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Registered clinical trials investigating ketamine for psychiatric disorders

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A B S T R A C T

As interest has grown in the potential psychiatric applications of ketamine, the number of registered clinical trials has grown substantially. Herein, we summarize and analyze clinical trials registered with ClinicalTrials.gov that assess the treatment of any psychiatric disorder with ketamine or ketamine enantiomers (e.g., S-ketamine, R-ketamine), with a focus on ongoing clinical trials. A ClinicalTrials.gov search on February 21, 2020 returned 140 registered trials. Frequency data was analyzed to determine the distribution of study designs. The majority of trials (70%) investigated the therapeutic effect of ketamine in mood disorders (unipolar: 60%, bipolar: 0.7%, both: 5.7%). Suicidal ideation (13.1%), post-traumatic stress disorder (5.4%), and obsessive-compulsive disorder (3.6%) were also investigated. Intravenous (IV) administration was the most common route with 87% of the studies using IV ketamine. Single-dose studies represented 50% of IV ketamine studies. Few studies were assessing maintenance treatment. Most studies were phase I or II with few definitive phase III trials registered. Given the large number of ongoing studies assessing psychiatric application of ketamine, researchers and relevant stakeholders should consider not only completed, published studies, but also ongoing registered studies in adjudicating the most relevant research questions. More definitive phase III trials and maintenance studies of IV ketamine for mood disorders are required, as numerous completed and ongoing studies have already assessed and demonstrated the proof-of-concept of acute antidepressant effects in phase I and II trials.

1. Introduction

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that is FDA (Food and Drug Administration) approved as an anesthetic agent, available since the 1970s (Dundee et al., 1970). Over the past two decades, ketamine has been repurposed to treat numerous psychiatric disorders, including but not limited to major depressive disorder (MDD). The use of intravenous (IV) ketamine for the rapid reduction of depressive symptoms and suicidal ideation has been of particular interest (Mion and Villevieille, 2013; Zanos et al., 2018). In 2000, the first randomized clinical trial (RCT) demonstrated that IV ketamine had rapid and robust antidepressant effects in approximately two-thirds of participants with treatment resistant depression (TRD) when administered at a sub-anesthetic dose of 0.5 mg/kg infused over 40 min (Berman et al., 2000). The antidepressant effects were sustained for approximately one week after a single infusion.

These preliminary results have been replicated in numerous phase II RCTs (Diazgranados et al., 2010; Zarate et al., 2012, 2006) and meta-analyses (Kishimoto et al., 2016; Newport et al., 2015) demonstrating rapid antidepressant effects of ketamine (e.g., within 24 h) with large effect sizes (Cohen's d = 0.9–1.2) for TRD. In these RCTs, ketamine has been found to be well-tolerated with only transient dissociative symptoms and minor transient increases in blood pressure. Meta-analytic level analysis has also demonstrated rapid and sustained reduction in suicidal ideation, whereas the effect on completed suicide and suicide attempts remains unknown (Wilkinson et al., 2018). More recently, the antidepressant effects of the S-enantiomer of ketamine (e.g., esketamine) has been demonstrated in large phase III RCTs, leading to the FDA approval of intranasal (IN) esketamine for TRD in March 2019 (Daly et al., 2019; Fedgchin et al., 2019).

Notably, other phase III RCTs assessing the acute antidepressant effects of esketamine were negative, with significant methodological limitations in all phase III studies, raising concerns about the FDA decision to approve esketamine, as further discussed by numerous experts (Mahase, 2020; Sial et al., 2020; Wei et al., 2020). As such, there remains significant controversy over the actual antidepressant effects of IN esketamine compared to IV racemic ketamine, that has consistently shown robust antidepressant effects with large effect sizes (Turner, 2019; Zheng et al., 2020).

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Given the robust antidepressant effects of ketamine (Kishimoto et al., 2016; Newport et al., 2015), the potential benefits of ketamine for other psychiatric disorders has also been of interest. Proof-of-concept studies have evaluated the effects of ketamine for anxiety disorders (Taylor et al., 2018), obsessive compulsive disorder (OCD) (Rodriguez et al., 2013), post-traumatic stress disorder (PTSD) (Feder et al., 2014) and substance use disorders (Dakwar et al., 2019) with preliminary positive results. Accordingly, numerous investigators are evaluating alternative applications of ketamine. With this large breadth of potential psychiatric application, the use of ketamine for psychiatric disorders has quickly become one of the most widely studied drugs in psychiatry. New clinical trials, review articles and meta-analyses on psychiatric applications of ketamine are being published on a weekly basis, given the rapid rate of studies being completed in this area worldwide. However, reviews often fail to capture details of ongoing studies, as the focus is on completed, published RCTs. Given the large number of ongoing studies assessing psychiatric applications of ketamine, a systematic assessment of all registered clinical trials (e.g., including ongoing studies, not only completed, published studies) would be of great importance.

The purpose of the current analysis is to systematically identify all registered clinical trials of ketamine for psychiatric disorders, including ongoing studies. In addition to understanding results from completed studies, appreciating the scope of registered ongoing studies is important to best allocate research resources to research questions that will not be answered by other registered studies. The results of the current analysis are intended to provide investigators and other stakeholders with a summary of ketamine-related research questions likely to be answered in the near future, and to highlight important unanswered questions. Of note, a review of the results of completed, published studies will not be performed, as numerous recent reviews have already summarized these findings (Kishimoto et al., 2016; Newport et al., 2015).

2. Methods

A search of National Institute of Health clinicaltrials.gov database was performed on February 21, 2020. The inclusion criteria were interventional clinical trials that investigate ketamine or esketamine as treatment to improve symptoms of psychiatric illness. Ketamine (and/or variant) was cross-referenced with the following terms (and/or variant): MDD, BD, OCD, PTSD, anxiety disorder, schizophrenia, schizoaffective disorder, delusional disorder, cognitive impairment, personality disorder, autism spectrum disorder, attention-deficit hyperactivity disorder and suicide. All completed, active and upcoming clinical trials involving randomized and non-randomized clinical trials in adults, older adults and pediatric patients were identified. Trials withdrawn prior to enrollment, terminated, or investigating ketamine effect in healthy individuals or in non-psychiatric disorders as primary condition and those investigating ketamine abuse were excluded, in order to have a more accurate overview of ongoing studies that investigate treatment applications of ketamine. Data recorded for each clinical trial included trial phase, inclusion criteria, estimated start and end dates, actual completion duration in completed trials, primary outcomes measures, number and duration of treatment, enrollment, sponsor, methods of administration, dose, placebo-controlled, other interventions and results. After extraction of relevant clinical trial parameters, data were analyzed using Microsoft Excel.

Notably, the research method has been adopted from similar studies in the field of oncology, which typically has high volumes of ongoing clinical trials (Barth et al., 2018; Cushman et al., 2018).

3. Results

Our search result returned 214 clinical trials that met inclusion criteria. Of these records, 167 were treatment trials which, after exclusion of withdrawn, terminated, and suspended trials, 140 were identified for further assessment (Fig. 1). Selected trials were analyzed for their characteristics. Of evaluated trials, 119 (85%) were investigating ketamine and 21 (15%) esketamine. The first trial submitted in 2004 and the number has increased with the largest number of submissions in 2015 (n = 20) (Fig. 2).

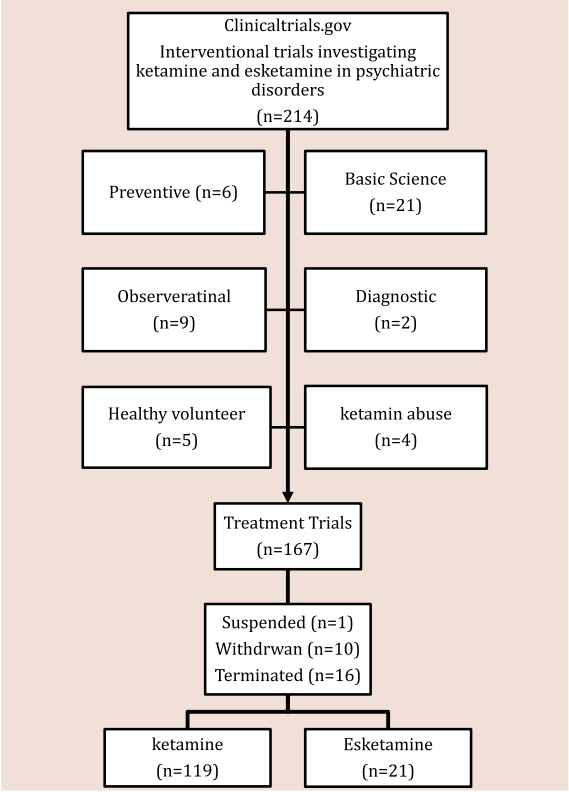


Fig. 1. Study selection schema.

3.1. Trial characteristics

At the time of data extraction (February 2020), 69 trials (49.3%) were completed, 35 (25%) were recruiting, 8 (5.7%) were active but not recruiting, 6 (4.3%) were enrolling by invitations, and 15 (10.7%) of the trials had an "unknown" status. One hundred ten (78.6%) were randomized trials, of which 88 (62.9%) were parallelly assigned. From an age perspective, 82 (58.6%) of trials enrolled only adults between 18 and 65 years. One hundred and thirty-three (95%) of the trials enrolled both genders with 7 (5%) trials recruiting only female participants. Academics (91; 65%) were the top sponsors followed by industry (20; 14.3%). Eighty-eight (62.9%) trials have opened site in North America (78 US and 10 Canada), 13 (9.3%) in Europe, 7 (5%) in Asia, 9 (6.4%) Middle east, 5 (3.6%) in South America, 3 (2.1%) in Australia and 15 (10.7%) multiple centers (Table 1).

Most submitted trials were in phase II (40; 28.6%), followed by phase IV (27; 19.3%) and phase III (18; 12.9%) (Table 2). A similar pattern was noticed among trials with completed status: phase II (22; 31.9%) and IV (11; 15.9%) (Fig. 3). In completed trials, 5362 participants had been enrolled and 5819 participants are expected to be enrolled in current treatment trials. Phase III trials had the greatest number of participants in total (n = 4922) and in completed trials (n = 2834) (Table 3). The mean predicted duration of studies were 26.47 months.

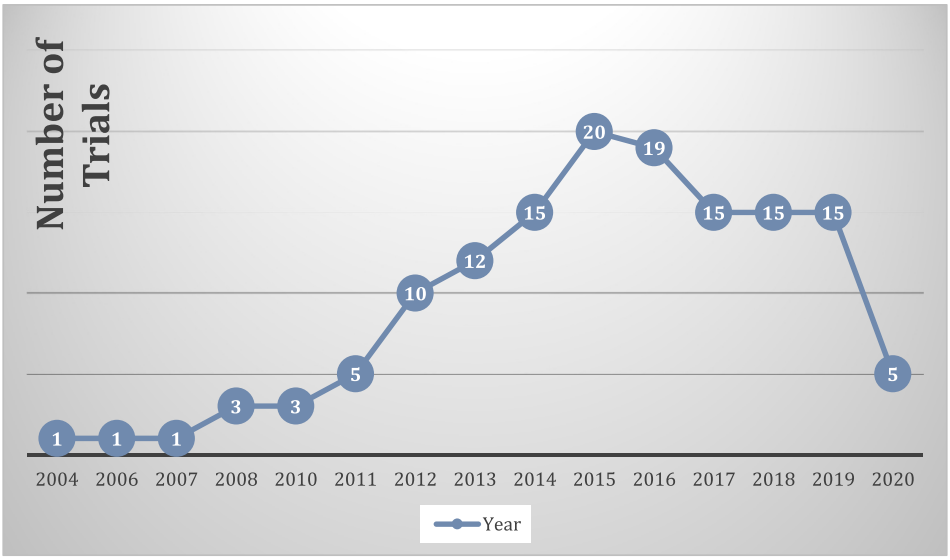


Fig. 2. Number of new trials that started in each year.

3.2. Clinical characteristics of trials

The majority of trials are investigating the therapeutic effect of ketamine or esketamine on major depressive episode (MDE) regardless of unipolar or bipolar depression diagnosis (98; 70%). Suicidal ideation (21; 15%), PTSD (7; 5%), OCD (5; 3.6%), autism spectrum disorder (2; 1.4%), anxiety disorder (1; 0.7%), borderline personality disorder (1; 0.7%), cognitive impairment (1; 0.7%) and schizophrenia (1; 0.7%) were other studied outcomes. In 55 (39.3%) of the MDE trials, the inclusion criteria was TRD defined as non-response to 2 or more antidepressants, 29 (20.7%) were MDD, 8 (5.7%) MDD or BD and 1 (0.8%) was BD. In the RCTs, saline (38; 27.1%), midazolam (23; 16.4%), methohexital (3; 2.1%), propofol (4; 2.9%) and diphenhydramine (2; 1.4%) were used as placebo. Thirty-one (22.1%) trials added other

Table 1
Characteristics of trials.

Characteristics	n (%) [a]	Characteristics	n (%)
Study status		**Gender**	
Active, not recruiting	8 (5.7)	Female	7 (5)
Completed	69 (49.3)	Male	0
Enrolling by invitation	6 (4.3)	Both	133 (95)
Recruiting	35 (25)	**Sponsor**	
Approved for marketing	1 (0.7)	Academic	91 (65)
Unknown	15 (10.7)	Industry	20 (14.3)
Allocation		NIH	3 (2.1)
Non-Randomized	29 (20.7)	US federal	9 (6.4)
Randomized	110 (78.6)	Consortium[d]	17 (12[c]
nterventional model		**Site locations**	
Case-only	1 (0.7)	Asia	7 (5)
Crossover	17 (12.1)	Australia	3 (2.1)
Factorial	1 (0.7)	Europe	13 (9.3)
Parallel	88 (62.5)	Middle East	9 (6.4)
Single group	30 (21.8)	North America	88 (62.9)
Sequential	2 (1.4)	USA	78 (88.6)
Masking model		Canada	10 (11.4)
Double[b]	32 (22.9)	outh America	5 (3.6)
Triple[c]	24 (17.1)	ulticenter	15 (10.7)
Quadruple[d]	45 (34.6)	**esult status**	
Single (investigator)	5 (3.6)	Has results	33 (23.6)
None (open label)	29 (20.7)	Submitted, not posted	7 (5)
Age group		No Results	100 (71.4)
Adult (18–65)	82 (58.6)		
Adult and older adult	47 (33.6)		
Child (< 18)	6 (4.3)		
Child and adult	2 (1.4)		
Older adult (> 65)	2 (1.4)		
All ages	1 (0.7)		

n, number; NIH, national institute of health.
*****Pharmaceutical and/or NIH and/or academic.
[a] All trials.
[b] Participant, investigator.
[c] Participant, care provider, investigator.
[d] Participant, care provider, investigator, outcome assessor.

Table 2
Trial Characteristics stratified by trial phase.

All Trials	Early I	I	I/II	II	II/III	III	IV	N.A
n (%)[a]	7 (5)	14 (10)	8 (5.7)	40 (28.6)	8 (5.7)	18 (12.9)	27 (19.3)	18 (12.9)
Therapy type								
Esketamine	1 (4.8)	1 (4.8)	–	9 (42.9)	–	9 (42.9)	–	1 (4.8%)
Ketamine	6 (5)	13 (10.9)	8 (6.7)	31 (26.1)	8 (6.7)	9 (7.6)	27 (22.7)	17 (14.3)
Allocation								
Non-Randomized	3 (10.3)	6 (20.7)	3 (10.3)	8 (27.6)	1 (3.4)	2 (6.9)	2 (6.9)	4 (13.8)
Randomized	4 (3.6)	8 (7.3)	5 (4.5)	32 (29.1)	7 (6.4)	16 (14.5)	25 (22.7)	13 (11.8)
Sponsor								
Academic	7 (7.7)	7 (7.7)	4 (4.4)	21 (23.1)	8 (8.8)	6 (6.6)	23 (25.3)	15 (16.5)
Pharmaceutical	–	2 (10)	–	7 (35)	–	10 (50)	–	1 (5)
NIH	–	–	1 (33.3)	2 (66.7)	–	–		–
U.S Federal	–	1 (11.1)	2 (2.2)	2 (22.2)	–	2 (22.2)	–	2 (22.2)
Corporations[b]	–	4 ()	1 ()	8 ()	–	–	4 ()	–
Study Status								
Active, not recruit	–	1 (12.5)	–	2 (25)	1 (12.5)	2 (25)	1 (12.5)	1 (12.5)
AFM	–	–	–	–	–	–	–	1 (100)
EBI	1 (16.7)	–	–	–	–	1 (16.7)	4 (66.7)	–
Completed	2 (2.9)	9 (13)	3 (4.3)	22 (31.9)	2 (2.9)	9 (13)	11 (15.9)	11 (15.9)
Recruiting	2 (5.7)	2 (5.7)	4 (11.4)	13 (37.1)	3 (8.6)	6 (17.1)	3 (8.6)	2 (5.7)
Not recruiting	1 (16.7)	1 (16.7)	–	1 (16.7)	–	–	3 (50)	–
Unknown	1 (6.7)	1 (6.7)	1 (6.7)	2 (13.3)	2 (13.3)	–	5 (33.3)	3 (20)
Psychiatric diagnosis								
Agitation	–	–	–	1 (100)	–	–	–	–
Anxiety disorder	1 (100)	–	–	–	–	–	–	–
ASD	–	1 (50)	–	1 (50)	–	–	–	–
BPD	–	–	–	1 (100)	–	–		–
CI	–	–	–	–	–	–	1 (100)	–
MDE	3 (3.1)	12 (12.2)	4 (4.1)	26 (26.5)	5 (5.1)	13 (13.3)	21 (21.4)	14 (14.3)
OCD	–	–	1 (20)	4 (80)	–	–	–	–
PTSD	–	1 (14.3)	1 (14.3)	3 (42.9)	1 (14.3)	–	–	1 (14.3)
Schizophrenia	–	–	–	–	–	–	1 (100)	–
Self harm (Non-suicidal)	–	–	1 (100)	–	–	–	–	–
SUD	–	–	–	1 (100)	–	–	–	–
SI	3 (14.3)	–	1 (4.8)	3 (14.3)	2 (9.5)	5 (23.8)	4 (19)	3 (14.3)
Interventional Mode								
Intranasal	1 (4)	2 (8)	–	8 (32)	1 (4)	10 (40)	1 (4)	2 (8)
Intramuscular	–	–	–	1 (50)	–	–	1 (50)	–
Intravenous	5 (4.8)	10 (9.5)	8 (7.6)	29 (27.6)	7 (6.7)	7 (6.7)	25 (23.8)	14 (13.3)
Oral	1 (33.3)	–	–	1 (33.3)	–	1 (33.3)	–	–
Patch	–	1 (100)	–	–	–	–	–	–
Variable	–	–	–	1 (50)	–	–	–	1 (50)
Not defined	–	1 (50)	–	–	–	–	–	1 (50)
Results status								
Has results	–	–	2 (6.9)	13 (44.4)	–	5 (17.2)	3 (10.3)	6 (20.7)
Submitted	–	–	–	–	1 (20)	–	4 (80)	–
No results	7 (7)	13 (13)	5 (5)	24 (24)	7 (7)	13 (13)	19 (19)	12 (12)

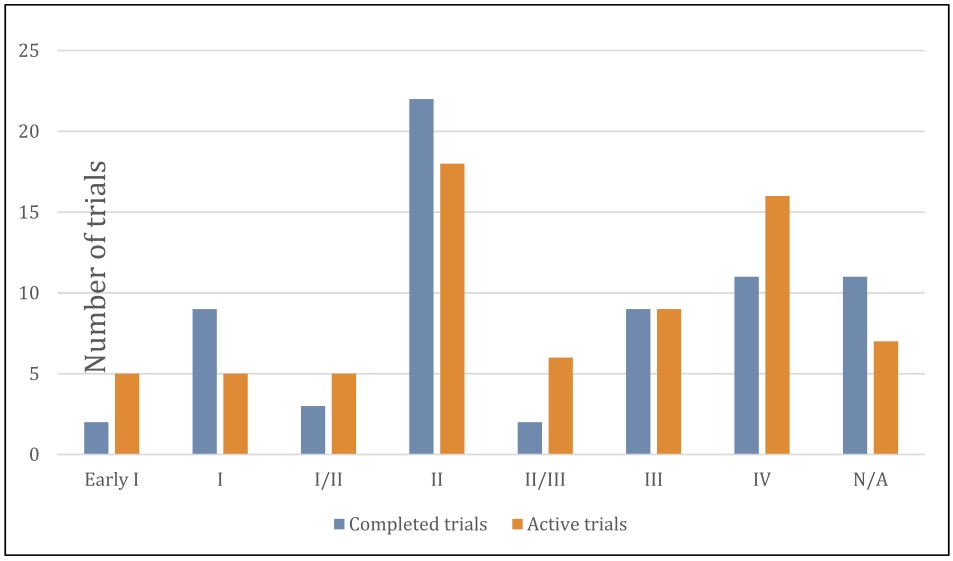
AFM, approved for marketing; ANR, active not recruiting; ASD, autism spectrum disorder; BD, bipolar disorder; BPD, borderline personality disorder; CI; cognitive impairment; EBI, Enrolling by invitation; MDE, major depressive episode, n, number; N/A, not applicable; NIH, National Institute of Health; OCD, obsessive compulsive disorder; PTSD, post-traumatic disorder; SI; suicide ideation; SUD, substance use disorder; U.S federal, United States Federal.

[a] Row total percentage.

[b] Pharmaceutical and/or NIH and/or academic.

psychotropic medications (i.e. antidepressants, antipsychotics) along with experimental medication. Eighteen (12.9%) trials used ketamine with electroconvulsive therapy (ECT) as an anesthetic or as adjuvant therapy. In 7 (5%) trials, cognitive behavior therapy (CBT) was integrated with ketamine treatment.

Regarding the methods of drug administration, 105 (75%) trials used IV infusion, 25 (17.9%) IN, 2 (1.4) intramuscular (IM), 3 (2.1%) oral, 1 (0.7) patch and 2 (1.4) compared different methods (Table 4). The dose of 0.5 mg/kg (73; 69.5%) was the most frequent dose used in trials with IV infusion protocol (Fig. 4A). In 57 (54.3%) of these trials, ketamine infused in 40 min and in 16 (15.2%) as bolus, while the duration of the infusion was not defined in 25 (23.8%) of trials (Fig. 4B). Fifty-two (49.5%) of these trials inject ketamine only once, 5 (4.8%) twice, 6 (5.7%) four times, 15 (15.3%) 6 times and 4 (3.8%) 8 times for the total duration of treatment (Fig. 4C). Total duration of treatment in trials with multiple injections of ketamine was 7 days in 3



N/A, not applicable

Fig. 3. Number of completed and active trials in each phase. N/A, not applicable.

Table 3
Enrollment based on trial's characteristics.

	Mean	Minimum	Maximum	Sum
All trials	80	1	1150	1181
Therapy type				
Esketamine	262	15	1150	5047
Ketamine	52	1	400	6134
Allocation				
Non-Randomized	84	5	1150	2452
Randomized	80	1	703	8752
Status				
Active, not recruiting	39	14	100	315
Enrolling by invitation	81	10	200	484
Completed	78	4	794	5362
Not recruiting	27	1	50	161
Recruiting	120	10	1150	4191
Unknown	45	10	132	668
Phase				
Early I	15	4	30	106
I	29	5	120	404
I/II	48	5	150	383
II	59	5	198	2363
II/III	108	10	400	860
III	273	25	1150	4922
IV	56	1	200	1517
Not applicable	37	10	90	626
Primary psychiatric condition				
Anxiety Disorder[a]	–	–	–	18
Agitation[a]	–	–	–	184
Autism Spectrum Disorder	36	21	50	71
Borderline personality disorder[a]	–	–	–	66
Cognitive impairment[a]	–	–	–	132
MDE	88	4	1150	8515
OCD	32	5	120	160
PTSD	58	15	198	404
Schizophrenia[a]	–	–	–	1
Self-harm (non-suicidal)	–	–	–	30
Substance use disorder[a]	–	–	–	8
Suicidal ideation	76	9	226	1592

MDE, major depressive episode; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.
[a] Only one trial.

Table 4
Clinical Characteristics of trials.

Characteristics	n (%)[a]	Characteristics	n (%)	
Primary psychiatric condition		Intervention mode	ketamine	Esketamine
Agitation	1 (0.7)	Intramuscular	1 (0.8)	1 (4.8)
Anxiety disorder	1 (0.7)	Intranasal	7 (5.9)	18 (85.7)
ASD	2 (1.4)	Intravenous	103 (86.6)	2 (9.5)
BPD	1 (0.7)	Oral	3 (2.5)	–
Cognitive impairment	1 (0.7)	Patch	1 (0.8)	–
MDE	98 (70)	Variable methods	2 (1.7)	–
OCD	5 (3.6)	Not defined	2 (1.7)	–
PTSD	7 (5)	**Placebo used in RCTs**		
Suicidal ideation	21 (15)	Diphenhydramine		2 (1.4)
Self-harm	1 (0.7)	Midazolam		23 (16.4)
Schizophrenia	1 (0.7)	Methohexital		3 (2.1)
Substance use disorder	1 (0.7)	Propofol		4 (2.9)
Suicidal ideation	21 (15)	Saline		38 (27.1)
MDE trials based on primary inclusion condition		Others		9 (8.8)
Alcohol use disorder	4 (2.9)	Not defined by study		25 (11.39)
Anxious Depression	2 (1.4)	**Type of imaging**		
BD	1 (0.7)	fMRI		4 (2.9)
Cancer related	2 (1.4)	MRI		14 (10)
MDD	29 (20.7)	PET		1 (0.7)
MDD or BD	8 (5.7)	No imaging studies		121 (86.4)
Postpartum Depression	1 (0.7)			
Preoperative	5 (3.6)			
TRD	55 (39.3)			
Substance use disorder (other than Alcohol)	1 (0.8)			
Not defined	8 (5.7)			
Studies with Additional interventions				
CBT	7 (5)			
ECT	18 (12.9)			
Other psychotropic medications	31 (22.1)			
r-TMS	1 (0.7)			

ASD, autism spectrum disorder; BD, bipolar affective disorder; BPD, CBT, cognitive behavior treatment; ECT, electroconvulsive therapy; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MDD, major depressive disorder; MDE, major depressive episode; MRI, magnetic resonance imaging; n, number; OCD, obsessive compulsive disorder; PET, positron-emission tomography; PTSD, post traumatic disorder; TRD, treatment resistant disorder.

[a] All trials.

(2.9%) trials, 14 days in 11 (10.5%) trials, 21 days in 7 (6.7%), 28 days in 8 (7.6%), 42 days in 2 (1.9%) and 56 days in 2 (1.9%) trial (Fig. 4D).

In trials with intranasal administration protocol, 12 (48%) were investigating different doses (mostly 28 mg, 56 mg and 86 mg). The other investigated doses were 20 mg (1; 4%), 40 mg (2; 8%), 50 mg (2; 8%), 84 mg (4; 16%) (Fig. 5A). Eleven (44%) administered medication for 8 times during the study (Fig. 5B) and in 12 (48%), the duration of treatment was 28 days (Fig. 5C).

Variants of the Montgomery-Asberg Depression Rating Scale (MADRS) was the most common method of outcome assessment in MDE trials (54; 55.1%) followed by the Hamilton Depression Rating Scales (HDRS) (19; 19.4%). In trials that investigate the treatment efficacy of ketamine in reducing suicidal ideation, MADRS (7; 33.3%) and the Beck Scale for Suicidal Ideation (BSSI) (7; 33.3%) were used more frequently. The Clinician Administered PTSD Scale (CAPS) (5; 71.4%), Impact of Event Scale – Revised (IES-R) (1; 14.3%) and PTSD Checklist (PCL) (1; 14.3%) were the assessment tools in PTSD trials. In OCD trials, the Yale-Brown Obsessive- Compulsive Scale (Y-BOCCS) was used as main assessment (5; 100%) (Table 5).

Thirty-three (23.6%) of trials posted their preliminary results on clinicaltrials.gov and 40 (28.5%) has a related published paper (Table 6).

4. Discussion

It is clear that the number of ketamine clinical trials has substantially increased since 2000 with the number of new trials peaking in 2015. In this systematic review of 130 registered trial protocols, most trials used ketamine or esketamine. The United States had the most opened sites. Majority of trials were in phase II in both active and completed trials. In addition, there is a higher rate of studying ketamine use for the treatment of depression and suicidal ideation in late-phase studies (phase III and IV), which could be translated to the perceived and anticipated value of this treatment for these conditions. Most of the trials were randomized with parallel assignment and used saline or midazolam as placebo. The majority of the trials enrolled or aim to enroll between 20 and 80 participants. The main outcome measure for the majority of the trials was the reduction of depressive symptoms measured by assessment of changes in MADRS or HDRS. A high proportion of the trials used single doses of 0.5 mg/kg of IV ketamine that had 40 min duration. The other common method was thrice and then twice infusion per week for the total period of two weeks for studies with more than a single dose.

Analysis of ongoing ketamine clinical trials has revealed numerous important trends. Areas without adequate ongoing or completed studies

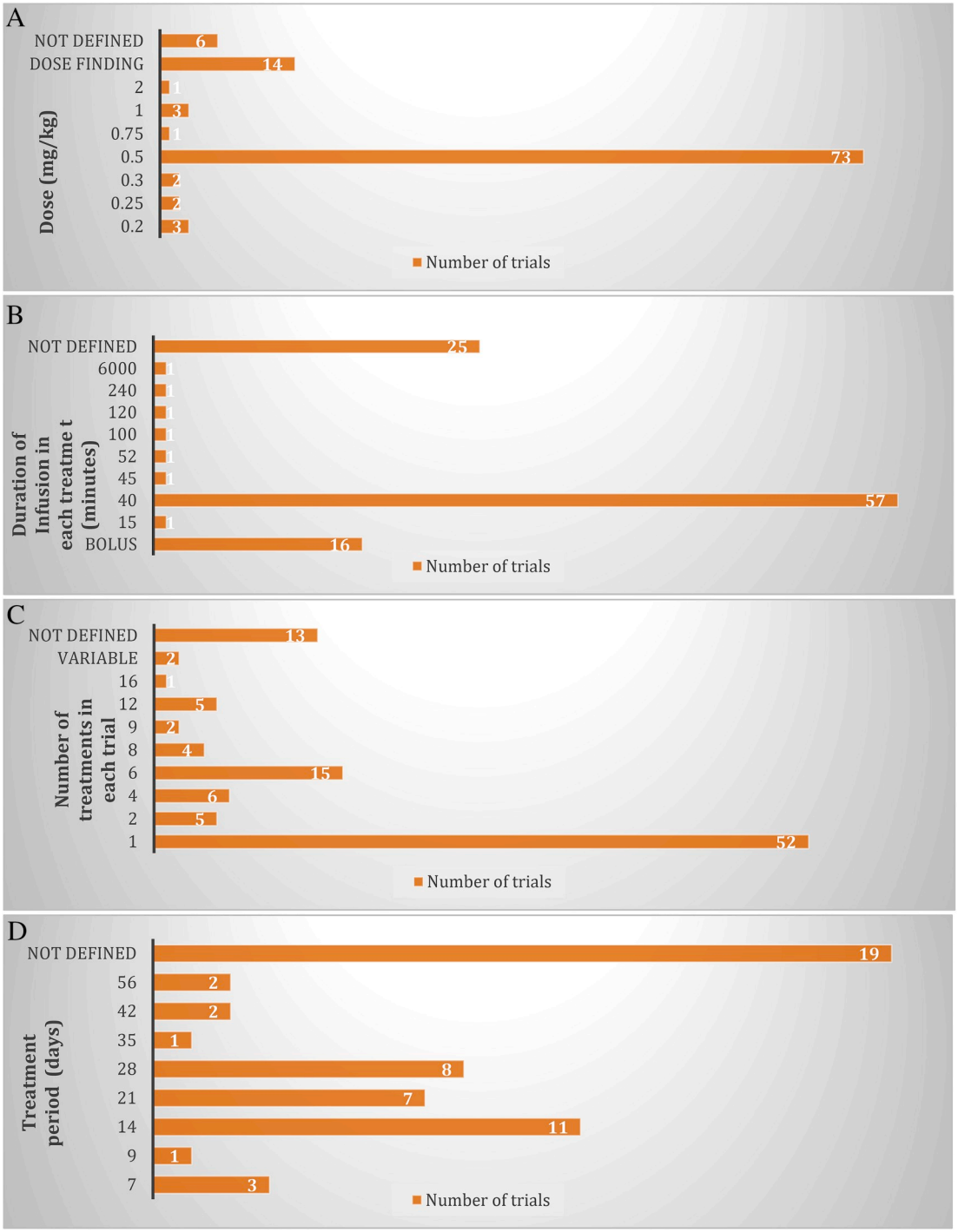


Fig. 4. Characteristics of trials with infusion protocol (A) Dose used, (B) Duration of infusion, (C) Number of treatments, (D) Treatment period in days.

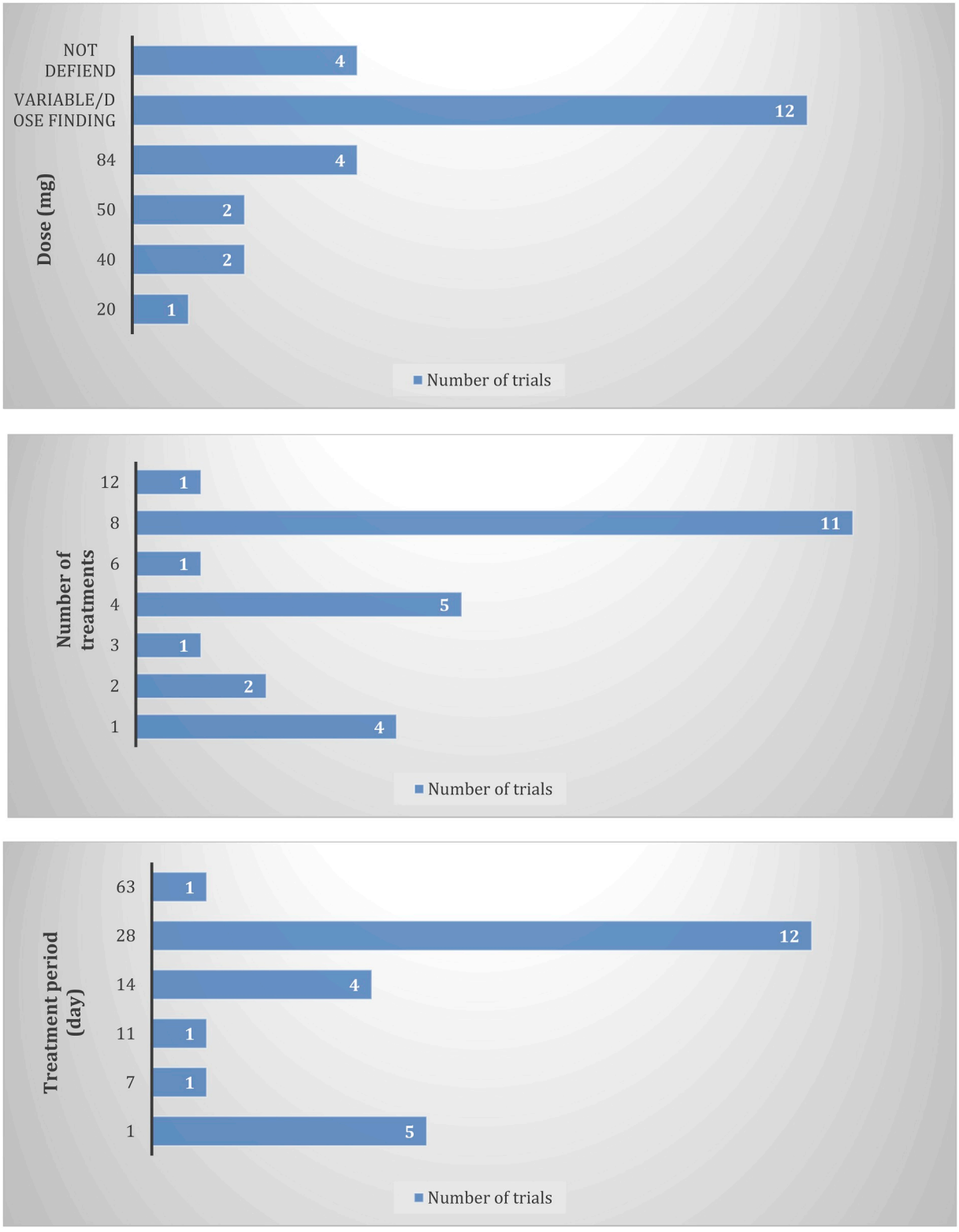


Fig. 5. Characteristics of trials with intranasal administering protocol. (A) Absolute dose, (B) Number of treatments, (C) Treatment period in days.

Table 5
Primary outcome assessment[a] in each trial.

Characteristics	n (%)	Characteristics	n (%)
Anxiety Disorder trials		**OCD trials**	
VAS	1 (50)	Y-BOCCS	5 (100)
ASD trials		**PTSD trials**	
ABC	1 (50)	CAPS	5 (71.4)
ADI	1 (50)	IES-R	1 (14.3)
BPD trial		PCL	1 (14.3)
MADRS variant	1 (100)	**Schizophrenia**	
MDE trials		CGI	1 (100)
CGI	2 (2)	**Substance use disorder**	
HDRS variants	19 (19.4)	VAS	1 (100)
HLVT	2 (2)	**Suicide trials**	
MADRS variants	54 (55.1)	BSSI	7 (33.3)
HADS-A	2 (2)	MADRS	7 (33.3)
PHQ-9	2 (2)	Other tests	4 (16.6)
Other tests	8 (8.2)	Not defined by study	3 (14.3)
Not defined by study	9 (12.2)		

ASD, Autism Spectrum disorder; BPD, borderline personality disorder; MDE, Major Depressive Episode; n, number; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.

[a] ADI, Autism Diagnostic Interview; ABC, autism behavior checklist; BSSI, Beck Scale for Suicidal Ideation; CAPS, Clinician Administered PTSD Scale; CGI, Clinical Global Impression; HADS-A, Hospital Anxiety and Depression Scale; HDRS, Hamilton Depression Rating Scale; HLVT, Hopkins Verbal Learning test; IES-R, Impact of Event Scale - Revised; MADRS, Montgomery-Asberg Depression Rating Scale; PCL, PTSD Checklist; PHQ-9, Patient Health Questionnaire-9; VAS, Visual Analog Scale; Y-BOCCS, Yale-Brown Obsessive Compulsive Scale.

include maintenance studies (e.g., safety and efficacy of repeated doses of ketamine for relapse prevention), comparative studies between enantiomers (e.g., racemic versus S-ketamine versus R-ketamine) and comparative studies between routes of administration (e.g., intranasal versus IV versus oral). Indeed, there are significant differences in bioavailability between intranasal (40–50%), IV (100%) and oral (10–20%) drug delivery that may have significant effects on efficacy and tolerability (Peltoniemi et al., 2016). Sex and gender differences also remain understudied with potential variability in benefits, tolerability and abuse liability of ketamine remaining unknown (Wright and Kabbaj, 2018). More definitive phase III studies are also needed to assess the antidepressant effects of IV ketamine, as the majority of registered trials are phase II proof-of-concept studies for mood disorders. Conversely, for PTSD, OCD and anxiety disorders, there is likely still merit for additional phase II studies to replicate the small number of ongoing and completed studies in these areas. Understanding the effects of ketamine on completed suicide also remains an unanswered research question, whereas the effect of ketamine and esketamine on suicidal ideations has numerous ongoing and completed studies. The effect of ketamine and esketamine in bipolar depression is also understudied, however, it is of great importance given the currently poor treatment outcomes for bipolar depression.

Ongoing and completed studies assessing the effects of R-ketamine are lacking compared to the abundance of studies investigating racemic ketamine and S-ketamine. Preclinical data suggests that the antidepressant effects of R-ketamine (and its metabolites) may even be greater than S-ketamine, while these effects have yet to be established in human studies (Hashimoto, 2019; Zanos et al., 2016). R-ketamine is being assessed in healthy controls for safety and tolerability (NCT04108234). This study also plans to compare racemic, R- and S-ketamine for the likelihood of important differences between ketamine enantiomers with no published results to date.

Researchers, granting agencies and expert reviewers should consider all registered ongoing trials to evaluate the relative novelty of ketamine projects being proposed to better evaluate if newly proposed studies are truly filling in gaps in knowledge, as opposed to attempting to answer research questions that are already in the process of being answered (i.e., through registered active, ongoing studies). Notably, while it is helpful to replicate findings, if a large number of similar trials are already ongoing, there is decreased merit of yet another study aiming to answer an identical research question.

A limitation of the current study is related to the registration of studies in the ClinicalTrials.gov database; there are presumably ketamine trials that are not registered, despite international guidelines encouraging study registration. Some registered trials also have missing information in their published protocol which can affect the analysis. Another important limitation is the inability to predict which clinical trials will be successfully completed. In our analysis, we identified many clinical trials that were registered but never completed (e.g., withdrawn and discontinued studies). Therefore, registered trials should be cautiously interpreted in trying to decide if a similar study should be proposed. Nevertheless, the current analysis may provide a broad summary of registered trials when planning future ketamine-related clinical trials.

Declaration of competing interest

RSM declares that he has been on advisory boards and/or received honoraria for educational activities and/or research grants from AstraZeneca, Bristol-Myers Squibb, Janssen-Ortho, Eli Lily, Forest, Lundbeck, Pfizer, Shire, Merck, Sepracor, and Otsuka. JDR is a subinvestigator for the COMPASS Psilocybin for Treatment Resistant Depression Study. RSM is the director of and JDR is a staff psychiatrist at a clinic that administers intravenous ketamine. All other authors in this manuscript have reported no relevant conflict of interest.

Table 6
Trials with publication.

NCT Number	Start	Con-dition	Study design	Phase	Age	Enroll-ment	Site	Assess-ments[a]	Protocol
NCT00088699	2004	MDD	RCT, QBS, crossover	I/II	18–65	67	U. S	MADRS	Single dose IV ketamine or saline over 40 min. After 7 days cross over.
NCT00419003	2006	MDD	RCT, TBS, factorial	IV	21–70	26	U. S	MARDS	300 mg of lamotrigine or placebo 2 h prior to ketamine infusion then responders receive either two capsules of riluzole (100 mg/d) or matching pill placebo
NCT00548964	2007	MDD	Non-RCT	I	21–80	36	U. S	MADRS	0.5 mg/kg of ketamine repeatedly over a period of one week +600–900 mg of Li carbonate
NCT00680433	2008	MDE	RCT, TBS, parallel	IV	18 <	83	Australia	–	6 adjunctive IV ketamine (0.25 mg/kg; 0.5 mg/kg) OR saline with regular maintenance ECT course
NCT00749203	2008	PTSD	RCT, QBS, parallel	II	21–55	41	U. S	IES-R	Single dose IV ketamine 0.5 mg/kg OR 0.045 mg/kg IV midazolam over 40 min
NCT00768430	2010	TRD	RCT, QBS, parallel	II	21–80	73	U. S	MADRS	Single dose of IV ketamine 0.5 mg/kg IV (in the vein) or 0.045 mg/kg midazolam
NCT01100255	2010	OCD	RCT, DBS, parallel	II	18–55	15	U. S	Y-BOCCS	0.5 mg/kg IV ketamine infusion over 40 min then IV saline over 40 min
NCT01179009	2010	TRD	RCT, DBS, parallel	–	18–65	40	U. S	CGI	100-h of ketamine infusion (0.0125 mg/kg-min). 5-day pre-treatment of clonidine (max. dose 1 mg/day divided doses), prior to and throughout the ketamine infusion OR 40-min ketamine infusion following a 100-h ± placebo (saline) infusion
NCT01209845	2010	TRD	Non-RCT	N/A	18 <	14	U. S	MARDS	Single intravenous ketamine (0.2 mg/kg) over 1–2 min
NCT01304147	2011	MDD	RCT, QBS, crossover	–	21–65	20	U. S	MADRS	single dose of intranasal ketamine up to 50 mg VS normal saline nasal spray
NCT01306760	2011	MDE	RCT, TBS, parallel	IV	18–65	40	U. K	MADRS	8 ECT treatments with IV ketamine (up to 2 mg/kg) OR IV propofol (up to 2.5 mg/kg) as anesthetic
NCT01349231	2011	OCD	Non-RCT	II	18–65	10	U. S	Y-BOCCS	single dose of IV Ketamine 0.5 mgékg over 40 min
NCT01441505	2011	MDE	RCT, DBS, crossover	II	18 <	42	Australia	BPRS, CADSS	Variable doses of IV, IM or SC ketamine (0.1–0.5 mg/kg) or saline, or midazolam (0.01 mg/kg weekly) for up to 6 weeks. Some may continue to receive ketamine weekly for up to 6 months
NCT01507181	2012	Suicide	RCT, QBS, parallel	IV	18–80	24	U. S	BSSI	single dose IV ketamine 0.5 mg/kg minutes OR midazolam, 0.45 mg/kg infused over 40 min
NCT01582945	2012	MDD	Non-RCT	–	18–65	14	U. S	HDRS 28	Ketamine IV 0.5 mg/kg infusion twice a week for 3 weeks as augmentation of ongoing antidepressant regimen
NCT01627782	2012	MDD	RCT, DBS, parallel	II	18–64	68	U. S	MADRS	Ketamine or placebo IV infusion 0.50 mg/kg, 2 or 3 times weekly for 4 weeks
NCT01640080	2012	MDD	RCT, TBS, parallel	II	18–64	30	Poland	MADRS	2 doses of IV esketamine 0.2/mg/kg or 0.4/mg/kg OR saline during 1 wk
NCT01700829	2012	Suicide	RCT, QBS, parallel	IV	18–65	80	U. S	–	Single dose of Ketamine (0.5 mg/kg) or Midazolam (0.02 mg/kg) infusion over 40 min
NCT01790490	2013	Substance use disorder	RCT, DBS, crossover	II	21–51	8	U. S	VAS, URICA	Three 52-min IV infusion of ketamin (0.41 or 0.71) or Lorazepam 2 mg treatments separated by 48 h
NCT01920555	2013	TRD	RCT, QBS, Parallel	II	18–70	99	U. S	HDRS- 6 MADRS	Single infusion of 0.1 or 0.2 or 0.5 or 1 mg/kg of ketamine vs 0.045 mg/kg midazolam
NCT01935115	2013	TRD	RCT, QBS, parallel	IV	18 <	27	Canada	MADRS	Twice/wk ECT for 4 wks with IV ketamine 0.75 mg/kg and remifentanil 1 mcg/kg OR propofol 1 mg/kg and remifentanil 1 mcg/kg
NCT01945047	2013	TRD	RCT, DBS, crossover	II	18–65	46	Canada	MADRS	Single Intravenous Bolus Infusion Ketamine Hydrochloride 0.50 mg/mL over 40 min
NCT01998958	2013	TRD	RCT, DBS, parallel	II	20–64	108	Nether-lands	MADRS	1 to 6 sprays of 14 mg IN esketamine for 4 days (Days 1, 4, 8, 11)
NCT02037503	2014	Suicide	RCT, TBS, parallel	III	18–65	100	Israel	–	1 mg/kg oral ketamine or placebo thrice weekly for 21 days
NCT02062658	2014	OCD	Non-RCT	II	18–55	10	U. S	Y-BOCCS	Single IV ketamine (0.5 mg/kg), followed by 10 1-h exposure sessions delivered over two weeks
NCT02083926	2014	Anxiety	RCT, QBS, crossover	Early I	18–65	18	U. S	VAS- Anxiety States	Single dose IV Ketamine (0.5 mg/kg) over 40 min or saline
NCT02094898	2014	Suicide	Non-RCT	II	18–65	12	U. S	MADRS	0.3 mg/kg/hr of ketamine infused for 100 min thrice weekly for up to 2 weeks. Responders receive once-weekly IV ketamine infusions for 4 weeks
NCT02133001	2014	MDE, suicide ideation	RCT, DBS, parallel	II	18–65	68	U. S	MADRS	Esketamine 84 mg will be self-administered by participants as intranasal spray as two times a week, for 4 weeks
NCT02165449	2014	TRD	Single Group Assignment	I	18–64	60	U. S	HDRS	4 subanesthetic dose of 0.5 mg/kg will be diluted in 60 cc of normal saline and administered via a slow IV infusion over 40 min
NCT02417064	2015	TRD	RCT, DBS, parallel	III	18–64	346	Multi-center	MADRS	Self-administer either 84 mg or 56 mg of esketamine, intranasally, twice per week as a fixed dose regimen + antidepressant of choice for 4 wks
NCT02418585	2015	TRD	RCT, DBS, parallel	III	18–64	236	Multicenter	MADRS	Participants will self-administer either 56 mg or 84 mg of esketamine, intranasally, twice per week as a flexible dose regimen for 4 wks
NCT02493868	2015	TRD	RCT, DBS, parallel	III	18–64	719	Multi-center	MADRS	Esketamine nasal spray (56 or 84 mg) plus an oral antidepressant. After 16 weeks of esketamine treatment, whom achieved stable remission or stable response entered the randomized withdrawal phase.
NCT02577250	2015	PTSD	Single group, open label	I	18–75	20	U. S	CAPS	Six infusions of 0.5 mg/kg of ketamine hydrochloride solution over 2 weeks
NCT02717052	2016	TRD	RCT, QBS, parallel	II	18–55	74	Austria	HDRS	0.25 mg/kg or 0.20 mg/kg or 0.50 mg/kg or 0.80 mg/kg (R, S)-ketamine IV over 40 Minutes

(*continued on next page*)

Table 6 (*continued*)

NCT Number	Start	Con-dition	Study design	Phase	Age	Enroll-ment	Site	Assess-ments[a]	Protocol
NCT02752724	2016	TRD	RCT, DBS, Parallel	N/A	18–100	52	U. S	PHQ9, MOCA	1.0 mg/kg IV ketamine (experimental arm) intravenously (IV) for the duration of their ECT index course over 2–3 weeks
NCT02766192	2016	PTSD	RCT, QBS, crossover	N/A	21–60	50	U. S	CAPS, PCL	single infusion of low dose ketamine (0.5 mg/kg) and TIMBER psychotherapy
NCT02911597	2016	TRD	RCT, DBS, crossover	I	18–70	16	U. S	HDRS, BDI	placebo or 50 mg of naltrexone preceding intravenous infusion of 0.5 mg/kg of ketamine after 45 min.
NCT03086148	2017	MDE	RCT, QBS, parallel	–	18–65	80	China	PDS	single dose IV ketamine 0.5 mg/kg minutes OR saline infused over 40 min
NCT03113968	2017	TRD	RCT, Open label	III	21–75	400	Canada	QIDS	0.5 mg/kg infusion over 40 min, 2 times a week up to a total of 6 treatment over 3–5 weeks
NCT03375671	2017	Agitation	RCT, TBS, parallel	II	19–60	184	Canada	RASS	single administration of 5 mg/kg, IM

DBS. Double blind study; hr (s), hour(s); IM, intramuscular; IN, intranasal; IV, intravenous; Kg, kilogram; MDD, major depressive disorder; MDE, major depressive episode; mg, milligram; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; QBS, Quadruple blind study; RCT, randomized clinical trial; SC, subcutaneous; TBS, triple blind study; TRD, treatment resistant depression; wk(s), week(s).

[a] ADI, Autism Diagnostic Interview; ABC, autism behavior checklist; BAES, Biphasic Alcohol Effects Scale; BSSI, Beck Scale for Suicidal Ideation; CAPS, Clinician Administered PTSD Scale; CDRS-R, Children's Depression Rating Scale-Revised; CGI, Clinical Global Impression; C-SSRS, Columbia Suicide Severity Rating Scale; CIWA, Clinical Institute Withdrawal Assessment; HDRS, Hamilton Depression Rating Scale; HLVT, Hopkins Verbal Learning test; IES-R, Impact of Event Scale - Revised; MADRS, Montgomery-Asberg Depression Rating Scale; m-YPAS, Modified Yale preoperative anxiety scale; PCL, PTSD Checklist; PHQ-9, Patient Health Questionnaire-9; QIDS, Quick Inventory of Depression Clinician; The Richmond Agitation and Sedation scale RASS; URICA, University Island Change Assessment; VAS, Visual Analog Scale; Y-BOCCS, Yale-Brown Obsessive Compulsive Scale.

Abbreviations

BD	bipolar disorder
BSSI	Beck Scale for Suicidal Ideation
CAPS	Clinician Administered PTSD Scale
CBT	cognitive behavior therapy
CGI	Clinical Global Impression
ECT	electroconvulsive therapy
FDA	Food and Drug Administration
HDRS	Hamilton Depression Rating Scales
IES-R	Impact of Event Scale – Revised
IM	intramuscular
IN	intranasal
IV	intravenous
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MDE	major depressive episode
NMDA	N-methyl-D-aspartate
PCL	PTSD Checklist
PHQ-9	Patient Health Questionnaire-9
PTSD	post-traumatic stress disorder
QIDS	Quick Inventory of Depression Clinician
RCTs	randomized controlled trials
TRD	treatment resistant depression
Y-BOCCS	Brown Obsessive- Compulsive Scale

Contributors

BP: study concept & design, literature review, data analysis & synthesis & presentation, primary draft of the manuscript (introduction, methods, results); RSM: study concept, manuscript review & supervision, LP: study concept and manuscript edit, LL: study concept and manuscript edit, HG: study concept and manuscript edit, AM: study concept and manuscript edit, FN: study concept and manuscript edit, JDR: supervision of BP, study concept & design, data analysis, primary draft of the manuscript (introduction, discussion).

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