Neuroscience and Biobehavioral Reviews 120 (2021) 78–85

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

The Effects of Ketamine on Cognition in Treatment-Resistant Depression: A Systematic Review and Priority Avenues for Future Research

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ARTICLE INFO

Keywords:
Neurocognition
Major depression
Racemic ketamine
Esketamine
Treatment-resistant depression

ABSTRACT

Replicated evidence has documented cognitive deficits in populations with treatment-resistant depression (TRD). Approximately 40 % of patients with MDD present with impairment of one or more cognitive domains. As such, there is an unmet need to discover treatments that have pro-cognitive effects in TRD patients. Ketamine has demonstrated efficacy as a rapid-onset intervention for the treatment of depression. The objective of the current review was to assess the effects of ketamine on cognition in TRD patients. We systematically searched PubMed, Google Scholar and PsycINFO between database inception to March 24th, 2020.

We identified five studies that evaluated cognition in TRD populations following ketamine treatment. All studies included a 0.5 mg/kg subanesthetic intravenous (IV) administration of ketamine. One study found significant improvements in complex ($p = .008$) and simple ($p = .027$) working memory and one study found improvements in visual learning memory following IV ketamine infusions ($p = .014$). Improvements in speed of processing and verbal learning memory were observed in anxious TRD participants only. Importantly, a subanesthetic dose of IV ketamine does not worsen cognitive function.

1. Introduction

Major depressive disorder (MDD) is characterized by significant cognitive and psychosocial impairments, compared to healthy subjects (Association and American Psychiatric Association, 2013). For example, nearly 40 % of patients with MDD present with impairment of one or more cognitive domains, including executive function, attention, memory, psychomotor speed and cognitive flexibility (Bortolato et al., 2015; Gualtieri and Morgan, 2008; Roger S. McIntyre et al., 2013; Motter et al., 2016). However, it is important to note that a dissociation exists between patient reports and objective assessments of cognitive deficits. Notwithstanding, persistent cognitive dysfunction contributes to occupational and psychosocial impairments, as well as diminished workplace productivity and functioning (i.e., presenteeism) or missed days at work (i.e., absenteeism) (Baune and Air, 2016; Lagerveld et al., 2010). Fewer than half of MDD patients achieve full symptom remission following first-line treatment options, with cognitive difficulties, sleep problems and low energy being the most common residual symptoms (Baune et al., 2010; Rush, 2007). Indeed, there is an ongoing debate on whether these deficits are an epiphenomenon of depression, with their own symptom progression, or a dimension of MDD. As such, this underscores the need for treatments that specifically improve cognitive functioning in patients with treatment-resistant depression (TRD; Knight and Baune, 2018).

Currently, antidepressants targeting the monoamine system provide modest improvements in depressive symptomatology for many individuals with MDD (Gaynes et al., 2009; Gitlin, 2006). Results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study indicated that approximately 35 % of individuals with depression experience complete remission, while 65 % remain symptomatic following multiple antidepressant medication trials (Rush et al., 2006). Individuals suffering from TRD experience substantially longer depressive episodes, and greater work-related impairment (Rizvi et al., 2014). As such, current first-line antidepressants offer only modest

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https://doi.org/10.1016/j.neubiorev.2020.11.020
Received 13 April 2020; Received in revised form 12 August 2020; Accepted 12 November 2020
Available online 23 November 2020
0149-7634/

improvements in neurocognition, with significant positive effects observed with only psychomotor speed and delayed recall in a subset of antidepressants, such as vortioxetine, with most antidepressants having no evidence for improving cognitive function (Rosenblat et al., 2015). The foregoing unmet needs underscore the need for a fast-acting, effective treatment for TRD with robust pro-cognitive effects (McIntyre et al., 2014).

Extant literature has evaluated the efficacy of ketamine, an N-methyl D-aspartate receptor antagonist, across numerous routes of administration, such as intravenous (IV), intranasal (IN), and oral routes (Coyle and Laws, 2015b; Fond et al., 2014; Rosenblat et al., 2019). The efficacy and safety of different ketamine formulations has also been assessed, such as racemic ketamine and the enantiomer esketamine and arketamine (Daly et al., 2018; Fava et al., 2018; Leal et al., 2020). For TRD, IV racemic ketamine and IN esketamine provide rapid onset antidepressant and anti-suicidal effects within 24 h following administration (Mathew and Zarate, 2016; Singh et al., 2016, 2017; van de Loo et al., 2017). The rapid efficacy of IV ketamine for patients with TRD has been further established through numerous randomized, double-blind, placebo-controlled trials, and large case-series from clinics providing off-label repeat-dose ketamine treatment for unipolar and bipolar TRD (aan het Rot et al., 2010; Berman et al., 2000; Coyle and Laws, 2015a; Daly et al., 2019; Kraus et al., 2017; Newport et al., 2016; Phillips et al., 2019). Our study assesses the effects of IV ketamine only, as the IN administration of esketamine lowers absorption predictability (Quintana et al., 2018).

Preliminary findings suggest that recreational abuse of ketamine may be associated with cognitive impairments in working memory, episodic memory and executive functioning (Morgan et al., 2009, 2014). The efficacy of ketamine in TRD patients provides the impetus to evaluate whether ketamine treatment can improve measures of cognition or limit anti-cognitive effects, as observed in the recreational use of ketamine. Notwithstanding the effects of typical monoamine-based antidepressants and recreational abuse of ketamine on cognition (Morgan et al., 2014; Rosenblat et al., 2015), the neurocognitive effects of ketamine in treatment-resistant depression is less clearly understood. Herein, we aim to systematically evaluate the effects of IV ketamine on cognition in TRD.

2. Methods

2.1. Literature search and study selection

Two independent reviewers (HG and BG) searched the literature for studies that evaluated cognition in TRD patients following ketamine treatment across all forms of administration (IV, IN and oral). We conducted a search on PubMed, Google Scholar and PsycINFO for English-language articles published between database inception to March 24th, 2020 using the following medical search heading (MeSH) terms and search strings: (Ketamine OR Esketamine OR S-Ketamine OR Arketamine OR R-ketamine) AND ((depression OR (major depressive OR treatment-resistant depression) AND (cognition OR neurocognition OR cogni*). An additional search was performed in the reference list of identified articles. Our systematic review reported results using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist was used to improve the reliability of included studies and comprehensively report the study methods and results (Moher et al., 2010).

2.2. Study outcomes

Although there is no agreed upon definition for TRD, it is commonly defined as an inadequate response to at least two prior antidepressant trials, following appropriate treatment dose and duration (Gaynes et al., 2020). Therefore, only studies that operationalized TRD in this way were included. Cognitive outcomes were not limited to any single criteria or definition. All domains of neurocognition were included.

2.3. Eligibility criteria

2.3.1. Inclusion criteria

Our inclusion criteria are as follows:

1 Clinician-confirmed diagnosis of MDD and/or MDD diagnosis according to validated scales (e.g., The Diagnostic and Statistical Manual of Mental Disorders (DSM)).
2 Validated objective or subjective measure of cognition.
3 Inadequate response to at least two antidepressant trials.
4 TRD as a primary or co-primary diagnosis and ketamine as a primary treatment with no adjunctive antidepressant treatments.

2.3.2. Exclusion criteria

Our exclusion criteria are as follows:

1 Unpublished data sets, case studies, conference reports, non-refereed abstracts, or observational studies.
2 Multiple reports from the same data set.
3 Absence of clinical assessment of depression and/or sample not meeting the criteria for TRD as part of MDD.
4 Absence of clinical assessment of cognition.
5 Adjunctive ketamine treatment (i.e., ketamine and ECT therapy).
6 Animal studies.

2.4. Study selection

Authors HG and BG reviewed all articles that met inclusion criteria to assess for the following primary outcome: evaluate the cognitive outcomes in TRD patients as part of MDD or following ketamine treatment across all methods of administration. Data were extracted using a standard data extraction form for: sample size, gender distribution, intervention features (i.e., method of assessment, details of controls), mean age, method of ketamine administration (i.e., IV, IN and/or oral), baseline and post-infusion cognitive measures (change, mean and SD), study design, outcome of interest, and reported findings. Where there was more than one intervention assessment of depression, the primary measure was used.

2.5. Assessment of bias

Study quality (i.e., risk of bias) was assessed using the *revised Cochrane risk-of-bias tool for randomized trials* (RoB 2: A revised Cochrane risk-of-bias tool for randomized trials, 2020). Bias was assessed in accordance with the six domains evaluating risk of bias: 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 (RoB 2: A revised Cochrane risk-of-bias tool for randomized trials, 2020). Complete results from the Cochrane risk-of-bias guidelines are presented in Table 1.

3. Results

3.1. Search results and study characteristics

After removal of duplicates, our database search returned 543 unique articles. An additional 3 articles were found through a manual search of the references. Subsequently, 546 titles and abstracts were independently reviewed for eligibility. The full text of 16 articles were screened for eligibility.

Following full-text review, 11 articles were excluded for not meeting the outlined inclusion criteria and primary study outcomes. The reasons for exclusion are as follows: seven articles were excluded for not having TRD as the primary diagnosis in the participant group, two articles were excluded for no/incomplete assessment of neurocognition (i.e.,

Table 1
Cochrane Risk of Bias Assessment Results.

Source	Domain 1: Risk of bias from the randomization process	Domain 2: Risk of bias due to deviations from the intended interventions	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 the selection of the reported result	Domain 6: Other bias	Overall assessment of bias
Liu et al., 2019	Low	Low	Low	Low	Unclear	Low	Low
Chen et al., 2018	Low	Low	Unclear	High	Low	Low	Low
Murrough et al., 2013	Low	Low	Low	Low	High	High	Low
Murrough et al., 2015	Low	Low	Low	Low	Low	Low	Low
Shiroma et al., 2014	High	Low	Low	Low	High	Low	Unclear

cognition evaluated at baseline and a separate timepoint), one article was excluded for providing ketamine treatment in combination with another modality (i.e., electroconvulsive therapy (ECT)), and one article was excluded for providing measurements from an already included dataset. A complete summary of search results is presented in accordance with the PRISMA guidelines (Fig. 1).

In all studies, participants received an IV infusion of ketamine (0.5 mg/kg) over 40 min. Two studies included six repeat-dose ketamine infusions across 12 days (baseline, day 3, 5, 8, 10 and 12 (Liu et al., 2019; Shiroma et al., 2014). Moreover, in combination with the 0.5 mg/kg treatment group, one study included a separate group of participants receiving 0.2 mg/kg infusion of ketamine over 40 min to measure dose effects on treatment response and cognition (Chen et al., 2018). A complete summary of study characteristics are presented in Table 2.

3.2. *Measurements of neurocognition across studies*

All studies assessed baseline measures of cognition. Three studies obtained baseline measures within one week prior to the initial ketamine infusion (Murrough et al., 2013, 2015; Shiroma et al., 2014). One study obtained baseline measures two days prior to their ketamine infusion (Chen et al., 2018). The final study did not specify when baseline measures were collected (Liu et al., 2019).

The timing of post-infusion cognitive measures varied between studies. The cognitive effects may vary widely based on timing during and immediately following the infusion. Therefore, the time-points for assessment are an important consideration. Shiroma et al. obtained cognitive measures after each follow-up visit (days 3, 5, 8, 10 and 12) (Shiroma et al., 2014). Meanwhile, Murrough et al., (2013) administered only one neurocognitive assessment immediately following IV ketamine infusion (Murrough et al., 2013). One study obtained follow-up cognitive measures seven days after the ketamine infusion (Murrough et al., 2015). Another study obtained follow-up cognitive measures following a single ketamine infusion (day 3), and then two weeks post-ketamine treatment (day 14) (Chen et al., 2018). The final study assessed cognitive measures one day after the final infusion (day 13), and two weeks following the final infusion (day 26; Liu et al., 2019) (Table 3).

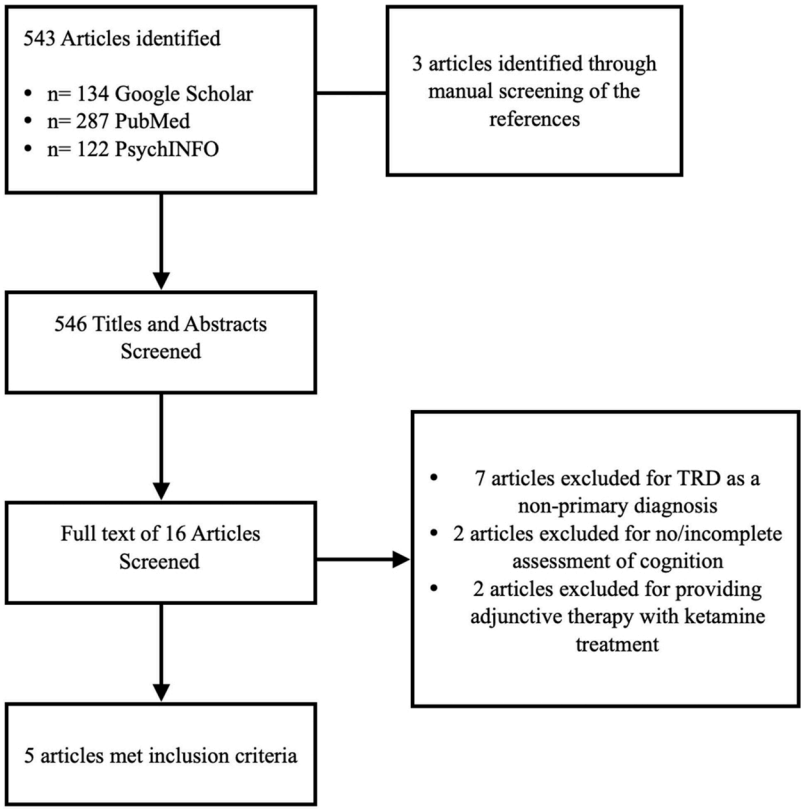

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) study selection flow diagram.

Table 2
Table illustrating the characteristics of included studies.

Source	Sample Size	Gender (No. %)	Mean Age (SD)	Ketamine Administration	Cognitive Assessment	Depression Assessment	Study Design
Liu et al., 2019	50	F:56 % M:44 %	34.00 (11.34)	IV 0.5 mg/kg at timepoints 1, 3, 5, 8, 10, 12 days	MCCB: SOP, WM, VBM, VSM	DSM-V, HDRS, MADRS	Open-label
Chen et al., 2018	24	F:87.5 % M:12.5 %	48.46 (11.01)	Single IV infusion of 0.5 mg/kg or 0.2 mg/kg	Go/no-go task, WM task	HDRS	Randomized, double-blind, placebo-controlled
Murrough et al., 2013	25	F:40 % M:60 %	49.00 (11.20)	Single IV infusion 0.5 mg/kg	WRAT-3 reading; WAIS-III Vocabulary and Reasoning; MCCB: SOP, WM, VBM, VSM	IDS-C_{30}, MADRS	Randomized, double-blind, placebo-controlled
Murrough et al., 2015	43	F:57 % M:43 %	47.1 (12.6)	Single IV infusion 0.5 mg/kg 7 days	MCCB: SOP, WM, VSM, VBM, reasoning	MADRS,	Randomized, double-blind, placebo-controlled
Shiroma et al., 2014	15	F:0% M:100 %		IV infusion 0.5 mg/kg at days 3, 5, 8, 10 and 12	Attention: IDN; WM: ONB, TWOB, GML; VM: CPAL, OCL, GMR; VBM: ISL, ISRL; SOP: GMCT, DET; set shifting: SETS	SCID, HDRS	Open-label

Abbreviations: Mmale, F = female, SD = standard deviation, IV = intravenous, MCCB = MATRICS consensus cognitive battery, SOP = speed of processing; SSset shifting, WM = working memory, VBM = verbal learning and memory, VSM = visual learning and memory, VM = visual memory, HDRS=Hamilton depression rating scale, MADRS = Montgomery–Asberg depression rating scale, IDS-C_{30}inventory of depressive symptomatology—clinician rated, IQ = intelligence quotient, WRAT-3=wide range achievement test 3, WAIS-II = Wechsler adult intelligence scale, SCID = structured clinical interview for the DSM-IV, IDN = identification task, ONB = one back task, TWOB = two back task, GML = Groton maze learning test, CPAL = continuous paired associate learning task, OCL = one card learning task, GMR = Groton maze learning test-delayed recall, ISL = international shopping list task, ISRL = international shopping list task-delayed recall, GMCT = Groton maze chase test, DET = detection task, SETS = set-shifting task.

Table 3
Table illustrating study outcomes and findings for the effects of ketamine on cognition.

Source	Study Outcomes	Primary Findings
Liu et al., 2019	Investigate differences in neurocognition following six IV ketamine infusions in participants with anxious and non-anxious TRD.	Anxious TRD patients reported improvements in working memory and speed of processing at day 13 and 26 post-infusion. No improvements were observed in the non-anxious TRD group.
Chen et al., 2018	Evaluating cognitive function before and after single low dose IV ketamine (0.3 mg/kg and 0.5 mg/kg) in TRD patients at baseline, day 3, day 14 post-infusion	No impairment in cognition following 0.3 mg/kg IV ketamine. Improvements in attention and response control with 0.5 mg/kg IV ketamine (day 14).
Murrough et al., 2013	Evaluated the relationship between baseline and post-infusion neurocognition in response to ketamine	Lower neurocognitive performance at baseline associated with better IV ketamine response. Impairments in memory recall 24 h following 0.5 mg/kg IV ketamine
Murrough et al., 2015	Evaluate the effect of IV ketamine on neurocognition 7 days post-infusion and whether baseline neurocognition predicts ketamine response.	No significant improvements in neurocognition 7 days post-infusion compared to controls.
Shiroma et al., 2014	Evaluate the neurocognitive performance in TRD patients at baseline and through six IV ketamine infusions. Also, assess whether neurocognitive changes were associated with treatment relapse.	Statistically significant improvements in visual memory, simple working memory, and complex working memory after the sixth ketamine infusion compared to baseline.

Abbreviations: TRD = Treatment-resistant depression, NOS = Newcastle-Ottawa Scale, IV = intravenous.

3.3. The effects of ketamine on working memory

Five studies assessed the effects of ketamine on working memory (WM) performance (n = 132) (Liu et al., 2019; Chen et al., 2018; Murrough et al., 2013, 2015; Shiroma et al., 2014). One study utilized the one-back test (ONB), two-back task (TWOB), and the Groton maze learning test (GML) to measure simple, complex, and spatial components of WM, respectively (Shiroma et al., 2014). Another study assessed WM by measuring reaction time to repeated numbers that were presented with only one number separating them. For example, the presentation of the number 23 followed by 45, and then 23 again (Chen et al., 2018). Meanwhile, Murrough et al. (2013) and Murrough et al. (2015) used the Wechsler Memory Scale-III (WMS-III) spatial span and the letter-number task to measure WM. One study did not specify the WM task used (Liu et al., 2019).

Four studies did not find statistically significant changes (i.e., improvements or worsening) in measures of WM following ketamine administration (Liu et al., 2019; Chen et al., 2018; Murrough et al., 2013, 2015). Shiroma et al. (2014) found significant improvements in complex (p =0.008) and simple (p =0.027) WM following the final ketamine infusion. No improvements were demonstrated for spatial WM (Shiroma et al., 2014). Moreover, when Montgomery-Asberg Depression Rating Scale (MADRS) scores were considered as a covariate, no significant differences were found in complex (p =0.230) or simple (p =0.917) WM in the treatment group (Shiroma et al., 2014).

3.4. The effects of ketamine on speed of processing

Four studies assessed speed of processing (SOP) following ketamine infusions (Liu et al., 2019; Murrough et al., 2015; Shiroma et al., 2014). One study did not specify the test used to measure SOP (Liu et al., 2019). Two studies used category fluency, trails A, and the Brief Assessment of Cognition in Schizophrenia (BACS) digit symbol tasks to assess SOP (Murrough et al., 2013, 2015). The fourth study used the Groton maze chase test (GMCT) and detection task (DET) to assess SOP (Shiroma et al., 2014).

Liu et al. (2019) evaluated SOP in patients with anxious TRD and non-anxious TRD. They found that patients with anxious TRD exhibited significant improvement in SOP both one day and two weeks following the completion of six serial ketamine infusions (ps <.001). In contrast, patients with non-anxious TRD displayed no significant differences in SOP (Liu et al., 2019). Another study assessed SOP in patients who received ketamine compared to an active control group who received 0.045 mg/kg of midazolam instead of ketamine. They found that seven days following treatment, both groups displayed significant improvements in SOP (p =0.013) (Murrough et al., 2015). Two studies did not find significant changes in SOP following ketamine infusions (Murrough

et al., 2013; Shiroma et al., 2014).

3.5. The effects of ketamine on verbal memory

Four studies assessed verbal memory (VBM) (Liu et al., 2019; Murrough et al., 2013, 2015; Shiroma et al., 2014). Of these, one study did not specify the test used (Liu et al., 2019). Two studies used the Hopkins verbal learning test (HVLT) and delayed recall tasks (Murrough et al., 2013, 2015). One study used the international shopping list task with and without delayed recall (Shiroma et al., 2014).

Liu et al. (2019) found significant improvements in VBM for participants with anxious TRD the day after the ketamine infusions were complete (p =0.028). However, these differences were not sustained two weeks after the final ketamine infusion (p =0.902). Significant VBM improvements were not found in participants with non-anxious TRD (Liu et al., 2019). In contrast, two studies did not find significant improvements in VBM following ketamine infusions (Murrough et al., 2015; Shiroma et al., 2014). Another study found significant decreases in HVLT delayed recall performance 40 min after IV ketamine administration (p = .001) (Murrough et al., 2013).

3.6. The effects of ketamine on visual learning memory

Four studies assessed visual learning memory (VSM) (Liu et al., 2019; Murrough et al., 2013, 2015; Shiroma et al., 2014). Two studies used the brief visual memory test (BVMT) learning component (Murrough et al., 2013, 2015). Shiroma et al. (2014) used the continuous paired associate learning task (CPAL), one card learning task (OCL), and the Groton maze learning test (delayed recall) to assess VSM (Shiroma et al., 2014). One study did not specify the test used (Liu et al., 2019).

Three studies found no improvements in VSM following ketamine administration (Murrough et al., 2013; Shiroma et al., 2014; Liu et al., 2019). One study found improvements in VSM for both ketamine and midazolam treatment (i.e., control) groups (p = .014). However, there was no direct effect of ketamine on VSM (Murrough et al., 2015).

4. Discussion

Our review explored the effects of ketamine on neurocognition in TRD populations. The primary cognitive measures amongst the included studies were WM, SOP, VBM and VSM. Improvements were observed in complex and simple WM (Shiroma et al., 2014). Similarly, improvements in SOP (one day and two weeks) and VBM (one day) were observed in anxious TRD patients following ketamine treatment (Liu et al., 2019). Meanwhile, only one study found improvements in VSM following IV ketamine infusions. However, ketamine did not offer greater improvement compared to midazolam (Murrough et al., 2015). Moreover, although it was not a primary aim, no worsening of cognitive function was seen in any study.

It is important to note that although there were no conclusive findings with regards to the pro-cognitive effects of ketamine in TRD, evidence for anti-cognitive effects were not present. However, further research regarding the cognitive effects of ketamine in TRD is essential. For example, Morgan et al. (2014) assessed the long-term impact of frequent, infrequent, and abstinent ketamine use on cognitive function in a sample of individuals with no history of psychiatric illness. Frequent use was defined as taking ketamine at least three times per week for one year. Researchers reported that long-term ketamine-induced cognitive deficits were present in frequent users only. Behavioural findings indicated declines in spatial WM, which were characterized by reduced hippocampal complex and left caudate activation (Morgan et al., 2014). On the other hand, in a double-blind clinical trial investigating the effects of ketamine on driving performance, participants were administered 84 mg of IN esketamine and 30 mg of oral mirtazapine. Driving performance is an important proxy for cognitive function. The findings demonstrated no driving impairment associated with IN esketamine eight hours following administration (van de Loo et al., 2017). While recreational use of ketamine indicates possible anti-cognitive effects, current findings suggest that subanesthetic administration of ketamine does not lead to significant cognitive impairment.

4.1. Ketamine and cognition

Extant findings from clinical and preclinical trials suggest that ketamine targets glutamate and brain-derived neurotrophic factor (BDNF) that are implicated in neuroplasticity. Modulation of glutamatergic receptors (N-methyl-D-aspartate [NMDA] and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) have important implications for both emotion regulation, as well as affective and cognitive processing (Lee et al., 2016). Structural changes such as neuronal atrophy and decreased synaptic connectivity in the prefrontal cortex (PFC) and hippocampus are commonly present in TRD patients (Bora et al., 2012; Sheline et al., 2003). This may occur due to dysregulation and hyperactivity of stress hormones, such as cortisol, which can be cytotoxic to neurons and glia (McEwen and Stellar, 1993). Chronic stress may shift the internal milieu to a proinflammatory state whereby neurogenesis, and therefore neurotrophic factors (i.e., BDNF), are downregulated. Moreover, higher serum levels of BDNF may predict antidepressant response (Wolkowitz et al., 2011). It is hypothesized that ketamine antagonizes the GABAergic interneuron NMDA receptors leading to a disinhibition of glutamatergic neurons that modulate AMPA (Zanos and Gould, 2018). Activation of these glutamatergic receptors leads to increased BDNF expression and downstream synaptogenesis in areas including the PFC and hippocampus (Duman, 2014). As such, ketamine is hypothesized to modulate neural substrates that subserve cognitive processes and this may be an important target for ketamine's antidepressant properties.

Based on current psychopathology and clinical-trial findings, it may be beneficial to discuss cognition as a pathophysiology of depression in accordance with the research domain criteria (RDoc) (Insel, 2014). In particular, studies should focus on the positive and negative valence systems. The preponderance of evidence, based on extant findings, gives a reason to believe that there may be benefits in general cognitive systems (e.g. working memory). Results demonstrate a particular effect of ketamine's efficacy in people with anhedonia (i.e., the positive valence systems), as well as people with anxious depression (i.e., the negative valence systems) (Ionescu et al., 2014; Lally et al., 2014). As such, it appears to be the case that ketamine is effective in these groups which have hitherto not been sufficiently responsive to conventional antidepressants.

4.2. Psychotherapy and ketamine for the treatment of cognitive deficits

Recent literature has explored the efficacy of ketamine and psychotherapy for the treatment of MDD. All forms of psychotherapy induce behavioural changes and current hypotheses involving ketamine suggests modulation in neuroplasticity with behavioural changes (Duman et al., 2016). For example, ketamine in combination with motivational enhancement therapy (MET) has shown improvements in drinking in subjects with alcohol use disorder, underscoring the potential for combination therapy including behavioural treatments and pharmacotherapy (Dakwar et al., 2020).

Moreover, recent findings using cognitive behaviour therapy (CBT) offer promising results that extend ketamine's antidepressant effects (Krystal et al., 2019). For example, Wilkinson et al. (2017) explored the effects of CBT in patients with TRD receiving IV ketamine treatment. Participants received two 0.5 mg/kg IV infusions of ketamine per week for two weeks. Next, they received concurrent CBT twice per week, with the first session being 24−48 hours following the first ketamine infusion. Patients continued to undergo CBT for eight additional weeks following the completion of ketamine infusions. Long-term follow-up demonstrated that median time to relapse was twelve weeks. This indicates that

the antidepressant response to ketamine was sustained throughout the duration of CBT for the majority of patients, thereby demonstrating its potential in prolonging and sustaining ketamine response in patients with TRD (Wilkinson et al., 2017). Combined with the aforementioned results indicating reduced cognitive function in frequent, long-term ketamine users, the need for ketamine therapies that produce sustained results with short-term exposure to ketamine is emphasized. With further research, ketamine combined with CBT may be able to achieve these results. Further empirical research on the effects of ketamine on cognition will help improve the selection of specific psychotherapies that enhance the antidepressant effects of ketamine.

5. Limitations and future directions

Current findings suggest that IV ketamine may have positive effects in working memory, anxious depression (the negative valence systems) and anhedonia (the positive valence system). Future studies should aim to expand on the effects of IV ketamine with these specific domains of cognition, as well as a transdiagnostic approach of evaluating cognition in accordance with the RDoc criteria. Moreover, due to the limited number of studies that have evaluated the effects of IV ketamine on cognition in a clinically-representative sample of TRD patients, clinicians should continue to adhere to post-treatment monitoring guidelines for adverse and dissociative effects.

A limitation of current findings evaluating the effects of ketamine on cognition in TRD is the paucity of real-world clinical studies. Only Liu et al. (2019) conducted the study in a real-world clinical setting. However, the study lacked a placebo-control group and replication of their findings is required with sufficient characterization of potential subgroups such as duration or number of depressive episodes. Illness duration and number of episodes influence cognition and greater heterogeneity is important for the translation of findings to real-world application (McIntyre et al., 2013).

Secondly, three studies employed a single dose IV paradigm. There is a need for repeat dose studies to further elucidate the relationship between cognitive functioning and ketamine's mechanism of action. A double-blind placebo controlled study by Ionescu et al. (2019) assessed the antidepressant efficacy of repeat-dose IV ketamine on patients with TRD and suicidal ideation. They found that, compared to placebo, ketamine did not produce significant improvements in depressive symptomatology, or in suicidal ideation (Ionescu et al., 2019). This is contrary to previous findings regarding the efficacy of single-dose ketamine, highlighting the need for greater research regarding the cognitive effects of repeat-dose ketamine. Moreover, a proprietary IN esketamine was approved by the United States Food and Drug Administration (FDA) in March 2019 as an adjunctive treatment for adults with TRD. In a randomized clinical trial with 67 adult patients, response to IN administered esketamine persisted for more than two months, and higher doses (56 mg or 84 mg) were associated with greater efficacy (Daly et al., 2018). However, there is a paucity of research with regards to IN ketamine and cognition. These limitations extend to oral administration of ketamine, as well as to esketamine.

Moreover, another limitation of the extant findings is the exclusion of anxiety, anhedonia and suicide measures. Liu et al. (2019) provided a comprehensive comparison of anxious TRD and non-anxious TRD subjects. However, neither of the remaining four studies included and/or controlled for anxiety in their participant samples. As conjectured by the Liu et al. (2019) findings, anxious and non-anxious TRD patients may vary in their response to IV ketamine treatment and exhibit a differential response to cognitive measures across multiple domains. Meanwhile, no study included an assessment for suicide or anhedonia. For example, Liu et al. (2019) had one participant discontinue due to suicidal behaviour. However, suicide was not assessed in their outcome measures (Liu et al., 2019). Ketamine has been previously shown to have potential anti-suicide properties. It can be conjectured that this benefit in suicidality may reflect improvement in cognitive function (Lee et al., 2016). Similarly, ketamine has been shown to reduce anhedonic symptoms in TRD subjects independent of depressive symptomatology (Lally et al., 2014). As such, the evaluation of neurocognitive measures should be supplemented by the inclusion of appropriate anxiety, anhedonia and suicide measures.

Fourth, only objective measures of cognition were administered for all included studies. Literature shows that there is a need for both objective and subjective measures to be assessed.

For example, a meta-analysis by McIntyre et al. (2016) evaluating the effects of vortioxetine on cognitive functioning demonstrated that objective measures of cognition varied compared to self-report measures (i.e., perceived deficits questionnaire (PDQ-5)) (McIntyre et al., 2016). As such, the addition of subjective measures may help to understand which cognitive domains are differentially affected following ketamine treatment.

Fifth, measures of cognition were assessed at varying time points in each study. This is important to note, as acute effects of ketamine differ from longer term effects. For example, in the case of IV ketamine infusions, patients may experience anti-cognitive effects during the infusion, as well as a few hours following completion of the infusion (Acevedo-Diaz et al., 2020). However, in the days to weeks following the infusion, patients may experience pro-cognitive effects. Therefore, it is important to recognize both acute and long term effects of ketamine.

Sixth, a major limitation of our current review was that only a qualitative analysis of the literature was performed. The authors for each included study were approached for raw data and a reasonable timeline of two weeks was given for a response. However, the methodological heterogeneity and available studies for each domain of cognition limited the power and feasibility of a quantitative analysis.

6. Conclusion

In conclusion, our review emphasizes the need for further research regarding ketamine and its impact on cognition in TRD patients. While few procognitive effects are observed, all studies report no cognitive impairments following subanesthetic administration of ketamine. This differs from current findings evaluating prolonged recreational use of ketamine, which demonstrate anti-cognitive effects. However, current research is limited and studies are primarily conducted in experimental settings with participant samples that are limited in their generalizability. Preliminary findings suggest potential enhancing effects of supplementing ketamine therapy with psychotherapy to sustain antidepressant efficacy and the further evaluation of ketamine in real-world clinical settings.

Contributors and funding source

Authors HG and RSM developed the research hypothesis and study design. Author HG and BG conducted the data extraction, data analysis and wrote the final draft of the manuscript. All authors contributed to the final manuscript proofreading, edits and approval for submission. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We want to extend our appreciation to all team members and co-authors for their contributions to this manuscript.

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