

Comparative efficacy between ketamine, memantine, riluzole and d-cycloserine in patients diagnosed with drug resistant depression: a meta-analysis

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ABSTRACT

Background: Glutamate modulators are having immense potential and are newer entities for treating drug resistant depression. The objectives were to generate statistical evidence on basis of existing data of ketamine, memantine, riluzole and d-cycloserine in resistant depression.

Methods: A total of 14 RCTs following PRISMA guidelines and matching inclusion and exclusion criteria were collected of ketamine (5), memantine (3), riluzole (2) and d-cycloserine (4) vs placebo in drug resistant depression. Only RCTs with primary diagnosis of drug resistant depression (Previously on two standard antidepressant therapy) were included. Studies with treatment response rate, 50% reduction in total score of the depression rating scale-Montgomery-Åsberg Depression Rating Scale or the Hamilton Depression Rating Scale or Beck Depression Inventory was chosen as clinical outcome measure. RevMan 5.3 software was used for the analysis.

Results: In ketamine group using random effect model SMD was 2.122 (95% CI 0.659-3.584). P-value was statistically significant (random effect $p < 0.005$ and in fixed effect < 0.001). In memantine group, using random effect model -0.963 was SMD and (95% CI -1.958-0.0324). P-value was < 0.001 , significant in fixed effect. In riluzole group, SMD was -0.564 with (95% CI -3.927-2.799) in random effect. P-value was 0.741. In d-cycloserine group SMD was 0.316 with (95% CI -1.252-1.885) in random effect. P-value was 0.690.

Conclusions: Ketamine showed best efficacy followed by memantine. Riluzole and DCS as such have no efficacy although its acts by same glutamate pathway. More molecular based research is required in use of glutamate modulators in resistant depression.

Keywords: D-cycloserine, Drug resistant depression, Efficacy, Ketamine, Meta-analysis, Memantine, Riluzole

INTRODUCTION

Drug resistant depression becomes a major debilitating disorder in this modern era. Major depression shows 10-30% poor and unsatisfactory response despite giving two anti-depressants which is termed as drug-resistant depression. In this type of patients exhibits difficulties in social and occupational function, decline of physical health, suicidal thoughts, and increased health care utilization. This is the most prime reason why researchers

always seek for developing newer anti-depressants which can treat drug resistant depression.¹

Animal studies have shown that stress enhances glutamate release in particularly limbic and cortical areas, and it induces dendritic remodelling and volumetric reduction of synapses. So, advent of newer glutamatergic modulators has very much hope for treatment of resistant cases of depression. Glutamatergic receptor subtype, ionotropic receptors like N-methyl-D-aspartate (NMDA) and α -

amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor get more attraction in research because of some preclinical and clinical corroboration.

Other metabotropic receptors (mGluRs) are also in pipeline of research.² Many established drugs like ketamine, memantine, riluzole and d-cycloserine have possible role in drug resistant depression are now being repurposed for the same.³⁻⁶

So, it is very much essential to generate statistical evidence for the efficacy of ketamine, memantine, riluzole and d-cycloserine in drug resistant depression.

The objective was to generate statistical evidence on basis of existing data of randomised clinical trials for the ketamine, memantine, riluzole and d-cycloserine in drug resistant depression patients.

METHODS

This is a meta-analysis between four different drugs acting on glutamate receptors.

Step 1: Identification and literature search

The search was done based on preferred reporting system for meta-analysis and systemic review (PRISMA) guideline.⁷ All the scientific database like clinical trials.gov, Pubmed central, NCBI, NIH, Cochrane Library and Google scholar were used for search by using terms like Drug resistant depression, Ketamine, Memantine, Riluzole and d-cycloserine. All the trials published after January 2000 to till date were included in search.

Step 2: Criteria for selection of studies

All study related Randomised controlled trials (RCTs) using either:

- An adequate method of allocation concealment (e.g. sealed opaque envelopes),
- Studies that were double-blind, single-blind or unblinded,
- Studies that included a comparison of glutamate receptor modulator ketamine, memantine, riluzole and d-cycloserine with placebo in individuals with drug resistant depression.

Step 3: RCT enrolment criteria

Inclusion criteria

- Primary diagnosis of drug resistant depression (previously on two standard antidepressant therapy),
- RCTs of ketamine, memantine, riluzole and d-cycloserine with placebo control trials in drug resistant depression

Exclusion criteria

- Behavioural therapy or non-pharmacological treatment in drug resistant depression vs glutamate modulators
- Unpublished research work or trials
- Observational study
- Preclinical studies

Step 4: Type of intervention

Ketamine or memantine or riluzole or d-cycloserine vs placebo in drug resistant depression.

Step 5: Clinical outcome measure

Treatment response rate (50% reduction in total score of the depression rating scale-Montgomery-Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HAM-D) or Beck Depression Inventory (BDI)).

Step 6: Data extraction

Data were extract from studies meeting above criteria. Those studies in which data was unclear asked from respective authors. In some studies, data could not obtain by enquiry were excluded. Data of study design, treatment comparator, which is placebo only, dosage and standardized depressive symptoms based on MADRS or HDRS or BDI score at baseline (placebo pre and drug pre) and at the end point (placebo post and drug post) were collected. Separate analytical data for ketamine, memantine, riluzole and d-cycloserine was retrieve from relevant RCTs.

Step 7: Nullification of bias

Authors assured to include studies in which allocation of control and experimental groups were adequately randomised and there was no any conflict of interest as well as match to inclusion and exclusion criteria.

Step 8: Measures of treatment effect

Direct comparison between active drug and placebo was done using fixed and random effect model and (standardised mean deviation) SMD was calculated. An SMD of zero means that the new treatment and the placebo have equivalent effects.

If improvement is associated with higher scores on the outcome measure, SMDs greater than zero indicate the degree to which treatment is more efficacious than placebo and SMDs less than zero indicate the degree to which treatment is less efficacious than placebo. If improvement is associated with lower scores on the outcome measure, SMDs lower than zero indicate the degree to which treatment is more efficacious than placebo and SMDs

greater than zero indicate the degree to which treatment is less efficacious than placebo.

Step 9: Summary measures

The principal summary measure was done with 95% Confidence Interval and funnel as well as forest plot. RevMan@Version5.38 were used for analysis. P-value less than 0.05 was considered significant.

RESULTS

Individual searches yield total 14 studies which were qualified for analysis (Figure 1). These Placebo controlled trials include ketamine (5 Trials), memantine (3 trials), riluzole (2 trials) and d-cycloserine (4 trials) for anti-depressant efficacy evaluation.⁹⁻²²

Individual analysis of glutamate receptor modulators

Ketamine

Total 5 placebo-controlled monotherapy RCTs in drug resistant depression has been found for meta-analysis. Studies were Berman et al, Zarate et al, Zarate et al, Sos et al, Lapidus et al.⁹⁻¹³

Total number of subjects in ketamine group was 61 whereas in placebo was 69. In random effect SMD was 2.122 and 95% CI was 0.659 to 3.584. P value in random effect was 0.005 and in fixed effect <0.001 which was significant in both model (Table 1 and Figure 2). So, that prove efficacy of ketamine as an anti-depressant in drug resistant depression.

Table 1: Standardised mean difference of ketamine vs placebo group in 5 RCTs.

Study	Ketamine (n)	Placebo (n)	Total	SMD	SE	95%CI	t	P	Weight (%)	
									Fixed	Random
Berman et al,	8	8	16	2.225	0.615	0.906 to 3.543			11.49	19.69
Zarate et al,	9	9	18	4.824	0.921	2.872 to 6.776			5.12	16.84
Zarate et al,	15	15	30	3.382	0.563	2.229 to 4.535			13.71	20.14
Sos et al,	11	19	30	0.0786	0.369	-0.677 to 0.834			31.93	21.58
Lapidus et al,	18	18	36	0.796	0.339	0.107 to 1.485			37.75	21.76
Total (fixed effects)	61	69	130	1.292	0.208	0.879 to 1.704	6.199	<0.001	100.00	100.00
Total (random effects)	61	69	130	2.122	0.739	0.659 to 3.584	2.871	0.005	100.00	100.00

Heterogeneity, Q=43.7623, Degree of Freedom=4, P <0.0001, I² (inconsistency)=90.86%, 95% Confidence Interval for I²=81.61 to 95.46.

Table 2: Standardised mean difference of memantine vs placebo group in 3 RCTs.

Study	Memantine (n)	Placebo (n)	Total	SMD	SE	95%CI	t	P	Weight (%)	
									Fixed	Random
Smith et al,	15	16	31	0.0631	0.350	-0.653 to 0.779			24.40	32.09
Omranifard et al,	30	30	60	-1.116	0.274	-1.665 to -0.566			39.70	34.13
Amidfar et al,	33	33	66	-1.784	0.289	-2.360 to -1.207			35.90	33.77
Total (fixed effect)	78	79	157	-1.068	0.173	-1.410 to -0.726	-6.176	<0.001	100.00	100.00
Total (random effect)	78	79	157	-0.963	0.504	-1.958 to 0.0324	-1.911	0.058	100.00	100.00

Heterogeneity, Q=16.6197, Degree of Freedom=2, P <0.0002, I² (inconsistency) = 87.97%, 95% Confidence Interval for I²=66.33 to 95.70.

Table 3: Standardised mean difference of riluzole vs placebo group in 2 RCTs.

Study	Riluzole (n)	Placebo (n)	Total	SMD	SE	95%CI	t	P	Weight (%)	
									Fixed	Random
Salardini et al,	32	32	64	-2.267	0.318	-2.903 to -1.632			42.02	49.88
Mathew et al,	25	40	65	1.132	0.271	0.591 to 1.673			57.98	50.12
Total (fixed effect)	57	72	129	-0.297	0.206	-0.705 to 0.111	-1.439	0.153	100.00	100.00
Total (random effect)	57	72	129	-0.564	1.699	-3.927 to 2.799	-0.332	0.741	100.00	100.00

Heterogeneity, Q=66.2218, Degree of Freedom= 1, P <0.0001, I² (inconsistency)=98.49%, 95% Confidence Interval for I²=96.70-99.31.

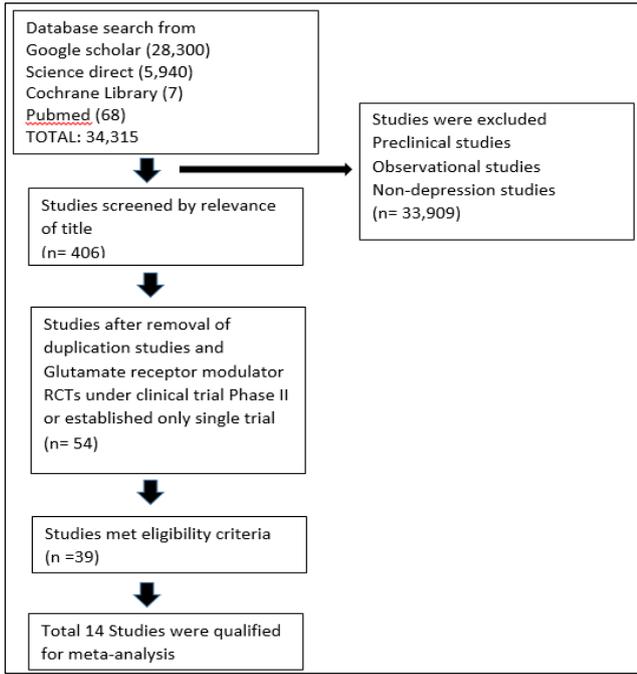


Figure 1: PRISMA flow diagram of included articles.

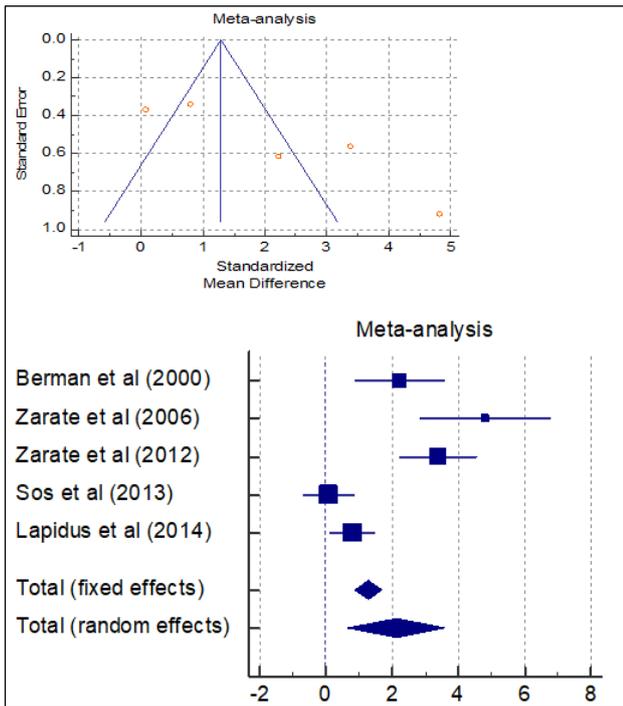


Figure 2: Funnel and forest plot results of ketamine vs placebo studies.

Memantine

There are 3 placebo-controlled trial Smith et al, Omranifard et al, Amidfar et al, were analysed with total of 78 subjects in memantine vs 79 in placebo arm. It shows -0.963 SMD and -1.958 to 0.0324 95% CI in random effect. P value was <0.001 significant in fixed effect (Table 2, Figure 3).¹⁴⁻¹⁶

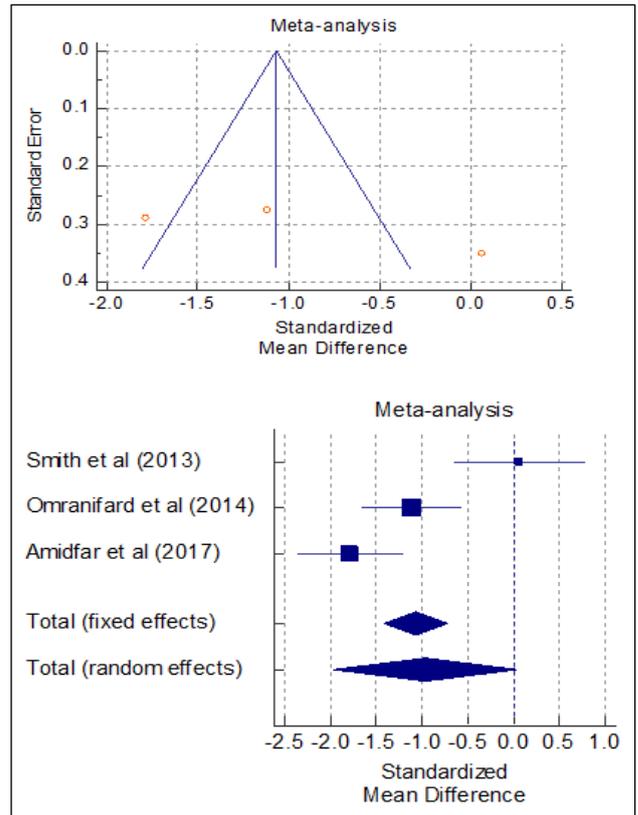


Figure 3: Funnel and forest plot results of memantine vs placebo studies.

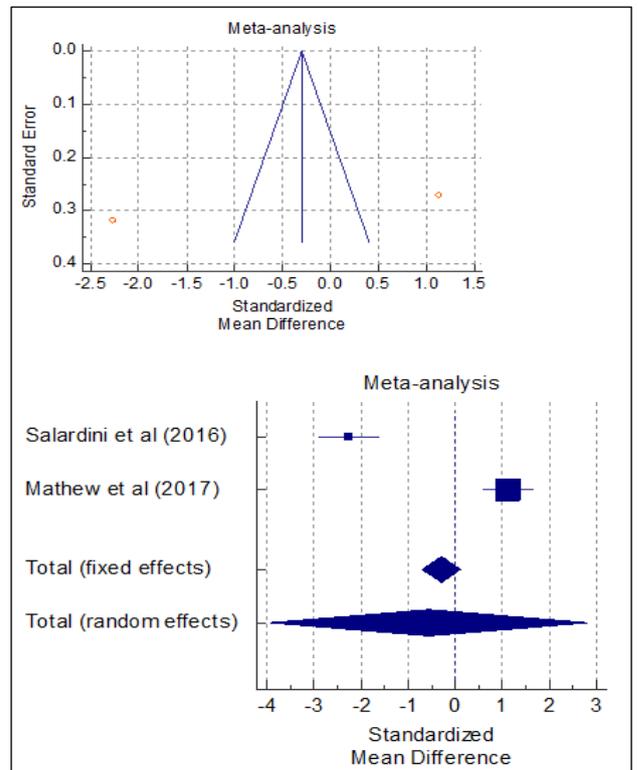


Figure 4: Funnel and forest plot results of riluzole vs placebo studies.

Riluzole

Two placebo-controlled trials Salardini et al, and Mathew et al, evaluated in which total subject in riluzole was 57 vs 72 in placebo arm.

SMD is -0.564 with -3.927 to 2.799 95% CI in random effect. There was statistically insignificant value found in both Fixed and random effect model. So, it states that riluzole has no role as an anti-depressant (Table 3 and Figure 4).¹⁷⁻¹⁸

d-cycloserine

A total of four RCTs Heresco et al, Kushner et al, Wilhelm et al, and Heresco et al, analysed, subjects involved in DCS group was 57 and in placebo 63. SMD was 0.316 with -1.252 to 1.885 of 95% CI in random effect. P value was 0.690 which was statistically insignificant shows no role of DCS in drug resistant depression (Table 4, Figure 5).¹⁹⁻²² Odds ratio for ketamine, d-cycloserine, Riluzole and Memantine was 3.26, 1.08, 0.93 and 0.92 respectively. This shows among all drugs ketamine in comparison to placebo showed efficacy in drug resistant antidepressant.

Table 4: Standardised mean difference of DCS vs placebo group in 2 RCTs.

Study	DCS (n)	Placebo (n)	Total	SMD	SE	95%CI	t	P	Weight (%)	
									Fixed	Random
Heresco et al,	19	20	39	-0.568	0.320	-1.217 to 0.0813			38.45	25.69
Kushner et al,	15	17	32	2.201	0.441	1.299 to 3.102			20.24	24.76
Wilhelm et al,	10	13	23	-1.542	0.465	-2.509 to -0.575			18.26	24.55
Heresco et al,	13	13	26	1.185	0.414	0.330 to 2.039			23.04	24.99
Total (fixed effect)	57	63	120	0.218	0.199	-0.175 to 0.612	1.100	0.274	100.00	100.00
Total (random effect)	57	63	120	0.316	0.792	-1.252 to 1.885	0.399	0.690	100.00	100.00

Heterogeneity, Q=45.9819, Degree of Freedom=3, P <0.0001, I² (inconsistency)=93.48%, 95% Confidence Interval for I²=86.49-96.85.

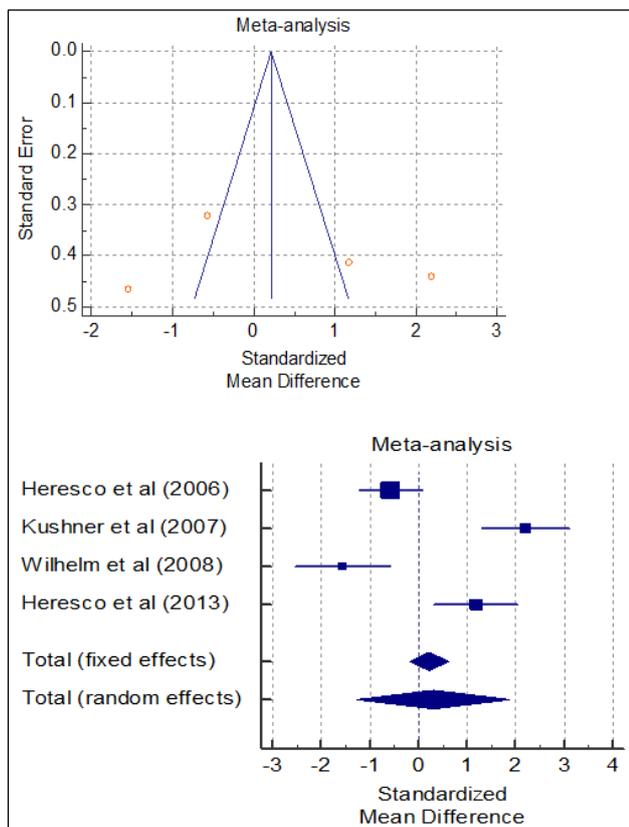


Figure 5: Forest plot results of DCS vs placebo studies.

DISCUSSION

It is well known that glutamate pathway plays a major role in pathophysiology of depression and its treatment. In the normal brain, glutamate regulates synaptic plasticity and neuron survival but under pathological conditions, increased levels of glutamate through excessive activation of the ionotropic glutamate receptors particularly NMDA receptors and consequent influx of extreme Ca²⁺ causes neurotoxicity.²³ Ketamine blocks pre-synaptic NMDAR signalling, resulting in increased glutamate release. Enhanced glutamate signalling activates post-synaptic AMPA receptors, and the resultant cell depolarization stimulates voltage-dependent calcium channels (VDCC), leading to calcium influx and BDNF exocytosis. BDNF release activates TrkB receptors and downstream signalling pathways, PI3K-Akt and MEK-Erk1/2. Both pathways activate mTOR complex1 through phosphorylation. The activity of mTOR can be potentiated by lithium through Akt activation and GSK-3 inhibition. mTOR then phosphorylates and activate sp70S6K, which inhibits eEF2K, halting the phosphorylation of eEF2, effectively inhibiting eEF2. In parallel, mTOR hyperphosphorylate 4E-BP1, reducing its interaction with eIF4E. Together, decreased eEF2 phosphorylation and the release of eIF4E from 4E-BP1 disinhibit protein translation, producing more synaptic proteins such as GluR1, PSD95, Arc, and synapsin I, as well as BDNF. This facilitates increased dendritic spine density and

synaptogenesis in the prefrontal cortex and hippocampus and leads to antidepressant-like behaviour.²⁴

One of the facts highlighted in C. Belzung study, that there were many encouraging preclinical evidence which pointed out for development of newer molecules, but somehow subsequent clinical trials have failed to show convincing results. Possibilities may be inappropriate animal models used for efficacy evaluation or may be clinical trials have not targeted appropriate dose or clinical population.²⁵

Although still some of preclinical studies shows ketamine play a role as fastest acting anti-depression but major drawback like psychomimetic symptoms, schizophrenia like symptoms and cognitive impairment are there.²⁶ Because of this reason ketamine is not widely used. To solve that one of proposed theory is addition of mood stabilizer lithium, shown to potentiate the behavioural and molecular antidepressant-like effects of ketamine.²⁷ On the basis of this other NMDA receptor antagonist, memantine also tested but its effectiveness in clinical trials have mixed and controversial evidence.²⁸ Glutamate modulator riluzole which inhibits presynaptic glutamate release and increases glial cell glutamate uptake also have some preclinical and clinical evidence of amelioration of stress induced depression.²⁹⁻³¹ D-cycloserine (DCS) is a broad-spectrum antibiotic and at doses greater than 100 mg/day, a functional NMDA glycine receptor partial agonist that may act by antagonizing the NMDA receptor.³² Efficacy of agents acting directly on the NMDA receptor found that DCS has been linked to acute antidepressant response at high doses (1000 mg) but not at low doses (250 mg).³³

Although many glutamate modulators are under research, this meta-analysis focus on ketamine, memantine, riluzole and DCS as these drugs have sufficient evidence-based data to get statistically importance. Amongst newer antidepressants ketamine till date being fastest and strongest efficacious along with some drawbacks. Whereas other drugs have found little or no role in depression so still more clinical trial has to be done to prove its efficacy.

CONCLUSION

This meta-analysis concludes four different drug efficacies in drug resistant depression. Ketamine shows efficacious in drug resistant depression. Memantine proven its little bit efficacy in depression yet more evidence based clinical trial needed to carry out. Riluzole and DCS as such have no role or efficacy in depression although its acts by same glutamate pathway. So, there are variability in pathophysiology of depression which still needed much more research for effective treatment in case of drug resistant depression.

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