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Research paper

# Does oral administration of ketamine accelerate response to treatment in major depressive disorder? Results of a double-blind controlled trial

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ABSTRACT

*Background:* Major depressive disorder (MDD) exerts a high health and financial burden on society. The conventional pharmacotherapies for MDD are partially effective and the response to medication often starts with some delay. There are recent reports of antidepressant effects for oral ketamine.
*Methods:* We employed a double-blind controlled trial to examine the time course of the therapeutic effect of ketamine when combined with the conventional administration of sertraline. A total of 81 patients participated in the study and were scored with the Hamilton Depression Rating Scale (HDRS) at baseline and at 2, 4 and 6 weeks after the start of the trial
*Results:* General linear model repeated measures demonstrated significant effect for time × treatment interaction on the HDRS scores, with significant difference at all time points post treatment. Early improvement was significantly greater in the ketamine group (85.4%) compared to the placebo group (42.5%). We did not observe any side effects for ketamine administration. Limitations: Our follow up was limited to 6 weeks post initiation of treatment and cannot reveal the potential long-term adverse effects of oral ketamine and the sustainability of its benefit.
*Conclusion:* Altogether, our results suggest that oral ketamine may be considered as suitable adjuvant to sertraline in relieving depressive symptoms.

## 1. Introduction

Depression is a common disease with a lifetime prevalence of 20–30% worldwide (Kruijshaar et al., 2005) and a huge burden on the healthcare system (Andrade et al., 2003). About one-third of patients with Major depressive disorder (MDD) do not respond successfully to conventional drugs (Rush et al., 2006). Even when effective, the conventional treatments typically require a delay before the depressive symptoms start to significantly diminish (Hillhouse and Porter, 2015). The slow response along with frequent side effects sometimes cause nonadherence and increase risk of suicide (Jick et al., 2004; Keyloun et al., 2017). Altogether, there seems to be a need for faster and more effective treatments.

A range of medications targeting diverse neurotransmitter receptors have been used to treat MDD. Glutamate, a neuroexcitatory mediator, is implicated in the pathogenesis of MDD. As such, N-methyl-D-aspartate (NMDA) receptor antagonists were found to be effective in treatment of patients diagnosed with MDD (Machado-Vieira et al., 2017). Ketamine is an NMDA receptor antagonist and was recently found to exhibit a rapid-onset treatment effect on MDD (Irwin et al., 2013; Yoosefi et al., 2014; Lee et al., 2015; Salardini et al., 2016). The rapid onset effect was even present in patients with treatment resistant depression (TRD); infusion of ketamine reduced the depressive scores after 24 h (Iadarola et al., 2015; Romeo et al., 2015). More recently, Feifel et al. (2017) reported that a single ketamine infusion caused 53.7% response and 41.5% remission in a real world TRD population with other psychiatric comorbidities. Therapeutic effects of ketamine in depression have been wildly studied by IV route. Besides IV infusion, alternative routes of ketamine delivery were examined, which include intramuscular (IM), subcutaneous (SC), intranasal and oral. The bioavailability of the drug via IV, IM and SC is nearly complete (Andrade, 2017), although Loo et al. showed that plasma concentration of ketamine is twice when used by IV route instead of IM or SC routes (Loo et al., 2016). The bioavailability of intranasal ketamine is diminished as some of the

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intranasal spray is swallowed via pharynx and thus undergoes first pass metabolism (Andrade, 2015). Oral ketamine has a high rate of first pass metabolism (Hijazi and Boulieu, 2002). However, its metabolite, norketamine, also has some antidepressant effects (Sałat et al., 2015). All routes of administration are known to be well tolerated by patients (Jafarinia et al., 2016; Lapidus et al., 2014; Lara et al., 2013). Although the bioavailability of oral ketamine is about 16% (Clements et al., 1982) and only a small portion of the drug reaches the brain, its acceptability for patients, presents clear advantages particularly for long-term use.

In a recent case series study, oral ketamine administration produced some improvement in depressive symptoms of approximately 30% of TRD cases. However, this effect was not well quantified as the study did not include a control group and was performed on a relatively small sample size of 22 (Al Shirawi et al., 2017). Overall, there is growing evidence for a potential role for various forms of ketamine administration in the treatment of MDD.

Here, we employed a double-blind controlled trial to investigate the effectiveness of oral ketamine in a population diagnosed with moderate to severe MDD. In particular, we were interested to establish the time course of the therapeutic effect of ketamine when combined with conventional medications. We also examined how the potential therapeutic effects are sustained over six weeks.

## 2. Materials and methods

### 2.1. Trial setting and design

A randomized, placebo-controlled double-blind trial was conducted over 6 weeks. Patients were recruited from the outpatient clinics of the Roozbeh Psychiatric Hospital (affiliated with Tehran University of Medical Sciences, Tehran, Iran) and assessed for inclusion criteria from August 2016 to September 2017. The study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. The trial was registered at the Iranian registry of clinical trials (www.irct.ir; registration number: IRCT201608071556N93). Written informed consent was obtained from all patients. The trial was approved by the institutional review board (IRB) of the Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1395.355). Patients were informed that they were free to withdraw from the study at any time without any ramifications on their relationship with their healthcare provider.

### 2.2. Patients

Patients with a clinical diagnosis of MDD, according to the Diagnostic and Statistical Manual 5 (DSM5), were recruited (Structured Clinical Interview). Patients included in the study were 18–60 years old and had a diagnosis of moderate to severe MDD defined by a Hamilton Depression Rating Scale (HDRS) score of ≥ 20 (Hamilton, 1960). Patients were excluded if they exhibited any psychotic symptoms or any other comorbid disorders. Other exclusion criteria were any cardiovascular or thyroid disease, alcohol or drug abuse, pregnancy, breastfeeding, or contraindications for ketamine or sertraline use. Finally, patients were also excluded from the trial if they had received antidepressant drugs within the previous month or Electroconvulsive Therapy (ECT) within the previous two months.

### 2.3. Interventions

Patients received sertraline (150 mg a day). As an adjuvant, they received either 50 mg/day ketamine or placebo. Formulation of ketamine capsules used in this study is delineated elsewhere. Different doses of oral ketamine have been used in previous studies; a number of studies have used a fixed dose 0.5 mg/kg or 150 mg/day (Irwin et al., 2013; Jafarinia et al., 2016) whereas others titrated the drug in a range from 0.5 mg/kg to 0.7 mg/kg or 25–300 mg/day (Al Shirawi et al., 2017; Hartberg et al., 2017). The frequency of administration also varies from once daily usage to three times a day (Irwin et al., 2013; Jafarinia et al., 2016). For IV administration, previous trials recommend an injection once every two or three days (Andrade, 2017). Here, we used ketamine as an adjuvant and thus a fixed low dose was chosen to minimize adverse effects. Sertraline was initiated at 25 mg/day and increased by 25 mg every three days. The maximum dose reached 150 mg. Ketamine prescription started with initial dose of sertraline and was prescribed at 25 mg twice daily. During the course of the trial, patients were not allowed to participate in psychotherapeutic sessions or receive any other medication, such as other antidepressants, anxiolytics or hypnotics. They were followed for six weeks and were asked to inform their therapist in case they experienced any adverse effects. Vital signs were recorded and physical examination was performed at the screening session and at each of the post-baseline visits. Upon high clinical suspicion for cardiovascular disease, electrocardiogram monitoring was performed and positive findings were excluded.

### 2.4. Outcomes

HDRS, a rating scale for measuring the severity of depressive symptoms, was used to assess patients at baseline and at weeks 2, 4, and 6 of therapy. This clinician-rated scale contains 17 questions measured either on a 5-point or a 3-point scale (Hamilton, 1960). The HDRS test is commonly applied in Iran (Arabzadeh et al., 2015; Shahmansouri et al., 2014; Zeinoddini et al., 2015). Side effects were recorded at each visit using a checklist administered by a psychiatrist. The checklist contained questions about frequent side effects such as abdominal pain, nausea, tremor, and dissociation. The checklist also included an open question where patients could indicate any other side effects, which was not in the list (Akhondzadeh et al., 2000; Abbasi et al., 2012). Our primary outcome measure was change in the HDRS score from baseline to week 2 across the two groups. Difference in the HDRS score at week 4 and 6 were assigned as secondary outcome measures. Other secondary outcome measures included the difference in early improvement (≥ 20% reduction in HRDS score within the first two weeks), response to treatment (≥ 50% reduction in the HDRS score at the termination of the trial), and remission (HDRS score ≤ 7 at the termination of the trial) between the two groups (Roohi-Azizi et al., 2017; Khajavi et al., 2012).

### 2.5. Allocation concealment, randomization, and blinding

Randomization of patients to either ketamine or placebo groups was done by a computerized random number generator (allocation ratio 1/1). Allocation was concealed using successively numbered, opaque, and sealed envelopes. The patients, the physician, and the statistician were all blind to allocation. The placebo and ketamine capsules were identical in shape, size, color, texture, and odor.

### 2.6. Sample size

A total sample size of 80 was calculated based on the following estimates: a difference of 2.5 on HDRS, a standard deviation of 3.5, a significance level of 5%, a power of 80%, and an attrition rate of 10%.

### 2.7. Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 20) was used for statistical analysis. Categorical variables were reported as frequency (percentage), and continuous variables were reported as mean ± SD. Baseline continuous variables were compared using the independent *t*-test. The mean difference (MD) between the ketamine and the placebo group was reported as MD and 95% confidence interval

(95% CI). We used two-factor repeated measure analysis of variance (ANOVA) to assess the effect of time × group (treatment) interaction. Results of Greenhouse-Geisser adjustment were reported if Mauchly's test of sphericity was significant. We used the independent *t*-test to compare HDRS score at each time point between the two study groups. A *p* value of $< 0.05$ was considered statistically significant. Categorical variables were compared using the $\chi 2$ or Fisher's exact test. The primary outcome measure for this trial was the efficacy of ketamine compared to placebo using general linear model repeated measures on the depressive symptoms. The two groups were also compared with respect to early improvement, response to treatment, and remission. All analyses were carried out based on the intention-to-treat sample with at least one post-baseline measurement. Graphs of repeated measure test were drawn using the sigma plot (version 12).

## 3. Results

### 3.1. Patients

A total of 126 patients were screened for eligibility. Ninety patients were randomly allocated to two groups: (i) Ketamine plus sertraline ($n = 45$) or (ii) placebo plus sertraline ($n = 45$). Eighty-one patients completed the study (Fig. 1). Baseline characteristics of participants were not significantly different between the two treatment groups (Table 1).

### 3.2. HDRS scores

There was no significant difference in baseline HDRS scores between the ketamine and the placebo groups (ketamine: 24.17 ± 2.31; placebo: 24.62 ± 3.52; [MD (95% CI) = 0.45 (− 1.76–0.85), t (79) = − 0.68, p = 0.49]). General linear model repeated measures demonstrated significant effect for time × treatment interaction on the HDRS scores [F (2.19, 173.01) = 5.70, p = 0.003] (Fig. 2). Significant differences were observed in the HDRS scores at week 2 ($p < 0.001$), week 4 (p = 0.001) and week 6 (p = 0.009 – Table 2). Early improvement was significantly greater in the ketamine group (85.4%) compared to the placebo group (42.5%) ($p < 0.001$, Table 3). The ketamine group exhibited a significantly greater response rate (85.4%) compared to the placebo group (57.5%) (p = 0.005 – Table 3). However, the remission rates were not significantly different between the two groups (Table 3).

### 3.3. Adverse events

Side effects were mild. No hepatic or cardiac adverse effect occurred. The frequency of side effects was not different between the two groups (Table 4). There were no complaints of dissociative symptoms. None of the discontinuations were related to side effects. In addition, none of the patients showed evidence of abuse or dependence to ketamine.

## 4. Discussion

Conventional pharmacotherapies of MDD typically require several days to reveal their antidepressant effects. Here we found that adding oral ketamine to sertraline enhances response to therapy. The most important finding was an early improvement of symptoms in patients that received ketamine compared to those that received placebo. The antidepressant effects of oral ketamine were still present after 6 weeks of treatment. Overall, these results are broadly compatible with previous reports on the effectiveness of oral ketamine treatment in depression (Al Shirawi et al., 2017; Irwin et al., 2013; Jafarinia et al., 2016).

Previous trials of oral ketamine administration often used a relatively small sample size. Irwin et al. (2013) gave ketamine to 14 patients with life limiting illness who were under hospice care. Only 8 of these completed the trial. Patients had a combination of depressive and anxiety symptoms. Administration of daily oral ketamine improved the depressive symptoms after 14 days with a sustained effect till the end of

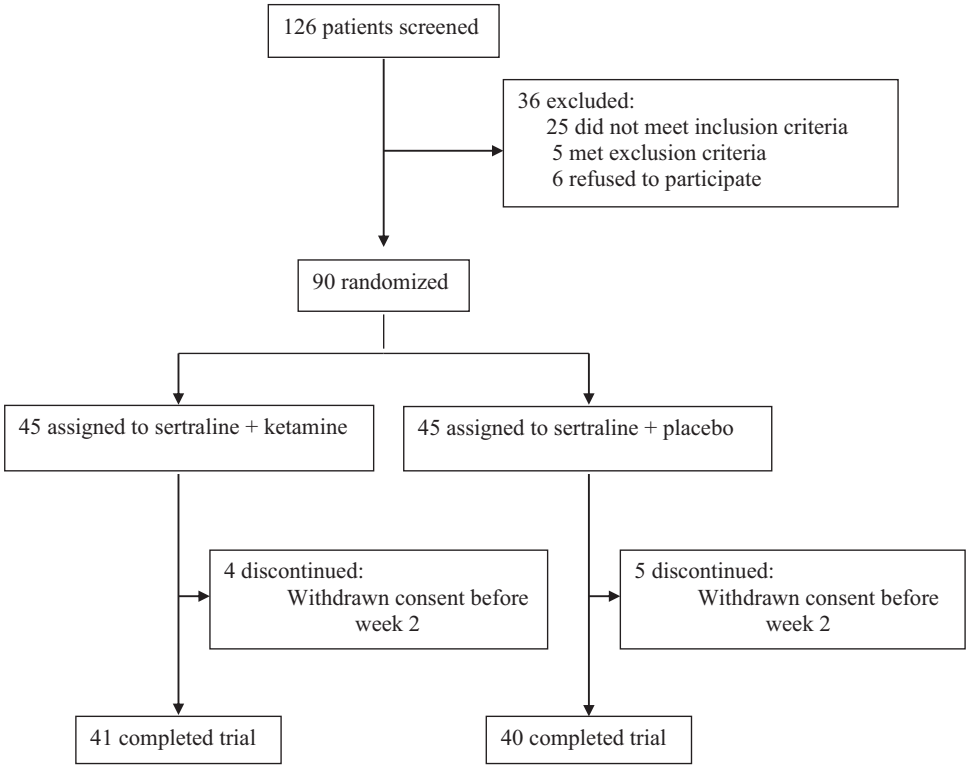


**Fig. 1.** Flow diagram of the study.

**Table 1**
Baseline characteristics of the participants.

| Variable | Ketamine group (n = 41) | Placebo group (n = 40) | P-value |
|---|---|---|---|
| **Age, year, mean ± SD** | 34.31 ± 6.73 | 33.72 ± 8.34 | 0.72 |
| **Gender, n (%)** | 15 (36.6%) | 16 (40.0%) | 0.75 |
| • **Female** | 26 (63.4%) | 24 (60.0%) | |
| • **Male** | | | |
| **Marital status, n (%)** | | | 0.67 |
| • **Single** | 11(26.8%) | 10 (25.0%) | |
| • **Married** | 28 (68.3%) | 26 (65.0%) | |
| • **divorce** | 2 (4.9%) | 4 (10.0%) | |
| **Smoking, n (%)** | 28 (68.3%) | 24 (60.0%) | 0.43 |
| **Educational level, n (%)** | | | 0.42 |
| ● **Under diploma** | 36(87.8%) | 32 (80.0%) | |
| • **High school diploma** | 4(9.8%) | 3 (7.5%) | |
| • **University degree** | 1(2.4%) | 5 (12.5%) | |
| **Weight, kg, mean ± SD** | 69.65 ± 11.35 | 70.67 ± 9.07 | 0.65 |
| **Duration of illness, year, mean ± SD** | 2.63 ± 0.85 | 2.82 ± 1.02 | 0.36 |
| **Baseline HDRS score, mean ± SD** | 24.17 ± 2.31 | 24.62 ± 3.52 | 0.49 |

SD, standard deviation; HDRS, Hamilton Depression Rating Scale; n, number.

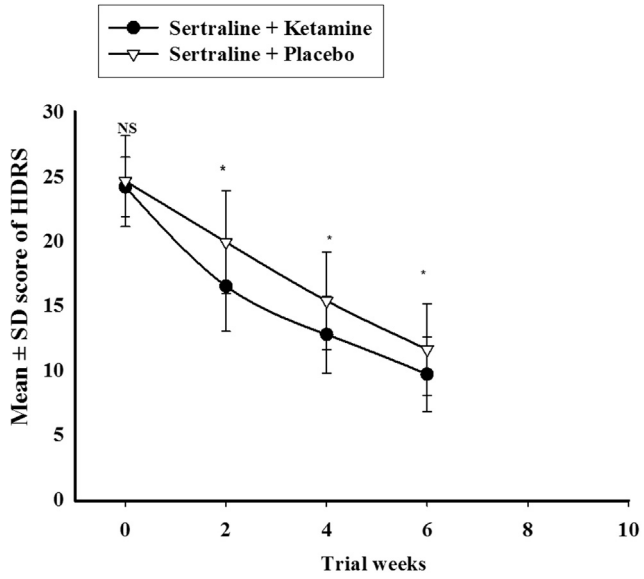


**Fig. 2.** Repeated measure to compare efficacy of ketamine and placebo on the Hamilton Depression Rating Scale (HDRS) scores. Values represent mean ± SD. P-values show the result of the independent *t*-test comparing HDRS scores between the two groups from baseline to each time point. NS indicates non-significant; *, $p < 0.05$.

the trial (28 days). Jafarinia et al. (2016) studied a subgroup of patients with chronic pain and mild to moderate depression and found that monotherapy with oral ketamine was more effective than diclofenac in reducing depressive symptoms. Alshirawi et al. (2017) tested oral ketamine on 22 patients with treatment resistant depression and assessed the severity of depressive symptoms by Beck Depression Inventory II scores. Greater than 50% reduction in symptoms was observed in 18% of patients, and 14% of patients reported a partial improvement in mood symptoms. However, 45% of patients showed no response and 23% showed a mild worsening in depressive symptoms. The mixed results are not surprising given that the test was done on treatment resistant patients who did not respond to several previous periods of antidepressant treatment. In the present study no major adverse events occurred in the ketamine group. Also no dissociative symptoms were observed after ketamine usage. This is consistent with previous research reporting fewer side effects with oral ketamine administration (Irwin et al., 2013; Schoevers et al., 2016). Dissociation is often linked to the initial high plasma levels of ketamine. When ketamine is administered orally the high first pass metabolism of ketamine may cause a safe profile and thus the dissociation symptoms would be less pronounced (Bowdle et al., 1998; Irwin et al., 2013).

There is growing evidence for involvement of the glutamatergic system and its dysfunction in the pathogenesis of depression (Huang et al., 2017). As such, it is expected that drugs that modulate the glutamatergic system via NMDA receptors exhibit antidepressant properties. Consistent with this idea, a number of drugs that interact with the glutamatergic system have been effective in treatment of depression (Machado-Vieira et al., 2017; Amidfar et al., 2017). Ketamine is one such NMDA receptor antagonists that exhibits antidepressant effects (Huang et al., 2017). However, the mechanisms by which ketamine exerts these effects are complex. Ketamine increases the presynaptic glutamate concentration and the brain-derived neurotrophic factor (BDNF) activity (Duman and Li, 2012; Niciu et al., 2014). In an animal model of depression, ketamine injection reduced depressive behaviors 27–48 h after injection (Zhang et al., 2014). The reduction of depression-like behaviors by ketamine was not observed in murine mutants that had conditional deletion of BDNF (Li et al., 2010). Thus, the pathways via which ketamine exerts its actions are yet to be fully understood.

A number of previous clinical studies reported that the antidepressant effects of ketamine begin soon after administration of the drug. Zarate et al. (2006) tested IV infusion of ketamine (0.5 mg/kg) on a group of treatment resistant patients. The antidepressant effects became prominent as early as 110 min after infusion, with a 29% remission and 71% response observed on the day following the infusion. The short lag between ketamine administration and alleviation of

**Table 2**
Comparison of HDRS scores between the two groups using independent T-test.

| HDRS score | Ketamine group | Placebo group | Mean difference ketamine-placebo (95% CI) | t | P-value |
|---|---|---|---|---|---|
| **Week 2, mean ± SD** | 16.48 ± 3.50 | 19.90 ± 3.98 | −3.41 (−5.07 to −1.75) | −4.09 | < 0.001 |
| **Week 4, mean ± SD** | 12.73 ± 2.97 | 15.35 ± 3.77 | −2.61 (−4.11 to −1.11) | −3.47 | 0.001 |
| **Week 6, mean ± SD** | 9.65 ± 2.90 | 11.57 ± 3.54 | −1.91 (−3.34 to −0.48) | −2.66 | 0.009 |

SD, standard deviation; CI, confidence interval; HDRS, Hamilton depression rating scale.

**Table 3**
Comparison of outcome indexes between the two groups.

| Outcome | Ketamine group (n = 41) | Placebo group (n = 40) | P-value | Odds ratio(95% CI) |
|---|---|---|---|---|
| **Number (%) of early improvers** | 35 (85.4%) | 17 (42.5%) | < 0.001 | 7.89 (2.70–22.98) |
| **Number (%) of responders at week 6** | 35 (85.4%) | 23 (57.5%) | 0.005 | 4.31 (1.48–12.55) |
| **Number (%) of remitters at week 6** | 9 (22.0%) | 6 (15.0%) | 0.42 | 1.59 (0.51–4.98) |

CI, confidence interval; HDRS, Hamilton depression rating scale.

**Table 4**
Number of patients with side effects in each group.

| Side effect, n (%) | Ketamine group (n = 41) | Placebo group (n = 40) | P value |
|---|---|---|---|
| **Abdominal pain** | 2 (4.8%) | 3 (7.5%) | 0.97 |
| **Loss of appetite** | 2 (4.8%) | 2 (5.0%) | 0.99 |
| **Nausea** | 3 (7.3%) | 2 (5.0%) | 0.99 |
| **Dizziness** | 3 (7.3%) | 2 (5.0%) | 0.99 |
| **Blurred vision** | 3 (7.3%) | 1 (2.5%) | 0.63 |
| **Tremor** | 4 (9.7%) | 3 (7.5%) | 0.99 |
| **Restlessness** | 3 (7.3%) | 2 (5.0%) | 0.99 |
| **Nervousness** | 2 (4.8%) | 3 (7.5%) | 0.97 |

n, number.

depressive symptoms makes ketamine a good option for the initiation of the treatment. However, IV infusion of ketamine has a number of complications such as painful phlebitis (Macklin, 2003). The bioavailability of ketamine via oral usage is about 16% (Clements et al., 1982). However, as a noninvasive route, oral use is often more acceptable for patients. Altogether, our results suggest that oral ketamine is a suitable adjuvant to sertraline in relieving depressive symptoms. As there is growing evidence about the efficacy of oral ketamine in treatment of depression, many researchers are now focusing on the topic in order to fully recognize the potential benefits and side effects of this new treatment. A number of clinical trials are currently undergoing such as a trial on oral ketamine versus placebo for treating depression in patients undergoing treatment for cancer (ClinicalTrials.gov Identifier: NCT02836288, Scott A. Irwin, Cedars-Sinai Medical Center).

### *4.1. Limitation*

The main limitation of our study is duration of follow-up. Given the potential adverse effects of long term ketamine usage, it would be useful to know at what time point the beneficial effects of ketamine as adjuvant diminishes. Our results show that at 6 weeks post initiation of treatment, the beneficial effects of ketamine are still present. A longer randomized clinical trial could; (i) identify the potential long-term adverse effects of ketamine, and (ii) investigate sustainability of the ketamine effect in alleviating depressive symptoms.

## 5. Conclusion

Here, we performed the first randomized clinical trial to assess the antidepressant effect of oral ketamine as an adjuvant to sertraline in treatment of patients diagnosed with moderate to severe major depression. Ketamine decreased the time lag for antidepressant effects of sertraline and produced an overall improvement compared to administration of sertraline with placebo. Future studies with longer follow-up periods can further evaluate the sustainability of these antidepressant effects. Our findings also encourage future studies to employ other NMDA receptor antagonists as adjuvant to conventional treatment to achieve faster and more effective responses.

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