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Review Article

The Glutamatergic System in Depression: A Review of the Clinical Evidence of Medications and Supplements Affecting Through It

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Abstract

Current therapies for depression are moderately effective, as response and remission rates were reported at 50% and 15-40%, following the first trial with current medications, respectively, and electroconvulsive therapy is not beneficial for more than half of the resistant patients. Recent research suggests that medication with glutamatergic modulatory properties may have antidepressant effects and would be of benefit to refractory patients. This study aims to review the efficacy of these medications in the treatment of unipolar depression. Ketamine, as the leading drug acting through the glutamatergic system, appears to be effective in treating depression IV and orally and in combination with electroconvulsive therapy. There is also clinical evidence of the promising effects of amantadine and lanicemine. Supplements and herbs such as L-carnosine, Crocus sativus (saffron), and Cinnamomum tamala, which were reported to be effective in randomized controlled trials on patients with depression, may act through this system as an antidepressant. Taken together, glutamate receptor modulators are alternative drugs for patients with resistant depression. Further high-quality clinical studies are recommended.

Keywords: Amantadine, Antidepressive agents, AZD6765, Carnosine, Cinnamomum, Crocus, Electroconvulsive therapy, Ketamine, Receptors, Glutamate

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Introduction

Considering the neuropathophysiology, there are several approaches to managing Major Depressive Misorder (MDD), including pharmacotherapy, psychotherapy, Electroconvulsive Therapy (ECT), vagus nerve stimulation, transcranial nerve stimulation, and deep brain stimulation. The last four mentioned strategies are usually used in more severe and resistant cases (1,2). For the initial treatment of MDD, previous studies suggest the combination of psychotherapy and pharmacotherapy, since it is much more effective than either treatment alone (3,4). Antidepressants can generally be divided into two generations. First-generation antidepressants include Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs) introduced in the 1950s. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are categorized as second-generation antidepressants. Based on their efficacy, tolerability, and side effect profile in comparison to other agents in Randomized Clinical Trials (RCTs), SSRIs are a widely prescribed class of antidepressants in this group and are recommended as first-line treatment by most guidelines (1,5-7). Current therapies are not largely effective, as response and remission rates were reported at 50% and 15-40% following the first trial with current medications (8), respectively, and ECT is not beneficial for more than half of the resistant patients (9).

Multiple lines of evidence, including neuroimaging findings and cellular and molecular studies, demonstrated that depression is associated with altered brain structure and function in different brain regions and several neurobiological cascades. Among these circuits, the dysfunction of the monoaminergic system (serotonin, norepinephrine, and dopamine) has been studied well for the past decades (10,11). With an increasing understanding of the neurobiology of depression over time, the glutamatergic system's role has received more attention. Glutamate is the main excitatory neurotransmitter of the Central Nervous System (CNS) and has roles in memory, learning, and cognition (12,13). Recent research suggests that medication with glutamatergic modulatory properties may have antidepressant effects and would be of benefit in patients suffering from MDD (14,15). Furthermore, emerging evidence has demonstrated that glutamate and glutamate receptor dysfunction might also play an essential role in the pathogenesis of other psychiatric illnesses, including mood and anxiety disorders, schizophrenia, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder, as well as neurodegenerative disorders (16).

Regarding the mechanism of the glutamatergic system and the promising effectiveness observed from medications that work with this mechanism, and the resistance to treatment observed in depressed patients, which reduces the quality of life and increases the cost of treatment, this study intends to briefly point out related studies and investigate the efficacy of these medications in treating depression.

Medications

To treat depression

Ketamine is a glutamate receptor antagonist. Berman *et al,* in a double-blind, randomized clinical trial in 2000, demonstrated its anti-depressive properties for the first time (17). Riluzole is a glutamate antagonist, too. In a clinical trial, Salardini *et al* administered riluzole as an augmentative therapy to citalopram in patients with MDD and showed a significant improvement in depressive symptoms in the riluzole group compared to the placebo group. Interestingly, the participants in the riluzole group demonstrated a shorter lag time to the onset of clinical effects and quicker improvements (93.3%) (14).

To treat resistant depression

Ketamine: In a preliminary study, 18 refractory depressed patients were candidates to receive a single shot of a standard dose of IV ketamine (0.5 *mg/kg*) or placebo. The evaluations revealed that ketamine caused improvement in depressive symptoms in 71% of patients in the ketamine group on the first day after injection, and 29% of the patients became almost asymptomatic (18). Although the analyses performed in this study seem simple, they point to the rapid effects of IV ketamine in improving symptoms of refractory depression.

Su *et al* conducted a randomized, double-blind, placebo-controlled, parallel-group trial in which 71 patients with Treatment-Resistant Depression

(TRD) were enrolled and divided into three treatment groups: ketamine 0.2 *mg/kg* (n=23), ketamine 0.5 *mg/kg* (n= 24), and placebo (n=24). Ketamine or placebo was administrated as a single shot over 40 *min*. The patients were assessed 40, 80, 120, and 240 *min* later, and telephone ratings were conducted 24, 48, 72, 96, 120, 144, and 288 *hr* after infusion based on the Hamilton Depression Rating Scale (HDRS). A significant interaction between group, time, and baseline HDRS in ketamine effects on the severity of depression was observed. Compared to placebo, 0.5 *mg/kg* ketamine caused significant improvements, but there was no difference between 0.5 *mg/kg* and 0.2 *mg/kg* ketamine. The response rate was 45.8, 39.1, and 12.5% in the ketamine 0.5 *mg/kg* and 0.2 *mg/kg* and placebo, respectively (19).

In a study by Albott *et al*, 15 patients with TRD participated, and each received six standard doses of IV ketamine (0.5 *mg/kg* for 40 *min*) for 12 days. Depressive symptoms of these patients were assessed based on the Montgomery-Asberg Depression Rating Scale (MADRS) at baseline and 40, 110, and 160 *min* after injection. Patients who met the clinical response criteria after 40 *min* of ketamine injection (50% reduction) were followed up for four weeks. Symptom assessment was performed at the end of each day until the onset of depressive symptoms. 13 out of 15 patients could complete six injections, and 12 (92%) responded to ketamine injections. Eight patients (61.5%) had a relapse, and five patients responded to treatment within four weeks. The mean time to recurrence of depressive symptoms after the last dose of ketamine injection was 16 days (range 7-28 days). Four of the 13 patients received oral lorazepam at an average dose of 2.75 *mg*. Analyses showed that at the end of the sixth ketamine injection, there was no difference in MADRS between benzodiazepine users and the other group (Benzodiazepine=11 *vs*. the other group=9). Also, the response time to ketamine in the two groups was significantly different (Benzodiazepine=11 *vs*. the other group=6.2). This study revealed that the use of benzodiazepines could delay the antidepressant effect of ketamine (20).

A randomized, double-blind study examined cognitive function in 43 TRD patients divided into two groups. The first group (n=25) received five injections of midazolam (0.045 *mg/kg*) followed by one injection of ketamine (0.5 *mg/kg*) over 12 days, and the second group (n=18) received six injections of ketamine (0.5 *mg/kg*) over 12 days. Patients' depressive symptoms were assessed at the baseline and after each injection, and the patients were followed up for 12 weeks. Patients' cognitive function was assessed at baseline and 24 *hr* after the last injection based on the CogState brief battery. The results of the evaluation of depressive symptoms in patients have been reported in a previous study. Examining neurocognitive symptoms after the fifth injection showed better performance in complex working memory, and visual memory was initially associated with a significant reduction in depressive symptoms. Post-hoc analysis indicated that in the second group (ketamine injections), there was a relationship between attention, visual memory, complex working memory, and reduction of MADRS (r=0.42, r=-0.45, and r=-0.44, respectively). Twenty-four hours after the last injection, it was found that in the group that received six ketamine injections, the speed of processing, set-shifting, complex working memory, and visual memory increased while the verbal memory decreased. In the group with only one injection of ketamine, the processing speed decreased (21).

Chen *et al* have investigated different doses of IV ketamine on glucose metabolism in different parts of the brain and its relationship with depressive symptoms. 24 TRD patients (21-64 years old) were divided into three treatment groups: 0.2 *mg/kg* IV ketamine (n=8), 0.5 *mg/kg* IV ketamine (n=8), and placebo (n=8). Assessment of glucose metabolism based on standardized uptake values (SU*Vs*) glucose by F-18-FDG positron-emission-tomography was performed at the beginning of the study and one day after injection. It was revealed that patients who took 0.5 *mg/kg* of IV ketamine had a higher SUV score on the Supplementary Motor Area (SMA) and dorsal Anterior Cingulate Cortex (dACC). Higher SUV scores in dACC had a significant relationship with a reduction of HDRS (22).

Sharon *et al*, in a preliminary study, investigated the effect of oral ketamine compared with placebo. In this study, 22 patients with TRD were divided into two groups of oral ketamine (12 patients) and placebo (10 patients) and were evaluated for depressive symptoms based on the MADRS for 21 days. Analyses showed

significant improvement in symptoms at the time and time×treatment interaction. This study revealed that oral ketamine could be as effective as intravenous ketamine in improving depressive symptoms (23).

In a number of studies, ketamine is used as an anesthetic before sessions of ECT. In a preliminary study by Yamada *et al*, 31 patients with TRD were candidates for eight ECT sessions and were divided into two groups: ketamine injection before ECT and propofol injection before ECT. Patients were evaluated based on HDRS after the second, fourth, sixth, and eighth sessions, and the results showed a significant advantage of the ketamine group in reducing depressive symptoms (24).

Besides, a number of studies have measured the effectiveness of ketamine compared to ECT sessions. Basso *et al* included 31 depressed patients treated with ketamine and 31 other depressed patients, gender- and age-matched, treated with ECT. Of these, 12 patients were excluded due to a low dose of ketamine injection (less than 3) or a high number of ECT sessions (more than 16 sessions). Fifty patients were divided into two treatment groups: serial ketamine injection and receiving ECT. Ketamine was injected at a standard dose of 0.5 *mg/kg* three times a week for a maximum of 6 to 9 times during the study. ECT sessions were performed three times a week using the standard method for a maximum of 9 to 16 sessions during the study. The patients' symptoms were assessed based on the MADRS at the beginning, middle, and end of the study. In the middle of the study, the MADRS scores in the ketamine and ECT groups were 13.38 (standard deviation 5.27) and 19.52 (standard deviation 7.07), respectively. Patients' symptoms in the ketamine group decreased more rapidly from the beginning to the middle of the study (mean reduction was 47.45±23.43% *vs*. 34.86±21.29%); however, the rate of symptom reduction was not significantly different between the two groups for the rest of the trial (ECT: 55.70±23.63%, ketamine: 49.88±27.30%). Evaluations also showed ketamine significantly improved cognitive activities, including verbal memory, executive functions, and attention (25).

Riluzole: Sakurai designed another study in 2019 to evaluate the long-term effect of riluzole. In this study, 104 patients were divided into three groups: placebo/placebo for eight weeks, riluzole (50 *mg* twice daily) for four weeks, and placebo and riluzole/riluzole (50 *mg* twice daily) for eight weeks. After the initial evaluation, 66 patients (12 responders and 54 non-responders) continued to take riluzole (50 *mg* twice daily) for 12 weeks, regardless of their primary group. By the end of week 12, the response rate was 8 out of 12 responders (66.7%) and 13 out of 54 (24.1%) in the non-responder group, and no significant difference was reported between riluzole and placebo (26).

In another study by Mathew *et al*, the patients were divided into groups A and B. Group A included people who were not taking antidepressants. They were given a therapeutic dose of sertraline for eight weeks. If these individuals did not respond well and had depressive symptoms, they would be selected for final randomization. Group B included individuals who had received an adequate SSRI dose, SNRI, or bupropion for at least eight weeks and had a fixed dose for at least four weeks prior to randomization. Finally, 104 patients were included in the study, and 85 completed the study. The patients were divided into three groups with a 2:3:3 ratio: drug/drug, placebo/placebo, and drug/placebo. Riluzole was administrated with a dose of 50 *mg* twice daily. The riluzole group had no significant advantage in MADRS over the placebo group. The speed of response to treatment was not significantly different between the two groups (27).

Amantadine: A study was conducted by Wrobel *et al*, which demonstrated the successful effect of adjunctive amantadine with imipramine in the treatment of refractory depression. Twelve depressed patients were treated with imipramine (100-150 *mg*) for six weeks with a two-week period without medication. Amantadine (100-150 *mg*) was then added to their treatment regimen for another six weeks, and their treatment continued for another two weeks with imipramine alone. Evaluations showed a decrease in HDRS from the beginning to the end of the study, from 32.2±1.2 to 6.12±3.1 (28).

Lanicemine: Lanicemine is a glutamate receptor inhibitor and antagonist. A clinical trial reported treatment-resistant depressed candidate patients divided into three groups receiving 100 *mg* and 150 *mg* intravenous AZD6765 over one *hr* and normal saline. Injections were performed three times a

week for three weeks. Evaluations in the third week demonstrated a significant reduction in MADRS reported at -5.5 and -4.8 for the 100 *mg* and 150 *mg* doses, respectively (29).

Chlorokynurenic acid: 7-chlorokynurenic acid also plays an antagonistic role in the glutamatergic system. In a study by Kadriu *et al*, 19 TRD patients (18 to 65 years) were divided into 4-Cl-KYN (1080 mg daily for seven days, up to 1440 *mg/day* for the next seven days) and placebo groups. Depression symptoms were assessed according to the HDRS on days 1, 2, 3, 7, and 13. Evaluations showed that there was no significant difference in the 4-Cl-KYN group. The peripheral and central biological markers were not significantly different between the two groups (30).

Supplements

Recent studies indicate that L-carnosine, a natural antioxidant dipeptide with a glutamate neuromodulation characteristic and neuroprotection activity, could be a putative antidepressant agent (31,32). A recently published clinical trial demonstrated that a six-week period of L-carnosine supplementation therapy significantly decreases time×treatment interaction on HDRS score compared to placebo with the same frequency of adverse events (15).

Studies suggested saffron extracts may have some effects on the glutamate system (33,34). Akhondzadeh *et al* have shown that saffron monotherapy was more effective than placebo in the treatment of mild-to-moderate depression (35). Another supplement that may be effective in this way is Cinnamomum tamala, which has been reported to be effective in a clinical study of MDD treatment (36).

Conclusion

Numerous published clinical studies support the hypothesis of the role of the glutamatergic system in the treatment of depressed patients, although these studies have limitations and are still insufficient. Although ketamine appears to be effective in the treatment of refractory depression as the mainstay of drugs acting through this mechanism, studies of other drugs are few and far between. Further high-quality studies are recommended.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

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Conflict of Interest

The authors had no conflicts of interest.

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