Memantine Enhances the Effect of Olanzapine in Patients with Schizophrenia: A Randomized, Placebo-Controlled Study

Ahmad Fakhri[1], Sirous Pakseresht[1], Mohammad Reza Haghdoost[1], Nasihat Hekmatkhah[1], Maria Torkashvand[2], and Behnam Ghorbanzadeh[3]

[1] *Department of Psychiatry, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[2] *Department of Internal Medicine, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[3] *Department of Pharmacology, School of Medicine, Dezful University of Medical Sciences, Dezful, Iran*

Received: 1 Nov. 2015; Accepted: 14 Aug. 2016

Abstract- Glutamate dysregulation may be involved in the neuropathology of schizophrenia. Memantine, a drug approved by the FDA for the treatment of moderate to severe Alzheimer's disease, acts as a partial uncompetitive NMDA receptor antagonist. The aim of this study was to examine the efficacy of memantine as an adjunctive treatment to olanzapine in patients with schizophrenia. In this double-blind, placebo-controlled studies, patients with schizophrenia according to DSM-IV clinical criteria were selected. Patients were randomly assigned to receive either memantine (week 1:10 mg/day; weeks 2-6:20 mg/day) plus olanzapine (15-20 mg/day) or olanzapine plus placebo. At baseline, no statistically significant difference regarding the mean total PANSS scores between treatment groups was found. Results showed that memantine significantly improved the positive and negative PANSS score in patients maintained on olanzapine after six weeks compared to olanzapine alone (P<0.001). Furthermore, female patients showed significantly better response than males, especially in positive PANSS score. No significant changes in extrapyramidal symptoms were observed.These findings indicate that olanzapine efficacy might be augmented with memantine. Furthermore, this effect is more remarkable in female patients with schizophrenia.

Acta Med Iran, 2016;54(11):696-703.

Keywords: Memantine; Schizophrenia; Combination therapy; Gender; NMDA receptors

Introduction

Schizophrenia is a chronic, severe, and disabling brain disorder that has affected people throughout history. Antipsychotics are the mainstay of schizophrenia treatment. However, some schizophrenic patients exhibit aninadequate or poor response, such as the persistence of positive and negative symptoms and cognitive deficits (1). This appears to be the case not only with the use of typical antipsychotic medications but also with the use of atypical antipsychotic medications such as olanzapine (2). Considering that both typical and atypical antipsychotics are not very effective on negative and cognitive symptoms of psychosis, several approaches have been considered by clinicians in order to deal with the clinical challenge. An attempt to improve antipsychotic therapies usually referred to as “augmentation” (3). For example, clinicians often treat patients with chronic schizophrenia with multiple medications, included combining antipsychotics or combining an antipsychotic with an antidepressant, a mood stabilizer, anxiolytic agents, or sedatives (4,5). This strategy intended to achieve one or more therapeutic goals, such as facilitating patient compliance, simplifying prescribing, improving efficacy without increasing adverse effects or decreasing adverse effects without loss of efficacy (6).

Glutamate system has been suggested to be involved in psychosis pathophysiology, and several neurochemical, neurodevelopmental and genetic data corroborate this view (7,8). The NMDA receptor is normally activated by the binding of glutamate, the major excitatory neurotransmitter in the central nervous system. It is believed that increased influx of calcium ions from the excessive activation of this channel may lead to excitotoxic damage to neurons in the brain (9). So, inhibition of glutamate release

Corresponding Author: B. Ghorbanzadeh
Department of Pharmacology, School of Medicine, Dezful University of Medical Sciences, Dezful, Iran
Tel: +98 614 2429533, Fax: +98 614 2429041, E-mail address: Ghorbanzadeh.b@dums.ac.ir

reduces neurotoxic damage from increased glutamate release as a consequence of NMDA receptor hypofunction, a condition that has been implicated in psychosis pathophysiology (10).

Memantine is a partial uncompetitive trapping blocker of NMDA channel receptors. This drug is licensed for the treatment of moderate to severe Alzheimer's disease, being well tolerated without psychotomimetic adverse effects (9,16). Besides this application, in few case reports memantine has been used off-label for psychiatric disorders (11). Memantine restores normal synaptic plasticity and prolongs theduration of NMDA-R-dependent postsynaptic long-term potentiation that is considered crucial for neuronal memory formation (12).

Memantine has been hypothesized to have a neuroprotective action in schizophrenia (13). Moreover, the efficacy of memantine in delaying thecognitive decline of patients with Alzheimer's disease reveals a potential role for treating cognitive impairment, as well as for preventing progression of the illness in schizophrenia (14). However, its use in combination with antipsychotic drugs in schizophrenia has given inconsistent results (11,15). So, the present study aimed to examine the efficacy of memantine as an addition to olanzapine in patients with schizophrenia and whether the side effects of olanzapine plus memantine would be similar to those of olanzapine alone. Furthermore, in this study, the possible effects of gender and age were considered.

Materials and Methods

Participants

Participants were male or female inpatients, 18-60 years at the time of screening. All patients were screened for treatment of schizophrenia based on DSM-IV-TR criteria. The exclusion criteria were clinically significant alcohol or substance abuse, developmental disability, kidney and liver diseases, and electroconvulsive therapy. Patients were selected based on total PANSS score of 50 or greater. Moreover, according to Hamilton Rating Scale for Depression, none of the patients displayed depressive disorder signs. Among the 71 patients interviewed during this period, 60 patients agreed to participate in the study and after giving informed consent letters entered the study. Overall, data were included for 30 subjects in the placebo treatment and for 30 subjects in the memantine treatment. Demographic data are shown in Table 1 for the study population who completed the entire study period. The study was approved by the Institutional and the Ministry of Health Review Boards.

Table 1. Demographic characteristics of study population

Characteristic	Olanzapine+Placebo	Olanzapine+Memantine
N	30	30
Male (n)	15	15
Female (n)	15	15
Age, years[a]	37.6±2.8	36.46±2.5
Age>30	15	14
Age≤30	15	16
Weight[a] **(kg)**	78.6±4.8	79.3±5.4

[a] Mean±SEM

Study design

The study was a randomized, double-blind, 6-week trial. After a week baseline assessment period, subjects were randomly allocated, without blocking, stratification, or other restrictions, to receive under double-blind conditions either memantine or placebo for 6 weeks. Patients' enrollment was performed by Golestan Hospital physicians; allocation sequence and assignments were generated by the principal investigator. Two parallel groups of patients with schizophrenia in Golestan Hospital of Ahvaz, Iran participated in this study from October, 2012 to September, 2014. Memantine (Sobhan Pharmaceutical, Iran) was started on day one at a single dose of 10 mg orally, as add-on to fixed dose of olanzapine (15-20 mg/day, p.o.). After the first week of treatment, dose of memantine was increased to 20 mg/day for additional 5 weeks. The maximal dose was chosen according to effective dose recommended for dementia (16). Drugs were dispensed into patient-coded containers by the non-blind study pharmacist. Clinical and research staff, as well as patients and their families, were unaware of and

could not determine the study drug assignment by appearance or otherwise.

Clinical assessments

The assessments included a psychiatric evaluation, side effects, and the completion of rating scales. Clinical assessments were performed on the week 0 (as baseline; prior to starting memantine or placebo), 3 and 6, using the Positive and Negative Syndrome Scale (PANSS) (17) and Simpson-Angus scale for extrapyramidal side effects (SAS) (18).

Safety

Safety assessments included arecording of adverse events, physical examination, monitoring of extrapyramidal symptoms (using the Simpson-Angus Scale), vital sign measurements (systolic and diastolic blood pressure, pulse rate, and body weight), and laboratory tests (including pregnancy tests). Patients were seen by a physician at each visit and the evaluation was documented.

Statistical analysis

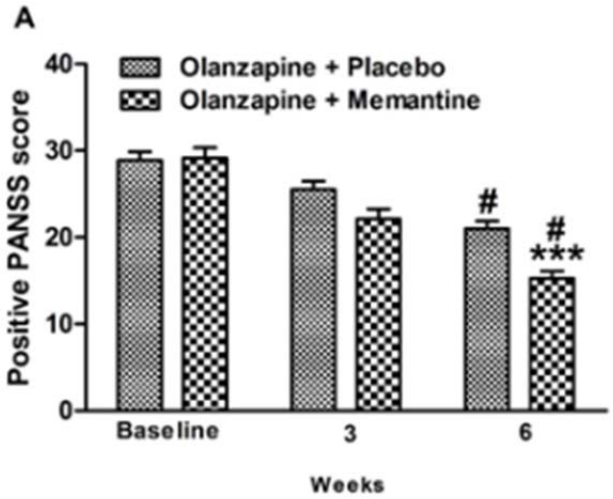
Analysis of variance (ANOVA) with repeated measures was used to compare the symptoms at all three-time points followed by Bonferroni post hoc test. The significance level was set at $P<0.05$. A paired *t*-test was used to assess changes before and after treatment. All results are expressed as mean±SEM.

Results

Efficacy

At baseline, no statistically significant difference regarding the mean total PANSS scores between treatment groups was found (data not shown). Also, the positive and negative symptom score did not differ between memantine and placebo groups at baseline. Significant between-group differences were seen in week 6 for the PANSS positive and negative symptoms. The decline in positive symptoms was significant which showed a 27.3% change as compared to olanzapine plus placebo at week 6. In addition, negative symptoms decreased by 26.6% as compared to olanzapine plus placebo at week 6 (Figure 1A and B).

In the present study, the effect of sex and age were also considered. Accordingly, the addition of memantine to olanzapine showed a significant reduction in positive response of female patients as compared to males at week 3 and 6. However, this effect was only observed at week 3 for negative scores (Figure 2A and B). There was no significant difference between females and males treated with olanzapine+placebo (data not shown). Furthermore, obtained results showed that there was no significant difference between groups>30 and≤30 years in positive and negative symptom score of memantine and placebo groups (Figure 3A and B; data of placebo group was not shown).



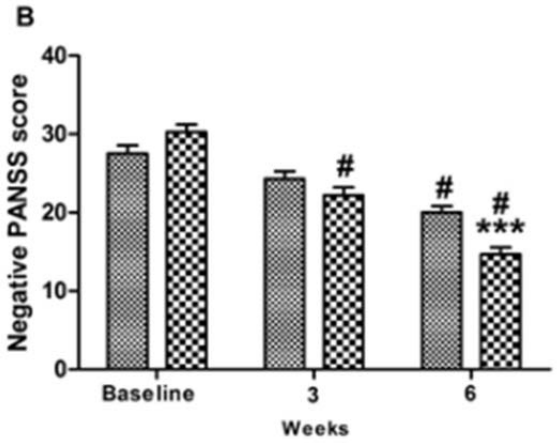


Figure 1. Scores for severity of symptoms at week 0 (baseline), 3 and 6 of the trial. There were significant differences in positive (A) and negative (B) scores between the memantine group and the placebo group at week 6. Bars are the means±S.E.M. $^{***}P<0.001$ compared to olanzapine + placebo at week 6. $^{\#}P<0.05$ compared to respective baseline.

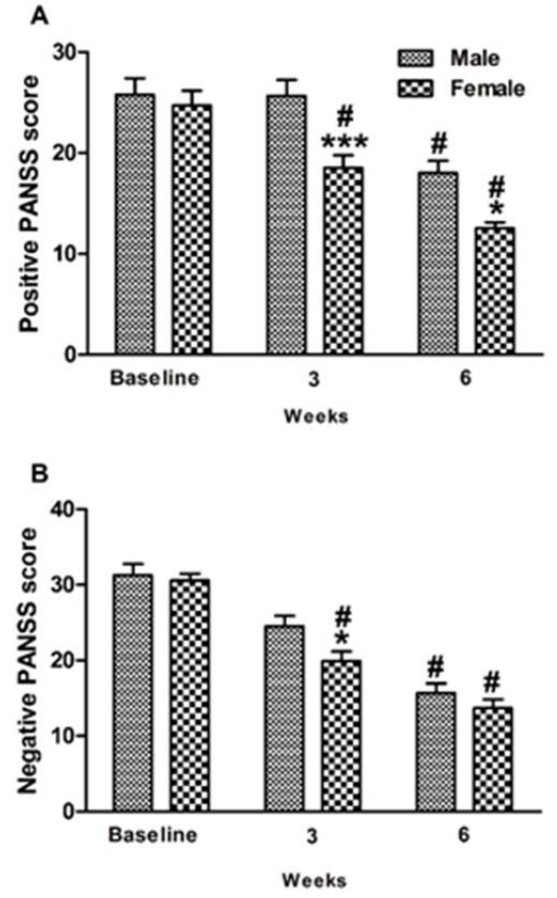


Figure 2. Effect of gender onpositive (A) and negative (B) scores of patients treated with olanzapine+memantine at week 0 (baseline), 3 and 6 of the trial. There was no significant difference between females and males treated with olanzapine+placebo (data not shown). Bars are themeans±S.E.M. $^{*}P<0.05$ and $^{***}P<0.001$ compared to themale group at respective week. $^{\#}P<0.05$ compared to respective baseline.

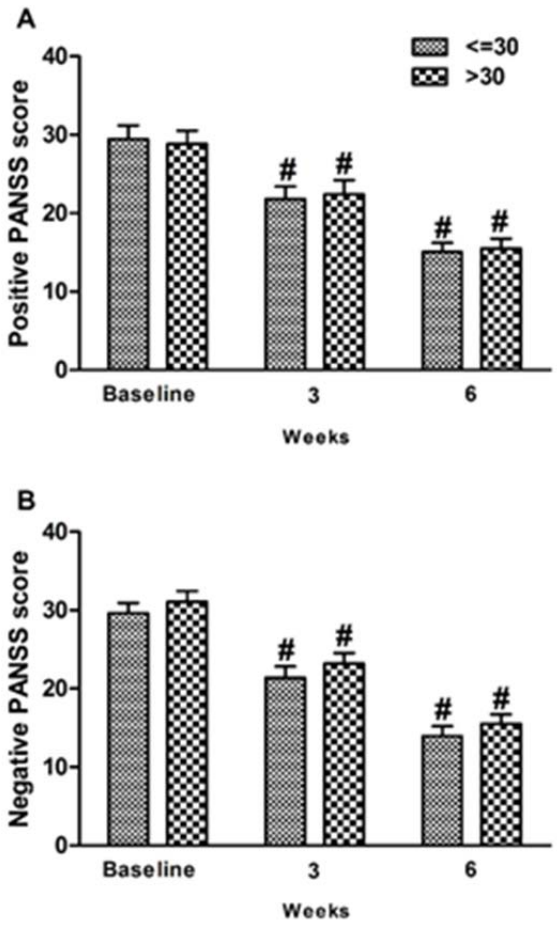


Figure 3. Effect of age onpositive (A) and negative (B) scores of patients treated with olanzapine+memantine at week 0 (baseline), 3 and 6 of the trial. There was no significant difference between groups>30 and ≤30 years treated with olanzapine+memantine. Bars are the means±S.E.M. $^{\#}P<0.05$ compared to respective baseline.

3.2. Safety

There were no patients who reported serious adverse effects or who discontinued the study because of adverse effects. The most frequent adverse effects in the memantine group were nausea, headache, insomnia, and fatigue. However, there were no significant different between memantine and placebo groups. Review of vital signs, laboratory, and extrapyramidal parameters showed clinically unremarkable changes from baseline and a low incidence of potentially clinically significant events (Table 2).

Table 2. Summary of adverse events reported in patients

		Number of patients	
		Olanzapine+Placebo	**Olanzapine+Memantine**
Nausea		2	3
Headache		3	4
Insomnia		3	3
Fatigue		2	3
SAS	**Baseline**	3.6±0.4	3.5±0.4
	Week 6	3.5±0.3	3.7±0.5

Values are mean±SEM. SAS, Simpson-Angus Scale for Extrapyramidal Symptoms

Discussion

The present study investigated the effects of memantine therapy in combination with olanzapine in patients with schizophrenia. As compared with placebo, augmentation with memantine in patients who are using olanzapine alone offered beneficial effects during the six-week, double-blind study, especially in female patients.

Approximately one-third of schizophrenic patients do not respond or respond poorly to antipsychotics (19). Therefore, there is a need for new approaches that can improve schizophrenia treatment significantly. The glutamate system and NMDA receptors is an attractive target for drug development. The glutamatergic system has been suggested in the pathophysiology of schizophrenia and is thought to mediate several psychopathological components of the disease including psychotic and cognitive symptoms (20). Paradoxically, it has been shown that schizophrenic symptoms may be improved by NMDA receptor allosteric agonists and also NMDA receptor antagonist (21,22). Recent research showed that glutamatergic antagonists could hypothetically not only provide symptom relief but also be disease-modifying (23).

Memantine, a NMDA receptor antagonist, is approved for the treatment of moderate to severe Alzheimer's disease. The efficacy of memantine in delaying cognitive decline reveals a potential for preventing progression of the illness in schizophrenia (14). In the present study, we showed that co-administration of memantine and olanzapine produced an improvement in positive and negative symptoms of schizophrenia, especially at week 6. In this regard, Krivoy *et al.*, (2008) colleagues reported that memantine produced a 21% decline in the PANSS negative scores (11). In that study, all the participants received first-generation antipsychotics (6 patients; one patient received a combination of clozapine and zuclopenthixol). On the other hand, Lieberman *et al.*, (2009) reported that there was no evidence of therapeutic benefits associated with adjunctive memantine treatment of residual psychopathology in patients with schizophrenia maintained on atypical antipsychotics (15). Based on theliterature, a large number of subtle differences in the pharmacological action of memantine have been proposed to account for such a dramatic clinical divergence, including its action onto two NMDA receptor sites and its propensity to behave as a partial trapping channel blocker, unlike psychotogenic NMDA receptor antagonists (24). In other words, the observed effects of memantine depending on whether the glutamatergic imbalance in schizophrenia involves a deficit or excess of glutamate release and synaptic neurotransmission.

The results of present study showed that memantine plus olanzapine could be more effective in female than male patients with positive and negative symptoms. Previous studies support the presence of significant differences between schizophrenic males and females arising from the interplay of sex hormones, neurodevelopmental and psychosocial sex differences (25). Animal studies also indicate thedifferent content of NMDA receptors in thehippocampus of males and females (26). On the other hand, females have been reported to be more sensitive than males to glutamate neurotoxicity (27). In accordance with our results, findings revealed that gender was a significant predictor of response based on the Clinical Global Impression (CGI) scale, with women having a better response. So, gender is a predictor of clinical response to antipsychotic treatment; However, its influence is not the same for all antipsychotic drugs (28).

In the current study, no differences in adverse events were observed between the memantine and placebo groups. In contrast to our study, Lieberman *et al.*, (2009) reported that memantine adjunctive therapy was associated with adverse treatment effects, although fewer adverse events were reported with memantine therapy in patients with chronic schizophrenia in their study compared with patients with Alzheimer’s disease (15). This discrepancy istween schizophrenia and Alzheimer’s disease in the occurrence of adverse effects might derive from differences in the physiological characteristics of patients. Furthermore, the lack of significant differences in adverse effects in our study could be related to the relatively short duration of memantine intervention.

In conclusion, our findings indicated that the addition of memantine to olanzapine leads to significant amelioration of negative and positive symptoms of schizophrenia after six weeks. Furthermore, female patients showed the most prominent improvement of schizophrenia symptom as compared to male patients.

Because only inpatients were included, long-term efficiency and benefits of the outlined therapy have to be further evaluated in prospective and randomized studies. Taken together, our study indicates that the combination of olanzapine with memantine represents a new therapeutic strategy in schizophrenic psychoses.

Acknowledgment

This paper is issued from thesis for psychiatry degree (NasihatHekmatkhah), and financial support was provided by the Vice Chancellor of Research, Ahvaz Jundishapur University of Medical Sciences (grant no. U-91087).Funding sources have no involvement in the manuscript writing and in the decision to submit the manuscript for publication.

References

1. Stahl SM, Grady MM. A critical review of atypical antipsychotic utilization: comparing monotherapy with polypharmacy and augmentation. Curr Med Chem 2004;11:313-27.
2. Toren P, Laor N, Weizman A. Use of atypical neuroleptics in child and adolescent psychiatry. J Clin Psychiatry 1998;59:6449-56.
3. Leucht S, Heres S, Kissling W, Davis JM. Evidence-based pharmacotherapy of schizophrenia. Int J Neuropsychopharmacol 2011;14:269-84.
4. Riedel M, Strassnig M, Schwarz MJ, Muller N. COX-2 inhibitors as adjunctive therapy in schizophrenia: rationale for use and evidence to date. CNS Drugs 2005;19:805-19.
5. Botts S, Hines H, Littrell R. Antipsychotic polypharmacy in the ambulatory care setting, 1993–2000. PsychiatrServ 2003;54:1086.
6. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. Br J Anaesth 2002;88:199-214.
7. Krystal JH, D'Souza DC, Mathalon D, Perry E, Belger A, Hoffman R. NMDA receptor antagonist effects, cortical glutamatergic function, and schizophrenia: toward a paradigm shift in medication development. Psychopharmacology (Berl) 2003;169:215-33.
8. Meador-Woodruff JH, Healy DJ. Glutamate receptor expression in schizophrenic brain. Brain Res Brain Res Rev 2000;31:288-94.
9. Lipton SA. Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurological disorders. J Alzheimer's Dis 2004;6:61-74.
10. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia Arch Gen Psychiatry 1995;52:998-1007.
11. Krivoy A, Weizman A, Laor L, Hellinger N, Zemishlany Z, Fischel T. Addition of memantine to antipsychotic treatment in schizophrenia inpatients with residual symptoms: A preliminary study. EurNeuropsychopharmacol 2008;18:117-21.
12. Parsons CG, Gilling K. Memantine as an example of a fast, voltage-dependent, open channel N-methyl-D-aspartate receptor blocker. Methods MolBiol 2007;403:15-36.
13. Rands GS. Memantine as a neuroprotective treatment in schizophrenia. Br J Psychiatry 2005;186:77-8.
14. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004;291:317-24.
15. Lieberman JA, Papadakis K, Csernansky J, Litman R, Volavka J, Jia XD, et al. A randomized, placebo-controlled study of memantine as adjunctive treatment in patients with schizophrenia. Neuropsychopharmacology 2009;34:1322-9.
16. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333-41.
17. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. Psychiatry Res 1987;23:99-110.
18. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. ActaPsychiatrScandSuppl 1970;212:11-9.
19. Freedman R. Schizophrenia. N Engl J Med 2003;349:1738-49.
20. Yang CR, Chen L. Targeting prefrontal cortical dopamine D1 and N-methyl-D-aspartate receptor interactions in schizophrenia treatment. Neuroscientist 2005;11:452-70.
21. Heresco-Levy U, Javitt DC, Ebstein R, Vass A, Lichtenberg P, Bar G, et al. D-Serine efficacy as add-on pharmacotherapy to risperidone and olanzapine for treatment-refractory schizophrenia. Biol Psychiatry 2005;57:577-85.
22. Homayoun H, Moghaddam B. NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. J Neurosci 2007;27:11496-500.
23. De Bartolomeis A, Sarappa C, Magara S, Iasevoli F. Targeting glutamate systemfor novel antipsychotic approaches: relevance for residual psychotic symptoms and treatment resistant schizophrenia. Eur J Pharmacol 2012;682:1-11.
24. Kotermanski SE, Wood JT, Johnson JW. Memantine binding to a superficial site on NMDA receptors contributes to partial trapping. J Physiol 2009;587:4589-

604.

25. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. ActaPsychiatrScandSuppl 2000;401:3-38.
26. Palomero-Gallagher N, Bidmon HJ, Zilles K. AMPA, kainate, and NMDA receptor densities in the hippocampus of untreated male rats and females in estrus and diestrus. J Comp Neurol 2003;459:468-74.
27. Arbogast LA, Voogt JL. Sex-related alterations in hypothalamic tyrosine hydroxylase after neonatal monosodium glutamate treatment. Neuroendocrinology 1990;52:460-7.
28. Usall J, Suarez D, Haro JM. Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. Psychiatry Res 2007;153:225-31.