MEMANTINE THERAPY AS AN AUGMENTATION IN TREATMENT-RESISTANT DEPRESSION: A CASE REPORT

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ABSTRACT

Evidence suggests that treatment-resistant depression (TRD), defined as the occurrence of an insufficient clinical response after adequate antidepressant therapy among patients diagnosed with major depression, is one of the most important public health problems and is associated with significant disability and psychosocial impairment. Here we present a case of depression resistance to the treatment of a 22-year-old man and the effects of Memantine augmentation. The first symptoms of depression appeared in January 2019, and pharmacotherapeutic treatment began in March of the same year. He was in a bad mood, sad, hopeless, tense, lacked energy, lost interest, and decreased libido. During his two-year pharmacotherapeutic therapy, he took SSRIs, SNRIs, TeCAs, SARIs, atypical antipsychotics with antidepressant effects, such as aripiprazole and cariprazine. Since the patient still did not have adequate therapeutic response and new drugs were available, the choice fell on Memantine after researching several databases and collecting the data listed at the beginning of the article. The initial dose was 5 mg daily and was gradually increased by 5 mg each week to a maximum of 20 mg. After 2 weeks at a stable dose, the patient reported feeling a little better. Significant improvement in symptoms was observed in the MADRS score, which was then applied to assess the effects of augmentation. After four weeks of therapy, he entered remission which is still ongoing.

Keywords: *Major depressive disorder, treatment-resistant depression, memantine, pharmacotherapy.*

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INTRODUCTION

Treatment-resistant depression (TRD) is broadly defined as the occurrence of an insufficient clinical response following adequate antidepressant therapy (in terms of dosage, duration, and compliance) among patients diagnosed with major depression (1).

According to the European Staging Method TRD is defined as:

A. Nonresponder to TCA, SSRI, MAOI, SNRI, ECT, other anti-depressants. No response to one adequate antidepressant trial in 6-8 weeks.
B. Resistance to 2 or more adequate antidepressant trials. Duration of the trial(s): TRD1:12-16 weeks; TRD2:18-24 weeks; TRD3:24-32 weeks; TRD4: 30-40 weeks; TRD5: 36 weeks-1year.
C. Chronic resistant depression - Resistance to several antidepressant trials, including augmentation strategy in the duration of the trial at least 12 months (2).

Evidence indicates that TRD is one of the most important public health problems and it is associated with significant disability and psychosocial impairment (3). Clinical practice has shown that individual treatment of almost every patient is necessary due to heterogeneity that exists in the psychiatric population. Various clinical studies have examined the effects of NMDA antagonists in mood disorders. Evidence indicates an alteration in the glutamatergic system in major depressive disorders as well as in treatment-resistant depression. Besides the well-known monoamine hypothesis, research suggests non-competitive modern affinity N-methyl-D-aspartate receptor antagonists (NDMA) in treatment resistance depression, due to changes in NMDA level in this patient (4).

Memantine is an NMDA receptor antagonist, indicated for the treatment of Alzheimer's disease. The fundamental role of these receptors is to bind glutamate: the main excitatory neurotransmitter in the brain believed to play a crucial role in neuronal plasticity and learning mechanisms. The relationship between depression and the NMDA pathway is reinforced by the fact that people with MDD (major depressive disorder) also demonstrate higher glutamate levels in the brain and blood(5). Memantine significantly slows neurodegenerative processes and it is effective in treating symptoms of dementia, shows good toleration by patients, in combination with various psychiatric medications offers great potential in treatment. Studies have shown that the effects of the glutamatergic system include the delayed, indirect effects of many antidepressants as well as the antidepressant effects of N-methyl-d-aspartate (NMDA) receptor antagonists in basic and clinical models of depression. (6-8)

In this article, we present the case of a 22-year-old man who has treatment-resistant depression. This case may help to enrich our understanding effects of Memantine augmentation in this condition.

CASE REPORT

The patient had the first episode of depressive symptoms in January 2019. He was in a bad mood, sad, hopeless, tense, lacked energy, lost interest, and decreased libido. At the beginning of March of the same year, pharmacotherapeutic treatment began. In the first episode from March 6th, 2019 the patient first took Escitalopram 10mg daily and Alprazolam 0,75mg daily. Due to poor tolerability and worsening of symptoms in terms of lethargy, lack of motivation, loss of emotions, and withdrawal from social communications, the drug was replaced. He started taking Venlafaxine from an initial dose of 75 mg daily, which was then increased to 150 mg daily. A few days later, the symptoms of depression became even more pronounced, he became very anxious due to the loss of all positive and negative emotions, and at the next follow-up visit, which was on April 3rd. 2019, the dose of Venlafaxine was adjusted to 75 mg daily and a new drug Olanzapine has introduced at the dose of 5mg which the patient did not tolerate well and which were quickly excluded from therapy. As a result, at the beginning of April 2019, he was entering remission, at that time he was only taking Venlafaxine in a dose of 75 mg daily. The remission lasted until July 2019. Then the symptoms worsen and the current depressive episode begins. Among the problems, he mentioned a depressed feeling, loss of interest in activities that were a pleasure, a feeling of emptiness, loss of energy ... The patient has been prescribed Maprotiline for the first time in a dose of 25 mg three times a day from July 20th, 2019. At the next follow-up, the patient did not report improvement in discomfort, and either a combination of the two antidepressants or augmentation was considered. We decided to increase the dose of Maprotiline to 100 mg/day from September 3rd, 2019, and introduce the drug Trazodone in an initial dose of 50 mg daily for the first 3 days, and then 100 mg daily. The patient appears to be therapeutically resistant and at the next follow-up, on September 17th, 2019, since he did not report any improvement, this therapy was excluded and Escitalopram 10 mg daily and Aripiprazole 5 mg daily were introduced, which he took regularly until November 22nd, 2019, when started treatment with Duloxetine at a dose of 30 mg and later 60mg daily. He did not come until June 5th, 2020, when he stated that the condition was much worse. Considering that patient in this episode still did not have an adequate therapeutic response and new medication (Cariprazine) which can be used for therapy of augmentation was available, Cariprazine was prescribed in the therapy.

At that moment, since he is a very young patient with severe problems and significant obstruction in his functioning, more intensive monitoring began.

At that moment, he was in a bad mood, slowed down, he had no wellness or energy, he was feeling empty, he lost interest in friends, family and all the things that used to be a pleasure, his concentration was bad, he had a drop in libido...

The diagnosis was confirmed according to the DSM-V criterion and confirmed according to the SCID-5 scale. The

diagnosis of treatment-resistant depression was made according to the criteria of therapy resistance. The patient did not have adequate response and improvement to more than two therapeutic protocols that were used long enough and at a sufficiently high dose (Table 1) (2).

Medical history was indicated that the patient is not treated for other significant medical conditions other than depression.

Evaluation of the severity of the disease with the Montgomery-Åsberg Depression Rating Scale (MADRS) has begun. The MADRS depression scale was performed on the first day of treatment with Cariprazine from July 30 and repeated until September 9th (Table 2). No significant improvement in symptoms was observed, so he left this therapy on his own.

At that moment, the authors of this article, considered which alternative protocol can be used in this case. After researching several databases and obtaining the data listed at the beginning of the article, the choice fell on Memantine. Memantine was prescribed together with Duloxetine. The patient was informed about the mechanism of action of memantine, its potential side effects, and the off-label use of the drug before starting it. The patient consented to add-on treatment with Memantine. In the beginning, the dose was 5mg, and every week it was increased by 5 mg to a maximum of 20 mg. Dosing was increased according to instructions used in previous trials (9). After 2 weeks on a dose of 20 mg, the patient reported feeling a little better and the psychiatric evaluation of the MADRS was 16 points. After another week, the total score on MADRS decreased to 13 points, and after another week to 11 points. When he came for an appointment after another month of treatment, the MDRS was 9 points. Table 3 The patient reported that he had not felt so well in a long time.

The patient reported that he felt better. His mood corresponded to the situation. He was not depressed. He had much more energy. His motivation and initiative were like in the period before the disease, his libido returned. Also, its functioning has improved. The patient started to achieve success at the faculty again and fulfilled all the planned obligations. Treatment did not change since then. From the beginning of the treatment, the patient tolerated the treatment well and no side effects were observed. The patient is still in stable remission.

DISCUSSION

In this case study, we reported a case of a 22-year-old man with depressive symptoms according to DSM-V, who had a significant improvement in symptoms after Memantine augmentation.

The first results on the efficacy of NMDA antagonists in treatment are shown by Berman et al. They found that a single dose of the high-affinity NMDA receptor antagonist ketamine resulted in a rapid antidepressant effect in patients with major depression. Unfortunately, possible lack of ketamine treatment is psychotomimetic effects which preclude its use as a chronic antidepressant (10)

Réus et al. (2009) suggest that acutely administration of Memantine (20mg/kg), significantly increased BDNF protein levels in the rat hippocampus as well as inhibition of the reuptake of serotonin and dopamine into mouse forebrain synaptosomes and effects on cholinergic signaling via muscarinic and sigma receptor in the brain tissue (11). Antidepressant-like effects of Memantine could be a consequence of interactions with several receptor systems involved in the modulation of behavioral and molecular actions of antidepressants. Moreover, Onogi et all (2009) showed increased locomotor activity after Memantine administration to mice. They also suggested that the D2 receptors of the nucleus accumbens could be involved in this effect. The administration of Memantine may inhibit MAO activity in the human brain, as well as have effects through NMDA receptor antagonism (12). The result of our case study is consistent with 12 weeks of open-label treatment study of 8 subjects with major depression conducted by Ferguson et al, which showed that Memantine may provide rapid and potent relief of depressive symptoms in patients with MDD. They administrated Memantine in dosage from 20 mg/day to 40mg/day and showed that therapy was well tolerated at the highest dosage 40 mg/d which is twice the dosage commonly prescribed for patients with Alzheimer's disease. The study limitations were lack of placebo and active controls were not used, and the possibility that results stem from a placebo response cannot be ruled out (13).

In contrast to previous research placebo-controlled trial of a selective NMDA antagonist in the treatment of major depressive disorder failed to show that Memantine has antidepressant effects in patients with major depression. Potential limitations of this study are the small number of subjects and low doses of Memantine (14).

CONCLUSION

Memantine therapy as an augmentation in TRD is successful in some cases. Considering that this drug is well tolerated and that the side effects are milder and less frequent than with some other augmentation drugs, it leaves room for further research in this field and can lead to progress in one of the most difficult fields of everyday psychiatric practice.

Table 1.

Medication	Dose (mg/ day)	Start / end time	Dose adjustment	Date/ time of dose adjustment
Escitatopram	10	06. March 2019/ 28. March 2019	NO	
Alprazolam	0,75	06. March 2019/ 28. March 2019	NO	
Venlafaxine	75 -150	29. March 2019/ June 2019	YES	Start dose 75 mg 29.03. - 04.04.2019 05.04-08.04. 150mg 08.04 - 06.2019. 75mg
Maprotiline	75 - 100	June2019/ September .2019	YES	06.2019-03.09.2019 - 75mg 04.09- 17.09. 10mg
Trazodon	100	03. September 2019	YES	03.09-10.09. 50mg
Escitaloprame	10	17. September 2019 / 22. November 2019	YES	17.09 - 24.09 5 mg, and than 10mg
Aripiprazole	5	17. September 2019 / 22. November 2019	NO	
Duloxetine	60	22. September 2019 -	YES	22.09-29.09 - 30mg, and than 60mg
Cariprazine	1.5-4.5	05. June 2020 - 09. September 2020	YES	05.06-19.06. 1.5mg; 20.06.-20.07. 3mg; 21.07-09.09. 4,5mg

Table 2.

Effects of Cariprazine therapy	
Visit date	MADRS score
30. July 2020	31
12.August 2020	31
19. August 2020	31
26. August 2020	29
09. September 2020	30

Table 3.

Effects of Memantine therapy	
Visit date	MADRS score
23. September 2020	16
30. September 2020	13
07. October 2020	11
04. November 2020	9

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