**Review Article**

# Ketamine and Other Glutamate Receptor Modulating Agents for Treatment-Resistant Depression: A Systematic Review of Randomized Controlled Trials

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**Abstract**

**Objective:** Available treatments of depression have limited efficacy and unsatisfactory remission rates. This study aims to review randomized controlled trials (RCTs) investigating effects of glutamate receptor modulators in treating patients with resistant depression.

**Method:** The study protocol was registered in PROSPERO (CRD42021225516). Scopus, ISI Web of Science, Embase, Cochrane Library, Google Scholar, and three trial registries were searched up to September 2020 to find RCTs evaluating glutamate receptor modulators for resistant depression. The difference between intervention and control groups in changing depression scores from baseline to endpoint was considered the primary outcome. Version 2 of the Cochrane risk-of-bias tool for randomized trials was used to assess the quality of the RCTs. No funding was received.

**Results:** Thirty-eight RCTs were included. Based on the included studies, compelling evidence was found for ketamine (with or without electroconvulsive therapy, intravenous or other forms), nitrous oxide, amantadine, and rislenemdaz (MK-0657); the results for MK-0657, amantadine, and nitrous oxide were only based on one study for each. Lithium, lanicemine, D-cycloserine, and decoglurant showed mixed results for efficacy, and, riluzole, and 7-chlorokynurenic acid were mostly comparable to placebo. A limited number of studies were available that addressed drugs other than ketamine.

**Conclusion:** The study cannot determine the difference between statistical and clinical significance between the agents and placebo due to high heterogeneity among the RCTs. Nevertheless, ketamine could be used as an efficacious drug in TRD; still, additional studies are needed to delineate the optimum dosage, duration of efficacy, and intervals. Further studies are also recommended on the effectiveness of glutamatergic system modulators other than ketamine on treatment-resistant depression.

**Key words:** *Behavioral Symptoms; Depressive Disorder; Glutamate Receptor; Glutamates; Resistant Depression; Systematic Review; Treatment*

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Major depressive disorder (MDD) is a tremendous public health problem and one of the most prevalent psychiatric illnesses, leading to increases in functional disability and mortality. Depression affects more than 264 million people worldwide (1). It has many negative impacts on society. Depression is often accompanied by negative impacts on quality of life in both personal and work life and impaired general health status. MDD imposes a great economic burden on society and is associated with a significant increase in both direct health care costs and workplace costs (2, 3). Estimates of the economic burden of depressive disorders on the U.S. health system are more than $210 billion annually - considering the costs of job problems and suicide (4). According to the World Health Organization reports, depression is among the top five causes of global burden of disease and is assumed to be the first leading contributor to disease burden by 2030 (1, 5).

Even though significant improvements have occurred in treating depression, several problems remain in managing the patients. Although the precise mechanisms of action and therapeutic activity have not been established yet, currently available treatments for depressive symptoms are of limited efficacy. They have clinically significant lag time to onset of action with unsatisfactory remission rates (6, 7). In an episode of major depression, the response and remission rates with standard treatment were reported to be 50% and 15-40%, respectively, indicating moderate efficacy of drugs (8). During a 6-year prospective study, Beekman *et al.* showed that remission only occurred in 23% of patients, and 32% experienced severe and chronic types of disease (9). More recent reviews and meta-analyses are also in line with these findings and have questioned the efficacy of these treatments (10, 11). On the other hand, electroconvulsive therapy (ECT) has brought considerable benefit for only about half of patients with treatment-resistant depression (TRD) (12).

The term TRD often refers to major depressive episodes that do not respond satisfactorily to at least two trials of antidepressant monotherapy from separate pharmacological classes with adequate doses and duration. As mentioned, due to the shortcomings of traditional antidepressants, there has been growing interest in fast-acting antidepressants, particularly among glutamate modulators, to both increase the patient's and the physician's feeling of satisfaction and to achieve a desirable response in psychiatric emergencies (13, 14). Berman and colleagues published the first clinical evidence of the rapid and robust antidepressant effect of single-dose ketamine in a randomized clinical trial. Thereafter, several randomized controlled trials (RCTs) of single-dose ketamine have also been conducted in TRD, all of which yielded the same results and demonstrated a consistent pattern (13, 15). Allbot *et al.* have shown that repeated ketamine infusion for comorbid post-traumatic stress disorder and TRD over a

12-day period could provide efficacious and safe treatment (16). Moreover, long-term management of TRD with IV ketamine has also been implicated in a case report in which ketamine was administered as augmentation therapy over 18 months (12).

There are systematic reviews on topics similar to this study without including the trials of the last five years, years in which glutamate receptor modulators received much attention. One study confirmed ketamine efficacy in treating depression by quantitatively analyzing trial data from trials up to September 2013 in which ketamine was prescribed for depressive disorders (17). By reviewing related trials up to November 2014, Serafini *et al.* reported the efficacy of ketamine specifically on TRD (18). In contrast, McCloud *et al.*, by systematically searching related studies up to 2015 and quantitatively analyzing the five included trials, found no reliable evidence of glutamate receptor modulator efficacy for treating depression in bipolar disorder (19). Due to the significant burden and high rate of treatment resistance in depression, the glutamatergic system has been of interest to researchers in recent years, especially focusing on modulator drugs. As mentioned above, some trials tried to appraise these agents and yielded different outcomes. Furthermore, no review scrutinized the whole glutamatergic system modulators and TRD alone (which is a challenge for the clinician). Therefore, there is a need to summarize the experiments. The idea behind this paper was to provide the first systematic review of glutamate receptor modulators in alleviating symptoms of TRD and assessing the adverse effects of these novel agents. This study aimed to review RCTs investigating the effects of glutamate receptor modulators on treatment of TRD.

## Materials and Methods

### *Information sources and search strategy*
The protocol of this study was prospectively registered under the code CRD42021225516 in PROSPERO. The search strategy aimed to identify studies investigating the effectiveness and efficacy of glutamate receptor modulator intervention for TRD. Scopus, ISI Web of Science Core Collection, Embase, Cochrane Library, and Google Scholar (the first 200 citations) electronic databases were searched by the first author to obtain systematic review information. The search was conducted in September 2020, without any restrictions on timespan, language, document type, and publication status. ClinicalTrials.gov, European Union Clinical Trials Registry, and Iranian Registry of Clinical Trials were manually searched to add missed related published articles, if any. This study aimed to find RCTs evaluating glutamate receptor modulators for TRD, so the terms searched were related to treatment (#1), depression (#2), resistance (#3), and glutamate receptor modulator drugs (#4), as mentioned below. Drug action mechanisms were then re-checked through the

DrugBank online database to match the study objectives (20).

#1. effect* OR efficacy OR impact OR therapy OR treat*

#2. depress*

#3. refractory OR resist*

#4a. amantadin* OR atomoxetin* OR *cycloserin* OR dextromethorphan OR rapastinel OR "GLYX 13" OR mk-0657 OR rislenemdaz OR ketamin* OR cerc-301 OR lanicemin* OR azd6765 OR memantin* OR quinolin* OR rellidep OR riluzol* OR tramadol* OR ets6103orviotra OR d-serine OR acetylcysteine OR nrx-1074 OR apimostinel OR sarcosin* OR glycin*

#4b. glutamat* OR glutamin*

The final search in all databases was as follows: #1 AND #2 AND #3 AND (#4a OR #4b). Finally, the included trials' references were reviewed to obtain non-replicated studies that met the selection criteria.

### Study inclusion and exclusion criteria

A.Aq. and A.H. independently and in parallel screened and selected the studies, and wherever there was a discrepancy, the opinion of the senior author was consulted. Published RCTs on patients with TRD diagnosis, who underwent therapeutic intervention with a glutamate receptor modulator, whose outcome was calculated based on a quantitative scale, were included. Having a passive control, a placebo control, or an antidepressant-comparison group was necessary for inclusion in the review. The settings were not restrictive criteria.

Since this study aimed to include all relevant published RCTs, conference papers whose full texts were not yet available were included. Book chapters, case reports, editorials, reviews, and non-randomized studies of intervention were excluded. This study included trials evaluating the effectiveness of drugs as monotherapy and adjunctive therapy. Both groups could be added to the same conventional treatment, such as ECT. In-vitro and animal studies were also not of interest. The diagnosis of TRD in these studies should have been made with a valid criterion, such as different Diagnostic and Statistical Manual of Mental Disorders (DSM) editions. Studies should also have used validated depression scales such as the Hamilton Depression Rating Scale (HDRS), the Montgomery – Åsberg Depression Rating Scale (MADRS), and the Beck Depression Inventory (BDI) to assess response to treatment. There was no restriction on age, gender, or ethnicity of the patients and the dose or duration of the interventions. There was no restriction on language of the studies. Authors of related articles were contacted for further information if needed.

### Data extraction

EndNote X9 (Clarivate, London, UK) was used to remove duplicate citations and the screening, and predefined Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) spreadsheets were used to record variables extracted from the included RCTs. S.H.M. and A.S.

independently extracted the data. Any disagreement was resolved through consultation with the senior author.

The formal narrative synthesis was performed in this study. The following variables were collected from each trial: inpatient or outpatient setting, design of each study, number of patients participating, age of patients, female to male ratio, diagnosis, the criterion of diagnosis, assessment scale of evaluating patients, treatment groups, drug dose in intervention groups, duration of each study, and statistical effectiveness of the intervention. S.A. reviewed funding sources of the included RCTs.

Significant differences between intervention and control groups in changing depression scores from baseline to endpoint was the primary outcome. Secondary outcomes were significant antidepressant effects earlier than the endpoint and significant side effects.

### Risk of Bias assessment

A.Ah. and A.S. assessed the risk of bias for all included RCTs using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (21). Studies were assessed for five domains, including randomization bias, intervention assignment bias, missing outcome data bias, outcome measurement bias, and selective reporting bias. The overall risk of bias was also estimated based on RoB 2 tool recommendations. Possible discrepancies were resolved by discussion, and, in some cases, the senior author was consulted to reach a consensus.

## Results

Figure 1 shows the process of selecting studies from the obtained citations. Thirty-eight RCTs were reviewed, including eighteen studies on ketamine without ECT, five studies on ketamine with ECT, two studies on lithium, one study on amantadine, four studies on riluzole, one study on 4-Cl-KYN, two studies on lanicemine (AZD6765), two studies on d-cycloserine, one study on decoglurant, one study on MK-0657, and one study on nitrous oxide. Lithium was not in the names of the drugs searched - based on previous studies - but in the final phrase, the studies related to it met the inclusion criteria. Obviously, the studies were not exactly homogenous with regard to the definition of TRD. Table 1 lists the risk of bias assessments for all included studies.

### Ketamine

Table 2 lists the characteristics of clinical trials on ketamine.

**Non ECT studies**

**Ketamine administration via the IV route**

*Ketamine administration as a single shot.* In six studies, the administration of single dose IV ketamine versus placebo (usually midazolam) was investigated in TRD patients, with three crossover and three parallel study designs (22-27). Three studies used HDRS, and three studies used MADRS as their primary method of depression assessment. All studies reported ketamine

effectiveness over placebo in reducing depressive symptoms with a minimum duration of one day and up to 14 days (22-27). One study noted that between ketamine doses of 0.1, 0.2, 0.5, and 1 mg/Kg, only the two higher doses were significantly superior to placebo (25).

It seems that administering a single shot of IV ketamine to reduce depressive symptoms is related to dose but determining the optimum dose relative to the side effects needs more research.

*Studies of the repeated-shot injection of ketamine*. Five trials were performed to evaluate the effects of cumulative doses of ketamine on reducing depression symptoms in TRD patients, and two of them were carried out in a crossover design (28-32). Four studies utilized MADRS, and one used HDRS questionnaires. Four of these papers found that ketamine was more effective on depressive symptoms than placebo, and a significantly larger proportion of ketamine receiving patients demonstrated response (> 50% reduction) and remission (MADRS < 10) compared to placebo (28-31). In one study, not only different doses of ketamine were compared, but also the efficacy of different injection methods (intravenous (IV), intramuscular (IM), subcutaneous (SC)) was examined. They revealed that ketamine's antidepressant effects were dose-dependent, but no significant difference was found between injection methods (30). On the other hand, the remaining study found no significant difference between ketamine and placebo groups (32).

## Studies of different methods of administering ketamine

*Studies on S-ketamine*. S-ketamine is a type of general anesthetic that is commonly used as a nasal spray. It is the S enantiomer of ketamine that, similarly, is an antagonist for the NMDA receptor but is 3 to 4 times more potent. In the four studies that assessed effectiveness of this drug in improving depressive symptoms, S-ketamine was significantly preferable over placebo at all-time points. All these studies had parallel designs and used MADRS for depression assessment (33-36). Interestingly, one study found that while a lower dose of 56 mg/Kg S-ketamine was significantly superior to placebo in improving depression, the 84 mg/Kg S-ketamine dosage (while still showing numerically better results) was not significantly more effective than placebo (35).

*Studies of ketamine administration in other forms*. Some studies have tried to use ketamine by other administration routes, such as oral, intramuscular, subcutaneous, or even nasal. Two of the included studies investigated the efficacy of orally taken ketamine on MADRS scores of TRD patients in a parallel design and demonstrated its superiority over placebo. Better response and remission rates were noted (37, 38). In a crossover design, another study that was concerned with intra-nasal ketamine demonstrated its superiority over placebo 24 hours after administration (39). In addition, a previously mentioned study in section 3.1.1.1.2 found no

significant difference between IV, IM, and SC methods (30).

## ECT studies

In some clinical trials, ketamine has been used as an anesthetic before ECT sessions. Five studies compared ketamine or its enantiomer S-ketamine with other anesthetic drugs such as propofol and thiopental sodium for reducing depression severity in TRD patients. All these studies were conducted with a parallel design. Only two studies found a significant difference between study groups (40, 41). One of them demonstrated ketamine superiority over thiopental in reducing HDRS scores only after the last (eighth) ECT session and showed that the duration of seizures in ECT sessions was shorter in the ketamine group (40). In addition to showing ketamine efficacy over propofol, the other study compared different intervals of ketamine injection and found no significant difference between repeated (before each ECT) and intermittent (once a week) ketamine injection for reducing HDRS scores. However, adverse effects such as hallucination and delirium were more prevalent in the repeated dosing group (41). The other three trials did not find any significant difference between study groups regarding HDRS (two studies) and MADRS (one study) scores (42-44).

### *Lithium*

Table 3 shows the characteristics of clinical trials on drugs other than ketamine. Lithium is a widely used psychiatric medication. Studies have shown that lithium and ketamine appear to have similar effects on NMDA receptors. Two parallel trials compared lithium therapy with placebo (45, 46). In one study that investigated its combination therapy with an SSRI, lithium was demonstrated to be superior over placebo plus SSRI in improving HDRS scores (45). However, in the other study, no difference was observed between lithium and placebo in reducing depression, which was assessed using MADRS (46).

### *Amantadine*

Amantadine can act as an NMDA receptor antagonist, and it has been evaluated as a single drug compared to SSRIs. In a randomized parallel study that compared the antidepressant effects of amantadine and fluoxetine, they found that while both treatment arms were effective and there was no significant difference in reducing HDRS scores, men responded significantly better to amantadine (47).

### *Riluzole*

Riluzole is a drug that is commonly known to play a role in treating amyotrophic lateral sclerosis (Lou Gehrig's disease), but some studies have shown its anti-glutamatergic effects. Four parallel design trials investigated riluzole efficacy in comparison to placebo in TRD patients (48-51). Riluzole was found to have comparable effects with placebo in reducing depressive symptoms when administered separately or after ketamine in two different studies (49, 51). In another study, no significant difference between riluzole and placebo was observed in preventing symptom recurrence

when administered in ketamine responsive patients (50). The mentioned studies utilized MADRS for their assessments. In contrast, one study found riluzole to be significantly more effective than placebo in reducing HDRS scores when administered in combination with citalopram (48).

### Cl-KYN

Seven-chlorokynurenic acid (7-Cl-KYNA) is an NMDA receptor antagonist that can cross the blood-brain barrier, and 4-Cl-KYN is a prodrug that has the same effects. However, a crossover study has found no significant therapeutic efficacy in HDRS score reduction for 4-Cl-KYN versus placebo (52).

### AZD6765

AZD6765 is another NMDA receptor antagonist, and two included studies compared its effects on depression scores in TRD patients (53, 54). In one crossover study, a small to moderate significant advantage was found for AZD6765 over placebo in acutely reducing MADRS scores only through 110 minutes (53). On the other hand, a parallel designed trial found no significant efficacy in reducing MADRS scores at sixth and 12th week after initiation of a three week AZD6765 treatment course (54).

### D-cycloserine (DCS)

D-cycloserine can act as a partial NMDA receptor agonist; however, it seems to play an antagonistic role for this receptor at higher doses. In two studies that assessed DSC efficacy, one crossover trial found no significant difference in HDRS reduction after six weeks of treatment (55). In contrast, the other study, which was conducted in a parallel design, demonstrated that the DCS treatment group had significantly improved symptoms compared to placebo (56).

### Decoglurant

Decoglurant is a drug with the selective inhibitory function of glutamate receptor type 2.3. One study compared the effects of placebo and different daily decoglurant doses of 5 mg, 15 mg, and 30 mg on MADRS scores. The results showed no difference in MADRS scores or response and remission rates between groups (57).

### Rislenemdaz (MK-0657)

MK-0657 is a selective NR2B antagonist. In a small sample crossover trial, significant reductions in depressive symptoms of TRD patients was observed based on HDRS and BDI (58).

### Nitrous oxide

Nitrous oxide is an important compound in general anesthesia. This compound can act as a competitive and non-competitive NMDA receptor antagonist. A crossover study demonstrated the effectiveness of nitrous oxide gas in improving depressive symptoms on the HDRS scale at 2 and 24 hours after inhalation compared to placebo (59).

## Discussion

Regarding the glutamate hypothesis of MDD, targeting N-methyl-D-aspartate (NMDA) receptors is becoming of great interest in various neuropsychological disturbances. In this article, we reviewed the antidepressant efficacy and safety of different glutamate receptor modulator agents in TRD in order to provide a clearer view of their benefits and potential harms. Glutamate is the chief excitatory neurotransmitter in the central nervous system, and glutamate signaling cascades are significantly involved in almost all brain circuits in both normal and pathological conditions (60, 61). There is accumulating evidence that dysfunction of these glutamatergic neurons and synapses, which play a fundamental role in mediating complex cognitive-emotional behaviors, can contribute to a variety of neuropsychiatric disorders, including major MDD (62). Even though the intrasynaptic function of glutamate is essential in information processing and synaptic plasticity, neuronal malfunction is an inevitable event in the presence of excessive extrasynaptic glutamate, which may eventually cause neuronal death. Consequently, the amount of glutamate in different synaptic areas of brain circuits and neurochemical systems must be controlled. Thus, neuronal endings and glial cells, mostly astrocytes, contain several transporters and antiporters on their surface that remove glutamate from synaptic clefts and prevent its destructive effects (63-66). Compelling evidence from clinical studies has demonstrated that glutamate transmission is aberrantly regulated in several brain regions of depressed patients, particularly in frontal and occipital cortices, which was also associated with the severity of depressive symptoms. Furthermore, a growing body of neuroimaging and histopathology literature suggests that abnormal glutamatergic signaling is associated with cytoarchitectural/morphological maladaptive changes in these brain areas (61, 67-71). Concurrently, the exciting results of animal studies are also in line with these studies and have highlighted the role of glutamate and NMDA receptor (NMDAR) complexes in different stressful situations in animal models (72-74). Taken together, the enormous plethora of emerging studies actually concentrated on the glial–neuronal glutamine/glutamate cycle related to glutamate receptors in order to shed more light on the glutamate hypothesis of MDD.

Glutamate receptors are divided into inotropic receptors, including NMDA, α-Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainite receptors and metabotropic receptors. Curiously, a wealth of data from recent basic research have implicated their place in the neurobiology of different mental illnesses (75). Wenji *et al.*, in a data meta-analysis of previous genetic experiments, have shown the association of metabotropic glutamate receptor type 7 and type 8 (GRM 7, 8) single nucleotide polymorphisms with schizophrenia and major depressive disorder (76). According to an interesting psycho-immunological systematic review, the possibility of developing and having elevated NMDA receptor antibody titers is about three times more likely among patients with

schizophrenia and MDD in comparison to control groups (77). Moreover, the possible connection between the neuroinflammatory hypothesis and the glutamate hypothesis of depression is also supported by the kynurenine pathway metabolites, which are endogenous inflammatory modulators of NMDA receptors (78). Besides, recent evidence has proposed that not only astrocytes and synaptic elements are involved in the synaptic function regulation, as mentioned above, but also microglia, as an inflammatory cell, can interact with synapses in a regulatory manner (79, 80). Another considerable aspect of MDD pathophysiology is neuroplasticity dysregulation. In a healthy brain, neural plasticity, which consists of several specific processes like synaptic plasticity and neural growth and remodeling, constantly occurs, leading to an appropriate inter-neural communication and reorganization (81, 82). Recent cumulative clinical and preclinical studies suggest that antidepressant activities of NMDA receptor antagonists are partially due to their various effects on neuroplastic processes by activating intracellular signaling pathways linked to synaptic plasticity (83). These are some of the other logical reasons for placing emphasis on NMDA receptors and their clinical relevance to major depressive disorder and broad spectrum of neuropsychiatric problems.

To date, according to a breakthrough in understanding various pathological mechanisms responsible for diverse mental and non-mental illnesses, researchers have conducted extensive studies and investigations on several anti-glutamatergic agents to verify the utility and also possible harm inherent to these novel therapeutics. Ketamine is one of the most popular glutamate receptor modulating drugs, which was first synthesized in the early 1960s. Although its precise mechanisms of action have not been elucidated yet, it is presumed that ketamine produces a rapid anti-depressive effect via binding to multiple receptors, especially NMDA, AMPA, and kainate receptors. Furthermore, ketamine elicits a unique form of functional plasticity, which alters the signal transduction pathway involved in neural plasticity (15, 84-86). Memantine is another noncompetitive NMDA receptor antagonist with rapid blocking kinetics, which was initially approved for treating moderate-to-severe Alzheimer's disease. Besides its role in improving glutamatergic tonus, mounting evidence from preclinical studies found that several downstream mechanisms enhancing brain-derived neuroprotective factor levels, inducing neurogenesis, regulating synaptic plasticity, adjusting the hypothalamic-pituitary-adrenal axis, and avoiding apoptotic cell death and neuronal atrophy are likely to be involved in generating the antidepressant-like properties of memantine. The clinical evidence is for and against the utility of memantine regimen in individuals with MDD, which is thought to be mostly attributed to memantine's specific receptor dynamics and methodological variations in studies (e.g., different

patients' baseline characteristics) (87). Riluzole is another glutamatergic modulator with additional neuroprotective properties that has been investigated recently in neuropsychiatric research. The presumptive mechanism of action of riluzole to counteract disturbed glutamate neurotransmission is related to its ability to increase glutamate metabolism and glutamate uptake by synaptic endplates and glial cells. Besides, a growing body of evidence suggests that riluzole is a neural plasticity enhancer and can also regulate the interaction between inflammatory mediators and glutamate (88-90). It should be noted that previous studies were not able to estimate the cost-effectiveness of intravenous ketamine for TRD exactly, which was due to the lack of sufficient evidence (91). Still, some reports propose the use of intranasal esketamine needs about 5000 to 8000 US dollar for the first month of treatment. The intranasal route is considered to be less costly than the infusion pump method, unlike the subcutaneous administration (92, 93).

In addition to these glutamate regulators with a wide range of efficacy, the last two decades of neuropsychopharmacology research has concentrated on complementary and herbal medicine to develop more effective and less expensive therapeutic agents with safer side effect profiles for alleviating symptoms of mood and behavioral disorders (94, 95). In an in-vivo experiment, Süer et al. reported that L-carnosine might also play a role in synaptic plasticity (96). Multiple studies have revealed that the application of L-carnosine would be of benefit in neuropsychiatric disorders, including autism, schizophrenia, obsessive-compulsive disorder, attention-deficit hyperactivity disorder, major depression disorder, Alzheimer's, and Parkinson's diseases (97, 98). Crocus sativus L., also known as saffron, is a medicinal plant that has been reported to have antidepressant features. Although serotonin and dopamine reuptake inhibitions are the main suggested mechanistic pathways for antidepressant properties of saffron and its active constituents, there have been some studies that show the potential effect of saffron extracts on glutamate system by focusing on NMDARs as well (99, 100). Saffron and its products have widely been investigated in both preclinical and clinical research, and its multiple neuropsychological properties, including anticonvulsant, anti- Alzheimer's, anti-schizophrenia, anti-Parkinson, and neuroprotective effects, have been scientifically proven (101).

Randomized controlled trials are the gold standard for evaluating the effectiveness of a drug (102). In many trials, the word effectiveness is used after obtaining a significant p-value (103). However, even a minimal effect can lead to a statistically significant analysis, which does not necessarily indicate effectiveness in the clinic (104). For a patient to be detectable with a minimal improvement in depression by a clinician, the HDRS must drop by at least seven points (105).
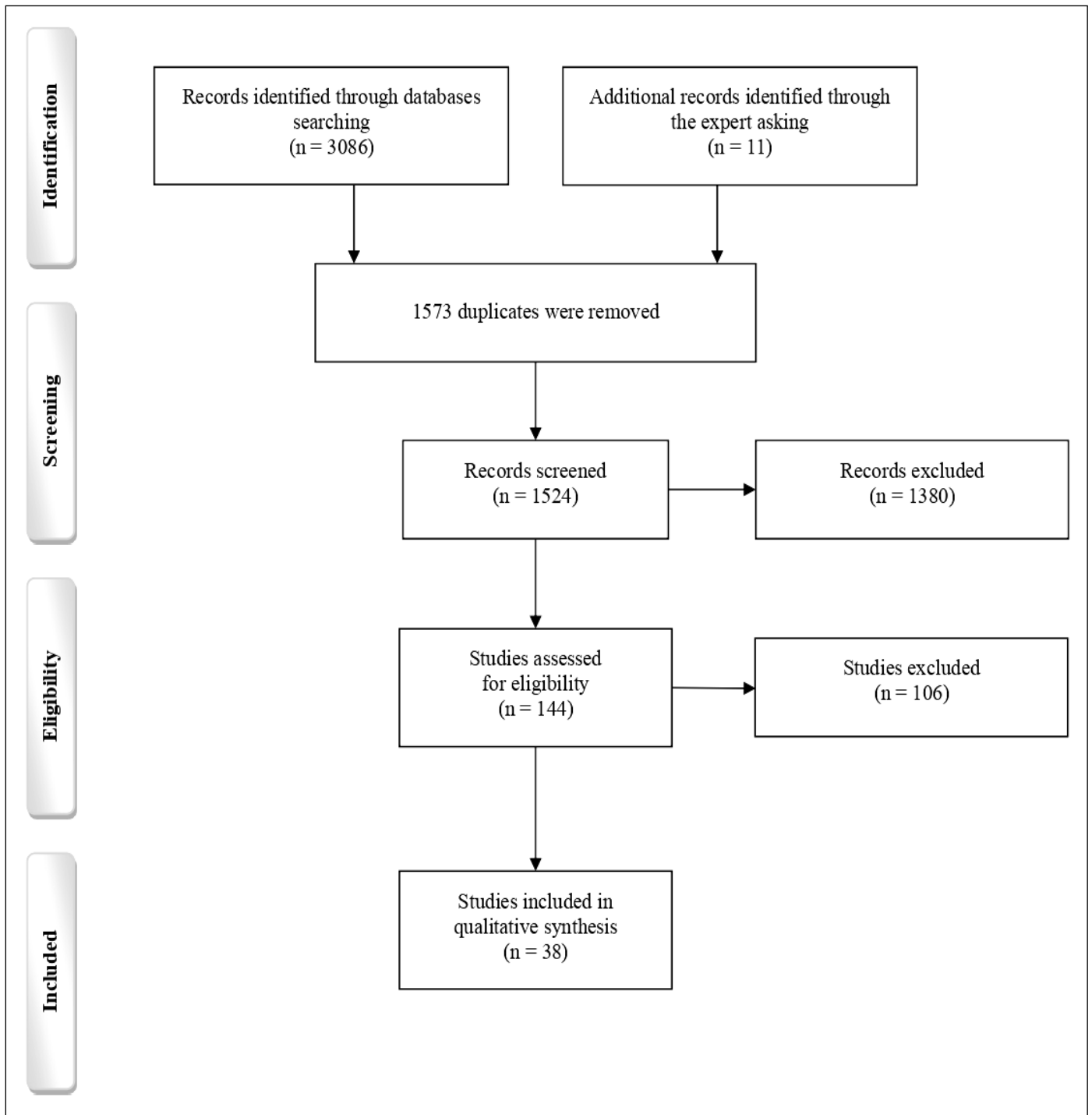
**Figure 1. Processing the Selection of Trials**

**Table 1. Risk of Bias Assessment for Depression Outcomes in Clinical Trials of Glutamate Receptor Modulators by Version 2 of the Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2)**

| 1st author, year | RD | AI | MD | OM | SL | Overall |
|---|---|---|---|---|---|---|
| Murrough, 2013 | L | L | L | L | L | L |
| Zarate, 2006 | L | L | L | L | L | L |
| Dwyer, 2021 | L | L | L | M | L | M |
| Fava, 2020 | M | L | L | L | L | M |
| Su, 2017 | L | L | L | L | L | L |
| Lai, 2014 | L | L | L | L | M | M |
| Singh, 2016a | L | L | L | L | L | L |
| Loo, 2016 | L | L | L | L | L | L |
| Phillips, 2019 | L | L | L | L | L | L |
| Ionesco, 2019 | L | M | L | L | L | M |
| Shiroma, 2020 | L | L | L | L | L | L |
| Popova, 2019 | L | M | L | L | L | M |
| Daly, 2018 | L | L | L | L | L | L |
| Fedgchin, 2019 | L | L | L | L | L | L |
| Singh, 2016b | L | L | L | L | L | L |
| Domany, 2016 | L | L | L | L | L | L |
| Domany, 2019 | L | L | L | L | L | L |
| Lapidus, 2014 | L | L | L | L | L | L |
| Salehi, 2015 | L | L | L | L | L | L |
| Dong, 2019 | L | L | L | L | L | L |
| Altinay, 2019 | L | L | L | L | H | H |
| Kuscu, 2015 | M | L | L | M | L | H |
| Jarventausta, 2014 | M | M | L | L | L | H |
| Bauman, 1996 | L | L | L | L | L | L |
| Costi, 2019 | L | L | L | L | L | L |
| Ruiz-Chow, 2010 | L | L | L | L | L | L |
| Salardini, 2016 | L | L | L | L | L | L |
| Mathew, 2017 | L | L | L | L | L | L |
| Mathew, 2010 | L | L | L | L | L | L |
| Ibrahim, 2012 | L | L | L | L | L | L |
| Park, 2020 | L | L | L | L | L | L |
| Zarate, 2013 | L | L | L | L | L | L |
| Sanacora, 2017 | L | L | L | L | L | L |
| Heresco-Levy, 2006 | L | M | L | L | L | L |
| Heresco-Levy, 2013 | L | L | L | L | L | L |
| Umbricht, 2020 | L | L | L | L | L | L |
| Ibrahim, 2012 | L | L | L | L | L | L |
| Nagele, 2015 | L | L | L | L | L | L |

RD: randomization; AI: assignment to intervention; MD: missing data; OM: outcome measurement; SL: selection; L: low risk; M: moderate risk; H: high risk.

**Table 2. Characteristics of the Randomized Clinical Trials Investigating Efficacy of Ketamine in Treatment-Resistant Depression**

| 1st author (year) | Design | Sample characteristics | Intervention | Main result(s) | Response and remission rates | Limitation(s) | Conclusion(s) |
|---|---|---|---|---|---|---|---|
| | | | Ketamine administration as a single IV shot | | | | |
| Murrough, JW (2013) | Randomized, blind, placebo controlled, parallel group trial | 73 TRD patients were divided into two treatment groups: ketamine 0.5 mg/kg and midazolam 0.045 mg/kg with a 2:1 ratio | Ketamine and midazolam were administered 0.5 mg/kg and 0.045 mg/kg as a single shot | A remarkable improvement in ketamine group compared to midazolam after 24 hours (ketamine group: CI95% (11.73-17.80), midazolam group: CI95% (18.85-26.59)) was seen | Response rate was reported 64% and 28% for ketamine and placebo groups, respectively | | Single shot of IV ketamine has rapid antidepressant effect compared to midazolam |
| Zarate, CA (2006) | Randomized, double blind, cross over trial | 18 patients were enrolled into trial | The patients took a single IV ketamine injection (0.5 mg/kg) or placebo and were assessed up to 7 days | There was a significant reduction in HDRS in time and time*treatment (p < 0.001) | During trial, 17 patients took ketamine and 71% of them responded and 29% of them reached remission | short time of trial | Single shot of IV ketamine has rapid antidepressant effect |
| Dwyer, J (2019) | Randomized, double blind, cross over trial | 18 patients were enrolled into trial | Ketamine and midazolam were administered 0.5 mg/kg and 0.045 mg/kg as a single shot | ketamine could reduce anxiety (p = 0.053) and also could reduce suicidal ideation | | | Single shot of IV ketamine has rapid antidepressant and antianxiety effects |
| Fava, M (2020) | Randomized, double blind, placebo controlled trial | 99 TRD patients were divided into five groups: ketamine 0.1 mg/kg, 0.2 mg/kg, 0.5 mg/kg, 1 mg/kg, and midazolam with a 1:1:1:1:1 ratio | Ketamine and midazolam were administered 0.1-1 mg/kg and 0.045 mg/kg as a single shot depending on patients` groups | There was a significant improvement in ketamine groups compared to placebo after 3 days (p = 0.02) and a significant different between ketamine groups was seen (p = 0.03) | After 3 days, the response rate range in ketamine groups was 37-57% and in placebo group it was 33% | 1- Small sample size 2- Inability to determine advantages of higher doses of ketamine | The IV ketamine (0.5 and 1 mg/kg) administration has efficacy to reduce depressive symptoms in TRD patients |
| Su, T (2018) | Randomized, double blind, placebo controlled trial | 71 TRD patients were divided into three treatment groups: ketamine 0.2 mg/kg (n = 23), 0.5 mg/kg (n = 24), and placebo (n = 24) | Patients took one shot IV ketamine (0.2 mg/kg or 0.5 mg/kg) depending their groups | A significant dose-related ketamine effect on scores on the HAMD. The results also show that the distinctive effects of ketamine 0.5 mg/kg relative to placebo or ketamine 0.2 mg/kg are more pronounced with increasing depression severity. | | | Evidence that ketamine has dose-related antidepressant effects that are moderated by baseline depression severity |

**Ketamine administration as repeated-shot injections studies**

| | | | | | | |
|---|---|---|---|---|---|---|
| Lai, R (2014) | Pilot cross over study | 4 TRD patients were enrolled in trial | Ketamine was administered up to 4 doses (0.1, 0.2, 0.3, and 0.4 mg/kg) over 2-5 minutes. | Three patients responded after 72 hours after injecting a dose of ketamine (2 of them were on the 0.1 mg ketamine), but the symptoms of all three patients recurred after one week. One patient entered the remission phase after receiving the maximum dose of ketamine (0.4 mg). | | 1- Small size group 2- Administration of saline as a placebo | Ketamine has an immediate antidepressant effect |
| Ionescu, DF (2019) | Randomized, double blind, placebo controlled trial | 26 TRD patients were allocated in two groups: ketamine (n = 13) and midazolam (n = 13) | The patients took ketamine in 6 doses of 0.5 mg/kg over 3 weeks | No significant reduction in depressive symptoms and suicidal idea was observed between two groups of study. (p = 0.47 and p = 0.32, respectively) | Response rate for ketamine and placebo groups were 25% and 17% and remission rate was 8% after 3 weeks | 1- Small sample size 2- Uncontrolled outpatient medication regimens 3- Restriction to outpatient | Repeated non-escalating doses of ketamine does not improve depressive symptom |
| Singh, JB (2016) | Randomized, double blind, placebo controlled parallel-group trial | 68 TRD patients were divided into four groups: 2x/wk or 3x/wk IV ketamine and 2x/wk or 3x/wk placebo with a 1:1:1:1 ratio | Ketamine was administered 0.5 mg/kg for each shot | 57 patients completed trial. After 15 days, ketamine groups had a lower MADRS significantly. (p < 0.001) | Response rates for 2x/wk ketamine and placebo were 68.8% and 15.4% and for 3x/wk ketamine and placebo were 53.8% and 6.3%. Remission rate were 37.5% and 23.1% for 2x/wk and 3x/wk ketamine, respectively. | 1- Short time of trial 2- No active placebo | Ketamine dosed 2X/wk or 3X/wk has similar effect in improving the MADRS and were generally well tolerated. |
| Shiroma, PR (2020) | Randomized, double blind, placebo controlled, parallel-group trial | 54 TRD patients were divided in two groups: five midazolam shots + one ketamine shot (n = 29) and six ketamine shots. (n = 25) | Ketamine and midazolam were administered 0.5 mg/kg and 0.045 mg/kg for each shot, respectively | A significant reduction in symptoms over study time was seen (p = 0.003). After 6th injection, no significant improvement was detected between two groups; however, it was remarkable after 5th injection (p = 0.13 and p = 0.012, respectively). | No significant difference in response rate and remission rate was detected after 6th injection between two group (p = 0.39 and p = 0.46, respectively) | 1- The population of study was remarkably male and old 2- There are some differences in results of this trial and previous studies. | Five injections of ketamine are superior to midazolam; however, when a single shot ketamine is added to midazolam, the difference fall short |

| Author (Year) | Design | Sample | Dose | Effectiveness | Response/Remission | Side effects | Limitations | Conclusion |
|---|---|---|---|---|---|---|---|---|
| Phillips, JL (2019) | Randomized, double blind, placebo controlled, cross over trial | 41 TRD patients were enrolled in trial | In the first phase, patients received an injection dose of ketamine (0.5 mg) and an injection dose of midazolam (0.045 mg) with an interval of one week. In the second phase, patients received six open labeled doses of ketamine over 2 weeks. | After the first injection, there was significant effectiveness for time (p < 0.001), drug (p < 0.001), and time*drug (p < 0.001) using random effect modeling. In the second phase, using random effect modeling, it was found that there was a significant effect for time (p < 0.001). | 24 hours after the first ketamine injection, 11 (27%) patients responded to treatment and 2 (5%) patients entered the remission phase. No patients responded to treatment after receiving midazolam and entered a remission phase. | 1- The absence of dissociative side effects with midazolam 2- The repeated and maintenance phases of the trial were open-label with no active control | | Repeated ketamine infusions have cumulative and sustained antidepressant effects |
| Loo, CK (2016) | Double blind, placebo controlled, cross over trial | 15 TRD patients were divided in four groups: IV ketamine, SC ketamine, IM ketamine, and midazolam | The initial dose of ketamine was 0.1 mg/kg, which was increased to a maximum of 0.5 mg/kg at intervals of 0.1 per week | 14 patients received midazolam. 12 patients entered both response and remission phases. The response / remission ratio in groups IV, IM, and SC were 75%, 60%, and 100%, respectively. | | | 1- Lack of randomization 2- Small sample size | Antidepressant response happens at a range of doses and at < 0.5 mg/kg. SC injection is as effective as IV injection. |

### S-Ketamine studies

| Author (Year) | Design | Sample | Dose | Effectiveness | Response/Remission | Side effects | Limitations | Conclusion |
|---|---|---|---|---|---|---|---|---|
| Popova, V (2019) | Randomized, double blind, placebo controlled, parallel group trial | 227 TRD patients were divided in two groups: oral antidepressant + s-ketamine (n = 114) and oral antidepressant + placebo (n = 109) | S-ketamine was administered 56 mg at the first of the trial and could be increased up to 84 mg. | The greater improvement was detected in s-ketamine group (p = 0.02) | 18 (16.5%) of s-ketamine's patients compared to 11 (10.8%) of placebo reached early response | | Exclusion of a lot of participants | S-ketamine has antidepressant effects and can be tolerated well |
| Daly, EJ (2018) | Randomized, double blind, placebo controlled, delayed start, parallel group trial | 67 TRD patients were divided in four groups: placebo, 28 mg s-ketamine, 56 mg s-ketamine, and 84 mg s-ketamine with a 3:1:1:1 ratio | S-ketamine was administered 28-84 mg depending on patients' group. | The greater improvement was detected in s-ketamine groups compared to placebo after 7 and 15 days (p < 0.05) | Response rate was 38%, 36%, and 50% for s-ketamine groups and 10% for placebo after 15 days. remission rate was 13%, 27%, and 40% for s-ketamine groups and 10% for placebo after 15 days. | | 1- Exclusion of a lot of participants 2- Small sample size | S-ketamine (28 mg, 56 mg and 84 mg) has antidepressant effects and can be tolerated well |

| Study | Design | Sample | Administration | Outcome | Response/Remission | Limitations | Conclusion |
|---|---|---|---|---|---|---|---|
| Fedgchin, M (2019) | Randomized, double blind, placebo controlled, parallel group trial | 346 TRD patients were divided in four groups: placebo, 56 mg s-ketamine, and 84 mg s-ketamine with a 1:1:1 ratio. | S-ketamine was administrated intranasal 56-84 mg twice in a week depending on the patients` group | The greater improvement was detected in s-ketamine groups compared placebo after 15 days; however, this improvement was not significant for s-ketamine 84 mg (p = 0.08) but significant for 56 mg (p = 0.02) | Response rate was reported 56.1%, 53.1%, and 38.9% at the end of the fourth week in the groups of 56 mg s-ketamine, 84 mg s-ketamine, and placebo, respectively. Remission rates reported 36.0%, 38.8%, and 30.6%, respectively. | 1- Exclusion of a lot of participants 2- Short time of trial | Statistical significance was not achieved with s-ketamine 84 mg compared to placebo |
| Singh, JB (2016) | Randomized, double blind, placebo controlled, parallel group trial | 30 TRD patients were divided in three groups: IV s-ketamine (0.2 mg/kg), IV s-ketamine (0.4mg/kg), and placebo | S-ketamine was administrated intravenous 0.2-0.4 mg/kg twice | S-ketamine was significantly superior to placebo (p = 0.001) | In the groups of 0.2 and 0.4 mg/kg s-ketamine, 6 (67%) and 7 (64%) treatment responses were observed, respectively, while no one responded to the treatment in the placebo group | | IV s-ketamine (0.2 mg/kg and 0.4 mg/kg) has a rapid antidepressant effect in TRD patients. Lower dose can be tolerated better. |

**Ketamine administration in other forms studies**

| Study | Design | Sample | Administration | Outcome | Response/Remission | Limitations | Conclusion |
|---|---|---|---|---|---|---|---|
| Domany, Y (2016) | Randomized, placebo controlled, double blind study | 27 TRD patients were divided in two groups: oral ketamine (n = 14) and placebo (n = 13) | | There was a clear difference in the reduction of MADRS between the two groups (p = 0.003) after 21 days | 4 (33%) patients in active groups reached clinical remission while this rate for the other group was 0 | | Oral ketamine can be as effective as IV ketamine in improving depressive symptoms |
| Domany, Y (2019) | Randomized, placebo controlled, double blind study | 41 TRD patients were divided in two groups: oral ketamine (n = 22) and placebo (n = 19) | Oral ketamine was administrated 0.1 mg/kg thrice a week for 21 days | There was a clear difference between the two groups in the reduction of MADRS (p < 0.001). | Responders were significantly different between two groups (7(31.8%) vs. 1(5.6%)). Remitters were also significantly higher in ketamine group (6 (27.3%) vs. 0). | 1- Efficient masking 2- lack of blood levels | Oral ketamine can be as effective as IV ketamine in improving depressive symptoms |
| Lapidus, KA (2013) | Randomized, placebo controlled, double blind, cross over study | 20 TRD patients were enrolled the trial. | Patients took intranasal ketamine (50 mg) and normal saline with an interval of one week | Preliminary analyzes showed that the depressive symptoms in the ketamine group improved significantly (p = 0.001) | 10 patients clinically responded to the medication (8 patients after administration of ketamine (42%) and 2 patients after placebo (11%)) | | Intranasal ketamine can be as effective as IV ketamine in improving depressive symptoms |

**ECT studies**

| | | | | | | |
|---|---|---|---|---|---|---|
| Salehi, B (2015) | Randomized, placebo controlled, double blind study | 160 TRD patients were divided in two groups: ketamine + ECT and thiopental sodium + ECT | Ketamine and thiopental sodium were administered 0.8 mg/kg and 1.5 mg/kg, respectively before ECT sessions for 8 sessions | Depressive symptoms decreased in both groups, regardless of the type of anesthetic, but this difference was significant only after the eighth ECT session (p = 0.04) | | Ketamine can prevent seizure during ECT sessions, so it can be used as an anesthetic drug |
| Altinay, M (2019) | Randomized, placebo controlled, double blind study | 15 TRD patients were divided in two groups: ketamine + ECT and midazolam + ECT | Ketamine and midazolam were administered 0.8 mg/kg and 0.045 mg/kg, respectively before ECT sessions for 8 sessions | There was no difference between the two groups based on MADRS and HDRS (p = 0.72) | 3 patients in the ketamine group (42%) reached remission, while this number was 0 for the other group / 1- Small sample size 2- High female male ratio | Ketamine is as effective as midazolam; however, ketamine causes faster relief symptoms |
| Kuscu, OO (2015) | Randomized, placebo controlled, double blind study | 58 TRD patients were divided in three groups: 4 mg/kg thiopental, 1 mg/kg ketamine, and 4 mg/kg thiopental plus 1 mg/kg ketamine as anesthetic before ECT session | Ketamine and thiopental were administered 1 mg/kg and 4 mg/kg, respectively, before ECT sessions for 8 sessions | No difference at any point in time in depressive symptoms based on the HDRS between the three study groups was detected (p = 0.54) | | Based on HDRS score, ketamine has no superiority to thiopental |
| Dong, J (2019) | Randomized, placebo controlled, double blind study | 172 TRD patients were divided in three groups: routine ECT group (n = 45), repeated ketamine assisted ECT group (n = 43), and intermittent ketamine assisted ECT group (n = 46) | Ketamine and propofol were administered 0.3 mg/kg and 1-1.5 mg/kg depending on patients` group | 134 patients completed the trial. All three groups changed compared to baseline, which was significantly higher in ketamine group (p = 0.04); however, there is no significant difference between two groups of ketamine (p> 0.05) | | Repeated ketamine injections assisted ECT session can improve significantly the symptoms of TRD patients and intermittent administration of ketamine assisted ECT session has the same effect |
| Jarventausta, KL (2014) | Randomized, pilot study | 32 TRD patients were divided into two groups: s-ketamine + propofol before ECT (n = 16) and saline + propofol before ECT (n = 16) | S-ketamine was administrated 0.4 mg/kg as a bolus shot | Both groups had a reduction in depressive symptoms but there was no significant difference in speed of response between the two groups | 1- Non fixed dose of propofol for the patients 2- Small sample size | Adjunct therapy of s-ketamine with propofol may not have extra advantages for ECT therapy |

TRD: treatment-resistant depression; CI: confidence interval; IV: intravenous; HDRS: Hamilton depression rating scale; MADRS: Montgomery – Åsberg depression rating scale; SC: subcutaneous; IM: intramuscular; ECT: electroconvulsive therapy.

**Table 3. Characteristics of the Randomized Clinical Trials Investigating the Efficacy of Glutamate Receptor Modulators Other than Ketamine in Treatment-Resistant Depression**

| 1st author (year) | Design | Sample characteristics | Intervention | Main result(s) | Response and remission rates | Limitation(s) | Conclusion(s) |
|---|---|---|---|---|---|---|---|
| | | | | **Lithium studies** | | | |
| Baumann, P. (1996) | Randomized, double blind, placebo controlled, parallel group trial | 24 TRD patients, who didn't answer to citalopram, were allocated to citalopram + Li (n = 10) and citalopram + placebo (n = 14) | The lithium was administrated in 2×400mg/d for 7 days | 6/10 patients in treatment group and 2/14 patients of placebo group were improved (p < 0.05) | | | Lithium can be an effective drug for TRD treatment |
| Costi, S (2019) | Randomized, double blind, placebo controlled, parallel group trial | 34 TRD patients, who answered to IV ketamine, were allocated to Li (n = 18) and placebo (n = 16) | The lithium was administrated in 600-1200 mg/d for 28 days. All patients took IV ketamine in 7th, 9th, and 11th days. | There was no significant different between two groups after 28 days (p = 0.91) | | 1- Using lithium as an adjunct. 2- The low range of lithium dosage for TRD treatment | There is no a significant antidepressant effect for lithium |
| | | | | **Amantadine studies** | | | |
| Ruiz-Chow, A (2010) | Randomized, double blind, controlled clinical trial | 49 TRD patients allocated two groups: fluoxetine (n = 25) and amantadine (n = 24) | | A significant reduction on HDRS was detected in both groups (55.5% and 58.3% , respectively, p < 0.05) | | | Amantadine is as effective as fluoxetine for TRD treatment |
| | | | | **Riluzole studies** | | | |
| Mathew, S. J (2010) | Randomized, double blind, placebo controlled, parallel group trial | 14 TRD patients received 0.5 mg/kg IV ketamine and were allocated two groups: riluzole (n = 6) and placebo (n = 8) | Patients received 100-200 mg riluzole or placebo for 4 weeks | 13 patients completed the trial. There is no difference between two groups in time to relapse (p = 0.68). | | 1- Open labeled ketamine admission 2- Small group size 3- Possibility of continuation | Riluzole can`t be an effective agent to prevent relapsing; however, more investigations should be done |
| Ibrahim, L. (2012) | Randomized, double blind, placebo controlled, parallel group trial | 42 TRD patients received 0.5 mg/kg IV ketamine and allocated two groups riluzole (n = 21) and placebo (n = 21) post infusion | Patients received 100-200 mg riluzole or placebo for 28 days | There is no difference between two groups in time to relapse (p = 0.11) and the mean recurrence time was 13.2 days | | Small group size | Riluzole can`t be an effective agent to prevent relapsing; however, more investigations should be done |

**Glutamate Modulators for Resistant Depression**

| Salardini, E (2016) | Randomized, double blind, placebo controlled, parallel group trial | 64 TRD patients allocated two groups, riluzole (n = 32) and placebo (n = 32) | All patients received citalopram and riluzole group patients received 50 mg riluzole for 6 weeks | Significant effect for treatment*time (p < 0.001) | Response rate for riluzole and placebo groups are 96.7% and 43.3% and remission rates are 26.7% and 10% | 1- Small group size 2- Short time of trial | Riluzole has some antidepressant effects |
|---|---|---|---|---|---|---|---|
| Mathew, S. J (2017) | Randomized, double blind, placebo controlled, parallel group trial | 104 TRD patients were allocated three groups, drug/drug, placebo/placebo, and drug/placebo with a 2:3:3 ratio | Patients received 100 mg riluzole or placebo for 8 weeks | 85 patients completed the trial. There is no significant reduction in MADRS between two groups (p = 0.1). | There is no difference in response rate and remission rate between two groups (p = 0.83 and p = 0.98, respectively) | | Riluzole has not an antidepressant efficacy compared to placebo |
| | | | **4-Cl-KYN studies** | | | | |
| Park, L. T (2020) | Randomized, placebo controlled, double blind, crossover study | 19 TRD patients were included | 4-Cl-KYN was administrated 1080-1440 mg/d for 14 days | 17 patients completed trial. No significant difference was detected in using 4-Cl-KYN as an antidepressant drug. | | 1- Small group size 2- Anxiety disorder in patients 3- Short time of trial | There is no antidepressant effect for 4-Cl-KYN |
| | | | **AZD6765 studies** | | | | |
| Zarate, C. A (2013) | Randomized, placebo controlled, double blind, crossover study | 22 TRD patients were included into trial and took 2 days drug with an interval of 1 week | AZD was administrated 150 mg IV in normal saline | A significant improvement was observed in reduction of symptoms in AZD group after 80 min lasted up to 110 min (p < 0.05) | Response rates for AZD and placebo groups were 32% and 15% and remission rates were 18% and 10% | 1- Small groups size 2- Comorbid anxiety in patients | AZD is tolerated well and can be an effective agent for reduction of TRD symptoms |
| Sanacora, G. (2017) | Randomized, placebo controlled, double blind, crossover study | 302 TRD patients were allocated into three groups: 50 mg AZD, 100 mg AZD, and saline | AZD was administrated 50-100 mg 3 times per week for 3 weeks | Taking AZD6765 had no significant effect in reduction of TRD symptoms after 6 and 12 weeks | | | AZD has no antidepressant effect for reduction of TRD symptoms |
| | | | **D-cycloserine studies** | | | | |
| Heresco-Levy, U (2006) | Randomized, placebo controlled, double blind, crossover study | 22 TRD patients were included into trial | DCS was administrated 250 mg/d for 6 weeks | 15 patients completed both period of trial. There is no significant improvement in TRD symptoms between two groups (p = 0.1). | | DCS was administrated as an adjunct therapy | There is no antidepressant effect for DCS |

| Study | Design | Sample | Dosage | Outcome | Response/Remission | Limitation | Conclusion |
|---|---|---|---|---|---|---|---|
| Heresco-Levy, U (2013) | Randomized, double blind, placebo controlled, parallel group trial | 26 TRD patients allocated two groups: DCS (n = 13) and placebo (n = 13) | DCS was administered 250 mg/d for 3 days, then 600 mg/d for 18 days, then 750 mg/d for 7 days, and then 1000 mg/d for 14 days | A significant time*treatment was seen at the end of the trial (p = 0.032) | Response rates for DCS and placebo groups were 54% and 15% and remission rates were 38% and 15% | 1- Small group size 2- Short time of trial 3- DCS was administrated as an adjunct therapy | DCS can be an effective agent for reduction of TRD symptoms |

**Decoglurant studies**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Umbricht, D (2020) | Randomized, double blind, placebo controlled, parallel group trial | 357 TRD patients were allocated in four groups: decoglurant 5 mg, 15 mg, 30 mg, and placebo | Decoglurant was administered 5-30 mg/d depending on patients' groups for 6 weeks | 310 patients completed trial. There is no significant improvement in reduction of TRD symptoms between two groups (p>0.05) | The response rate range was 35-47% and the remission rate range was 29-38% | | There is no antidepressant effect for decoglurant |

**MK studies**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ibrahim, L (2012) | Randomized, placebo controlled, double blind, crossover, pilot study | 5 TRD patients were randomized into trial | MK was administered 4 mg/d up to 8 mg/d for 12 days | 5 patients completed both period of trial. A significant improvement based on HDRS and BDI was observed (p = 0.001 and p = 0.01, respectively). | | 1- Small group size 2- Short time of trial | MK is tolerated well and can be an effective agent for reduction of TRD symptoms |

**Nitrous oxide studies**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nagele, P (2015) | Randomized, placebo controlled, double blind, crossover study | 20 TRD patients were included into trial | Active treatment was $O_2$ (50%)/NO (50%) and placebo was $O_2$ (50%)/$N_2$ (50%) for 1 hour | 15 patients completed trial. A significant improvement was seen after 2 and 24 h after taking NO (p = 0.002 and p < 0.001, respectively). | Response rates for NO and placebo groups were 20% and 5% and remission rate was 15% for active group | Drug abuse | NO can be an effective agent for improving TRD symptoms; however, its indications is limited |

TRD: treatment-resistant depression; IV: intravenous; HDRS: Hamilton depression rating scale; MADRS: Montgomery – Åsberg depression rating scale.

## Limitation

The current study cannot address the difference between statistical and clinical differences between the agents and placebo - an issue that casts doubt on the efficacy of typical antidepressants (103). We were not able to perform a quantitative meta-analysis because of great heterogeneity in the included RCTs (different drugs, dosages, administration routes, and measured outcomes). We suggest that future investigations be implemented using similar methods to reduce the heterogeneity. Researchers and clinicians should consider this issue before jumping to conclusions. Also, conducting a meta-analysis is required to judge whether there is a clinically significant difference between drugs and placebo.

## Conclusion

This study supports the function of the glutamatergic system in patients with depression. By reviewing controlled clinical trials evaluating the effectiveness of glutamate receptor modulator agents in treating TRD, many results favoring these agents' effectiveness and safety in patients with TRD were obtained. There is even evidence in favor of reducing suicidal ideation. It can be concluded from this study that the use of glutamate receptor modulators for TRD is statistically different from using placebo.

Since most studies have used antagonists of receptors involved in the glutamatergic system - most notably, ketamine - as an intervention, studying of drugs with specific antagonistic functions in this system may increase understanding of the disorder. In order to prove the efficacy of glutamate receptor modulators in treating TRD, studies with superior methodology and large sample sizes are still needed. The glutamatergic system and especially the drug ketamine are among the methods developed for the treatment of TRD, for which there is great evidence in favor of improving effects. Therefore, if necessary and despite skeptical views of definitive efficacy, the use of ketamine can be considered for therapeutic purposes by psychiatrists to help patients. Further studies of other agents are recommended.

## Acknowledgment

## Conflict of Interest

None.

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