses/patient (avg.): 8 Isomer(s): Esketamine Depression Scale(s) (MCID): MADRS (1.9), PHQ-9 (3), Other(s): CGI-S(1) Suicidality Scale(s): Comorbidities: unknown Concomitants: duloxetine, escitalopram, sertraline, venlafaxine (XR)	**Main Outcome:** Twice a week intranasal doses for 4 weeks produced highly favourable antidepressant effects. **Discontinuations:** non-response (84), lack of efficacy (21), patient withdrawal (22), TEAEs (52), and other reasons (19).	78.4	31.6	52.6	–	Y
Wilkinson et al. (2017)	Design: Open-label study Location: Connecticut, USA Sample (N): 16 Sex (Female): n = 12, 75% Mean Age (years): 42.7 Dose (mg/kg): 0.5 #Doses/patient (avg.): 4 Isomer(s): Racemic Depression Scale(s) (MCID): MADRS (1.9), QIDS-SR16 Suicidality Scale(s): Other Morbidities: unknown Concomitants: CBT, AD (9), antipsychotics (7), mood stabilizers (4)	**Main Outcomes:** Twice weekly infusions for 2 weeks with CBT sessions on non-ketamine days facilitated remission in some. **Secondary Outcome:** Relapse seemed to be offset by CBT and the researchers called for an RCT to verify this finding. **Note:** Remission happened early in ketamine treatment, if ever, and response happened after 4 infusions in most cases.	21.3	–	–	–	Y
Wilkinson et al. (2018)	Design: Open-label Study (Longitudinal) Location: New Haven, Connecticut, USA Sample (N): 44 Sex (Female): n = 33, 61.1% Mean Age (years): 46.7 Dose (mg/kg): 0.5 #Doses/patient (avg.): Isomer(s): Racemic Depression Scale(s) (MCID): QIDS-SR-16 (28.5%), MADRS (1.9) Suicidality Scale(s): Other Morbidities: BD (6), Schizoaffective (3), Catatonia (1) Concomitants (n = 52): Ondansetron, labetalol, AD (39), antipsychotic (29), sedative/hypnotic (27), stimulant (12), lithium (10), and others.	**Main Outcomes:** Over the course of 4 standard infusions, clinically significant improvements were evident. 5 patients remitted after a single infusion, and 9 remitted after 4 infusions. **Followup:** 14 of the patients received treatment for at least 14 weeks, and change from baseline at 12 months post-initial treatment was 47.1% **Discontinuations:** 4 patients due to insufficient AD effect, and 1 due to intolerable dissociation.	45.5	27.3	38.1	–	Y
Yoon et al. (2018)	Design: Open-label Study Location: Netherlands Sample (N): 5 Sex (Female): Unknown Mean Age (years): Unknown Dose (mg/kg): 0.5 #Doses/patient (avg.): 4 Isomer(s): Racemic Depression Scale(s) (MCID): MADRS (1.9) Suicidality Scale(s): Comorbidities: Alcohol Use Disorder (AUD) Concomitants: Naltrexone (380 mg)	**Main Outcomes:** Naltrexone + ketamine therapy alleviated both sets of symptoms in patients with MDD-AUD comorbidity. **TEAEs:** Authors report favourable safety and tolerability; no TEAEs reported in the publication.	100.0	60.0	–	–	N

Percentage of responders %Rs; percentage of remitters %Rm; percent change from baseline %Δ; anti-suicidal effect reported (yes/no) AS; treatment resistant depression (yes/no) TRD; minimal clinically important difference MCID.

corresponding 95% prediction interval ranged from 8.24 to 88.5% (Fig. 5). The mean remission rate was 30 ± 5.9% ($p < 0.0001$), and its 95% prediction interval was 15.7–49.7% (Fig. 6). The standardized mean symptomatologic improvement score was a Hedges' g value of 1.44 ± 0.609 ($p < 0.0001$), with a 95% prediction interval of −0.758 to 3.63 (Fig. 7).

The following Q and I2 statistics are difficult to interpret but are nevertheless reported here for full disclosure; $\tau 2$ and the consequent prediction interval are more conducive to interpretation. The total between study variance Q, and the respective percentage of this variance estimated to represent true variation in real-world populations I^2, was Q = 351 ($p < 0.0001$) with $I^2 = 90.6\%$ for the meta-analysis of response rates, Q = 48.7 ($p < 0.001$) with $I^2 = 54.8\%$ for the meta-analysis of remission rates, and Q = 331 ($p < 0.0001$) with $I^2 = 96.1\%$ for the meta-analysis of change scores. The estimated variances in true effects for the meta-analyses of logit-response rates, logit-remission rates, and standardized symptomatologic change scores were $^2 = 1.24$, $\tau^2 = 0.174$, and $\tau^2 = 1.20$, respectively. As shown by the prediction intervals computed from these variances (Figs. 5–7), the variability of effectiveness was substantial and meta-regressions were necessary to explain it.

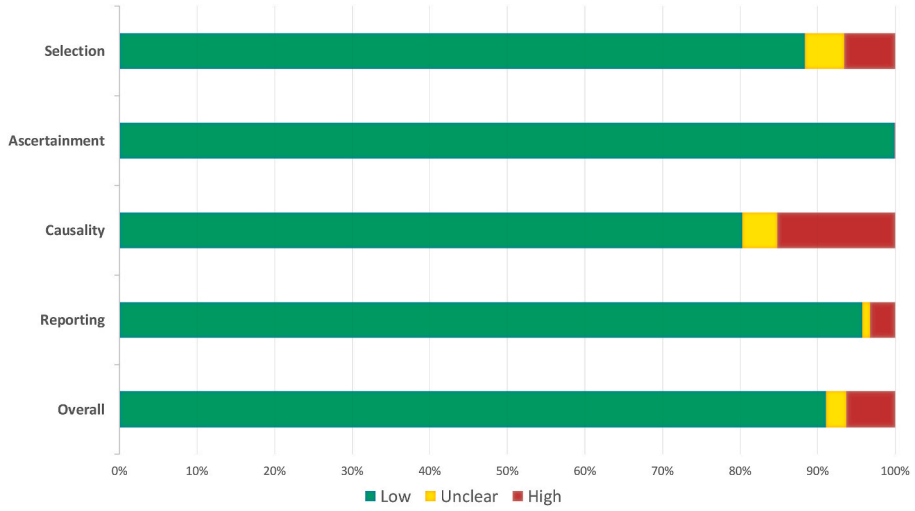

Fig. 3. Weighted distributions of risk of bias assessment results for all studies included in the systematic review, representing judgements for **k = 79 studies** with a pooled sample size of **n = 2665 patients.** Judgements were weighted by sample size; domains are defined in Table 2.

Fig. 4. Weighted distributions of risk of bias assessment results for studies included in meta-analyses, wherein judgements are weighted by sample size for the overall collection **(Meta-analyses)**, and weighted with respective random-effects inverse variance values for each synthesis; domains are defined in Table 2.

3.4. True discoveries from linear meta-regressions

Six out of 32 regressions were significant in the present study ($p \leq 0.05$). As shown in Fig. 8, two of these positive results were identified as false discoveries (see **Supplementary Methods** and **Synthesis Workbook: FDR Estimation** for all relevant details), leaving four putatively true discoveries (reported in Table 4). A negative effect of treatment resistance on remission rates accounted for 52.4% of the true variance and a smaller effect was seen with symptomatologic scales in the same meta-analysis. After controlling for the smaller effect of scale, treatment resistance did not account for any more variance than it did as a sole moderator, and the converse regression was a false discovery. Additionally, average age had a positive influence on symptomatological improvement, and the effect explained 46.1% of the variance in the analysis of change scores.

Importantly, the dosing regimen and the duration from baseline to endpoint had no effect on any of the three outcomes ($p \geq 0.05$). Two-week antidepressant washouts also had no effect on any of the three outcomes ($p \geq 0.05$). There were also no effects of the percentages of bipolar patients or patients using benzodiazepines, anticonvulsants, lithium, or unprescribed drugs with respect to response rates ($p \geq 0.05$) (see **Supplementary Material: JASP Outputs** for all negative results). The same was true for remission rates except for the %patients using unprescribed drugs; data were insufficient for an adequate regression (i.

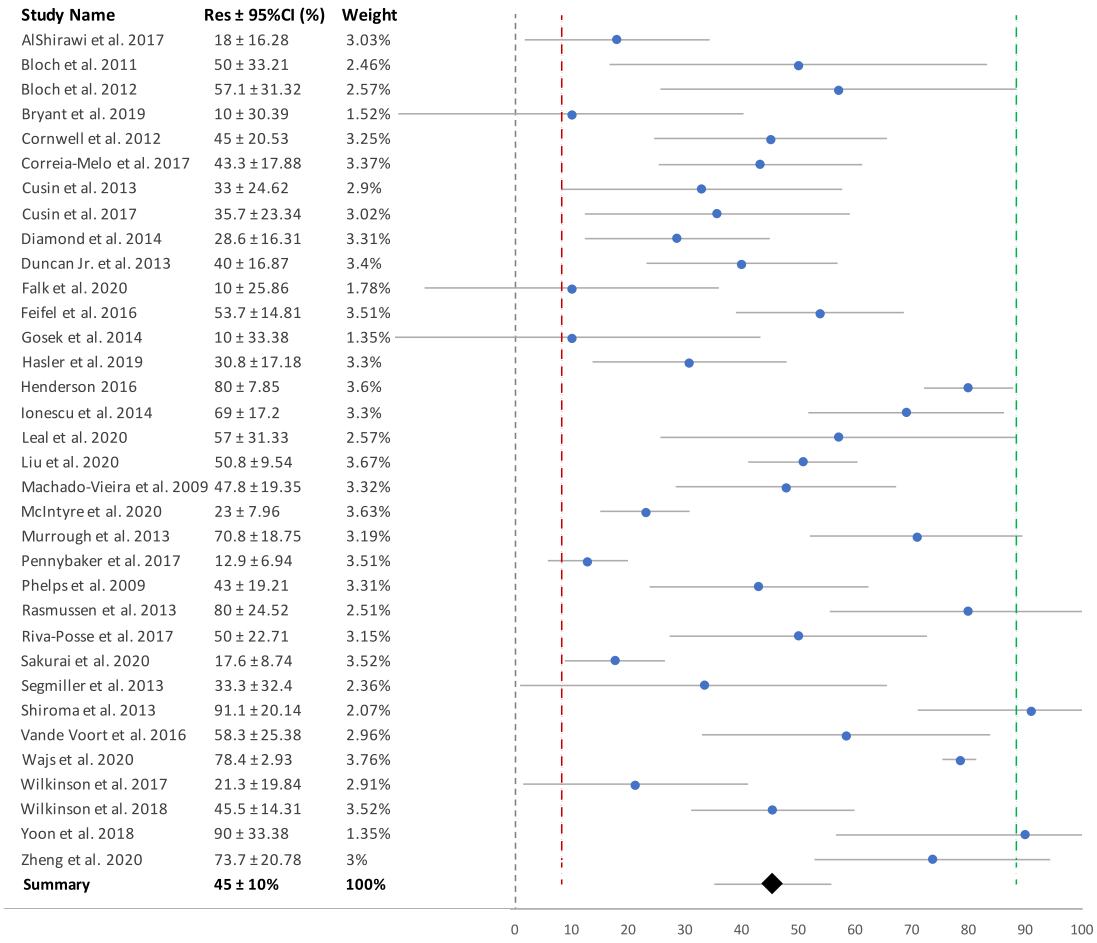

Fig. 5. Forest plot depicting the distribution of response rates as percentages, wherein the **red** and **green** dashed lines represent the **lower** and **upper** limits of the **95% prediction interval** computed by adding and subtracting 2τ to and from the **point estimate (black diamond)** ($p < 0.0001$), which represents **k = 34 studies** and **pooled n = 1722**. Both the prediction interval and the **95% confidence intervals (error bars)** were computed on the natural log-scale then back-transformed to percentages.

e., $df < 10$). The dosage (mg/kg) and route of administration data were also inadequate for regression, as they were too homogeneous to produce meaningful results.

3.5. Sensitivity analysis with recent studies

The date of last search for the main syntheses presented herein was 22/07/2020. In order to assess whether the general trends of the present syntheses are representative of more recent studies, the systematic review was replicated on 25/12/2021 (YA and DC). The search identified 330 new publications of which 46 were deemed relevant by abstract screening. Vetting the full texts for non-redundant data identified five new studies to be included in meta-analysis (Artin et al., 2021; Kang et al., 2021; Lucchese et al., 2021; Szarmach et al., 2020; Wilkowska et al., 2021). The updated means were then compared to their predecessors by Z-tests; this was a short-hand method of assessing the robustness of the results herein. There were no significant differences ($p > 0.1$) between any of the pairs of means for the three outcomes, and all three pairs of prediction intervals overlapped by ~90% or more (see **Supplementary Material: Synthesis Workbook** for all relevant details). Given these results and the ongoing rapid growth of the ketamine literature, the meta-regressions were not re-run and the original meta-analytic values were consequently retained to avoid confusing the two datasets.

4. Discussion

4.1. Overall pattern of effectiveness

The results herein consistently demonstrate that ketamine is significantly effective in TRD ($p < 0.0001$), and that this persists across repeated treatments. The estimated means ± 95% CI were 45 ± 10% ($p < 0.0001$) for response rates, and 30 ± 5.9% ($p < 0.0001$) for remission rates; crude estimates in Fig. 2A are similar. However, considerable variability in the magnitude of ketamine's effectiveness was an equally consistent finding across all metrics. The reported results of the effectiveness literature (shown in Fig. 2B) corroborate those of the efficacy literature (McIntyre et al., 2021; Ng et al., 2021), as they suggest that ketamine exerts a robust antidepressant effect, and a less consistent but clinically significant antisuicidal effect. Fig. 2B also confirms that the two effects often occur despite ≥2 failed antidepressant trials in the current depressive episode. Notwithstanding, crude 95% prediction intervals extrapolated from Fig. 2A would cover values below 0% and above 100%. While negative event rates are statistical artifacts, the prediction of worsening symptoms is veridical in rare cases.

Indeed, throughout the entire collection of 79 publications, only one study reported a worsening in the sample-wide mean change score (Zhuo C. et al., 2020). At the individual patient level, a retrospective chart review including 162 patients with TRD found that only 1.83–5.49% of patients experienced a worsening of symptoms due to

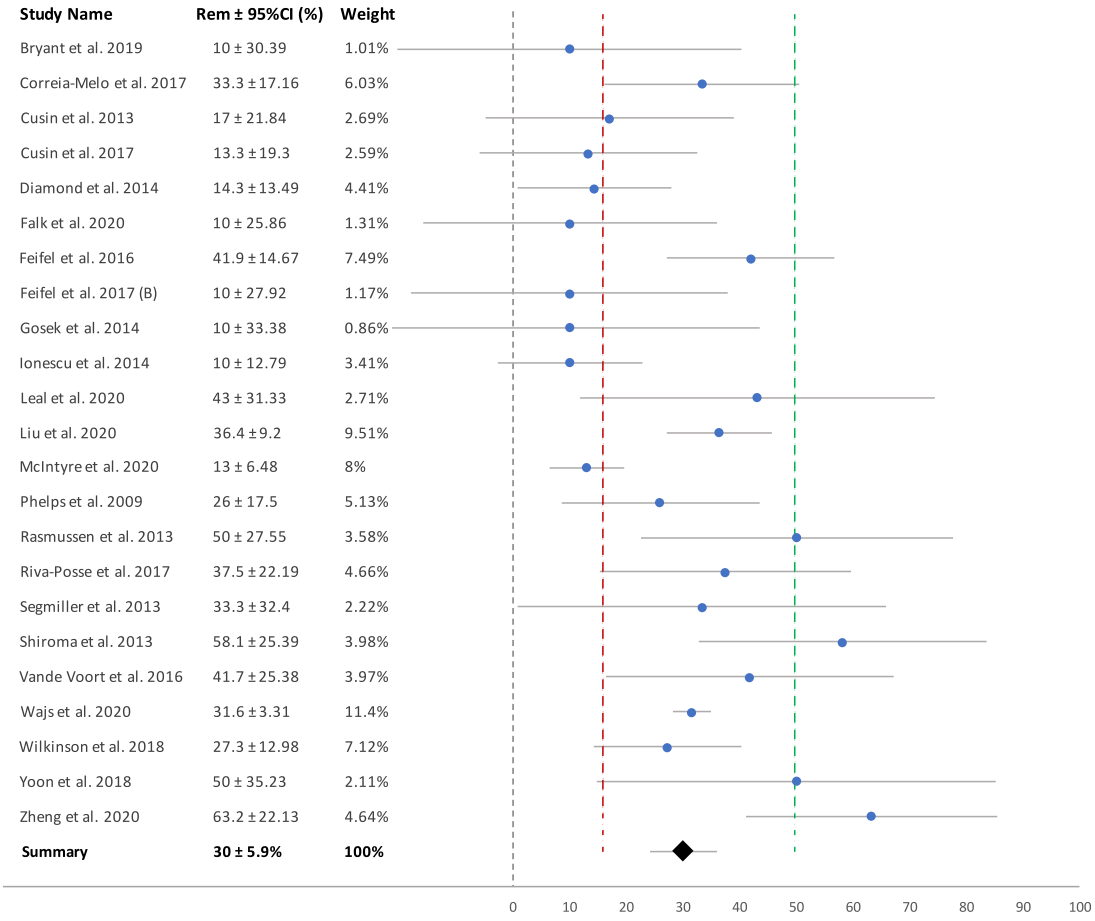

Fig. 6. Forest plot depicting the distribution of remission rates as percentages, wherein the **red** and **green** dashed lines represent the **lower** and **upper** limits of the **95% prediction interval** computed by adding and subtracting 2τ to and from the **point estimate (black diamond)** ($p < 0.0001$), which represents $\mathbf{k = 23}$ **studies** and **pooled** $\mathbf{n = 1291}$. Both the prediction interval and the **95% confidence intervals (error bars)** were computed on the natural log-scale then back-transformed to percentages.

ketamine (Di Vincenzo et al., 2022). Despite these results highlighting the promise of ketamine, the imprecision of the crude analysis and the stark variability of effects apparent in it (Fig. 2A) demanded further investigation. This was the impetus for the three meta-analyses and respective meta-regressions. All these analyses and their 95% prediction intervals demonstrate the same general pattern: ketamine exerts a powerful antidepressant effect on average, and a highly variable therapeutic effect across TRD populations.

4.2. *Implications of treatment resistance & dosing regimens*

The results from the meta-analysis of response rates recapitulate much of the heterogeneity apparent in the larger crude synthesis. The 95% prediction intervals shown in Figs. 5–7 demonstrate that the effectiveness of ketamine varies widely in the real-world clinical context. Furthermore, the majority of moderators were not predictive, and the negative effect of treatment resistance is unsurprising. Crucially, this effect was a false discovery in the case of response rates ($p \approx 0.05$), and only significant when tested on remission rates ($p < 0.01$). This suggests that while the prospect of ketamine-induced remission is remote for the most treatment resistant patients, achieving response in these patients is possible nevertheless. However, the extent of symptomatologic improvement is largely a question of individual differences (Meshkat et al., 2022). As shown by the interval in Fig. 7, the extent of symptomatologic change varies so widely that even worsening is possible but rare; a finding that corroborates prior results (Di Vincenzo et al., 2022). As of yet, the factors that determine the extent of symptomatological improvement, or the infrequent exacerbation of symptoms, are largely a matter of speculation.

Importantly, the negative effect of treatment resistance explained 52.4% of the variation in remission rates, which shows that a non-trivial proportion of TRD patients would require novel treatments to stably remit. It may seem plausible that some aspects of the dosing regimen could be tuned to facilitate remission in the more treatment-resistant patients. However, none of the dosing moderators (i.e., number of doses administered, doses/week, or duration from baseline to endpoint) were significant predictors of any outcomes ($p \geq 0.05$). While this underscores the need for diverse and novel treatments, it also constitutes strong evidence that mid-to-long term maintenance infusions are effective for many TRD patients. Overall, these results imply that the antidepressant benefit-to-cost ratio of ketamine therapy in depression follows an inverted U-shaped curve when expressed as a function of treatment resistance. Concretely, ketamine is generally effective in TRD, but as failed antidepressant trials accumulate, an inflection point is reached, and diminishing returns begin to apply. It is prudent to estimate this inflection point, but given the current dearth of options, ketamine remains indispensable in TRD.

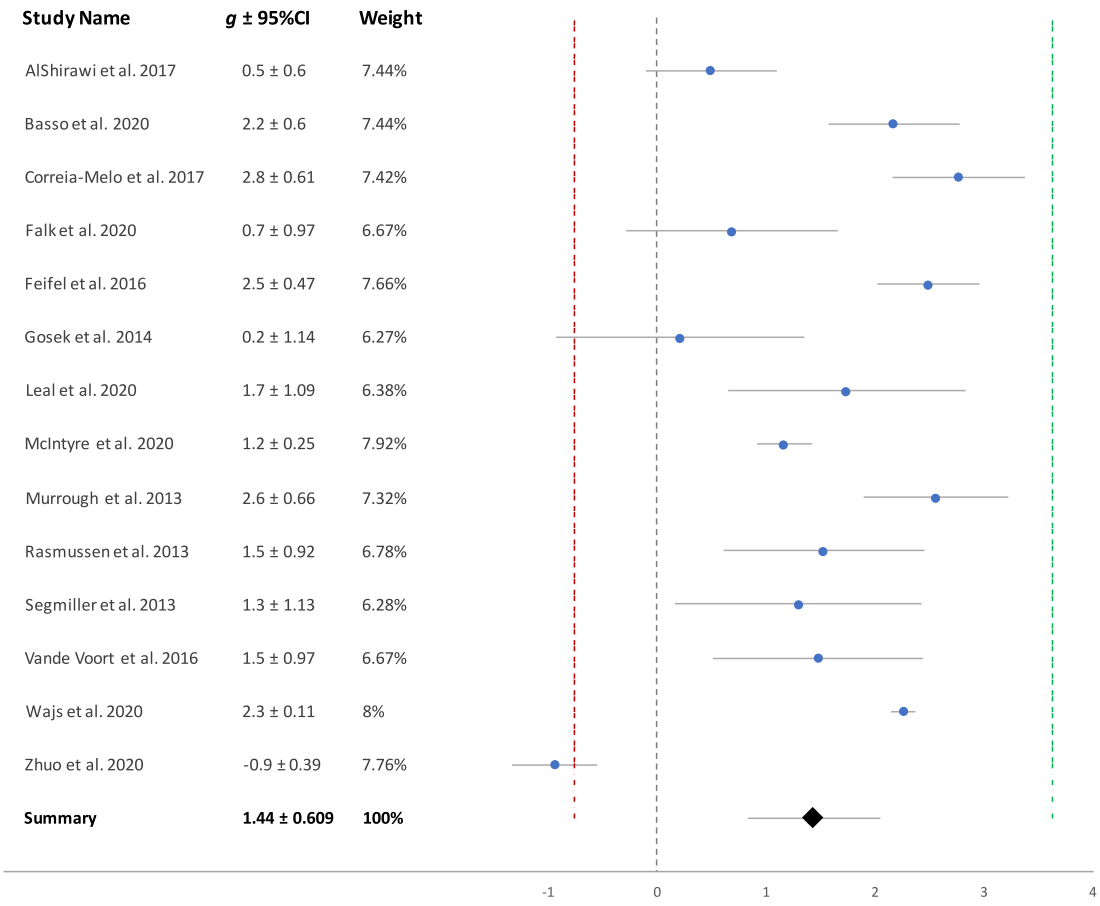

Fig. 7. Forest plot depicting the distribution of standardized symptomatologic improvement scores (Hedges' *g*), wherein the **red** and **green** dashed lines represent the **lower** and **upper** limits of the **95% prediction interval** computed by adding and subtracting 2τ to and from the **point estimate (black diamond)** ($p < 0.0001$), which represents **k = 14 studies** and **pooled n = 1079**.

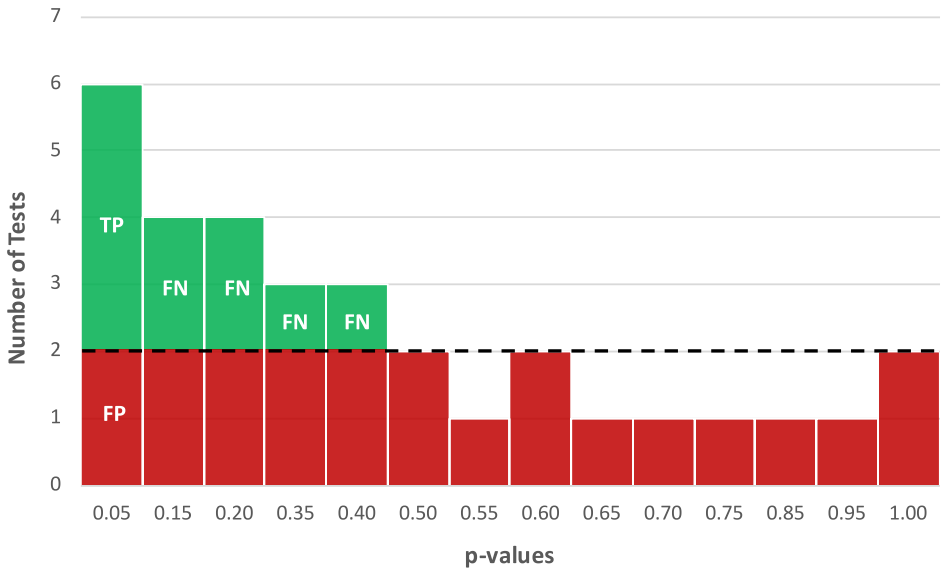

Fig. 8. Distribution of p-values for each of the 32 meta-regressions conducted in the present study, wherein the bins include p-values within consecutive **ranges** (0.05 increments) specified by the **x-axis** and the **number** of p-values per bin is shown on the **y-axis**; five empty bins are not shown. The **dashed line** represents the **noise-floor** which is extrapolated from the approximately uniform distribution of true null p-values evident above 0.40; **red** sections represent **true null** hypotheses, and **green** sections represent **false null** hypotheses. Abbreviations: True positive TP, false positive FP, false negative FN.

Table 4
Putatively true discoveries made by meta-regression.

Outcome	Moderator (Confounder)	*df*	R^2 (%)	Q_M	*p*	Residual Heterogeneity		
						Q	τ^2	I^2 (%)
Logit (Remission Rates)	Treatment Resistance	19	52.4	8.39	0.0038	30.5	0.0827	37.8
	Scale	21	14.3	4.99	0.0255	40.4	0.1490	48.0
	Treatment Resistance (Scale)	19	52.4	8.39	0.0038	30.5	0.0827	37.8
Hedges g (Change)	Average Age	12	46.1	4.93	0.0263	121	0.6479	90.1

4.3. Post-hoc analysis of prolonged effectiveness

One of the most important findings herein is that the effectiveness of ketamine does not significantly decline with repeated treatments or time. Two such regressions (i.e., mean # of doses administered and mean duration from baseline to endpoint) were intended for each of the three outcomes, but the data were insufficient (df $<$ 10) to regress duration on symptomatologic improvement. The smallest p-value of these tests was p = 0.3 from a regression of duration on remission rates (df = 16). Among the five regressions, the one with the greatest degrees of freedom was a regression of dose # on response rates (df = 30) which gave p = 0.6. This pattern of results speaks to the prolonged effectiveness of ketamine, but a reasonable objection can be made in this regard.

It is possible that these results are artifacts of patient discontinuations due to lack of effectiveness. To investigate this, all studies whose sample sizes diminished within the duration of the extracted response rates were excluded, and the two regressions were re-run to reveal whether a significant decline in effectiveness occurs. Upon filtering the response data accordingly, both regressions give p $\geq$ 0.3 with n = 337, 382 (df = 14, 18) for duration and dose # respectively. Applying the same restrictions to a regression of dose # on remission rates still gives p = 0.3 with n = 161 (df = 11); data were insufficient for the other regressions (df $<$ 10). The robustness of these results validates the finding that the effectiveness of ketamine does not decline with repeated dosing or time, despite suspicions suggested in prior studies (Gálvez et al., 2018; Gass et al., 2020; Ionescu et al., 2019).

4.4. Distinguishing artifacts from real effects

The results from the comparison of symptomatologic scales demonstrate that the apparent bias of the MADRS was a false discovery. Furthermore, the apparently significant impact of age on change scores may be just as artificial given the few degrees of freedom (*df* = 12). However, the continuity of the standardized change score renders it sensitive to the effects of true predictors, as moderator effects do not have to reach the threshold of response or remission to be detected. With this in mind, the regression of age on change scores suggests that younger patients tend to be somewhat less responsive than older ones. However, since the effect was not significant in the larger and less sensitive regressions on the log-odds of response and remission, the therapeutic effect in younger patients is appreciable nevertheless.

It is also noteworthy that some of the negative results (see **Supplementary Material: JASP Outputs** for complete reports) have settled suspicions that tend to echo throughout the literature; namely, the ideas that benzodiazepine users and bipolar patients are less responsive to ketamine (Andrashko et al., 2020; McGirr et al., 2015) did not survive scrutiny ($p > 0.05$). Typical concomitant benzodiazepine dosing has little impact on the therapeutic effects of ketamine (T. Henderson, 2016), but this is not true of high doses (Andrashko et al., 2020). Notwithstanding, the most important suspicion settled herein is that ketamine is only effective in the short term. Dose frequency, dose number, and duration did not affect any of the three outcomes, which demonstrates that ketamine's effectiveness is not limited to the short term (see section 4.3).

4.5. Limitations

Close to half of the overall weight in the meta-analysis of remission rates corresponded to studies exhibiting a high risk of bias in the causality domain. In some of the included studies, the endpoint measurements were taken several weeks after the initial ketamine dose. *A priori*, the longer the duration from baseline to endpoint, the greater the probability of confounding influences. The most common issue in this respect was the uncontrolled dosing of concomitants, and this was true for all four syntheses herein. Furthermore, the choice of the extracted time points was not determined quantitatively (see section 2.2). While these choices aimed to balance sample sizes across time, the lack of an adequate optimization formula for the temporal/dosing and sample size variables was not ideal. However, given the concordance between the efficacy literature (McGirr et al., 2015; McIntyre et al., 2021; Ng et al., 2021) and the mean effects reported herein (see **Section 3.1**), the influence of these confounds is likely to be minimal. While the crude synthesis (k = 79 studies) appeared less confounded (see Fig. 3.), its results are less generalizable, as it did not adequately correct for the imprecision of the included studies (i.e., only sample size could be used as weights) nor did it estimate the true variance (i.e., τ^2 was not accounted for). However, the general pattern apparent in this set of results was recapitulated in robust meta-analyses which were not limited by these confounds. Despite limitations, the present study provides a uniquely representative quantitative assessment of ketamine's real-world effectiveness.

5. Conclusion & outlook

The present study confirms that ketamine is effective overall, and that its effectiveness varies considerably across clinical populations. Four overlapping syntheses estimating the effectiveness of ketamine based on data from a total of 2665 patients demonstrate this trend conclusively. The overall results of the meta-regressions also confirm that ketamine is a viable mid-to-long term treatment strategy for many TRD patients, as dose frequency, dose number, and the duration until followup had no effect on any treatment outcomes. Notwithstanding, novel treatments are needed to achieve stable remission in the more treatment-resistant patients, despite many of these patients drawing some benefit from ketamine. It would thus be interesting to explore head-to-head comparisons with emerging augmentation options (Bartoli et al., 2021; Nuñez et al., 2022), as patients who reap minimal benefits from ketamine may benefit more from some of these combinations. However, research on these newer augmentation strategies will require greater rigor in its future iterations, as the evidence remains tenuous in most cases (Bartoli et al., 2021; Nuñez et al., 2022). While the effectiveness of ketamine varies across TRD populations, the current dearth of well-established treatment options underscores its importance, as the mean effect of ketamine is substantial, and reliably persists with repeated treatments.

CRediT statement

Conceptualization: JDR, YA; Methodology: JDR, NBR, MYJ, YA; Validation: JDR, RSM, YL, RCMH, HG, JDV, NBR, MYJ, DC, YA; Formal Analysis: YA; Investigation: EK, DC, MYJ, YA - all authors contributed to

evidence collection; Resources: All authors; Data Curation: MYJ, EK, DC, YA; Writing - Original Draft: YA; Writing - Review & Editing: All authors - extensive contributions from FC; Visualization: YA; Project administration: JDR, DC, YA; Supervision: JDR, RSM, YL; Software and Funding Acquisition: N/A.

Declaration of competing interest

JDR has received research grant support from CIHR, the Canadian Cancer Society, Canadian Psychiatric Association, American Psychiatric Association, American Society of Psychopharmacology, University of Toronto, University Health Network center for Mental Health, Joseph M. West Family Memorial Fund and Timeposters Fellowship and industry funding for speaker/consultation/research fees from Janssen, Allergan, Lundbeck, Sunovion and COMPASS. He is the medical director of a private clinic providing intravenous ketamine infusions and intranasal esketamine for depression.

RSM has received research grant support from CIHR/GACD/Chinese National Natural Research Foundation; speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Abbvie. Dr. Roger McIntyre is a CEO of Braxia Scientific Corp.

YL received salary support from the Global Alliance for Chronic Diseases/Canadian Institutes of Health Research (CIHR)/National Natural Science Foundation of China's Mental Health Team Grant and the CIHR Frederick Banting and Charles Best Canada Graduate Scholarship; personal fees from Braxia Scientific Corp.

RCMH has received research grant support from National Medical Research Council (Singapore), National Parks Board (Singapore); speaker/consultation fees from Lundbeck, Janssen, Eisai, Pfizer, DKSH, and OBELAB.

DC, JDV, SM, and KMT have received personal fees or grant(s) from Braxia Scientific Corp.

Acknowledgements

The project was conceived by JDR, and co-supervised by JDR and RSM. The systematic review was conducted by YA, DC, and EK. A second pass of extensive data refinement and quality control was carried out by YA and MYJ. DC and YA replicated the original systematic review. YA conducted the quantitative data analyses and drafted the article. All authors approved this manuscript and made significant contributions towards quality control and fact-checking efforts.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2022.04.037.

References

Sources cited in the article

Abdallah, C.G., 2017. What's the buzz about hydroxynorketamine? Is it the history, the story, the debate, or the promise? Biol. Psychiatr. 81 (8), e61–e63. https://doi.org/10.1016/j.biopsych.2017.01.002.

Alnefeesi, Y., Tamura, J.K., Lui, L.M.W., Jawad, M.Y., Ceban, F., Ling, S., Nasri, F., Rosenblat, J.D., McIntyre, R.S., 2021. Trace amine-associated receptor 1 (TAAR1): potential application in mood disorders: a systematic review. Neurosci. Biobehav. Rev. 131, 192–210. https://doi.org/10.1016/j.neubiorev.2021.09.020.

Andrashko, V., Novak, T., Brunovsky, M., Klirova, M., Sos, P., Horacek, J., 2020. The antidepressant effect of ketamine is dampened by concomitant benzodiazepine medication. Front. Psychiatr. 11, 844. https://doi.org/10.3389/fpsyt.2020.00844.

Artin, H., Bentley, S., Mehaffey, E., Liu, F., Sojourner, K., Bismark, A., Printz, D., Lee, E., Martis, B., De Peralta, S., Baker, D., Mishra, J., Ramanathan, D., 2021. Effects of intranasal (S)-ketamine on veterans with co-morbid treatment-resistant depression and PTSD: a retrospective case series. Neuropsychopharmacology 46, 113–114. https://doi.org/10.1038/s41386-021-01236-7 ((Artin, Bentley, Mehaffey, Liu, Sojourner, Bismark, Printz, Lee, Martis, De Peralta, Baker, Mishra, Ramanathan) UCSD School of Medicine, San Diego, CA, United States).

Banwari, G., Desai, P., Patidar, P., 2015. Ketamine-induced affective switch in a patient with treatment-resistant depression. Indian J. Pharmacol. 47 (4), 454–455. https://doi.org/10.4103/0253-7613.161277.

Bartoli, F., Cavaleri, D., Bachi, B., Moretti, F., Riboldi, I., Crocamo, C., Carrà, G., 2021. Repurposed drugs as adjunctive treatments for mania and bipolar depression: a meta-review and critical appraisal of meta-analyses of randomized placebo-controlled trials. J. Psychiatr. Res. 143, 230–238. https://doi.org/10.1016/j.jpsychires.2021.09.018.

Björkholm, C., Monteggia, L.M., 2016. BDNF — a key transducer of antidepressant effects. Neuropharmacology 102, 72–79. https://doi.org/10.1016/j.neuropharm.2015.10.034.

Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Methods 1 (2), 97–111. https://doi.org/10.1002/jrsm.12.

Borenstein, M., Higgins, J.P.T., Hedges, L.V., Rothstein, H.R., 2017. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity: I^2 is not an absolute measure of heterogeneity. Res. Synth. Methods 8 (1), 5–18. https://doi.org/10.1002/jrsm.1230.

Brunoni, A.R., Lopes, M., Fregni, F., 2008. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int. J. Neuropsychopharmacol. 11 (8), 1169–1180. https://doi.org/10.1017/S1461145708009309.

Carhart-Harris, R.L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J.N., Wall, M.B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H. V., Nutt, D.J., 2017. Psilocybin for treatment-resistant depression: FMRI-measured brain mechanisms. Sci. Rep. 7 (1), 1–11. https://doi.org/10.1038/s41598-017-13282-7.

Chen, M.-H., Lin, W.-C., Tsai, S.-J., Li, C.-T., Cheng, C.-M., Wu, H.-J., Bai, Y.-M., Hong, C.-J., Tu, P.-C., Su, T.-P., 2021. Effects of treatment refractoriness and brain-derived neurotrophic factor Val66Met polymorphism on antidepressant response to low-dose ketamine infusion. Eur. Arch. Psychiatr. Clin. Neurosci. 271 (7), 1267–1274. https://doi.org/10.1007/s00406-021-01264-w.

de Pins, B., Cifuentes-Díaz, C., Thamila Farah, A., López-Molina, L., Montalban, E., Sancho-Balsells, A., López, A., Ginés, S., Delgado-García, J.M., Alberch, J., Gruart, A., Girault, J.-A., Giralt, A., 2019. Conditional BDNF delivery from astrocytes rescues memory deficits, spine density and synaptic properties in the 5xFAD mouse model of Alzheimer disease. J. Neurosci. 39, 2441–2458. https://doi.org/10.1523/JNEUROSCI.2121-18.2019, 2121–18.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Contr. Clin. Trials 7 (3), 177–188. https://doi.org/10.1016/0197-2456(86)90046-2.

Di Vincenzo, J.D., Lipsitz, O., Rodrigues, N.B., Jones, B.D.M., Gill, H., Lee, Y., Lui, L.M. W., Teopiz, K.M., Ho, R., Lin, K., Nasri, F., McIntyre, R.S., Rosenblat, J.D., 2022. Frequency analysis of symptomatic worsening following ketamine infusions for treatment resistant depression in a real-world sample: results from the canadian rapid treatment center of excellence. Psychiatr. Res. 307, 114321. https://doi.org/10.1016/j.psychres.2021.114321.

Duman, R.S., Voleti, B., 2012. Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. Trends Neurosci. 35 (1), 47–56. https://doi.org/10.1016/j.tins.2011.11.004.

Farmer, C.A., Gilbert, J.R., Moaddel, R., George, J., Adeojo, L., Lovett, J., Nugent, A.C., Kadriu, B., Yuan, P., Gould, T.D., Park, L.T., Zarate, C.A., 2020. Ketamine metabolites, clinical response, and gamma power in a randomized, placebo-controlled, crossover trial for treatment-resistant major depression. Neuropsychopharmacology 45 (8), 1398–1404. https://doi.org/10.1038/s41386-020-0663-6.

Fukumoto, K., Fogaça, M.V., Liu, R.-J., Duman, C., Kato, T., Li, X.-Y., Duman, R.S., 2019. Activity-dependent brain-derived neurotrophic factor signaling is required for the antidepressant actions of (2 *R* ,6 *R*)-hydroxynorketamine. Proc. Natl. Acad. Sci. Unit. States Am. 116 (1), 297–302. https://doi.org/10.1073/pnas.1814709116.

Gálvez, V., Li, A., Huggins, C., Glue, P., Martin, D., Somogyi, A.A., Alonzo, A., Rodgers, A., Mitchell, P.B., Loo, C.K., 2018. Repeated intranasal ketamine for treatment-resistant depression – the way to go? Results from a pilot randomised controlled trial. J. Psychopharmacol. 32 (4), 397–407. https://doi.org/10.1177/0269881118760660.

Gass, N., Becker, R., Reinwald, J., Cosa-Linan, A., Sack, M., Weber-Fahr, W., Vollmayr, B., Sartorius, A., 2020. The influence of ketamine's repeated treatment on brain topology does not suggest an antidepressant efficacy. Transl. Psychiatry 10 (1), 1–10. https://doi.org/10.1038/s41398-020-0727-8.

Gosek, P., Chojnacka, M., Bienkowski, P., Swiecicki, L., 2014. Effectiveness of ketamine in depressed patients resistant to ECT or rTMS therapy. Psychiatr. Pol. 48 (1), 49–58.

Grunebaum, M.F., Galfalvy, H.C., Choo, T.-H., Parris, M.S., Burke, A.K., Suckow, R.F., Cooper, T.B., Mann, J.J., 2019. Ketamine metabolite pilot study in a suicidal depression trial. J. Psychiatr. Res. 117, 129–134. https://doi.org/10.1016/j.jpsychires.2019.08.005.

Guo, W., Machado-Vieira, R., Mathew, S., Murrough, J.W., Charney, D.S., Grunebaum, M., Oquendo, M.A., Kadriu, B., Akula, N., Henter, I., Yuan, P., Merikangas, K., Drevets, W., Furey, M., Mann, J.J., McMahon, F.J., Zarate, C.A., Shugart, Y.Y., 2018. Exploratory genome-wide association analysis of response to ketamine and a polygenic analysis of response to scopolamine in depression. Transl. Psychiatry 8 (1), 280. https://doi.org/10.1038/s41398-018-0311-7.

Hashimoto, K., 2012. A BDNF Val66Met polymorphism and ketamine-induced rapid antidepressant action. https://doi.org/10.9758/cpn.2012.10.1.59, 10, 1, 59-60.

Henderson, T., 2016. Practical application of the neuroregenerative properties of ketamine: real world treatment experience. Neural Regeneration Res. 11 (2), 195. https://doi.org/10.4103/1673-5374.177708.
Herzog, D.P., 2021. Longitudinal CSF proteome profiling in mice to uncover the acute and sustained mechanisms of action of rapid acting antidepressant (2R,6R)-hydroxynorketamine (HNK). Neurobiol. Stress. 13.
IntHout, J., Ioannidis, J.P.A., Rovers, M.M., Goeman, J.J., 2016. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open 6 (7), e010247. https://doi.org/10.1136/bmjopen-2015-010247.
Ionescu, D.F., Bentley, K.H., Eikermann, M., Taylor, N., Akeju, O., Swee, M.B., Pavone, K. J., Petrie, S.R., Dording, C., Mischoulon, D., Alpert, J.E., Brown, E.N., Baer, L., Nock, M.K., Fava, M., Cusin, C., 2019. Repeat-dose ketamine augmentation for treatment-resistant depression with chronic suicidal ideation: a randomized, double blind, placebo controlled trial. J. Affect. Disord. 243, 516–524. https://doi.org/10.1016/j.jad.2018.09.037.
JASP Team, 2021. JASP (*version 0.16*)*[Computer software]*. https://jasp-stats.org/.
Kang, M.J.Y., Kulcar, E., Chandrasena, R., Anjum, M.-R., Fairbairn, J., Hawken, E.R., Vazquez, G.H., 2021. Subanesthetic ketamine infusions for suicide ideation in patients with bipolar and unipolar treatment refractory depression. Psychiatr. Res. 296, 113645 https://doi.org/10.1016/j.psychres.2020.113645.
Kavalali, E.T., Monteggia, L.M., 2012. Synaptic mechanisms underlying rapid antidepressant action of ketamine. Am. J. Psychiatr. 169 (11), 1150–1156. https://doi.org/10.1176/appi.ajp.2012.12040531.
Laje, G., Lally, N., Mathews, D., Brutsche, N., Chemerinski, A., Akula, N., Kelmendi, B., Simen, A., McMahon, F.J., Sanacora, G., Zarate, C., 2012. Brain-derived neurotrophic factor Val66Met polymorphism and antidepressant efficacy of ketamine in depressed patients. Biol. Psychiatr. 72 (11), e27–e28. https://doi.org/10.1016/j.biopsych.2012.05.031.
Lapidus, K.A.B., Levitch, C.F., Perez, A.M., Brallier, J.W., Parides, M.K., Soleimani, L., Feder, A., Iosifescu, D.V., Charney, D.S., Murrough, J.W., 2014. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol. Psychiatr. 76 (12), 970–976. https://doi.org/10.1016/j.biopsych.2014.03.026.
Lin, L., Chu, H., 2018. Quantifying publication bias in meta-analysis. Biometrics 74 (3), 785–794. https://doi.org/10.1111/biom.12817.
Lucchese, A.C., Sarin, L.M., Magalhães, E.J.M., Del Sant, L.C., B Puertas, C., Tuena, M.A., Nakahira, C., Fava, V.A., Delfino, R., Surjan, J., Steiglich, M.S., Barbosa, M., Abdo, G., Cohrs, F.M., Liberatori, A., Del Porto, J.A., Lacerda, A.L., B Andreoli, S., 2021. Repeated subcutaneous esketamine for treatment-resistant depression: impact of the degree of treatment resistance and anxiety comorbidity. J. Psychopharmacol. 35 (2), 142–149. https://doi.org/10.1177/0269881120978398.
Macaskill, P., Walter, S.D., Irwig, L., 2001. A comparison of methods to detect publication bias in meta-analysis. Stat. Med. 20 (4), 641–654. https://doi.org/10.1002/sim.698.
McGirr, A., Berlim, M.T., Bond, D.J., Fleck, M.P., Yatham, L.N., Lam, R.W., 2015. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol. Med. 45 (4), 693–704. https://doi.org/10.1017/S0033291714001603.
McIntyre, R.S., Carvalho, I.P., Lui, L.M.W., Majeed, A., Masand, P.S., Gill, H., Rodrigues, N.B., Lipsitz, O., Coles, A.C., Lee, Y., Tamura, J.K., Iacobucci, M., Phan, L., Nasri, F., Singhal, N., Wong, E.R., Subramaniapillai, M., Mansur, R., Ho, R., Rosenblat, J.D., 2020. The effect of intravenous, intranasal, and oral ketamine in mood disorders: a meta-analysis. J. Affect. Disord. 276, 576–584. https://doi.org/10.1016/j.jad.2020.06.050.
McIntyre, R.S., Rosenblat, J.D., Nemeroff, C.B., Sanacora, G., Murrough, J.W., Berk, M., Brietzke, E., Dodd, S., Gorwood, P., Ho, R., Iosifescu, D.V., Lopez Jaramillo, C., Kasper, S., Kratiuk, K., Lee, J.G., Lee, Y., Lui, L.M.W., Mansur, R.B., Papakostas, G.I., et al., 2021. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. Am. J. Psychiatr. 178 (5), 383–399. https://doi.org/10.1176/appi.ajp.2020.20081251.
Meshkat, S., Rodrigues, N.B., Di Vincenzo, J.D., Ceban, F., Jaberi, S., McIntyre, R.S., Lui, L.M.W., Rosenblat, J.D., 2022. Pharmacogenomics of ketamine: a systematic review. J. Psychiatr. Res. 145, 27–34. https://doi.org/10.1016/j.jpsychires.2021.11.036.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, T.P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), e1000097 https://doi.org/10.1371/journal.pmed.1000097.
Murad, M.H., Sultan, S., Haffar, S., Bazerbachi, F., 2018. Methodological quality and synthesis of case series and case reports. BMJ Evidence Based Med. 23 (2), 60–63. https://doi.org/10.1136/bmjebm-2017-110853.
National Institute of Mental Health (NIMH), 2022. *A Double-Blind, Placebo-Controlled, Single Ascending Dose (SAD), Multiple Ascending Dose (MAD) and CSF Capture Study Of the Safety, Pharmacokinetics And Pharmacodynamics Of (2R,6R)-Hydroxynorketamine In Healthy Volunteers* (Clinical Trial Registration No. NCT04711005). clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04711005.
Ng, J., Rosenblat, J.D., Lui, L.M.W., Teopiz, K.M., Lee, Y., Lipsitz, O., Mansur, R.B., Rodrigues, N.B., Nasri, F., Gill, H., Cha, D.S., Subramaniapillai, M., Ho, R.C., Cao, B., McIntyre, R.S., 2021. Efficacy of ketamine and esketamine on functional outcomes in treatment-resistant depression: a systematic review. J. Affect. Disord. 293, 285–294. https://doi.org/10.1016/j.jad.2021.06.032.
Nuñez, N.A., Joseph, B., Pahwa, M., Kumar, R., Resendez, M.G., Prokop, L.J., Veldic, M., Seshadri, A., Biernacka, J.M., Frye, M.A., Wang, Z., Singh, B., 2022. Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis. J. Affect. Disord. 302, 385–400. https://doi.org/10.1016/j.jad.2021.12.134.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ n71. https://doi.org/10.1136/bmj.n71.
Sathyanarayana Rao, T.S., Andrade, C., 2017. A possible role for ketamine in suicide prevention in emergency and mainstream psychiatry. Indian J. Psychiatr. 59 (3), 259–261. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_345_17.
Szarmach, J., Cubała, W.J., Włodarczyk, A., Gałuszko-Węgielnik, M., 2020. Metabolic risk factors and cardiovascular safety in ketamine use for treatment resistant depression. Neuropsychiatric Dis. Treat. 16, 2539–2551. https://doi.org/10.2147/NDT.S273287.
Vevea, J.L., Hedges, L.V., 1995. A general linear model for estimating effect size in the presence of publication bias. Psychometrika 60 (3), 419–435. https://doi.org/10.1007/BF02294384.
Wilkowska, A., Szalach, L., Słupski, J., Wielewicka, A., Czarnota, M., Galuszko-Wegielnik, M., Wiglusz, M.S., Cubala, W.J., 2020a. Affective switch associated with oral, low dose ketamine treatment in a patient with treatment resistant bipolar I depression. Case report and literature review. Front. Psychiatr. 11, 516. https://doi.org/10.3389/fpsyt.2020.00516.
Wilkowska, A., Włodarczyk, A., Gałuszko-Węgielnik, M., Wiglusz, M.S., Cubała, W.J., 2021. Intravenous ketamine infusions in treatment-resistant bipolar depression: an open-label naturalistic observational study. Neuropsychiatric Dis. Treat. 17, 2637–2646. https://doi.org/10.2147/NDT.S325000.
Zanos, P., Gould, T.D., 2018. Mechanisms of ketamine action as an antidepressant. Mol. Psychiatr. 23 (4), 801–811. https://doi.org/10.1038/mp.2017.255.
Zanos, P., Moaddel, R., Morris, P.J., Riggs, L.M., Highland, J.N., Georgiou, P., Pereira, E. F.R., Albuquerque, E.X., Thomas, C.J., Zarate, C.A., Gould, T.D., 2018. Ketamine and ketamine metabolite Pharmacology: insights into therapeutic mechanisms. Pharmacol. Rev. 70 (3), 621–660. https://doi.org/10.1124/pr.117.015198.
Zanos, P., Moaddel, R., Morris, P.J., Georgiou, P., Fischell, J., Elmer, G.I., Alkondon, M., Yuan, P., Pribut, H.J., Singh, N.S., Dossou, K.S.S., Fang, Y., Huang, X.-P., Mayo, C.L., Wainer, I.W., Albuquerque, E.X., Thompson, S.M., Thomas, C.J., Zarate, C.A., Gould, T.D., 2016. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533 (7604), 481–486. https://doi.org/10.1038/nature17998.
Zarate, C.A., Brutsche, N., Laje, G., Luckenbaugh, D.A., Venkata, S.L.V., Ramamoorthy, A., Moaddel, R., Wainer, I.W., 2012. Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. Biol. Psychiatr. 72 (4), 331–338. https://doi.org/10.1016/j.biopsych.2012.03.004.
Zhuo, C., Ji, F., Tian, H., Wang, L., Jia, F., Jiang, D., Chen, C., Zhou, C., Lin, X., Zhu, J., 2020a. Transient effects of multi-infusion ketamine augmentation on treatment-resistant depressive symptoms in patients with treatment-resistant bipolar depression—an open-label three-week pilot study. Brain. Behave. 10, e01674. https://doi.org/10.1002/brb3.1674.

Additional sources included in formal syntheses

Aan het Rot, M., Collins, K.A., Murrough, J.W., Perez, A.M., Reich, D.L., Charney, D.S., Mathew, S.J., 2010. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol. Psychiatr. 67 (2), 139–145. https://doi.org/10.1016/j.biopsych.2009.08.038.
Al Shirawi, M.I., Kennedy, S.H., Ho, K.T., Byrne, R., Downar, J., 2017. Oral ketamine in treatment-resistant depression. J. Clin. Psychopharmacol. 37 (4), 464–467. https://doi.org/10.1097/JCP.0000000000000717.
Albott, C., Shiroma, P., Erbes, C., Thuras, P., Wels, J., Lim, K., 2016. Serial IV ketamine infusions are effective for the treatment of comorbid post-traumatic stress disorder and treatment-resistant major depression. Neuropsychopharmacology 41 (Suppl. 1), S152. https://doi.org/10.1038/npp.2016.240.
Barbosa, M.G., Delfino, R.S., Sarin, L.M., Jackowski, A.P., 2020. Repeated subcutaneous esketamine administration for depressive symptoms and pain relief in a terminally ill cancer patient: a case report. Palliat. Med. 34 (6), 822–825. https://doi.org/10.1177/0269216320910351.
Basso, L., Bonke, L., Aust, S., Gartner, M., Heuser-Collier, I., Otte, C., Wingenfeld, K., Bajbouj, M., Grimm, S., 2020. Antidepressant and neurocognitive effects of serial ketamine administration versus ECT in depressed patients. J. Psychiatr. Res. 123, 1–8. https://doi.org/10.1016/j.jpsychires.2020.01.002 ((Basso, Bonke, Aust, Gartner, Heuser-Collier, Otte, Wingenfeld, Bajbouj, Grimm) Charite-Universitatsmedizin Berlin, Corporate Member of Freie Universitat Berlin, Humboldt-Universitat zu Berlin, Berlin Institute of Health, Campus Benjamin Franklin, Hin).
Best, S., Pavel, D.G., 2017. Combined transcranial magnetic stimulation and ketamine for treatment of refractory mood disorder, anxiety, and pain: a case report. Curr. Neurobiol. 8 (1), 1–4.
Best, S.R.D., 2015. Combined ketamine and transcranial magnetic stimulation for treatment resistant depression in the context of chronic OCD: a case report. Neuropsychioatric. Electrophysiol. 1 (1), 2. https://doi.org/10.1186/s40810-015-0003-y.
Best, S.R.D., Griffin, B., 2015. Combination therapy utilizing ketamine and transcranial magnetic stimulation for treatment-resistant depression: a case report. Int. J. Neurosci. 125 (3), 232–234. https://doi.org/10.3109/00207454.2014.933834.
Best, S.R.D., Griffin, B.P., Pavel, D.G., 2015. Ketamine and transcranial magnetic stimulation treatment for bipolar II disorder: a case report. J. Med. Case Rep. 9 (1), 73. https://doi.org/10.1186/s13256-015-0520-0.

Bloch, M.H., Leckman, J.F., Krystal, J.H., Bhagwagar, Z.H., Sanacora, G., Pittenger, C., 2011. Ketamine for treatment-refractory obsessive-compulsive disorder. Neuropsychopharmacology 36 (Suppl. 1), S294–S295. https://doi.org/10.1038/npp.2011.292.

Bloch, M.H., Wasylink, S., Landeros-Weisenberger, A., Panza, K.E., Billingslea, E., Leckman, J.F., Krystal, J.H., Bhagwagar, Z., Sanacora, G., Pittenger, C., 2012. Effects of ketamine in treatment-refractory obsessive-compulsive disorder. Biol. Psychiatr. 72 (11), 964–970. https://doi.org/10.1016/j.biopsych.2012.05.028.

Bobo, W., Voort, J.V., Morgan, R., Rico, J., Ritter, M., Tye, S., Frye, M., 2016. Continuation phase intravenous ketamine in adults with treatment-resistant depression. Neuropsychopharmacology 41 (Suppl. 1), S168–S169. https://doi.org/10.1038/npp.2016.240.

Bryant, K.A., Altinay, M., Finnegan, N., Cromer, K., Dale, R.M., 2019. Effects of repeated intravenous ketamine in treatment-resistant geriatric depression: a case series. J. Clin. Psychopharmacol. 39 (2), 158–161. https://doi.org/10.1097/JCP.0000000000001006.

Bryson, E.O., Ahle, G.M., Liebman, L.S., Aloysi, A.S., Majeske, M.F., Lapidus, K.A., Kellner, C.H., 2014. Dosing and effectiveness of ketamine anesthesia for electroconvulsive therapy (ECT): a case series. Australas. Psychiatr. 22 (5), 467–469. https://doi.org/10.1177/1039856214545547.

Bustillo, I.L., Olazabal, N., Bustamante, S., Madrazo, M.A., Osa, L., Gonzalez-Torres, M. A., 2019. P.319 Intravenous ketamine long-term use in two bipolar depression cases: 1-year follow-up. Eur. Neuropsychopharmacol 29 (Suppl. 6), S228. https://doi.org/10.1016/j.euroneuro.2019.09.339.

Chan, L.F., Eu, C.L., Soh, S.Y., Maniam, T., Kadir, Z.S., Chong, B.T.W., Loo, J.L., Sharip, S., Wong, V.C.W., Loo, T.H., Ng, Y.P., Kahn, D.A., 2018. Is ketamine the future clozapine for depression? A case series and literature review on maintenance ketamine in treatment-resistant depression with suicidal behavior. J. Psychiatr. Pract. 24 (4), 279–291. https://doi.org/10.1097/PRA.0000000000000316.

Cornwell, B.R., Salvadore, G., Furey, M., Marquardt, C.A., Brutsche, N.E., Grillon, C., Zarate Jr., C.A., 2012. Synaptic potentiation is critical for rapid antidepressant response to ketamine in treatment-resistant major depression. Biol. Psychiatr. 72 (7), 555–561. https://doi.org/10.1016/j.biopsych.2012.03.029.

Correia-Melo, F.S., Argolo, F.C., Araujo-de-Freitas, L., Leal, G.C., Kapczinski, F., Lacerda, A.L., Quarantini, L.C., 2017. Rapid infusion of esketamine for unipolar and bipolar depression: a retrospective chart review. Neuropsychiatric Dis. Treat. 13, 1627–1632. https://doi.org/10.2147/NDT.S135623 ((Correia-Melo, Argolo, Araujo-de-Freitas, Leal, Quarantini) Psychiatry Service, University Hospital, Federal University of Bahia, Salvador, Brazil(Araujo-de-Freitas, Quarantini) Federal University of Bahia, Salvador, Brazil(Kapczinski) Department of Psych).

Correll, G.E., Futter, G.E., 2006. Two case studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. Pain Med. 7 (1), 92–95. https://doi.org/10.1111/j.1526-4637.2006.00101.x.

Cusin, C., Eikermann, M., Zaremba, S., Pavone, K., Durham, K., Chang, T., Cassano, P., Dording, C., Soskin, D., Mischoulon, D., Fava, M., 2013. Preliminary investigation of EEG predictors in an open-label, flexible-dose, repeated infusions of ketamine as augmentation in treatment resistant depression. Neuropsychopharmacology 38 (Suppl. 2), S526–S528. https://doi.org/10.1038/npp.2013.281.

Cusin, C., Ionescu, D.F., Pavone, K.J., Akeju, O., Cassano, P., Taylor, N., Eikermann, M., Durham, K., Swee, M.B., Chang, T., Dording, C., Soskin, D., Kelley, J., Mischoulon, D., Brown, E.N., Fava, M., 2017. Ketamine augmentation for outpatients with treatment-resistant depression: preliminary evidence for two-step intravenous dose escalation. Aust. N. Z. J. Psychiatr. 51 (1), 55–64. https://doi.org/10.1177/0004867416631828.

Diamond, P.R., Farmery, A.D., Atkinson, S., Haldar, J., Williams, N., Cowen, P.J., Geddes, J.R., McShane, R., 2014. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J. Psychopharmacol. 28 (6), 536–544. https://doi.org/10.1177/0269881114527361.

DiazGranados, N., Ibrahim, L.A., Brutsche, N.E., Ameli, R., Henter, I.D., Luckenbaugh, D. A., Machado-Vieira, R., Zarate Jr., C.A., 2010. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J. Clin. Psychiatr. 71 (12), 1605–1611. https://doi.org/10.4088/JCP.09m05327blu.

Dore, J., Turnipseed, B., Dwyer, S., Turnipseed, A., Andries, J., Ascani, G., Monnette, C., Huidekoper, A., Strauss, N., Wolfson, P., 2019. Ketamine assisted psychotherapy (KAP): patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. J. Psychoact. Drugs 51 (2), 189–198. https://doi.org/10.1080/02791072.2019.1587556.

Duncan Jr., W.C., Selter, J., Brutsche, N., Sarasso, S., Zarate Jr., C.A., 2013. Baseline delta sleep ratio predicts acute ketamine mood response in major depressive disorder. J. Affect. Disord. 145 (1), 115–119. https://doi.org/10.1016/j.jad.2012.05.042.

Dunner, D.L., Fugate, R.M., Demopulos, C.M., 2020. Safety and efficacy of esketamine nasal spray in a depressed patient who was being treated with tranylcypromine: a case report. Neurol. Psychiatr. Brain Res. 36, 30–31. https://doi.org/10.1016/j.npbr.2020.02.008 ((Dunner, Fugate, Demopulos) Center for Anxiety and Depression, 7525 SE 24th Street, Suite 400, Mercer Island, WA 98040, United States).

Falk, E., Schlieper, D., van Caster, P., Lutterbeck, M.J., Schwartz, J., Cordes, J., Grau, I., Kienbaum, P., Neukirchen, M., 2020. A rapid positive influence of S-ketamine on the anxiety of patients in palliative care: a retrospective pilot study. BMC Palliat. Care 19 (1), 1. https://doi.org/10.1186/s12904-019-0499-1.

Feifel, D., Malcolm, B., Boggie, D., Lee, K., 2016. Efficacy and safety of intravenous low-dose ketamine for depression in an academic clinical practice. Neuropsychopharmacology 41 (Suppl. 1), S159. https://doi.org/10.1038/npp.2016.240.

Feifel, D., Peppa, P., Boggie, D., Lee, K., 2017. Long-term treatment of depression with repeated intramuscular ketamine. Neuropsychopharmacology 43 (Suppl. 1), S173. https://doi.org/10.1038/npp.2017.264.

Harihar, C., Dasari, P., Srinivas, J.S., 2013. Intramuscular ketamine in acute depression: a report on two cases. Indian J. Psychiatr. 55 (2), 186–188. https://doi.org/10.4103/0019-5545.111461.

Hasler, G., Suker, S., Schoretsanitis, G., Mihov, Y., 2019. Ketamine improves negative attitudes toward self in treatment-resistant depression. Neuropsychopharmacology 44 (Suppl. 1), 429. https://doi.org/10.1038/s41386-019-0547-9.

Hassamal, S., Spivey, M., Pandurangi, A.K., 2015. Augmentation therapy with serial intravenous ketamine over 18 months in a patient with treatment resistant depression. Clin. Neuropharmacol. 38 (5), 212–216. https://doi.org/10.1097/WNF.0000000000000104.

Henderson, T.A., 2016. Practical application of the neuroregenerative properties of ketamine: real world treatment experience. Neural Regeneration Res. 11 (2), 195–200. https://doi.org/10.4103/1673-5374.177708.

Ionescu, D.F., Luckenbaugh, D.A., Niciu, M.J., Richards, E.M., Slonena, E.E., Vande Voort, J.L., Brutsche, N.E., Zarate, C.A., 2014. Effect of baseline anxious depression on initial and sustained antidepressant response to Ketamine. J. Clin. Psychiatr. 75 (9), e932–e938. https://doi.org/10.4088/JCP.14m09049.

Irwin, S.A., Iglewicz, A., 2010. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. J. Palliat. Med. 13 (7), 903–908. https://doi.org/10.1089/jpm.2010.9808.

Kallmunzer, B., Volbers, B., Karthaus, A., Tektas, O.Y., Kornhuber, J., Muller, H.H., 2016. Treatment escalation in patients not responding to pharmacotherapy, psychotherapy, and electro-convulsive therapy: experiences from a novel regimen using intravenous S-ketamine as add-on therapy in treatment-resistant depression. J. Neural. Transm. 123 (5), 549–552. https://doi.org/10.1007/s00702-015-1500-7.

Kwon, J.H., Sim, W.S., Hong, J.P., Song, I.S., Lee, J.Y., 2018. Intravenous ketamine infusion for a patient with treatment-resistant major depression: a 10-month follow-up. J. Clin. Pharm. Therapeut. 43 (4), 581–583. https://doi.org/10.1111/jcpt.12669.

Leal, G.C., Bandeira, I.D., Correia-Melo, F.S., Telles, M., Mello, R.P., Vieira, F., Lima, C.S., Jesus-Nunes, A.P., Guerreiro-Costa, L.N.F., Marback, R.F., Caliman-Fontes, A.T., Marques, B.L.S., Bezerra, M.L.O., Dias-Neto, A.L., Silva, S.S., Sampaio, A.S., Sanacora, G., Turecki, G., Loo, C., et al., 2020. Intravenous arketamine for treatment-resistant depression: open-label pilot study. Eur. Arch. Psychiatr. Clin. Neurosci. 271, 577–582. https://doi.org/10.1007/s00406-020-01110-5 (Leal, Quarantini) Hospital Universitario Professor Edgard Santos, Servico de Psiquiatria, Universidade Federal da Bahia, 3 andar, Rua Dr. Augusto Viana S/N, Salvador, Bahia 40110-060, Brazil (Leal, Bandeira, Correia-Melo, Telles, Mello, Vieira, Lima, Jesu.

Liebrenz, M., Borgeat, A., Leisinger, R., Stohler, R., 2007. Intravenous ketamine therapy in a patient with a treatment-resistant major depression. Swiss Med. Wkly. 137 (15–16), 234–236.

Liebrenz, M., Stohler, R., Borgeat, A., 2009. Repeated intravenous ketamine therapy in a patient with treatment-resistant major depression. World J. Biol. Psychiatr. 10 (4 PART 2), 640–643. https://doi.org/10.1080/15622970701420481.

Liu, W., Zhou, Y., Wang, C., Zheng, W., Zhan, Y., Lan, X., Zhang, B., Li, H., Chen, L., Li, M., Ning, Y., 2020. Baseline insomnia as a predictor of antidepressant efficacy to repeated intravenous ketamine for unipolar and bipolar depression: a preliminary study. J. Affect. Disord. 271, 1–8. https://doi.org/10.1016/j.jad.2020.03.048 ((Liu, Zhou, Wang, Zheng, Zhan, Lan, Zhang, Li, Chen, Li, Ning) The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China(Liu, Zhou, Wang, Zheng, Zhan, Lan, Zhang, Li, Chen, Ning) Guangdong Engineering Techn).

Lopez-Diaz, A., Fernandez-Gonzalez, J.L., Lujan-Jimenez, J.E., Galiano-Rus, S., Gutierrez-Rojas, L., 2017. Use of repeated intravenous ketamine therapy in treatment-resistant bipolar depression with suicidal behaviour: a case report from Spain. Therapeutic. Adv. Psychopharmacol. 7 (4), 137–140. https://doi.org/10.1177/2045125316675578.

Lu, B.Y., Agapoff, J.R., Olson, D.J., Williams, S.R., Roller, A., Goebert, D., 2020. Rapid and sustained improvement in treatment-refractory depression through use of acute intravenous ketamine and concurrent transdermal selegiline: a case series. J. Affect. Disord. 262. https://doi.org/10.1016/j.jad.2019.10.050 ((Lu, Agapoff, Olson, Williams, Goebert) University of Hawai'i at Manoa, John A. Burns School of Medicine, Department of Psychiatry 1356 Lusitana St., 4th Fl., Honolulu, HI 96813, United States, United States(Lu, Williams, Roller, Goebert) Queen's Medical), 40-42.

Machado-Vieira, R., Yuan, P., Brutsche, N., DiazGranados, N., Luckenbaugh, D., Manji, H.K., Zarate Jr., C.A., 2009. Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist. J. Clin. Psychiatr. 70 (12), 1662–1666. https://doi.org/10.4088/JCP.08m04659.

Mandal, S., Sinha, V.K., Goyal, N., Mukherjee, N., 2019. Ketamine therapy and its efficacy in treatment of depression. Indian J. Psychiatr. 61 (9 Suppl. 3), S542.

McIntyre, R.S., Lipsitz, O., Rodrigues, N.B., Lee, Y., Cha, D.S., Vinberg, M., Lin, K., Malhi, G.S., Subramaniapillai, M., Kratiuk, K., Fagiolini, A., Gill, H., Nasri, F., Mansur, R.B., Suppes, T., Ho, R., Rosenblat, J.D., 2020. The effectiveness of ketamine on anxiety, irritability, and agitation: implications for treating mixed features in adults with major depressive or bipolar disorder. Bipolar Disord. 22, 831–840. https://doi.org/10.1111/bdi.12941 (McIntyre, Lipsitz, Rodrigues, Lee, Cha, Subramaniapillai, Gill, Nasri, Mansur, Rosenblat) Mood Disorders Psychopharmacology Unit, Poul Hansen Family Centre for Depression, ON, University Health Network, Toronto, Canada(McIntyre, Lipsitz, Rodrigues, Lee.

McIntyre, R.S., Rodrigues, N.B., Lee, Y., Lipsitz, O., Subramaniapillai, M., Gill, H., Nasri, F., Majeed, A., Lui, L.M.W., Senyk, O., Phan, L., Carvalho, I.P., Siegel, A., Mansur, R.B., Brietzke, E., Kratiuk, K., Arekapudi, A.K., Abrishami, A., Chau, E.H., Rosenblat, J.D., 2020. The effectiveness of repeated intravenous ketamine on

depressive symptoms, suicidal ideation and functional disability in adults with major depressive disorder and bipolar disorder: results from the Canadian Rapid Treatment Center of Excellence. J. Affect. Disord. 274, 903–910. https://doi.org/10.1016/j.jad.2020.05.088 ((McIntyre, Rodrigues, Lee, Lipsitz, Subramaniapillai, Gill, Nasri, Majeed, Lui, Phan, Carvalho, Siegel, Mansur, Rosenblat) Mood Disorder Psychopharmacology Unit, University Health Network; University of Toronto, Toronto, ON, Canada(McIntyre, Rodrigues, Le).

Medeiros da Frota Ribeiro, C., Riva-Posse, P., 2017. Use of ketamine in elderly patients with treatment-resistant depression. Curr. Psychiatr. Rep. 19 (12), 107. https://doi.org/10.1007/s11920-017-0855-x.

Messer, M.M., Haller, I.V., 2010. Maintenance ketamine treatment produces long-term recovery from depression. Prim. Psychiatr. 17 (4), 48–50.

Messer, M.M., Haller, I.V., 2017. Ketamine therapy for treatment-resistant depression in a patient with multiple sclerosis: a case report. Innovation Clinic. Neurosci. 14 (1–2), 56–59.

Murrough, J.W., Perez, A.M., Pillemer, S., Stern, J., Parides, M.K., Aan Het Rot, M., Collins, K.A., Mathew, S.J., Charney, D.S., Iosifescu, D.V., 2013. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol. Psychiatr. 74 (4), 250–256. https://doi.org/10.1016/j.biopsych.2012.06.022.

Nakahira, C., Steglich, M.S., Ferreira, M.B., Ferreira, C.B.N.D., Magalhaes, E.J.M., Del Sant, L.C., Lucchese, A.C., Sarin, L.M., Del Porto, J.A., Lacerda, A.L.T., 2017. Safety and efficacy of ketamine infusion in treatment-resistant depression with multiple medical comorbidities: a case report. Eur. Neuropsychopharmacol 27 (Suppl. 4), S866–S867.

Niciu, M.J., Grunschel, B.D.G., Corlett, P.R., Pittenger, C., Bloch, M.H., 2013. Two cases of delayed-onset suicidal ideation, dysphoria and anxiety after ketamine infusion in patients with obsessive-compulsive disorder and a history of major depressive disorder. J. Psychopharmacol. 27 (7), 651–654. https://doi.org/10.1177/0269881113486718.

Olazabal, N., Bustamante, S., Madrazo, M., Priego, G., Osa, L., Catalan, A., O'Neil Of Tyrone, A., Gonzalez-Torres, M., 2017. Intravenous ketamine for depression and congruent psychotic symptomatology: description of two consecutive cases. Eur. Neuropsychopharmacol 27 (Suppl. 4), S854.

Paslakis, G., Gilles, M., Meyer-Lindenberg, A., Deuschle, M., 2010. Oral administration of the NMDA receptor antagonist S-ketamine as add-on therapy of depression: a case series. Pharmacopsychiatry 43 (1), 33–35. https://doi.org/10.1055/s-0029-1237375.

Pennybaker, S.J., Niciu, M.J., Luckenbaugh, D.A., Zarate Jr., C.A., 2017. Symptomatology and predictors of antidepressant efficacy in extended responders to a single ketamine infusion. J. Affect. Disord. 208, 560–566. https://doi.org/10.1016/j.jad.2016.10.02610.1016/j.jad.2016.10.026 (aan het Rot, M., Collins, K. A., Murrough, J.W., Perez, A.M., Reich, D.L., Charney, D.S., Mathew, S.J. (2010). Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol. Psychiatry, 67, 139-145.Anand, A., Charney,).

Phelps, L.E., Brutsche, N., Moral, J.R., Luckenbaugh, D.A., Manji, H.K., Zarate Jr., C.A., 2009. Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. Biol. Psychiatr. 65 (2), 181–184. https://doi.org/10.1016/j.biopsych.2008.09.029.

Rasmussen, K.G., Lineberry, T.W., Galardy, C.W., Kung, S., Lapid, M.I., Palmer, B.A., Ritter, M.J., Schak, K.M., Sola, C.L., Hanson, A.J., Frye, M.A., 2013. Serial infusions of low-dose ketamine for major depression. J. Psychopharmacol. 27 (5), 444–450. https://doi.org/10.1177/0269881113478283.

Riva-Posse, P., Galendez Snead, G., McDonald, W.M., 2017. Ketamine infusions after failure to respond to electroconvulsive therapy: a case series report. Brain Stimul. 10 (2), 491. https://doi.org/10.1016/j.brs.2017.01.433.

Sakurai, H., Jain, F., Foster, S., Pedrelli, P., Mischoulon, D., Fava, M., Cusin, C., 2020. Long-term outcome in outpatients with depression treated with acute and maintenance intravenous ketamine: a retrospective chart review. J. Affect. Disord. 276, 660–666. https://doi.org/10.1016/j.jad.2020.07.089.

Sampath, H., Sharma, I., Dutta, S., 2016. Treatment of suicidal depression with ketamine in rapid cycling bipolar disorder. Asia Pac. Psychiatr. 8 (1), 98–101. https://doi.org/10.1111/appy.12220.

Scheele, D., Zimbal, S., Feinstein, J.S., Delis, A., Neumann, C., Mielacher, C., Philipsen, A., Hurlemann, R., 2019. Treatment-resistant depression and ketamine response in a patient with bilateral amygdala damage. Am. J. Psychiatr. 176 (12), 982–986. https://doi.org/10.1176/appi.ajp.2019.18101219.

Segmiller, F., Ruther, T., Linhardt, A., Padberg, F., Berger, M., Pogarell, O., Moller, H.J., Kohler, C., Schule, C., 2013. Repeated S-ketamine infusions in therapy resistant depression: a case series. J. Clin. Pharmacol. 53 (9), 996–998. https://doi.org/10.1002/jcph.122.

Shiroma, P.R., Johns, B., Kuskowski, M., Wels, J., Thuras, P., Albott, C.S., Lim, K.O., 2014. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. J. Affect. Disord. 155, 123–129. https://doi.org/10.1016/j.jad.2013.10.036.

Stefanczyk-Sapieha, L., Oneschuk, D., Demas, M., 2008. Intravenous ketamine "burst" for refractory depression in a patient with advanced cancer. J. Palliat. Med. 11 (9), 1268–1271. https://doi.org/10.1089/jpm.2008.9828.

Sultan, R., Riva-Posse, P., Garlow, S.J., Schwartz, A.C., 2014. Beneficial pre-ECT ketamine infusion in a patient with treatment-resistant depression. Psychosomatics 55 (4), 396–399. https://doi.org/10.1016/j.psym.2013.12.002.

Szymkowicz, S.M., Finnegan, N., Dale, R.M., 2013. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment-resistant depression. J. Affect. Disord. 147 (1–3), 416–420. https://doi.org/10.1016/j.jad.2012.10.015.

Wajs, E., Aluisio, L., Holder, R., Daly, E.J., Lane, R., Lim, P., George, J.E., Morrison, R.L., Sanacora, G., Young, A.H., Kasper, S., Sulaiman, A.H., Li, C.-T., Paik, J.-W., Manji, H., Hough, D., Grunfeld, J., Jeon, H.J., Wilkinson, S.T., Singh, J.B., 2020. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). J. Clin. Psychiatr. 81 (3) https://doi.org/10.4088/JCP.19m12891.

Wang, M., Xiong, Z., Su, B., Wang, L., Yang, Y., Fang, J., Li, Z., 2020. Repeated ketamine injections in synergy with antidepressants for treating refractory depression: a case showing 6-month improvement. J. Clin. Pharm. Therapeut. 45 (1), 199–203. https://doi.org/10.1111/jcpt.13041.

Wilkinson, S.T., Katz, R.B., Toprak, M., Webler, R., Ostroff, R.B., Sanacora, G., 2018. Acute and longer-term outcomes using ketamine as a clinical treatment at the yale psychiatric hospital. J. Clin. Psychiatr. 79 (4), 17m11731 https://doi.org/10.4088/JCP.17m11731.

Wilkinson, S.T., Wright, D., Fasula, M.K., Fenton, L., Griepp, M., Ostroff, R.B., Sanacora, G., 2017. Cognitive behavior therapy may sustain antidepressant effects of intravenous ketamine in treatment-resistant depression. Psychother. Psychosom. 86 (3), 162–167. https://doi.org/10.1159/000457960.

Wilkowska, A., Szalach, L., Slupski, J., Wielewicka, A., Czarnota, M., Galuszko-Wegielnik, M., Wiglusz, M.S., Cubala, W.J., 2020b. Affective switch associated with oral, low dose ketamine treatment in a patient with treatment resistant bipolar I depression. Case report and literature review. Front. Psychiatr. 11, 516. https://doi.org/10.3389/fpsyt.2020.00516 ((Wilkowska, Szalach, Slupski, Wielewicka, Czarnota, Galuszko-Wegielnik, Wiglusz, Cubala) Department of Psychiatry, Medical University of Gdansk, Gdansk, Poland).

Yoon, G., Ralevski, E., Arias, A.J., Limoncelli, D., Newcomb, J., Levy, L., Jane, J.S., Krystal, J.H., Petrakis, I.L., 2018. Naltrexone plus ketamine for the treatmentofmajor depressive disorder and alcohol use disorder. Alcohol Clin. Exp. Res. 42 (Suppl. 1), 236A. https://doi.org/10.1111/acer.13747.

Zanicotti, C.G., Perez, D., Glue, P., 2012. Mood and pain responses to repeat dose intramuscular ketamine in a depressed patient with advanced cancer. J. Palliat. Med. 15 (4), 400–403. https://doi.org/10.1089/jpm.2011.0314.

Zhang, J., Tian, H., Li, J., Ji, S., Chen, S., Zhu, J., Jiang, D., Wang, L., Li, G., Chen, M., Wang, W., Lin, X., Zhuo, C., 2020. Ketamine plus propofol-electroconvulsive therapy (ECT) transiently improves the antidepressant effects and the associated brain functional alterations in patients with propofol-ECT-resistant depression. Psychiatr. Res. 287, 112907 https://doi.org/10.1016/j.psychres.2020.112907 ((Zhang, Chen, Zhu, Jiang, Zhuo) Department of Psychiatric-Neuroimaging-Genetics Laboratory (PNG_Lab), Wenzhou Seventh People's Hospital, Wenzhou, Zhejiang Province 325000, China(Tian, Ji) Department of Radiology, Tianjin 4th Centre Hospital, Tianjin 30014).

Zheng, W., Zhou, Y.-L., Liu, W.-J., Wang, C.-Y., Zhan, Y.-N., Lan, X.-F., Zhang, B., Ning, Y.-P., 2020. A preliminary study of adjunctive ketamine for treatment-resistant bipolar depression. J. Affect. Disord. 275, 38–43. https://doi.org/10.1016/j.jad.2020.06.020.

Zhuo, C., Ji, F., Tian, H., Wang, L., Jia, F., Jiang, D., Chen, C., Zhou, C., Lin, X., Zhu, J., 2020b. Transient effects of multi-infusion ketamine augmentation on treatment-resistant depressive symptoms in patients with treatment-resistant bipolar depression—an open-label three-week pilot study. Brain. Behave. 10, e01674. https://doi.org/10.1002/brb3.1674 *(*Zhuo, Ji) Department of Psychiatry, School of Mental Health, Jining Medical University, Jining, China*(Zhuo, Tian, Wang, Jia) Department of Psychiatry and Imaging-Genetics and Co-morbidity (PNGC-Lab), Tianjin Anding Hospital*, Tianjin Mental Health Center.