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Review article

The effect of intravenous, intranasal, and oral ketamine in mood disorders: A meta-analysis

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ABSTRACT

Background: Ketamine is established as a rapid and effective treatment in adults with treatment-resistant depression (TRD). The availability of different formulations and routes of delivery invites the need for evaluating relative effect sizes.

Methods: Effect size with respect to depression symptom reduction for each formulation and route of delivery was compared at discrete time-points (i.e., 24 h, 2–6 days, 7–20 days, 21–28 days) in adults with TRD. A random-effects meta-analysis was conducted to evaluate the effect size across intravenous, intranasal and oral routes of administration. Analysis was also conducted evaluating the effect size of racemic ketamine to esketamine.

Results: The pooled effect size for intranasal ketamine/esketamine at 24 h was $g = 1.247$ ($n = 5$, 95% CI: 0.591–1.903, $p < 0.01$). At 2–6 days, the pooled effect size for intravenous ketamine/esketamine was $g = 0.949$ ($n = 14$, 95% CI: −0.308–2.206, $p = 0.139$). At 7–20 days, intranasal ketamine had a pooled effect size of $g = 1.018$ ($n = 4$, 95% CI: 0.499–1.538, $p < 0.01$). At 21–28 days, oral ketamine had a pooled effect size of $g = 0.633$ ($n = 2$, 95% CI: 0.368–0.898, $p < 0.01$).

Limitations: Additional comparative studies are needed with regards to the efficacy of different formulations and routes of delivery.

Conclusions: The short-term efficacy of intravenous and intranasal ketamine/esketamine for adults with TRD was established. Interpreting the efficacy of oral ketamine was limited by the need for studies with larger samples across independent sites. No conclusions regarding comparative efficacy of the disparate formulations and routes of delivery can be derived from this analysis. Direct comparative studies are needed to further inform treatment options for TRD.

1. Introduction

Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) indicate that acute remission rates are approximately 10–15% after two prior inadequate treatment trials in major depressive disorder (MDD) (Rush et al., 2006; Zisook et al., 2008). In addition to suboptimal remission rates, individuals achieving symptomatic remission with third-stage therapy are less likely to report commensurate improvements in patient reported-outcomes (PROs) (e.g., quality of life) and psychosocial function, and are more likely to

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experience relapse and treatment emergent adverse events (Rush and Jain, 2019).

Moreover, the therapeutic lag time for monoamine-based antidepressants is unacceptable to many patients, inviting the need for rapid onset treatments. Consensus exists that novel molecular targets are required in mood disorders to improve both symptomatic and PROs in MDD. Many empirically supported targets have emerged, including but not limited to, glutamate and gamma-aminobutyric acid (GABA) (Rosenblat et al., 2015; Tomasetti et al., 2019).

Evidence indicates that the dissociative anesthetic ketamine offers rapid, robust, and reproducible symptom-mitigating effects in adults with treatment-resistant depression (TRD). Available evidence also suggests a rapid reduction of suicidal ideation following a single sub-anesthetic dose of ketamine in depressed individuals (Grunebaum et al., 2018). Ketamine, a known N-methyl-D-aspartate (NMDA) antagonist, is hypothesized to reduce depressive symptoms in MDD via disparate targets (e.g., glutamatergic, opioidergic, neurotrophic) (Krystal et al., 2013).

Ketamine is hypothesized to exert its biological effects through the disinhibition of NMDA receptors expressed on inhibitory GABA interneurons (Zanos and Gould, 2018). This non-competitive receptor inhibition leads to enhanced glutamatergic activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Zanos and Gould, 2018). In turn, activation of these receptors facilitates transcription of pro-synaptogenesis proteins associated with antidepressant effects (Abdallah et al. 2016).

Extant studies in TRD have evaluated the efficacy of ketamine across different routes of administration including, but not limited to, intravenous (IV), intranasal (IN), and oral (Coyle and Laws, 2015; Fond et al., 2014; Rosenblat et al., 2019). In addition, different formulations of ketamine have been evaluated including racemic ketamine and the enantiomer esketamine (Correia-Melo et al., 2020, 2018). In March 2019, the U.S. Food and Drug Administration (FDA) approved a proprietary IN formulation of esketamine as adjunctive treatment in adults with TRD.

Several factors provide impetus for this meta-analysis: the FDA-approval of esketamine for adults with TRD; the availability of different ketamine formulations; different acquisition and implementation costs associated with available formulations; differences in pharmacokinetics (and possibly pharmacodynamics); infrastructure and resource requirements to deliver different ketamine formulations; the need for guidance with respect to effect sizes of the available routes of delivery and formulations; and the need to identify methodological differences across formulations and routes of administration in TRD.

The overarching aim of this meta-analysis is to quantify effect sizes of ketamine formulations across different routes of administration in adults with TRD.

2. Methods

2.1. Search methods for identification of trials

PubMed/MedLine and Google Scholar were searched to identify suitable articles from database inception date to June 24, 2019. The articles selected were limited to human studies (i.e., observational studies, meta-analyses, reviews) and studies written in the English language. The following combinations of search terms were used to select relevant articles: (major depressive disorder *or* MDD *or* depression *or* unipolar disorder *or* bipolar disorder *or* manic depression *or* treatment-resistant depression *or* TRD) *and* (ketamine *or* esketamine *or* s-ketamine *or* r-ketamine *or* intravenous ketamine *or* IV ketamine *or* intranasal ketamine *or* IN ketamine *or* spravato *or* oral ketamine *or* intramuscular ketamine *or* IM ketamine *or* subcutaneous ketamine *or* SC ketamine) *and* (randomized control trial *or* RCT *or* double-blind *or* placebo-controlled).

Additional relevant articles were identified using the following search terms in various combinations: randomized, controlled-trial, double-blind, ketamine, esketamine, s-ketamine, r-ketamine, depression, major depression, MDD, unipolar, bipolar disorder, manic depression, TRD, treatment resistant, and spravato. Furthermore, the reference lists of identified articles were manually searched to select additional relevant studies. Reviewers (IPC, RSM, ACC) selected the articles included in the qualitative and quantitative analysis. Articles were organized according to the PICO worksheet (Miller, 2001). Methodological quality was also assessed using the AMSTAR checklist (Shea et al., 2017). Discussion took place when there was disagreement about the inclusion of an article and consensus was reached.

2.2. Inclusion criteria

Articles were selected based on the following inclusion criteria: (i) Human studies where participants were 18 years of age or older; (ii) diagnosis of depression (i.e., unipolar or bipolar) in accordance with the Diagnostic and Statistical Manual (DSM) criteria with no restriction on edition; (iii) studies that were limited to randomized, double-blind, placebo-controlled trials; and (iv) data available at key time points of interest (i.e., 24 h, 2–6 days, 7–20 days, 21–28 days).

2.3. Exclusion criteria

Articles were excluded based on the following exclusion criteria: (i) conference abstracts, poster projects, observational studies, open-label trials, or studies that included unpublished data; (ii) multiple studies reporting from the same data set; and (iii) articles where the full-text was unavailable (i.e., abstract only).

2.4. Data extraction and statistical analysis

Towards the aim of comparing effect sizes across studies that implemented disparate rating scales, mean differences were obtained and/or calculated for each study (comparing baseline scores to scores at 24 h, 2–6 days, 7–20 days, or 21–28 days). When original articles did not report on outcomes at the points of interest, corresponding authors were contacted and provided with a request for information and up to thirty days to respond (of which none responded with actionable information).

The quantitative outcomes were later transformed into Hedge's *g* scores. Data extraction was performed by IPC using a standardized data collection form. The following information was collected: (1) study features (author names, sample size, relevant inclusion data, study length, study design, and depression scale used); (2) intervention features (ketamine dose, ketamine administration route (i.e., IV, IN, oral), and quantity of doses); (3) tolerability of the intervention (side effects listed); and (4) intervention outcomes (mean differences, or baseline and post-intervention scores, as well as a standard deviation [SD]). When studies included more than one measure of depressive symptom severity, the stated primary outcome measure was included in the analysis.

All statistical analyses were conducted using Comprehensive Meta-Analysis 3.0. A random-effects model was used to account for the predictably high between-study heterogeneity. For each study, mean differences were initially taken before being transformed into Hedge's *g* scores within the program. Effect size measures were a function of the difference between baseline scores and scores reported at the time points of interest (i.e., 24 h, 2–6 d, 7–20 d, 21–28 d). Trim-and-fill analysis did not identify any outliers when using a random effects model; consequently, no reanalysis was required.

A subgroup analysis was performed with the aim of identifying the presence of potential moderational effects of the selected time points of interest. Further exploratory meta-regression analyses were conducted with the aim of identifying whether sample size, dosing frequency, and dosage administration moderated outcomes of interest. Critical values

Table 1
Risk of bias assessment.

Study Name	Domain 1: Risk of bias arising from the randomization process	Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Domain 3: Risk of bias due to missing outcome data	Domain 4: Risk of bias in measurement of the outcome	Domain 5: Risk of bias in selection of the reported result	Domain 6 (other bias i.e., for profit)	Overall Risk of Bias
Intravenous							
Berman et al. (2000)	Low	Low	High	Low	Low	Low	Low
Chen et al. (2018)	Low	Low	Unclear	Low	Low	Low	Low
Diazgranados et al. (2010)	Low	Low	Unclear	Low	Low	Low	Low
Fan et al. (2017)	Low	Low	Low	Low	Low	Low	Low
Fava et al. (2018)	Low	Low	Low	Low	Low	Unclear	Low
Hu et al. (2016)	Low	Low	Low	Low	Low	Low	Low
Ibrahim et al. (2012)	Low	Low	Unclear	Low	Low	High	Unclear
Murrough et al. (2013)	Low	Low	Low	Low	High	High	Unclear
Murrough et al. (2015)	Low	Low	Low	Low	Low	Unclear	Low
Phillips et al. (2019)	Low	Low	Low	Low	Low	Unclear	Low
Singh et al. (2016)	Low	Low	Unclear	Low	Low	Unclear	Low
Sos et al. (2013)	Low	Low	Unclear	Low	Low	Low	Low
Su et al. (2017)	Low	Low	Low	Low	Low	High	Low
Zarate et al. (2006)	Low	Low	Unclear	Low	Low	Low	Low
Intranasal							
Canuso et al., 2018	Low	Low	Unclear	Low	Low	High	Unclear
Daly et al., 2018	Low	Low	Unclear	Low	Low	High	Unclear
Fedgchin et al. (2019a)	Low	Low	Low	Low	Low	High	Low
Lapidus et al., 2014	Low	Low	Low	Low	Low	Unclear	Low
Oral							
Arabzadeh et al. (2018)	Low	Low	Low	Low	Low	Low	Low
Domany et al. (2019)	Low	Low	Low	Low	Low	Low	Low
Jafarinia et al. (2016)	Low	Low	Low	Low	Low	Low	Low

for pooled effect sizes were set to 0.05.

Heterogeneity was calculated using the I^2 statistic. For the I^2 statistic, 25% = small, 50% = moderate, and 75% = high heterogeneity.

2.5. Assessment of bias

Study quality (such as risk of bias) was assessed for all studies using the *revised Cochrane risk-of-bias tool for randomized trials* (Sterne et al., 2019). The tool examines bias through the following six domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in the selection of the reported result, and bias arising from conflicts of interest (Sterne et al., 2019). The results of the Cochrane risk-of-bias assessments are displayed in Table 1.

Risk of publication bias was analyzed using an Egger's regression test. A trim and fit analysis found no outliers while using a random effects model.

3. Results

3.1. Search results

The initial search yielded 248 records (Table 2). Following the removal of duplicates, 144 records remained of which 41 articles were excluded following abstract review (Fig. 1). These articles were excluded if the indication for ketamine was not depressive disorders, administered in a specific population (i.e., elderly or youth), was a conference paper or study protocol, not published in English, was not double-blinded or placebo controlled, or if ketamine was administered adjunctively. From the 103 full-text articles that were assessed, 78 records were excluded due to study design (i.e., not randomized-controlled trials, double-blinded, placebo- or active-controlled, did not evaluate a depressed population), did not include standard deviation (SD), mean difference, or mean values, utilization of ketamine for primary purpose beyond mitigating depressive symptoms and/or did not have the full text available through the institutional subscription services of the University of Toronto, University Health Network, or Dalhousie University.

Included in the final qualitative analysis were twenty-five studies: the majority assessed the efficacy of IV ketamine (n = 17) (Berman et al., 2000; Chen et al., 2018; Diazgranados et al., 2010; Fan et al., 2017; Fava et al., 2018; Grunebaum et al., 2017, 2018; Hu et al., 2016; Ibrahim et al., 2012; Murrough et al., 2015, 2013; Phillips et al., 2019; Singh et al., 2016; Sos et al., 2013; Su et al., 2017; Zarate et al., 2006, 2013), some evaluated IN ketamine (n = 5), and the remainder evaluated oral ketamine (n = 3). Of the IN ketamine studies, three studies evaluated esketamine (Canuso et al., 2018; Daly et al., 2018; Fedgchin et al., 2019a), and two studies evaluated racemic ketamine (Gálvez et al., 2018; Lapidus et al., 2014). All oral ketamine studies evaluated racemic ketamine (Arabzadeh et al., 2018; Domany et al., 2019; Jafarinia et al., 2016) using a liquid oral suspension or ketamine capsules. Of note, liquid ketamine is bitter and no masking flavours were added to the liquid suspension (Domany et al., 2019). Each of the foregoing studies were included in the qualitative analysis.

Twenty-one studies (Table 3) were included in the final quantitative analysis (Arabzadeh et al., 2018; Berman et al., 2000; Canuso et al., 2018; Chen et al., 2018; Daly et al., 2018; Diazgranados et al., 2010; Domany et al., 2019; Fan et al., 2017; Fava et al., 2018; Fedgchin et al., 2019b; Hu et al., 2016; Ibrahim et al., 2012; Jafarinia et al., 2016; Lapidus et al., 2014; Murrough et al., 2013, 2015; Phillips et al., 2019; Singh et al., 2016; Sos et al., 2013; Su et al., 2017; Zarate et al., 2006). The remaining 4 studies were excluded for lack of data (i.e. no data could be extrapolated from graphs or calculated from values given). Only randomized controlled trials (RCTs) were included in the study to reduce the influence of factors outside the experimental treatment group. We could not identify SC or IM studies that had the data required for our analysis.

In cases where more than one dosage was tested within the paper, each dosage condition was evaluated as an individual submission.

3.2. Effects of intranasal versus intravenous versus oral administrations on depressive symptoms

A random effects meta-analysis revealed large and significant effects

Table 2
Summary of study characteristics, dosage, and efficacy.

Administration type	Study	Study design	Dose	Time point	*N*	Mean difference	Hedges g	Standard error	Depression outcome measure
Intravenous	Murrough et al. (2015)	Randomized, double-blind, placebo-controlled	0.5 mg/kg	24 h	12	16.2	0.369	0.279	MADRS
				2–6 d		15.9	0.408	0.281	
				7–20 d		13.5	0.355	0.278	
	Murrough et al. (2013_	Randomized, double-blind, placebo-controlled	0.5 mg/kg	24 h	47	17.89	0.873	0.169	MADRS
				7–20 d		14.75	0.215	0.145	
	Sos et al. (2013)	Randomized, double-blind, placebo-controlled	0.54 mg/kg	24 h	9	6.4	0.79	0.354	MADRS
				2–6 d		5.9	0.775	0.352	
				7–20 d		6.1	0.815	0.357	
	Su et al. (2017)	Randomized, double-blind, placebo-controlled	0.2 mg/kg	24 h	23	7.84	0.24	0.204	HAMD-6
				7–20 d		6.01	0.185	0.203	
				21–28 d		7.53	0.254	0.205	
			0.5 mg/kg	24 h	24	9.75	0.316	0.203	
				7–20 d		7.88	0.271	0.201	
				21–28 d		6.5	0.215	0.2	
	Zarate et al. (2006)	Randomized, double-blind, crossover, placebo-controlled	0.5 mg/kg	24 h	18	14.58	0.675	0.252	HDRS
				2–6 d		12.5	0.578	0.245	
				7–20 d		6.25	0.289	0.23	
	Chen et al. (2018)	Randomized, double-blind, placebo-controlled	0.2 mg/kg	24 h	8	6.86	0.361	0.327	MADRS
			0.5 mg/kg			12	0.952	0.394	
	Singh et al. (2016)	Randomized, double-blind, placebo-controlled	0.2mg/kg	2–6 d	9	16.8	1.686	0.499	MADRS
			0.4 mg/kg		11	16.9	1.598	0.44	
	Fan et al. (2017)	Randomized, double-blind, placebo-controlled	0.5 mg/kg	24 h	20	10.43	0.278	0.219	MADRS
				2–6 d		9.8	0.278	0.219	
				7–20 d		6.09	0.155	0.216	
	Hu et al. (2016)	Randomized, double-blind, placebo-controlled	0.5 mg/kg	24 h	13	10.7	0.275	0.265	MADRS
				2–6 d	12	13.8	0.408	0.281	
				7–20 d		16	0.5	0.287	
				21–28 d		18.9	0.639	0.299	
	Berman et al. (2000)	Randomized, double-blind, placebo-controlled	0.5 mg/kg	24 h	7	11	1.629	0.545	HDRS
				2–6 d		12.69	1.958	0.618	
	Fava et al. (2018)	Randomized, double-blind, placebo-controlled	0.1 mg/kg	24 h	18	3.18	0.163	0.227	HAMD
				2–6 d		2.04	0.097	0.226	
			0.2mg/kg	24 h	20	1.13	0.055	0.215	
				2–6 d		0.36	0.017	0.215	
			0.5 mg/kg	24 h	22	4.79	0.243	0.209	
				2–6 d		3.21	0.151	0.207	
			1 mg/kg	24 h	20	3.76	0.181	0.217	
				2–6 d		1.84	0.083	0.215	
	Ibrahim et al. (2012)	Randomized, double-blind, placebo-controlled	0.5 mg/kg	24 h	21	9.76	0.377	0.218	MADRS
				2–6 d		10.05	0.388	0.218	
				7–20 d		8.29	0.32	0.216	
				21–28 d		6.82	0.248	0.213	
	Phillips et al. (2019)	Randomized, double blind, crossover, placebo-controlled	0.5 mg	24 h	43	10.9	0.183	0.151	MADRS
	Diazgranados et al. (2010)	Randomized, double-blind, placebo-controlled	0.5 mg/kg	24 h	17	12.5	0.628	0.255	MADRS
				2–6 d		14.5	0.749	0.264	
				7–20 d		5.26	0.249	0.235	
Intranasal	Canuso et al. (2018)	Randomized, double-blind, placebo-controlled	84 mg	24 h	35	18.82	0.467	0.174	MADRS
				2–6 d		20.88	0.487	0.175	
				7–20 d		19.41	0.516	0.176	
				21–28 d		22.35	0.152	0.166	
	Daly et al. (2018)	Randomized, double-blind, delayed-start, placebo-controlled	28 mg	24 h	11	14.8	1.471	0.419	MADRS
				7–20 d		9.8	1.003	0.351	
			56 mg	24 h	11	15.7	1.595	0.439	
				7–20 d		12.4	1.297	0.392	
			84 mg	24 h	12	16.4	1.668	0.434	
				7–20 d		15.3	1.605	0.424	
	Lapidus et al. (2014)	Randomized, double-blind, crossover, placebo-controlled	50 mg	24 h	9	13.5	1.31	0.431	MADRS
				2–6 d	9	7.72	0.691	0.342	
	Fedgchin et al. (2019a)	Randomized, double-blind, active-controlled	56 mg	21–28 d	111	19	0.481	0.1	MADRS
			84 mg		98	18.8	0.501	0.106	
Oral	Domany et al. (2019)	Randomized, double-blind, placebo-controlled	1 mg	2–6 d	22	8.2	0.386	0.214	MADRS
				7–20 d		9.5	0.439	0.216	
				21–28 d		12.5	0.588	0.224	
	Arabzadeh et al. (2018)	Randomized, double-blind, placebo-controlled	50 mg	7–20 d	41	16.24	0.839	0.179	HDRS
				21–28 d		11.44	0.659	0.17	
	Jafarinia et al. (2016)	Randomized, double-blind, placebo-controlled	150 mg	2–6 d	20	5.53	0.398	0.224	HDRS

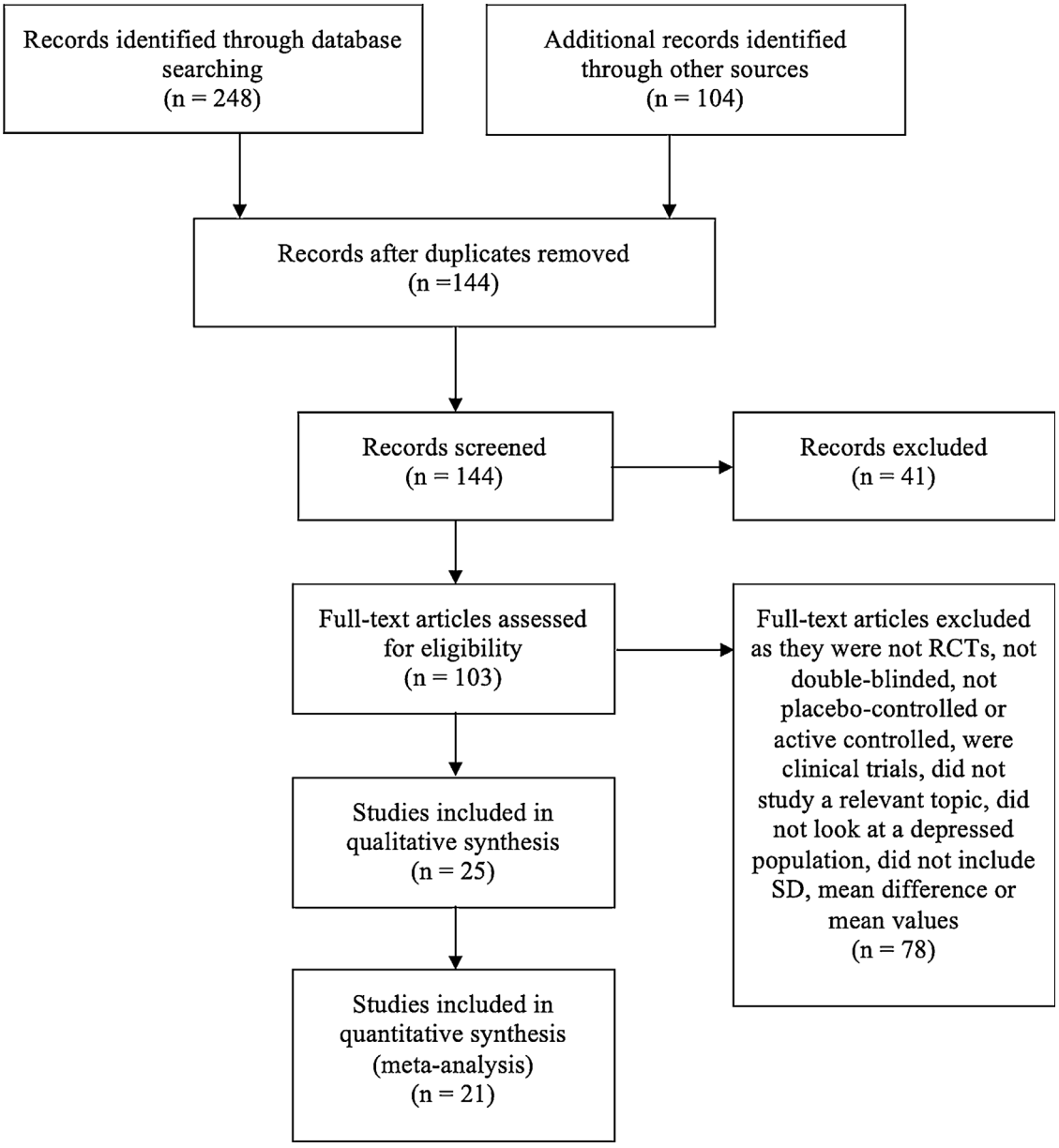

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study selection flow diagram.

for all formulations of ketamine administration (Table 4). The pooled effect sizes for IV, IN, and oral administrations over all recorded time points was $g = 0.529$ ($N = 31$, 95% CI: 0.328 to 0.729, $p < 0.01$) indicative of a moderate to large effect size (Fig. 2). The pooled effect size for IV administration was $g = 0.406$ ($N = 20$, 95% CI: 0.261 to 0.552, $p < 0.01$). The pooled effect size for IN administration was $g = 0.667$ ($N = 8$, 95% CI: 0.451 to 0.882, $p < 0.01$). The pooled effect size for oral administration was $g = 0.556$ ($N = 3$, 95% CI: 0.224 to 0.887).

At 24 hours, the IV route of administration had $g = 0.395$ ($N = 18$, 95% CI: 0.258 to 0.533, $p < 0.01$). At 2–6 days, the IV route of administration had $g = 0.949$ ($N = 14$, 95% CI: −0.308 to 2.206, $p = 0.139$). At 7–20 days, the IV route of administration had $g = 0.280$ ($N = 10$, 95% CI: 0.145 to 0.416, $p < 0.01$). At 21–28 days, the IV route of administration had $g = 0.293$ ($N = 4$, 95% CI: 0.077 to 0.509, $p < 0.01$).

At 24 h, the IN route of administration had $g = 1.247$ ($N = 5$, 95% CI: 0.591 to 1.903, $p < 0.01$). At 2–6 days, the IN route of administration had $g = 0.529$ ($N = 2$, 95% CI: 0.223 to 0.835, $p < 0.01$). At 7–20 days, the IN route of administration had $g = 1.018$ ($N = 4$, 95% CI: 0.499 to 1.538, $p < 0.01$). At 21–28 days, the IN route of administration had $g = 0.417$ ($N = 3$, 95% CI: 0.238 to 0.596, $p < 0.01$).

There was no recorded data for the 24-hour point in the oral administration category. At 2–6 days, the oral route of administration had g = 0.392 ($N = 2$, 95% CI: 0.089 to 0.694, $p = 0.01$). At 7–20 days, the oral route of administration had $g = 0.657$ ($N = 2$, 95% CI: 0.267 to 1.048, $p < 0.01$). At 21–28 days, the oral route of administration had $g = 0.633$ ($N = 2$, 95% CI: 0.368 to 0.898, $p < 0.01$).

The heterogeneity of IV studies is moderate and significant ($p = 0.015$, $I^2 = 59.74\%$). The heterogeneity of IN studies is low to moderate and significant ($p = 0.016$, $I^2 = 45.07\%$). As the oral category had a d.f. of 2, an I^2 value could not be calculated. The heterogeneity across all studies was moderate and significant ($p < 0.01$, $I^2 = 50.38\%$).

Table 3
Ovid MEDLINE search record.

#	Searches	Results
1	Exp Depression/	111367
2	Exp Depressive Disorder, Major/	28379
3	MDD.mp.	12010
4	Manic depression.mp.	374
5	Unipolar depression.mp.	2621
6	Unipolar disorder.mp.	210
7	Exp Bipolar Disorder/	39076
8	Bipolar depression.mp.	2335
9	BD.mp.	19381
10	Exp Depressive Disorder, Treatment-Resistant/	1079
11	TRD.mp.	1401
12	Exp Ketamine/	11879
13	Esketamine.mp.	84
14	s-ketamine.mp.	551
15	r-ketamine.mp.	145
16	Intravenous ketamine.mp.	536
17	IV ketamine.mp.	224
18	Intranasal ketamine.mp.	79
19	IN ketamine.mp.	653
20	Spravato.mp.	2
21	Oral ketamine.mp.	152
22	PO ketamine.mp.	6
23	Subcutaneous ketamine.mp.	31
24	SC ketamine.mp.	7
25	Intramuscular ketamine.mp	165
26	IM ketamine.mp.	62
27	Exp Randomized Controlled Trial/	489427
28	RCT.mp.	20502
29	Placebo-controlled.mp.	82750
30	Exp Double-Blind Method/	153130
31	Exp Meta-Analysis/	104541
32	MA.mp.	53352
33	Exp "Review"/	2558637
34	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	192410
35	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	12641
36	27 or 28 or 29 or 30 or 31 or 32 or 33	3194645
37	34 and 35 and 36	261
38	Limit 37 to English language	248

3.3. Effects of IV racemic ketamine versus IV esketamine on depressive symptoms

A random effects meta-analysis revealed large and significant effects for both IV racemic ketamine and IV esketamine (Table 5).

At 24 h, racemic IV ketamine had a *g* value of $g = 0.395$ ($N = 18$, 95% CI: 0.258 to 0.533, $p < 0.01$). At 2–6 days, racemic IV ketamine and IV esketamine had g values of $g = 0.355$ ($N = 12$, 95% CI: 0.173 to 0.537, $p < 0.01$) and $g = 1.637$ ($N = 2$, 95% CI: 0.990 to 2.283, $p < 0.01$). At 7–20 days, racemic IV ketamine had a g value of $g = 0.280$ ($N = 10$, 95% CI: 0.145 to 0.416, $p < 0.01$). At 21–28 days, racemic IV ketamine had a *g* value of $g = 0.293$ ($N = 4$, 95% CI: 0.077 to 0.509, $p < 0.01$).

The heterogeneity of the racemic ketamine formulation for IV administration was small and insignificant ($p = 0.314$, $I^2 = 11.713\%$). The heterogeneity of the esketamine formulation for IV administration could not be calculated due to a low quantity of studies. The heterogeneity across all IV formulations was small to moderate and significant ($p = 0.016$, $I^2 = 45.07\%$).

3.4. Effects of IN racemic ketamine versus IN esketamine on depressive symptoms

A random effects meta-analysis revealed a large but insignificant effect for IN racemic ketamine, and large and significant effects for IN esketamine (Table 6).

At 24 h, IN racemic ketamine and IN esketamine had *g* values of $g = 1.310$ ($N = 1$, 95% CI: 0.465 to 2.156, $p < 0.01$) and $g = 1.233$ ($N = 4$, 95% CI: 0.506 to 1.960, $p < 0.01$), respectively. At 2–6 days, IN racemic ketamine and IN esketamine had *g* values of $g = 0.691$ ($N = 1$, 95% CI: 0.020 to 1.362, $p = 0.044$) and $g = 0.487$ ($N = 1$, 95% CI: 0.143 to 0.830, $p < 0.01$). At 7–20 days, IN esketamine had a *g* value of $g = 1.018$ ($N = 4$, 95% CI: 0.499 to 1.538, $p < 0.01$). At 21–28 days, esketamine had a *g* value of $g = 0.417$ ($N = 3$, 95% CI: 0.238 to 0.596, $p < 0.01$).

The heterogeneity of the esketamine formulation for IN administration was moderate to high, and significant ($p = 0.014$, $I^2 = 62.54\%$). The heterogeneity of the racemic ketamine formulation for IN administration could not be calculated due to a low quantity of studies. The heterogeneity across all IN formulations was high and significant ($p = 0.015$, $I^2 = 59.74\%$).

4. Discussion

Herein, we replicate other meta-analytic studies by observing a significant overall antidepressant effect of disparate ketamine formulations (i.e., notably IV and IN) in the treatment of adults with TRD (Han et al., 2016; Zheng et al., 2020). To our knowledge, this is the first meta-analysis to contemporaneously evaluate effect-sizes across routes of delivery and formulations. Unfortunately, we are not able to arrive at any comparative efficacy claims as a consequence of the significant heterogeneity across studies. We also note that a recent underpowered study comparing IV ketamine to esketamine demonstrated non-inferiority of the two formulations with respect to depression symptom improvement as well as dissociation risk (Correia-Melo et al., 2020).

It was observed that the effect-size was greatest for IV ketamine at 2–6 days while for IN esketamine was greatest at 24 h. The difficulty in interpreting this result, however, is that most IV ketamine studies are single infusion studies whilst for IN ketamine, they are repeat-dose studies. Moreover, in several esketamine studies, a concomitant antidepressant was initiated with esketamine.

We also observed that oral ketamine had demonstrated efficacy notably at 21–28 days. We had previously reported in a separate meta-analysis that oral ketamine had yet to establish rapid and robust antidepressant effects; it can be conjectured that the benefits of oral ketamine are increasingly apparent with multiple doses across several weeks perhaps reflecting accumulated bioavailability (Peltoniemi et al., 2016). It is also worth noting that two of the studies which reported oral ketamine with significant effect sizes were conducted at the same center; it would be important to replicate these findings with oral ketamine at other centers (Arabzadeh et al., 2018; Jafarinia et al., 2016).

Interpreting the study results requires caution with respect to

Table 4
Effects of INl versus IVs versus oral administrations on depressive symptoms, combining esketamine and racemic ketamine.

	IV administration	IN administration	Oral administration	Pooled sample size IV	Pooled sample size IN	Pooled sample size oral
24 h	0.395 ($N = 18$)	1.247 ($N = 5$)	N/A	350	78	N/A
2–6 days	0.949 ($N = 14$)	0.529 ($N = 2$)	0.392 ($N = 2$)	216	44	42
7–20 days	0.280 ($N = 10$)	1.018 ($N = 4$)	0.657 ($N = 2$)	203	69	63
21–28 days	0.293 ($N = 4$)	0.417 ($N = 3$)	0.633 ($N = 2$)	80	244	63
Pooled within Category	0.406 ($N = 20$)	0.667 ($N = 8$)	0.556 ($N = 3$)	849	435	168
Combined	0.529 ($N = 31$)			1452		

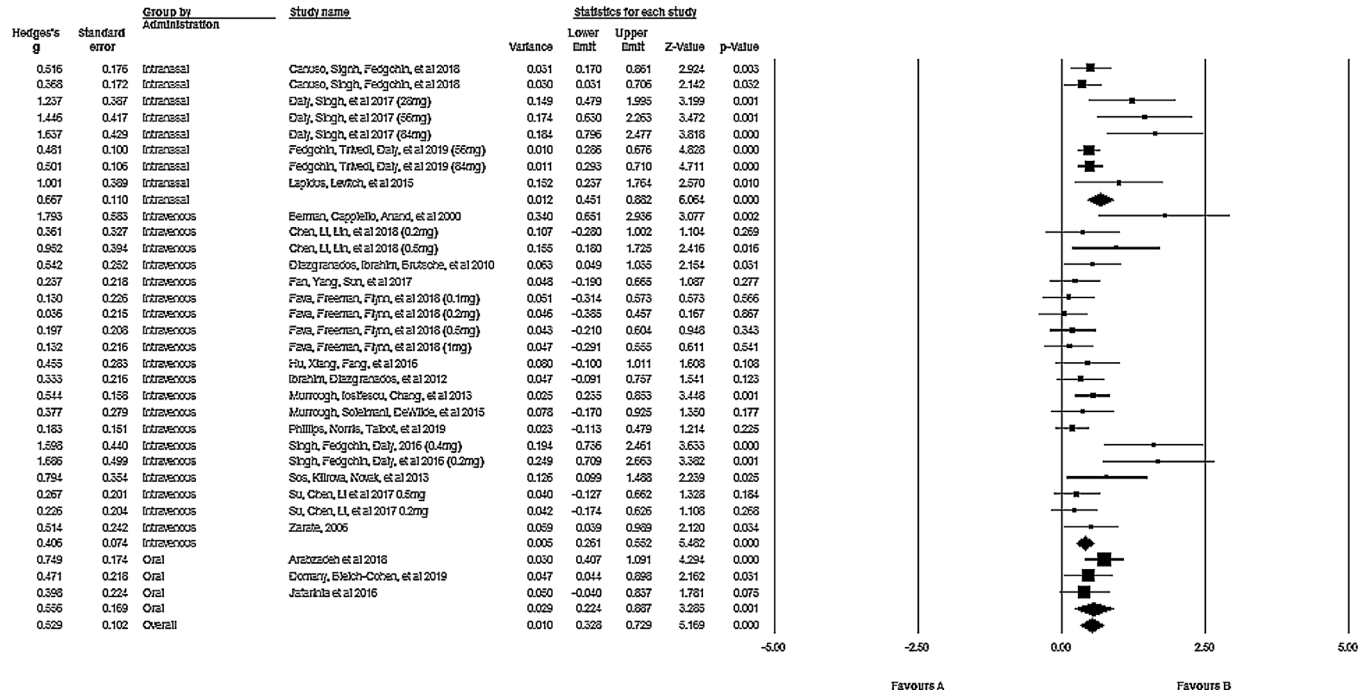

Fig. 2. Forrest plot for all studies included, grouped by administration. Squares plot effect size of individual studies, diamonds plots summary measures of each formulation and overall findings.

Table 5
Effects of IV racemic ketamine versus IV esketamine on depressive symptoms.

	IV Racemic Ketamine	IV Esketamine
24 h	0.395 (N = 18)	N/A
2–6 days	0.355 (N = 12)	1.637 (N = 2)
7–20 days	0.280 (N = 10)	N/A
21–28 days	0.293 (N = 4)	N/A
Pooled effect sizes	0.333 (N = 18)	1.637 (N = 2)

Table 6
Effects of IN racemic ketamine versus IN esketamine on depressive symptoms.

	IN Racemic Ketamine	IN Esketamine
24 h	1.310 (N = 1)	1.233 (N = 4)
2–6 days	0.691(N = 1)	0.487 (N = 1)
7–20 days	N/A	1.018 (N = 4)
21–28 days	N/A	0.417 (N = 3)
Pooled effect sizes	0.945 (N = 1)	0.728 (N = 3)

heterogeneity across the studies included in this meta-analysis. For example, there is heterogeneity with respect to sample composition (e.g., sociodemographics), illness characteristics, definitions of treatment resistance, histories of prior modalities of therapy, rating instruments employed, and frequency of administration. Additionally, studies evaluating IN ketamine administered IN ketamine on a repeat basis, while most studies with IV ketamine were single-infusion studies.

The extant studies were highly variable in their timepoints of measuring efficacy. We took a pragmatic approach and used time intervals in an attempt to have parsimony in comparing formulations and routes of delivery. Additionally, alleviation of depression was not the primary outcome in all studies included in our analysis. For example, some studies primarily evaluated the effect of ketamine on suicidality with depression as a secondary outcome. Moreover, we confine our analysis of efficacy to depression symptom reduction and did not look at other relevant outcome measures (e.g., suicidality, functional improvement, workplace productivity) that should be included in any comprehensive assessment of a treatment's overall benefit in mood disorders. The analysis also did not attempt to assess relative tolerability and safety across the different ketamine formulations, which may affect reported efficacy.

Standards of care with respect to ketamine administration in mood disorders have been published on behalf of the American Psychiatric Association (Sanacora et al., 2017). There is a need to refine best practices with respect to ketamine administration and appropriate patient selection in clinical practice. In addition, questions remain with respect to which route of administration and formulation are most effective at select timepoints, and which formulations/routes of administration are most safe and cost-effective is also uncertain. Moreover, our analysis was not able to address the question of ketamine formulation efficacy as a function of its sequence in treatment. That is, we are unable to determine whether individuals who initiated treatment with IV ketamine and then transitioned to another formulation (e.g., IN, PO) exhibit differential therapeutic and/or cost outcomes.

The FDA requires that the recently approved esketamine be administered only in settings capable of implementing a Risk Evaluation and Mitigation Strategy (REMS). Although not mandated by the FDA due to its off-label use, it is also recommended that individuals receiving IV ketamine be observed for up to 60 to 120 minutes for safety surveillance. Cost analysis will need to consider FDA mandated REMS in the case of branded esketamine, as well as best practices safety surveillance and infrastructure requirements for IV ketamine.

In conclusion, the results of our meta-analysis support the efficacy of IV (racemic, esketamine), IN (racemic, esketamine), and oral (racemic) ketamine formulations in adults with TRD. A head-to-head adequately powered controlled study comparing IV and IN ketamine is warranted and would inform the question we are addressing (i.e., efficacy). Indeed, such a study could also potentially inform relative safety and tolerability, patient acceptability, adherence, and cost-effectiveness.

5. Limitations

This analysis should be considered within the context of several

limitations. The included trials used different ranges of time in order to evaluate antidepressant effects of the medication. Although ketamine is viewed as a rapid-acting antidepressant, this analysis had to use date ranges as the outcome variables to accommodate the differences between trials. In addition, data was unavailable at certain timepoints depending on the formulation or delivery method. Moreover, TRD has not been systematically defined, and therefore individual trials decided on appropriate definitions of treatment-resistance within their sample, which may not be representative of the population. Although existing data has established the use of ketamine within the context of clinical trials, there remains a paucity of data for the effectiveness of ketamine in community-based samples. Comparative studies are needed to reach definitive conclusions with regards to the efficacy of different formulations and routes of delivery.

6. Conclusions

Herein, the short-term efficacy of intravenous and intranasal ketamine/esketamine for adults with TRD was established. Interpreting the efficacy of oral ketamine was limited by the need for studies with larger samples across independent sites. No conclusions regarding comparative efficacy of the disparate formulations and routes of delivery can be derived from this analysis. Direct comparative studies are needed to further inform treatment options for TRD.

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Authorship Contribution Statement

RSM contributed to the overall design, article selection and review, and manuscript preparation. IPC contributed to article selection and review, manuscript preparation, data extraction, data analysis, and plot/table creation. JDR contributed to the overall design, article selection and review, and manuscript preparation. All other authors contributed to the review, manuscript preparation, editing and submission.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.06.050.

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