Clin Schizophr Relat Psychoses
Volume 14:2, 2020
DOI: 10.3371/CSRP.PMRF.101920

Clinical Schizophrenia & Related Psychoses

Research Article

Hybrid Open Access

The Evaluation of Atypical Antipsychotic Augmentation with Atomoxetine in the Reduction of Negative Symptoms in Patients with Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Maryam Pourshams[1], Forough Riahi[1], Ashraf Tashakori[1] and Fatemeh Erfanifar[2*]

[1]*Department of Child and Adolescent Psychiatry, Department of Psychiatry, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

[2]*Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

Abstract

Background and purpose: Schizophrenia is one of the most severe psychiatric disorders with a chronic and debilitating condition. Negative symptoms are common in patients with schizophrenia that have not yet responded well to drugs. The aim of this study is to evaluate the effect of adding Atomoxetine to atypical antipsychotics in reducing the negative symptoms in schizophrenic patients.

Materials and methods: In this randomized, double-blind, placebo-controlled clinical trial during 2018-2020, 60 DSM-V based schizophrenic patients were enrolled to the study. They were divided into case (n=30) and control (n=30) groups. Case group received Atomoxetine, 40 mg daily in the first week and 40 mg daily in the following weeks and the control group received placebo. The effect of medication on negative symptoms in both groups was compared by PANSS scale at baseline and weeks 4 and 8. The data analyzed by using SPSS software version 22.

Result: The mean age of the patients was 30.00 ± 8.50 years and the majority of patients were male (55%). There was no statistically significant difference between the negative symptoms of case and control group at the beginning of the study (19.86 ± 3.00 vs. 20.83 ± 3.51 p=0.257) and in the fourth week (16.53 ± 2.56 vs. 17.46 ± 3.00 p=0.201). But in the eighth week, general (26.90 ± 5.33 vs. 31.50 ± 7.41 p=0.008), negative (11.83 ± 1.87 vs. 15.83 ± 2.98 p=0.001), and Total symptoms (52.16 ± 8.33 vs. 62.33 ± 9.37 p=0.002) were significantly lower in the case group than in the control group.

Conclusion: This study showed that Atomoxetine significantly reduces the negative, general and total PANSS score in schizophrenic patients. This can improve treatment and quality of life in these patients. Therefore, the findings of this study confirmed the addition of Atomoxetine to the treatment of schizophrenia to improve treatment of negative symptoms.

Keywords: Schizophrenia • Atomoxetine hydrochloride • Antipsychotic agents • Quality of life

Introduction

Today, psychiatric disorders as one of the major problems in global health have become more and more important for researchers, and efforts to better manage the treatment of patients and find new pharmacological and non-pharmacological methods have become particularly important [1-3]. One of the most common psychiatric disorders is schizophrenia. Schizophrenia is one of the most severe psychiatric disorders with a chronic and debilitating condition [4,5]. The main manifestations of the disease include positive and negative symptoms [6,7]. Positive symptoms include hallucinations, delusions, confused behaviors, and confusion [8,9]. Negative symptoms include a lack of willpower, inability to initiate and purposeful activities, a lack of understanding and enjoyment of activities, and an emotional slowdown as well as a decrease in verbal communication and word production. Negative symptoms are the most important symptoms of schizophrenia [10,11]. Generally, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, the diagnosis of schizophrenia requires at least two symptoms: delusions, hallucinations, Disorganized speech, Grossly disorganized or catatonic behavior, and negative symptoms for a period of one month. In addition, symptoms should be on the threshold or stay for at least 6 months and should be accompanied by a significant decrease in social or occupational performance. Symptoms should not be due to medical conditions or medication use [12,13]. Negative symptoms in schizophrenia are less known than positive symptoms, but it can be claimed that negative symptoms are the most important symptoms in schizophrenia because they represent the best predictor of future schizophrenia disability [14].

Negative symptoms associated with demographic characteristics such as male gender, pre-existing academic and occupational performance, early onset of illness, and longer duration of related illness [15]. Negative symptoms can be considered a major deficiency in the underlying systems involved in interpersonal relationships by a patient with schizophrenia. Treatment strategy for this patient include atypical antipsychotic and typical antipsychotic drugs. Atypical antipsychotic drugs that are newer have fewer motor side effects than typical antipsychotic drugs. But in spite of this superiority in treating the negative symptoms of the disease, only a slight superiority has been achieved [16-18]. No effective treatment has been known to treat the negative symptoms of the disease, which are the most harmful symptoms of schizophrenia. Progressive damage to the noradrenergic pathway has been shown to cause negative symptoms of schizophrenia [19]. Recently, booster therapy with norepinephrine reuptake inhibitors has been proven to be a treatment for schizophrenia [20]. Studies of the efficacy of Atomoxetine in the treatment of schizophrenia have shown that Atomoxetine has little benefit in improving cognitive symptoms [21].

***Corresponding Author:** Dr. Fatemeh Erfanifar, Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, Tel: +09192961401; E-mail: vakili.f63@gmail.com*

Received 09 October, 2020; **Accepted** 23 October, 2020; **Published** 30 October, 2020

Atomoxetine is a drug that is approved for the treatment of Attention deficit hyperactivity disorder (ADHD) and is used today to treat it. It is a selective non-stimulatory inhibitor of norepinephrine re-uptake. Norepinephrine reuptake inhibitors increase the extracellular level of norepinephrine neurotransmitter in the central nervous system by inhibiting its reuptake to the synapse through the norepinephrine transporter. This study aims to examine more specifically the effect of Atomoxetine on the negative symptoms of schizophrenia.

Materials and Methods

After obtaining permission from the Ethics Committee (Code: IR.AJUMS.REC.1397.416) of the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, in A randomized, double-blind, placebo-controlled clinical trial, during 2018-2020, 78 patients admitted to the neurological ward or referred to the psychiatric clinic of Golestan Hospital of Ahvaz with schizophrenia were enrolled. 18 patients withdrew from the study for various reasons, including failure to answer the phone, failure to follow up, difficulty navigating, and observation of drug side effects (dizziness was observed in two patients and high blood pressure in one patient), so 60 patients continued the study. Diagnosis was made by clinical interview based on DSM-V or Structured Clinical Interview for DSM (SCID). The semi-structured diagnostic interview at SCID starts with questions about demographic information and then questions about mood disorders, psychotic disorders, substance abuse, physical, eating and adaptive disorders. All available information sources such as patient records, companions and observations were used for diagnosis. After explaining the plan to the patients, if they completed the consent form and obtained consent by considering the inclusion and exclusion criteria based on a randomized list previously prepared by the statistical consultant, they were divided into case (n=30) and control (n=30) groups. Case group received Atomoxetine, 40 mg daily in the first week and 80 mg daily in the following weeks and the control group received placebo. The placebo is a tablet that is similar in shape, color, odor and taste to Atomoxetine and was prepared at the Faculty of Pharmacy of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. The drug was ordered by a psychiatrist and administered to patients by psychiatric ward nurses and the project manager was not aware of this selection and prescription. The effect of medication on negative symptoms in both groups was compared by the Positive and Negative Syndrome Scale (PANSS) at baseline (or week 0), week 4 and week 8 after intervention. The validity and reliability of this questionnaire has been studied in our country and its validity is 0.89 according to Cronbach's alpha coefficient [22] (Figure 1).

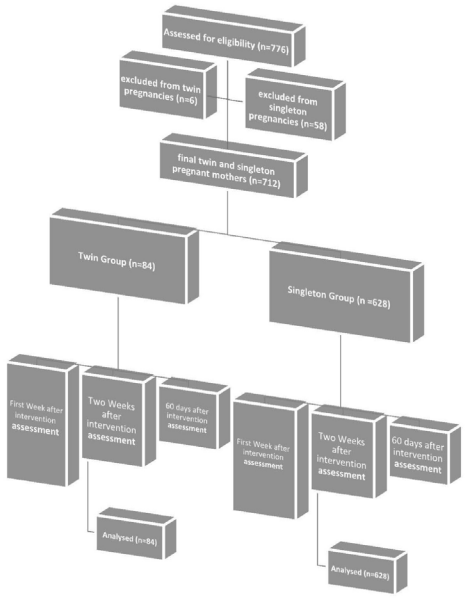

Figure 1. Schematic material and methods.

Inclusion criteria

DSM-5-based schizophrenia, no liver disease (based on the patient's history and examination), no treatment with ECT in the last six months, the illness lasted more than a year, Ages 18 to 70 years.

Exclusion criteria

Depression based on clinical interview and DSM-5, Mental retardation, schizoaffective, bipolar disorder, history of allergy or serious side effects with study drugs, pregnant or lactating women, substance abuse during the last month, use of antidepressant or lithium for any reason, neurological diseases such as epilepsy and Parkinson's disease, suicidal ideation and other active suicides, reluctance of patients to participate in this project, extramural complications, patients with cardiovascular problems, patients with closed-angle glaucoma , History of urinary obstruction and history of ADHD.

Randomization

A random number table was used in this study. In this table, random numbers do not follow any explicit pattern for randomization. This table contains numbers 0 to 9 with probability of occurrence approximately equal.

Statistical analysis

In this study, after data collection, these results were analyzed by SPSS 22 software. To describe the data, the mean and standard deviation (or median and quadratic range) of the quantitative variables and the frequency and percentage of the qualitative variables were used. Pearson correlation coefficient or Spearman correlation coefficient, t-test, chi-square test and regression were used for data analysis and the significance level was assumed less than 0.05.

Results

The mean age of the case group was 30.36 ± 7.16 and the control group was 29.63 ± 9.77 years. No significant difference was found between two groups (p=0.74). Also, the study of patients' gender showed that in general 33 men (55%) and 27 women (45%) participated in our study. Among the case group, 16 were men (53.30%) and 14 were women (46.7%). Of the control group, 17 were male (56.70%) and 13 were female (43.30%). There was no statistically significant difference between the gender of two groups (p=0.79).

Results of the PANSS scale in the case group showed that the mean of negative symptoms at the beginning of the study was 19.86 ± 3.00, in the fourth week after the intervention was 16.53 ± 2.56 and in the 8th week was 11.83 ± 1.87. The results of the control group also showed that at the beginning of the study the mean score of negative symptoms was 20.83 ± 3.51, in the 4th week it was 17.46 ± 3.00 and in the 8th week it was 15.83 ± 2.98. Based on the results of Mann-Whitney test, it was found that the mean of negative symptoms of PANSS scale at week 0 was not significant at the 1% and 5% level between the two groups (p=0.225). Also, despite a decrease in negative symptoms at week 4, this difference was not statistically significant (p=0.026), But at the 8th week of study, the mean of the case group was significantly lower than the control group, indicating statistical difference between the two groups (p=0.001). The Positive Symptom Scores, General and Total Scores are also shown in Table 1. The mean score of positive symptoms showed that at the beginning of the study and in the fourth and eighth weeks there was no significant difference between the two groups.

Table 1. PANSS Scores in case and control group.

PANSS	Time	Group	Mean	SD	p-value
Positive Score	Week 0	Case	24.93	4.36	0.104
		Control	27.03	5.43	
	week 4	Case	17.83	3.8	0.491
		Control	16.93	6.01	
	Week 8	Case	13.43	3.63	0.196
		Control	15	5.45	
Negative Score	Week 0	Case	19.86	3	0.257
		Control	20.83	3.51	
	Week 4	Case	16.53	2.56	0.201
		Control	17.46	3	
	Week 8	Case	11.83	1.87	0.001
		Control	15.83	2.98	
General psychopathology	Week 0	Case	36.8	5.07	0.11
		Control	34.73	4.77	
	Week 4	Case	33.46	6.05	0.509
		Control	32.43	5.98	
	Week 8	Case	26.9	5.33	0.008
		Control	31.5	7.41	
Total Score	Week 0	Case	81.6	9.01	0.601
		Control	82.6	5.19	
	Week 4	Case	67.83	9.36	0.65
		Control	66.83	7.9	
	Week 8	Case	52.16	8.33	0.002
		Control	62.33	9.37	

The mean score of general symptoms showed that there was no statistically significant difference between the two groups at the beginning of the study and the fourth week, but in the eighth week of study the mean score of general symptoms in the case group was significantly lower than the control group (p=0.008). The mean of total scores also showed that there was no significant difference between the two groups at the beginning of the study and the fourth week but in the eighth week the mean score of the patients in the case group was significantly lower than the control group (p=0.002).

Discussion

Schizophrenia is a clinical syndrome with variable but highly destructive psychopathology that involves cognition, emotion, perception, and other aspects of behavior [23]. The symptoms of schizophrenia are attributed to impaired lobe function, but its mechanism is unclear. It may be due to a disorder of dopamine transmission in the frontal cortex in the chronic phase of the disease because in patients with high levels of HVA in the CSF, the function of the frontal lobe is at the lowest level [24]. Atomoxetine inhibits the selective reuptake of norepinephrine. The exact mechanism is unknown, but the effects of the drug are thought to be related to the selective inhibition of norepinephrine precursor transport, which increases norepinephrine in the brain [25]. Due to the lack of study on the effects of this drug on the negative symptoms of schizophrenia, the present study was performed. The results of this study showed that the combination of Atomoxetine with atypical antipsychotic drugs, although reduced the PANSS symptom score in the subgroups during the fourth week, but none of the positive, negative, general, and total score of case group in the fourth week of treatment were significantly different from the control group. Overall results showed that there was a significant difference between the case and control groups at week 8, for the negative, General, and total PANSS score but there was no statistically significant difference between two groups in PANSS positive score. In fact, the addition of Atomoxetine to atypical antipsychotic drugs significantly improved the treatment of negative symptoms in schizophrenic patients. There was no significant difference between the two groups in terms of clinical features including demographic characteristics at baseline so these variables cannot be the cause of the result. In order to compare the results of the present study with other studies, we reviewed some articles in this subject. Kelly et al. studied 92 patients in the US in 2013 and found that Atomoxetine had little benefit in the recovery of schizophrenia patients, although their sample size was larger than the present study, their findings are consistent with our study [26]. Ganguli et al. in Canada also studied the effect of Atomoxetine on the negative symptoms of 60 schizophrenic patients with dominant negative symptoms and showed no statistically significant difference between the placebo and control groups in symptoms and quality of life. Which is inconsistent with the current study [27]. In other study, Kishi et al., in Japan noted that they studied Atomoxetine and reboxetine in 298 schizophrenic patients and concluded that there were no significant clinical benefits for treating the general and negative symptoms of schizophrenia [25]. Although they used the PANSS scale, as in our study, their results are contrary to our study. Friedman et al. in the United States noted that they examined the effect of adding Atomoxetine to second-generation antipsychotic drugs on cognitive deficits in 20 schizophrenic patients. In their study, the cognitive effects of Atomoxetine were evaluated as a placebo-controlled study in schizophrenia patients, with no significant improvement in cognitive function [28]. If more studies are carried out with greater volume and duration, or at higher doses, it may help to identify the cause of this discrepancy. Other researchers have also added other drugs to atypical antipsychotic drugs, But the results have not been effective. For example, In the US in 2008, Lieberman et al performed a study of 70 schizophrenic patients with residual symptoms, for patients treated with atypical antipsychotic for 8 weeks and 20 mg Memantine was administered on a daily basis, but there was no significant difference between them and the patients receiving placebo in the Total PANSS Score after 8 weeks. Also, the Memantine group showed more complications than placebo. Their study, like our study, used the PANSS scale to evaluate patients, the duration of the study was similar and the sample size was approximately similar, but the results were not consistent with our study [29]. Erhart et al. in the United States studied the effect of addition of Reboxetine along with atypical antipsychotic drugs on schizophrenia patients and found that their drug was effective in treating patients [30].

There have been many studies on this topic, and reviewing meta-analysis articles can give us a better overall conclusion of other studies, in a meta-analysis performed by Singh et al., The effect of antidepressants on reducing the negative symptoms of chronic schizophrenia was investigated. None of the drugs sertraline, reboxetine, citalopram, and serine did not improve the negative symptoms, which is inconsistent with the results of the current study regardless of the drug type [31]. In a meta-analysis conducted by Sepehri et al. on the effect of adding SSRIs to negative symptoms in schizophrenic patients, the results showed that these drugs had no effect on reducing negative symptoms that did not match the results of the present study, but the drugs were not separated and it was unclear which drug was ineffective [32].

Conclusion

In conclusion, it is concluded that addition of Atomoxetine to atypical antipsychotic drugs can decrease negative, general and total PANSS score after eight weeks, but there was no significant change in the results of positive symptom subtype in the case and control groups. As seen in the present study, Atomoxetine significantly reduced the negative, general, and overall symptoms of PANSS in patients, which could increase their acceptability of treatment and improve their quality of life. Based on the results, and given the low side effects, Atomoxetine is a good drug for the treatment of negative symptoms of schizophrenia and may be useful in improving their quality of life. We suggest that in future studies, extend the duration of follow-up in patients to evaluate the persistence of the effect of Atomoxetine on symptoms. Also design studies to examine the negative symptoms separately and determine which symptoms respond best to combination therapy and determine the response time of each symptom separately.

Conflicts of interest

All authors declare that they have no conflict of interest with regard to this study.

Acknowledgements

The present research article has been extracted from the "Thesis" conducted as a research project funded by Research Deputy of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

References

1. Riahi, Forough, Mehdi Tehrani Doost, Zahra Shahrivar and Javad Alaghb et al. "Efficacy of Reboxetine in Adults with Attention-Deficit/Hyperactivity Disorder: A Randomized, Placebo-Controlled Clinical Trial." *Hum Psychopharmacol* 25(2010): 570-576 .
2. Riahi, Forough, Ashraf Tashakori and Sakineh Izadi Mazidi. "Effectiveness of Reboxetine in Treatment of Outpatient Children and Adolescents with Attention Deficit-Hyperactivity Disorder with Comorbid Anxiety Disorders." *Iran J Psychiatry* 8(2013): 195.
3. Riahi, Forough, Ashraf Tashakori and Ghazal Salehi Vanani. "Effects of Folic Acid on Appetite in Children with Attention Deficit Hyperactivity Disorder (ADHD) Treated with Methylphenidate: A Randomized Double-Blind Clinical Trial." *Iran J Psychiatry* 43(2018): 9.
4. Sekar, Aswin, Allison R. Bialas, Heather de Rivera, Avery Davis, Timothy R. Hammond, Nolan Kamitaki and Katherine Tooley et al. "Schizophrenia Risk from Complex Variation of Complement Component 4." *Nature* 530(2016): 177-183.
5. Ruiz, Pedro. Comprehensive Textbook of Psychiatry. Benjamin J Sadock, Virginia Alcott Sadock (eds) Vol. 1. Philadelphia, PA: Lippincott Williams & Wilkins, 2000.
6. Ghosh, Abhishek, Kaustav Chakraborty and Surendra Kumar Mattoo. "Newer Molecules in the Treatment of Schizophrenia: A clinical Update." *Indian J Pharmacol* 43 (2011): 105.
7. Kring, Ann M and Erin K Moran. "Emotional Response Deficits in Schizophrenia: Insights from Affective Science." *Schizophr Bull* 34 (2008): 819-834.
8. Dietz, Martin J., Yuan Zhou, Lotte Veddum, Christopher D. Frith and Vibeke F. Bliksted. "Aberrant Effective Connectivity is Associated with Positive Symptoms in First Episode Schizophrenia." *NeuroImage Clin* (2020): 102444.
9. Ardizzi, Martina, Marianna Ambrosecchia, Livia Buratta and Francesca Ferri, et al. "Interoception and Positive Symptoms in Schizophrenia." *Front Neurol* 10 (2016): 379.
10. Galderisi, Silvana, Armida Mucci, Robert W Buchanan and Celso Arango. "Negative Symptoms of Schizophrenia: New Developments and Unanswered Research Questions." *Lancet Psychiatry* 5(2018): 664-677.
11. Veerman, Selene RT, Peter FJ Schulte and Lieuwe de Haan. "Treatment for Negative Symptoms in Schizophrenia: A Comprehensive Review." *Drugs* 77 (2017): 1423-1459.
12. Harvey, Rebecca C, Anthony C James and Gemma E Shields. "A Systematic Review and Network Meta-Analysis to Assess the Relative Efficacy of Antipsychotics for the Treatment of Positive and Negative Symptoms in Early-Onset Schizophrenia." *CNS Drugs* 30(2016): 27-39.
13. Graham, KA, RS Keefe, JA Lieberman and AS Calikoglu, et al. "Relationship of Low Vitamin D Status with Positive, Negative and Cognitive Symptom Domains in People with First-Episode Schizophrenia." *Early Interv Psychia* 9(2015): 397-405.
14. Häfner, H, Löffler W, Maurer K and Hambrecht M et al. "Depression, Negative Symptoms, Social Stagnation And Social Decline in the Early Course of Schizophrenia." *Acta Psychiatrica Scandinavica* 100(1999): 105-118.
15. Cools, Roshan. "Role of Dopamine in the Motivational and Cognitive Control of Behavior." *The Neuroscientist* 14(2008): 381-395.
16. Krause, Marc, Maximilian Huhn, Johannes Schneider Thoma and Philipp Rothe, et al. "Antipsychotic drugs for elderly patients with schizophrenia: A systematic review and meta-analysis" *Eur Neuropsychopharmacol* 28(2018): 1360-1370.
17. Monti, Jaime M, Pablo Torterolo and Seithikurippu R Pandi Perumal. "The Effects of Second Generation Antipsychotic Drugs on Sleep Variables in Healthy Subjects and Patients with Schizophrenia." *Sleep Med Rev* 33 (2017): 51-57.
18. Huang, Xu Feng and Xueqin Song. "Effects of Antipsychotic Drugs on Neurites Relevant to Schizophrenia Treatment." *Med Res Rev* 39(2019): 386-403.
19. Veerman, Selene RT, Peter FJ Schulte and Lieuwe de Haan. "Treatment for Negative Symptoms in Schizophrenia: A Comprehensive Review." *Drugs* 77(2017): 1423-1459.
20. Mitra, Sayantanava, Tathagata Mahintamani, Anjana Rao Kavoor and S Haque Nizamie. "Negative Symptoms in Schizophrenia." *Indian J Psychol* 25(2016): 135.
21. Raveendranathan, Dhanya, Mukund G Rao, Shivarama Varambally and Ganesan Venkatasubramanian, et al. "Atomoxetine-Induced Vocal Tics in a Patient with Schizophrenia" *J Neuropsychiatry Clin Neurosci* 24(2012): E45-E46.
22. Pad, Belgheis, Kaveh Alavi and Ahmad Hajebi. "A Randomized Controlled Trial of Telephone Follow-Up in Patients with Severe Mental Illness: Study Protocol." *Iran J Psychiatry* 23(2017): 108-117.
23. Correll, Christoph U, Chris Abbott, Samuel J Keith and Peter Haddad. "Antipsychotic Treatment and Adherence in Schizophrenia." *Oxford University Press* (2016): 1-29.
24. Cools, Roshan. "Role of Dopamine in the Motivational and Cognitive Control of Behavior." *The Neuroscientist* 14(2008): 381-395.
25. Kishi, Taro, Tomohiko Mukai, Yuki Matsuda and Masatsugu Moriwaki, et al. "Efficacy and Safety of Noradrenalin Reuptake Inhibitor Augmentation Therapy for Schizophrenia: A Meta-Analysis of Double-Blind Randomized Placebo-Controlled Trials." *Psychiatry Res* 47(2013): 1557-1563.
26. Sarpal, Deepak K, Delbert G Robinson, Todd Lencz and Miklos Argyelan, et al. "Antipsychotic Treatment and Functional Connectivity of the Striatum in First-Episode Schizophrenia." *JAMA psychiatry* 72 (2015): 5-13.
27. Ganguli, Rohan and Jaspreet Brar. "Effect of Atomoxetine on Negative Symptoms of Schizophrenia: A Randomized Double-Blind Placebo-Controlled Clinical Trial." *Schizophr Res* 1(2008): 254.
28. Friedman, Joseph I, David Carpenter, Jing Lu and Jin Fan, et al. "A Pilot Study of Adjunctive Atomoxetine Treatment to Second-Generation Antipsychotics for Cognitive Impairment in Schizophrenia." *Journal of clinical psychopharmacology* 28(2008): 59-63.
29. Lieberman, Jeffrey A, Kelly Papadakis, John Csernansky and Robert Litman, et al. "A Randomized, Placebo-Controlled Study of Memantine as Adjunctive Treatment in Patients with Schizophrenia." *Neuropsychopharmacology* 34(2009): 1322-1329.
30. Erhart, Stephen M, Stephen R Marder and William T Carpenter. "Treatment of Schizophrenia Negative Symptoms: Future Prospects." *Schizophr Bull* 32 (2006): 234-237.
31. Singh, Surendra P, Vidhi Singh, Nilamadhab Kar and Kelvin Chan. "Efficacy of Antidepressants in Treating the Negative Symptoms of Chronic Schizophrenia: Meta-Analysis." *Br J Psychiatry* 197(2010): 174-179.
32. Sepehry, Amir Ali, Stéphane Potvin, Robert Élie and Emmanuel Stip. "Selective Serotonin Reuptake Inhibitor (SSRI) Add-On Therapy for the Negative Symptoms of Schizophrenia: A Meta-Analysis." *J Clin Psychiatry* 68(2007): 604-610.

How to cite this article: Pourshams, Maryam, Forough Riahi, Ashraf Tashakori and Fatemeh Erfanifar. "The Evaluation of Atypical Antipsychotic Augmentation with Atomoxetine in the Reduction of Negative Symptoms in Patients with Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial." *Clin Schizophr Relat Psychoses* 14 (2020): 2. DOI:10.3371/CSRP.PMRF.101920