AKADÉMIAI KIADÓ

Journal of Psychedelic Studies

6 (2022) 3, 176–187

DOI:
10.1556/2054.2022.00234

SYSTEMATIC REVIEW, META-ANALYSIS

Registered clinical trials investigating ketamine and esketamine for treatment-resistant depression: A systematic review

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Received: September 8, 2022 • Revised manuscript received: November 20, 2022 • Accepted: November 28, 2022

ABSTRACT

Background and Aims: Ketamine and esketamine have garnered interest in both psychiatric research and clinical practice for treatment-resistant depression (TRD). In this review, we examined registered trials investigating the therapeutic use of ketamine or esketamine for TRD, with the aim of characterizing emerging trends and knowledge gaps. *Methods:* The ClinicalTrials.gov electronic registry and results database was queried from inception to February 5, 2022, adhering to elements of the PRISMA guideline, we evaluated trial eligibility in the qualitative synthesis. Data regarding study design, drug regimens, and measures were subsequently abstracted and descriptively analyzed. *Results:* The search returned 86 records, of which 56 trials were included in the final review. The number of trials investigating ketamine and esketamine for TRD increased since 2008, with higher peaks observed in 2015 (n = 9) and 2021 (n = 9). Most trials were Phase 2 (13, 23.2%) or Phase 3 (11, 19.6%), gathering preliminary data on efficacy and/or further data on safety and efficacy with variant dosing and pharmacological approaches. By and large, trials examined ketamine and esketamine as individual versus combination treatments (45% and 25%, respectively). The Montgomery-Asberg Depression Rating Scale (MADRS) was most commonly used to assess clinical outcomes (75%). *Conclusions:* There are increasingly large-scale and late-phase trials of esketamine over ketamine for TRD, coupled with efforts to centralize evidence on these medications. Yet several trials do not assess patient characteristics that may affect treatment response, such as age, sex, and race. By understanding these design limitations, scientists and clinicians can avoid research waste and funding bodies can judiciously direct support towards high priority research.

KEYWORDS

ketamine, esketamine, treatment-resistant depression, antidepressant, clinical trials, systematic review

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INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychiatric conditions in the United States (US), and a leading cause of years lived with disability (YLD) worldwide (Johnston, Powell, Anderson, Szabo, & Cline, 2019; NIMH, 2022). First-line treatment for MDD is generally comprised of monoaminergic antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (NIMH, 2022). However, even when optimally delivered, up to 67% of patients show clinical non-response, a subset of whom progress to a chronic refractory state (Johnston et al., 2019; Warden, Rush, Trivedi, Fava, & Wisniewski, 2007). Moreover, each treatment failure is associated with a decline in successful intervention experience. A study evaluating the trajectory of antidepressant response to treatment found remission rates, based on a standard depression inventory, of 36.8, 30.6, 13.7, and 13.0% for the first, second, third, and fourth acute treatment steps, respectively (Rush et al., 2006). Furthermore, those who required additional treatment steps demonstrated higher relapse rates, even when benefit was eventually noted (Rush et al., 2006). Treatment-resistant depression (TRD) is characterized as failure to respond to two or more antidepressant trials of adequate dose and duration, aimed at treating the current depressive episode (Hough, 2019; Ionescu, Rosenbaum, & Alpert, 2015). The prevalence of TRD among patients with MDD is estimated at 30%, disproportionally accounting for MDD's burden of disease (Amos et al., 2018; Ionescu et al., 2015; Rush et al., 2006). Importantly, patients with TRD have an all-cause mortality rate that is 7–16 times higher than those responsive to first-line treatments (Brenner, Reutfors, Nijs, & Andersson, 2021).

At present, few interventions exist for TRD (Ionescu et al., 2015). Several pharmacotherapy regimens are thus used in clinical practice including switching or combining antidepressants as well as augmentation with second-generation antipsychotics or lithium (Ionescu et al., 2015; Luan, Wan, Wang, Li, & Zhang, 2017; NIMH, 2022). Olanzapine, an atypical antipsychotic, combined with fluoxetine is specifically indicated for TRD; though, this combination can produce undesired side effects, such as weight gain and extrapyramidal symptoms (i.e., tremors or involuntary muscle contraction) (Moser, 2018; Sanacora, Treccani, & Popoli, 2012). Further, most oral antidepressants take several weeks to initiate symptom improvement, resulting in considerable increased risk for suicidal behavior and mortality in the interim (Machado-Vieira et al., 2010; NIMH, 2022). Non-pharmacological treatment for TRD includes somatic therapies, namely transcranial magnetic stimulation (TMS), in addition to electroconvulsive therapy (ECT) and deep brain stimulation (DBS) (Cusin & Dougherty, 2012; Dandekar, Fenoy, Carvalho, Soares, & Quevedo, 2018; Li, Cui, Li, Liu, & Chen, 2021). However, TMS, ECT, and DBS are time-intensive and costly, with each carrying significant limitations (Cusin & Dougherty, 2012). First, TMS is not fully supported by trials on TRD, with small sample sizes, variable treatment schedules, and high drop-out rates (Cusin & Dougherty, 2012). Second, ECT, despite its efficacy, is linked to acute cognitive deficit as well as amnesia (Cusin & Dougherty, 2012). Finally, DBS is an experimental surgical procedure associated with substantial risk and slow onset of action to relieve depressive symptoms (Cusin & Dougherty, 2012). Taken together, there is a serious unmet need for novel, rapid-acting treatments for patients with TRD who may be at imminent risk of suicidal ideation (Hasin et al., 2018; Jakuszkowiak-Wojten et al., 2019; Kim, Farchione, Potter, Chen, & Temple, 2019).

Ketamine, which was first approved by the US Food and Drug Administration (FDA) in 1970 as an anesthetic and analgesic agent, has been increasingly used as an off-label treatment for psychiatric disorders when delivered at low doses (Sanacora et al., 2017). The drug is a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors, and a 1:1 racemic mixture of its *S*- and *R*-enantiomers (Kim et al., 2019; Sanacora et al., 2017). Compared to the *R*-enantiomer, the *S*-enantiomer binds to the NMDA receptor with greater affinity and has stronger anesthetic and analgesic action, producing less lethargy and cognitive impairment (Agboola, Atlas, Touchette, Fazioli, & Pearson, 2020). Common reported physiological effects of ketamine include dissociation, changes in sensory perception, and slight increases in blood pressure (Szarmach, Cubała, Włodarczyk, & Wiglusz, 2019; Zanos & Gould, 2018). Ketamine can be administered through various routes; however, most research to date is on intravenous (IV) infusions, with dose ranges of 0.5–1.0 mg kg^{-1} over 40–60 min (Andrade, 2017; R. S. McIntyre et al., 2021). Of significance, the bioavailability (BA) of ketamine is a function of the route of administration (i.e., IV: BA = 100%, intramuscular (IM): BA = 90–95%, intranasal (IN): BA = 30–50%, oral: BA = 10–20%) (R. S. McIntyre et al., 2021).

While ketamine is administered off-label for psychiatric disorders, the *S*-enantiomer (esketamine) was synthesized into a prescription nasal spray by Janssen Pharmaceuticals, gaining FDA approval in March of 2019 for adults with TRD (Agboola et al., 2020; Janssen, 2019; Kim et al., 2019). This represented the first novel treatment for the condition since the advent of SSRIs in 1987. In terms of efficacy, a meta-analysis of four phase 3 randomized controlled trials (RCTs) on esketamine (initiated with an oral antidepressant) and TRD reported significant pooled risk ratios for response (RR = 1.40 $P < 0.0001$) and remission (RR = 1.45, $P < 0.0001$) compared to an oral antidepressant alone (Papakostas et al., 2020). Moreover, in a longer-term, randomized withdrawal study, esketamine reduced the risk of relapse by 51 and 70% among stable remitters and responders, respectively (Daly et al., 2019). In regard to, there have been several trials demonstrating its short-term efficacy for TRD (Murrough et al., 2013; Newport et al., 2015; Singh et al., 2016). A recent meta-analysis found that patients given a single ketamine infusion experienced rapid reduction in depressive symptoms during the first 24 h, with effects decreasing at seven days post-infusion (Marcantoni et al., 2020). These findings are especially pertinent to individuals requiring immediate intervention, as in the case of concurrent, active suicidality.

The literature on ketamine and esketamine for TRD is promising, yet there remain urgent questions regarding their comparative and long-term safety and efficacy, as well as patient suitability (R. S. McIntyre et al., 2021). Additionally, there are uncertainties around the infrastructure and personnel required for safe use, the appropriate setting for administration, and the dosing schedule for continued treatment (R. S. McIntyre et al., 2021; Sanacora et al., 2017). These concerns are further magnified by the rapid increase in healthcare providers who have introduced ketamine and esketamine into their scope of practice, despite the lack of real-world, evidence-based practice guidelines (R. S. McIntyre et al., 2021; Thielking, 2018; Wilkinson, Howard, & Busch, 2019; Wilkinson et al., 2017).

Given that trials frequently take years to conclude, publish results, and translate findings to clinical care, we chose to systematically investigate registered trials of ketamine and esketamine for TRD. This review aims to characterize pipeline trends, identify strengths and gaps in study design, and inform resource allocation. It also seeks to supplement existing knowledge on these medications published in the literature (Agboola et al., 2020; McIntyre et al., 2020; R. S. McIntyre et al., 2021; Papakostas et al., 2020).

METHOD

We performed a systematic review combining elements from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline with methods for examining ongoing trials of serotonergic and classical psychedelics in psychiatric research (Peyrovian et al., 2020; Shamseer et al., 2015; Siegel et al., 2021). The review protocol was registered *a priori* through the Open Science Framework (Center for Open Science), which can be accessed via the digital object identifier (DOI): 10.17605/OSF.IO/BM6V4. Trial records were identified by searching the publicly available electronic database, ClinicalTrials.gov, operated by the U.S. National Library of Medicine (NLM) at the National Institute of Health (NIH). The query was executed from inception (i.e., establishment of the database) to February 5, 2022, using the following search string: ((“ketamine” [other terms] OR “esketamine” [other terms]) AND (“treatment-resistant depression” [condition or disease])). No publication date nor language restrictions were applied.

Inclusion criteria consisted of a) patients diagnosed with TRD of any age and biological sex, per trial eligibility criteria; b) ketamine or esketamine investigated as a primary intervention, either mechanistically (basic science) and/or therapeutically (treatment); c) non-randomized or randomized trials (Early Phase through Phase 4) that had concluded (status: “completed”), were active or active plus recruiting (status: “recruiting”, “enrolling by invitation”, or “active, not recruiting”), or were preparing for recruitment (status: “not yet recruiting”); and d) records posted in the English language. Trials failing to meet full inclusion criteria and/or were specified as “unknown”, “suspended”, “terminated”, or “withdrawn” were excluded.

Search results were independently screened by two authors (M.S. and S.C.) who examined titles (“official title”) and abstracts (“brief summary”). Relevant trials were subsequently identified for full text screening and assessed for eligibility. Discrepancies were resolved by discussion and involvement of a third member (M.B.) of the research team, as applicable. Data was then extracted from eligible trials, including: condition/disease, intervention/treatment, study population, groups/cohorts, study type and phase, target enrollment, estimated start and end date, allocation, interventional model, masking, outcome measures, drug regimen, sample characteristics, results, location, and funder type/sponsor. Following extraction of pertinent parameters, data were descriptively analyzed using STATA 16 (StataCorp, 2019).

RESULTS

The initial search returned 86 records in ClinicalTrials.gov. Of these, 56 met criteria for inclusion in the final review (35% excluded) (Fig. 1). The number of trials investigating ketamine and esketamine for TRD increased since 2008, with higher peaks in 2015 ($n = 9$) and 2021 ($n = 9$) (Fig. 2). Most trials were Phase 2 (13, 23.2%) or Phase 3 (11, 19.6%), gathering preliminary data on efficacy and/or further data on safety and efficacy with variant dosing and pharmacological approaches (Table 1, Fig. 3).

By and large, trials investigated ketamine or esketamine as sole therapeutics (ketamine: 25 [45%], esketamine: 14 [25%]). The overwhelming majority were interventional in nature (91%), with a small number of mechanistic trials (9%) (Table 1). Others evaluated them as combination therapies (ketamine: 12 (21%), esketamine: 5 (9%)). In ketamine trials, this included clonidine (sedative, antihypertensive), lithium (mood stabilizer), brexpiprazole (atypical antipsychotic), and permpanel (antiepileptic) as well as TMS, ECT, cognitive behavioral therapy (CBT), and music therapy. Several routes of administration were employed, spanning IV (28, 76%), IN (6, 16%), and IM (1, 3%) (Supplementary Table S2). Two (5%) trials had unknown routes for ketamine administration. Comparatively, in esketamine trials, only oral antidepressants were used as a combination treatment. The IN administration route was leveraged most often for esketamine (17, 89%), except for two (11%) trials that utilized IV infusion.

To assess outcomes of ketamine or esketamine treatment, 22 (39%) trials used subjective measures, 3 (5%) used objective measures, and 31 (55%) employed both (Table 1). Of the trials utilizing subjective measures, the following were most prevalent: Montgomery–Åsberg Depression Rating Scale (MADRS; 42, 75%), Clinical Global Impressions Scale (CGI; 21, 38%), Patient Health Questionnaire-9 (PHQ-9; 12, 21%), European Quality of Life Five Dimension (EQ-5D-5L; 11, 20%), Clinician-Administered Dissociative States Scale (CADSS; 10, 18%), Generalized Anxiety Disorder-7 (GAD-7;

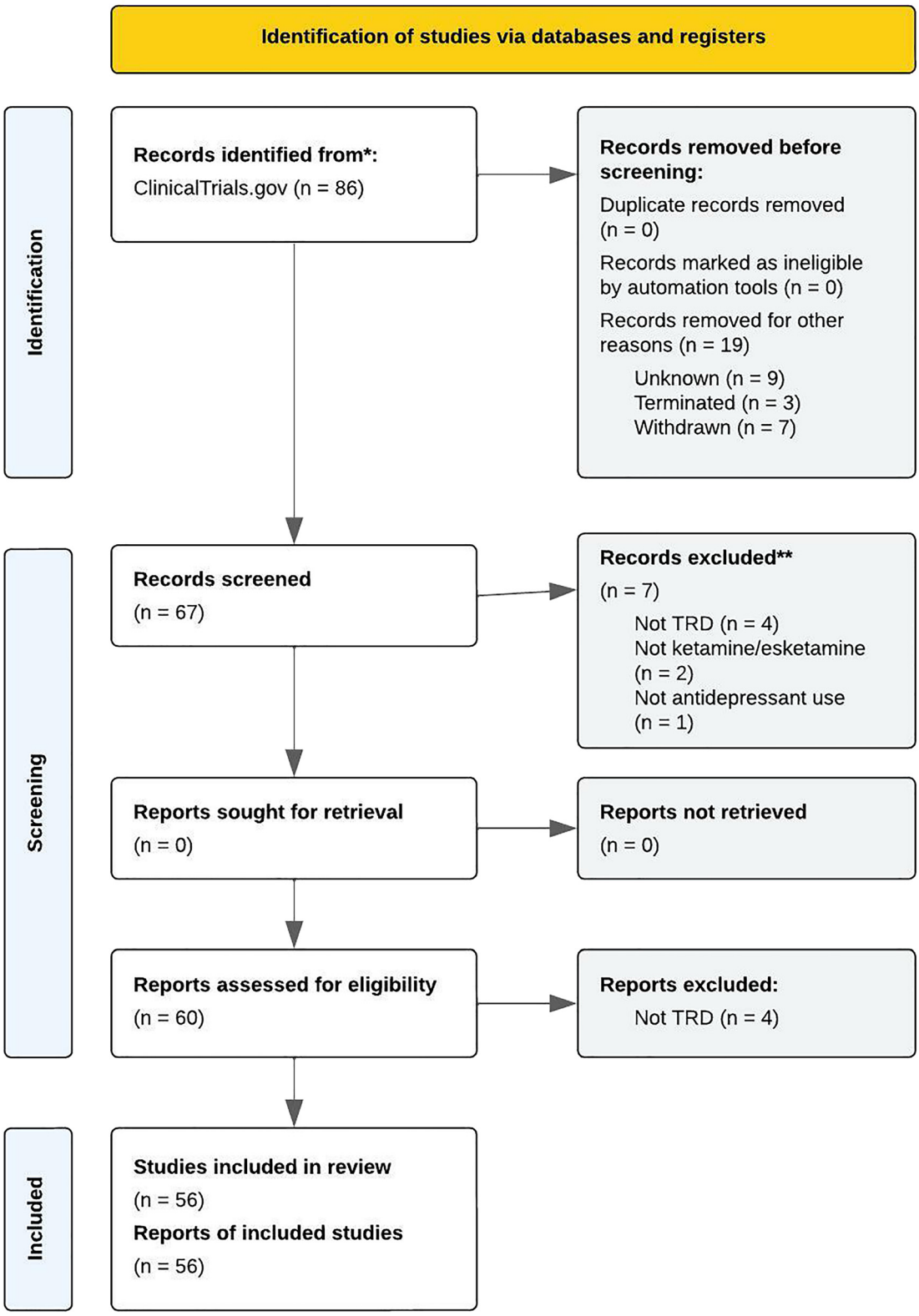

Fig. 1. PRISMA flow diagram

9, 16%), Columbia Suicide Severity Rating Scale (CSSRS; 8, 14%), Sheehan Disability Scale (SDS; 8, 14%), Hamilton Depression Rating Scale (HAM-D; 7, 13%), and Quick Inventory of Depression Symptomatology (QIDS; 5, 9%) (Supplementary Table S2). There were additionally 5 (8.9%) trials that leveraged neuroimaging techniques, including magnetic resonance spectroscopy, magnetic resonance imaging, and functional magnetic resonance imaging (Table 1).

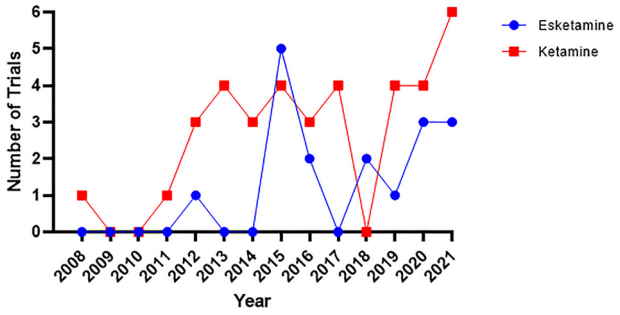

Fig. 2. Number of new trials initiated each year investigating esketamine or ketamine for TRD

No trials were exclusive based on sex, and the majority enrolled adults and/or older adults (36, 64.3%) (Table 1). Target trial enrollment ranged from 9 to 1,148 participants (Table 2). The largest number of estimated or actual participants in esketamine trials were enrolled in randomized, parallel assignment, Phase 3 trials among adults and/or older adults. The majority of participants in ketamine trials were enrolled in trials with the same characteristics as esketamine trials with majority enrollment except for the study phase. Most participants enrolled in ketamine trials were enrolled in Phase 2 trials or those wherein phase was not applicable (i.e., observational).

Sponsor type varied across trials included in this review, with 26 (46.4%) university sponsored, 20 (35.7%) industry sponsored, 4 (7.1%) federally-sponsored, and 6 (10.7%) sponsored by other organizations. Moreover, the majority of trials were single site and located in the US (30, 53.6%). Other single site locations included Canada (4, 7.1%), Austria (2, 3.6%) Poland (2, 3.6%), Japan (1, 1.8%), Mexico (1, 1.8%), Taiwan (1, 1.8%), and England (1, 1.8%). The remaining 14 (25%) trials were multiple site (Table 1).

Table 1. Characteristics of trial records

Characteristics	*n* (%)	Characteristics	*n* (%)
Therapy		*Intervention model*	
Esketamine	14 (25.0)	Parallel	31 (55.4)
Esketamine combination	5 (8.9)	Single Group	20 (35.7)
Ketamine	25 (44.6)	Crossover	4 (7.1)
Ketamine combination	12 (21.4)	Sequential	1 (1.8)
Sex		*Masking*	
Inclusive	56 (100)	Single	3 (5.4)
Age group		Double	14 (25)
Child/adolescent (<18)	2 (3.6)	Triple	5 (8.9)
Adult (18–64)	16 (28.6)	Quadruple	9 (16.1)
Adult/older adult (18++)	36 (64.3)	None	25 (44.6)
Older adult (>64)	2 (3.6)	*Data monitoring committee*	
Primary purpose		Monitoring committee	26 (46.4)
Treatment	51 (91.1)	No monitoring committee	30 (53.6)
Basic Science	5 (8.9)	*Neuroimaging methods*	
Study type		Neuroimaging	5 (8.9)
Interventional	48 (85.7)	No neuroimaging	51 (91.1)
Observational	6 (10.7)	*Site location (country)*	
Patient Registries	1 (1.8)	United States	30 (53.6)
Expanded Access	1 (1.8)	Canada	4 (7.1)
Study phase		Austria	2 (3.6)
Early phase I	1 (1.8)	Poland	2 (3.6)
Phase I	3 (5.4)	Japan	1 (1.8)
Phase I/II	1 (1.8)	Mexico	1 (1.8)
Phase II	13 (23.2)	Taiwan	1 (1.8)
Phase II/III	2 (3.6)	United Kingdom	1 (1.8)
Phase III	11 (19.6)	Multisite	14 (25.0)
Phase IV	8 (14.3)	*Sponsor type*	
Not applicable	17 (30.4)	Academic	26 (46.4)
Study status		Industry	20 (35.7)
Completed	32 (57.1)	Federal	4 (7.1)
Recruiting	15 (26.8)	Other	6 (10.7)
Enrolling by Invitation	1 (1.8)	*Results posted*	
Active – Not Recruiting	4 (7.1)	Results	20 (35.7)
Approved for Marketing	1 (1.8)	No results	36 (64.3)
Not Yet Recruiting	3 (5.4)	*Publications*	
Allocation		Publications	32 (57.1)
Randomized	34 (60.7)	No publications	24 (42.9)
Non-randomized	2 (3.6)		
Not applicable	20 (35.7)		

DISCUSSION

Registered trials of ketamine and esketamine for TRD revealed critical trends in the research pipeline. Compared to ketamine, there are more large-scale and late-phase trials investigating esketamine for TRD. This reflects the time period initiated in 2015 of large Phase 3 trials on esketamine, which are included in this review, leading to the FDA approval of esketamine for TRD in 2019 (FDA, 2019b). However, due to economic factors and patent law in the pharmaceutical industry, it is unlikely that such trials on ketamine will be conducted (Sanacora et al., 2017). Ketamine's expired patent is specifically unprofitable for pharmaceutical companies to conduct further research under, given its anesthetic and analgesic use for over half a century (Wei, Chang, & Hashimoto, 2020). Without large-scale trials to provide data on safety and efficacy, as required by the FDA, a TRD indication for ketamine will likely not be subject to FDA review (FDA, 2019a). Hence, there are major knowledge gaps surrounding the acute and maintenance use of ketamine for this condition (R. S. McIntyre et al., 2021; Sanacora et al., 2017).

Furthermore, there is a paucity of research on combination approaches to ketamine, namely with psychotherapy. This is otherwise known as ketamine-assisted psychotherapy (KAP). As a prototypical psychoplastogen, ketamine has been shown to rapidly promote structural and functional neuroplasticity, which may enhance (or be enhanced by) the

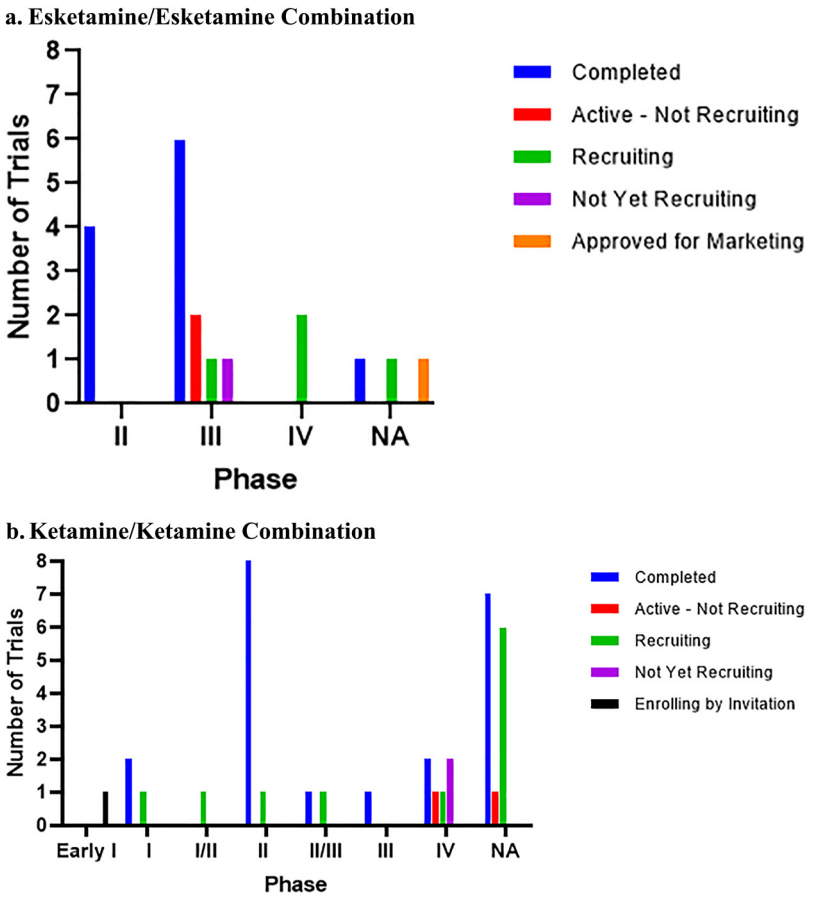

Fig. 3. Number of new trials initiated each year investigating esketamine or ketamine for TRD by study phase. NA, not applicable (i.e., observational study). a. Esketamine/Esketamine Combination. b. Ketamine/Ketamine Combination

effects of psychotherapy to maximize treatment outcomes (Joneborg et al., 2022; Olson, 2018). The formation of new neural connections, restructuring of thought patterns, and promotion of emotional learning are potential mechanisms of behavior change within this context (Drozdz et al., 2022; Hasler, 2020). Additionally, ketamine may enhance treatment adherence and patient engagement, carrying high capacity as a psychotherapeutic adjunct (Drozdz et al., 2022). In clinical practice, KAP often comprises preparatory therapy, the ketamine experience, and integration therapy; however, several approaches exist and are being explored. One method is administering a low dose ketamine prior to psychotherapy as a way of decreasing fear and resistance to exploring psychological material (Dore et al., 2019). Of the trials included in this review, one trial that utilized CBT following IV ketamine to sustain antidepressant effects, a current primary goal in the field (R. S. McIntyre et al., 2021; S. Wilkinson, 2020). Yet, no trials utilized ketamine prior to or during therapy. More open-label, pilot, and randomized trials are thus warranted to determine whether ketamine and psychotherapy act synergistically, are efficacious together, and are superior to ketamine alone. Future trials should also examine these questions at variant dosing schedules to best capture response rates and durability (Drozdz et al., 2022).

Descriptive analyses further revealed important gaps in demographic and clinical characteristics. Patients with TRD have increased rates of psychiatric comorbidity, the most common being anxiety, substance use, post-traumatic stress disorder (PTSD), personality disorders, and non-organic psychosis (Abdallah et al., 2019, 2022; Huang et al., 2020). In this review, only one trial clearly examined ketamine for TRD with a psychiatric comorbidity, PTSD (Albott et al., 2018). Thus, more definitive trials investigating the safety and efficacy of these mediations in TRD with psychiatric comorbidities are needed.

Importantly, there is limited knowledge regarding age- and sex-specific response to ketamine and esketamine (Benitah et al., 2022; Di Vincenzo et al., 2021). The majority of trials in this review enrolled adults (18 + years of age), per eligibility criteria, while only two trials examined ketamine for adolescents (12–19 years of age) and two trials examined ketamine or esketamine for older adults (>64 years of age) (Doty et al., 2021; Lenze, 2020; Mu-Hong, 2021; Roy et al., 2021). Conversely, trials were not exclusive based on sex; however, it is unclear whether the investigators plan to evaluate sex differences and/or have the statistical power to do so. These are noteworthy considerations, as pre-clinical data suggests the underlying mechanisms ketamine's antidepressant response could be differential based on sex (Herzog, Wegener, Lieb, Müller, Treccani, 2019; Ponton, Turecki, & Nagy, 2022; Wright, 2018). Although, at this time, few published studies have directly investigated sex

Table 2. Enrollment based on trial characteristics

	Esketamine/Esketamine combination					Ketamine/Ketamine combination				
All trials	Trials (n = 19) n (%)	Participants				Trials (n = 37) n (%)	Participants			
		Median	Minimum	Maximum	Sum		Median	Minimum	Maximum	Sum
Age group										
Child/adolescent	–	–	–	–	–	2 (5)	34	14	54	68
Adult	9 (47)	202	30	719	2,011	7 (19)	36	9	110	341
Adult/older adult	8 (42)	320	10	1,148	3,383	26 (70)	31	9	400	1,445
Older adult	1 (5)	139	139	139	139	1 (3)	30	30	30	30
Primary purpose										
Treatment	18 (95)	196	10	1,148	5,533	31 (84)	33	9	400	1,685
Basic Science	–	–	–	–	–	5 (14)	36	9	70	199
Study Type										
Interventional	17 (89)	202	30	1,148	5,523	31 (84)	30	9	400	1,570
Observational	1 (5)	10	10	10	10	5 (14)	60	13	120	314
Patient Registries	–	–	–	–	–	1 (3)	NA	NA	NA	NA
Expanded Access	1 (5)	NA	NA	NA	NA	–	–	–	–	–
Study Phase										
Early phase I						1 (3)	20	20	20	20
Phase I	–	–	–	–	–	3 (8)	10	16	24	60
Phase I/II	–	–	–	–	–	1 (3)	70	70	70	70
Phase II	4 (21)	98	30	202	428	9 (24)	60	9	99	465
Phase II/III	–	–	–	–	–	2 (5)	205	9	400	409
Phase III	10 (53)	299	30	1,148	4,385	1 (3)	33	33	33	33
Phase IV	2 (11)	320	190	450	640	6 (16)	41	20	62	244
Not applicable	2 (11)	40	10	70	80	13 (35)	28	13	120	583
Study Status										
Completed	11 (58)	202	10	802	2,932	21 (57)	28	9	99	773
Recruiting	4 (21)	130	37	450	747	10 (27)	60	20	400	877
Enrolling by Invitation	–	–	–	–	–	1 (3)	20	20	20	20
Active – Not Recruiting	2 (11)	912	676	1,148	1,824	2 (5)	70	30	110	140
Approved for Marketing	1 (5)	NA	NA	NA	NA	–	–	–	–	–
Not Yet Recruiting	1 (5)	30	30	30	30	2 (5)	37	20	54	74
Allocation										
Randomized	13 (68)	202	30	719	3,346	21 (57)	46	15	400	1,349
Non-randomized	–	–	–	–	–	2 (5)	45	30	60	90
Not applicable	5 (26)	190	10	1,148	2,187	13 (35)	20	9	120	445
Intervention model										
Parallel	13 (68)	202	30	719	3,346	18 (49)	57	15	400	1,303
Single Group	5 (26)	190	10	1,148	2,187	13 (35)	20	9	120	445
Crossover	–	–	–	–	–	4 (11)	22	16	46	106
Sequential	–	–	–	–	–	1 (3)	30	30	30	30

differences in ketamine or esketamine treatment; and of those that have, strong differences in antidepressant response were not detected (Benitah et al., 2022; Freeman et al., 2019; Jones et al., 2022; Williams, 2018). However, these trials may not have been sufficiently powered to detect sex differences (Williams, 2018). This has significant implications on health disparity, as understanding the processes driving sex differences in response to treatment is necessary for developing effective intervention protocols. Future research is thus encouraged to assess the safety and efficacy of ketamine and esketamine for TRD across sexes, as well as consider other confounding factors such as ethnicity, age, gender, and their interplay in addition to menstruation and pregnancy (Gerhard & Duman, 2018; Williams, 2018).

Ethnoracial health disparities were also evident in the samples included in the large-scale, phase 3 trials investigating esketamine for TRD. There was a particular lack of inclusion of black, indigenous, and people of color (BIPOC). This was shown, for example, in two short-term RCTs evaluating esketamine (i.e., TRANSFORM-1 and -2) where the study population was 79% White, 6% Black or African American, 2% Asian, 7% other, 0% American Indian or Alaskan Native, and 0% multiple races (Hudgens et al., 2021). Sexual and gender minorities were also excluded

and/or unreported in trials. This reflects existing evidence, or the lack thereof, on ketamine or esketamine for TRD among these minority populations, such as non-binary or transgender individuals (Herzog et al., 2019). Future research stands to benefit from more inclusive study designs, and targeted recruitment strategies in underrepresented communities, that likely translate to and influence real-world access, quality, and affordability of care.

Notwithstanding the foregoing, there are several trials aiming to increase the knowledge base of ketamine for TRD, as demonstrated in this review. Importantly, one trial is establishing a psychiatric service registry for patients receiving ketamine infusions or esketamine nasal spray (Niciu, 2020). This is a critical development, as there is pressing need to centralize evidence on ketamine and esketamine for mood disorders, which can inform long-term safety and effectiveness, as well as populations that are most likely to benefit (Sanacora et al., 2017). This can also aid in efforts surrounding reproducibility of evidence with clarity in clinical and methodological characteristics of treatment. Additionally, the registry can be extended to other institutions, providing a path to collaborative research among scientists and clinicians, and be leveraged to develop clinical practice guidelines.

LIMITATIONS

This review was limited to trials registered with ClinicalTrials.gov, which is principally based in the US. There are likely other trials, not included in this review, that were not registered in this database and/or registered outside of the US. Additionally, some trials that assessed TRD may not have been identified with the search strategy if they did not explicitly state TRD as the condition under study. Furthermore, some trials had missing information that affected the overall analysis and subsequent interpretation, including data regarding intervention protocol as well as route of administration. Finally, there is a possibility that ongoing trials are withdrawn and/or terminated with incomplete, unpublishable data and, therefore, should be examined cautiously.

CONCLUSION

The research pipeline for ketamine and esketamine for TRD shows increasing trends in the number of trials investigating their safety and efficacy, with a larger proportion of late phase esketamine trials compared to ketamine. Trials were heterogeneous in methodological and clinical characteristics. Trials further underscore limitations in assessing patient characteristics that may affect treatment response, such as age, sex, and race. While replication plays a role in accumulating evidence to support these treatments for TRD, the field serves to benefit from making trial inclusion more equitable, particularly for developing evidence-based practice guidelines. By understanding these emerging gaps, scientists and clinicians can avoid research waste (i.e., squandering limited resources by asking low priority questions), and funding bodies agencies can judiciously direct support towards high priority research.

Ethics approval: Not applicable. This was a review of the literature.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: A.R. is the Founding Director of the Integrated Research Literacy Group. R.R. serves as Chief Clinical Officer of Numinus Wellness and is an equity holder in the company. He is also the Co-Founder of Cedar Psychiatry, the Medical Director of Center for Change, and an Investigator for MAPS-sponsored trials. L.A.A serves as a Consultant, Speaker and/or Advisory Board Member for Guidepoint, Transcend Therapeutics, Source Research Foundation, Reason for Hope, and Ampelis. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding: This study was not funded.

Authors' contributions: M.B. and A.R. conceptualized and designed the study. M.B., M.S., and L.S. extracted and analyzed data and completed the manuscript writeup. A.R., M.Z., P.S., M.S.G., L.A.A., and R.R. reviewed the data analysis and presentation and critically reviewed/revised the manuscript writeup. All authors have read and approved the final article.

SUPPLEMENTARY MATERIALS

Supplementary data to this article can be found online at https://doi.org/10.1556/2054.2022.00234.

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Appendix: List of abbreviations

Term	Definition
BA	Bioavailability
CADSS	Clinician-Administered Dissociative States Scale
CGI	Clinical Global Impressions
CSSRS	Columbia Suicide Severity Rating Scale
DBS	Deep Brain Stimulation
DOI	Digital Object Identifier
ECT	Electroconvulsive Therapy
EQ-5D-5L	European Quality of Life Five Dimension
FDA	Food and Drug Administration
GAD-7	Generalized Anxiety Disorder-7
HAM-D	Hamilton Depression Rating Scale
IM	Intramuscular
IN	Intranasal
IV	Intravenous
KAP	Ketamine-assisted psychotherapy
MADRS	The Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
NMDA	*N*-methyl-D-aspartate
NIH	National Institute of Health
NLM	National Library of Medicine
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Post-Traumatic Stress Disorder
QIDS	Quick Inventory of Depression Symptomatology
RCT	Randomized Controlled Trials
SDS	Sheehan Disability Scale
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
TMS	Transcranial Magnetic Stimulation
TRD	Treatment Resistant Depression
US	United States
YLD	Years Lived with Disability