

## Comparison of the effect of Olanzapine, Haloperidol and quetiapine on the resolution of individual delirium symptoms in ICU patients: a double-blind, clinical trial study

### Abstract

**Introduction:** Considering that haloperidol is a first-generation antipsychotic drug known as the primary treatment for delirium, it causes extrapyramidal side effects, and olanzapine and quetiapine are second-generation antipsychotic drugs without extrapyramidal side effects. In this study, we compared the effects of olanzapine and quetiapine with haloperidol on the resolution of individual delirium symptoms.

**Materials and Methods:** In a double-blind clinical trial study, 90 patients admitted to the ICU in three groups received haloperidol at a dose of 2.5 mg/day, while in the second group, patients received olanzapine at an amount of 2.5- 10.5mg/day. In the third group, they received quetiapine at a dose of 12.5 to 75 mg daily. Then, patients' sedation levels were measured according to RASS criteria, and their disease severity was evaluated according to APACHE II criteria.

**Results:** During 15 work shifts in the first, second, third, seventh, and tenth days, sedation scores in all three groups decreased significantly ( $p < 0.05$ ), and all three drugs were effective in subsiding patients' agitation in 10 days. In the evening and night of the first day, the sedation score in the quetiapine group was higher than the other two groups; however, after the treatment period and in the work shifts of the seventh and tenth days, the patients in the quetiapine group had the lowest sedation score on the RASS scale. Also, after starting drug treatment in the three groups, the mean severity of the disease was significantly different in the three groups ( $p < 0.05$ ), so that on the third and seventh day, the olanzapine group had the lowest and the haloperidol group had the highest disease severity. But on the tenth day, the severity of the disease was lowest in the patients in the quetiapine group.

**Conclusion:** As a result of this study, it was found that quetiapine, olanzapine, and haloperidol had the most significant effect in improving the sedation level of patients with delirium according to RASS criteria, respectively, and the use of atypical antipsychotic drugs had more favorable outcomes than typical ones in controlling patients' delirium.

**Keywords:** Quetiapine, Olanzapine, Haloperidol, Delirium

## Introduction

Delirium is a relatively common mental disorder characterized by a sudden onset of disturbance of consciousness (a marked decrease in environmental awareness and impairment of attention) and a change in cognition (such as memory deficit, disorientation, and language disturbance). The disorder usually makes progress over a short period and fluctuates diurnally. In critical patients, many factors can play a role in the prognosis of this condition, including hypoxemia, infection, and systemic inflammation. (1) Delirium frequently occurs in patients with critical conditions. It may be followed by negative consequences such as increased ventilating, Hospitalization, and ICU admission time and is also associated with an escalation in cognitive impairment after being discharged from the ICU. (2) The risk of delirium depends on complex interactions between predictors and prognostic factors. Because current treatment options for delirium are scarce, some studies suggest that efforts should prevent the condition's onset. A study on delirium showed that the prevalence of delirium in hospital samples was 19.6% per day. (4) another study found that the prevalence of delirium in patients undergoing heart surgery in the ICU was 23.5%, and the patients who developed delirium after these surgeries were significantly older ones (5). One study observed that the death rate in delirium patients suffering an active delirium state increases by 11% every 48 hours (6), which indicates the importance of on-time diagnosis and treatment of this disorder. Both pharmacological and non-pharmacological methods and strategies successfully prevented methods, but not globally. Various studies have considered pharmacological and non-pharmacological interventions in advanced delirium states, but none have verified the benefits of these methods. (7) Haloperidol is a first-generation antipsychotic drug. The primary mechanism of this drug is its antagonistic effect on cortical dopamine receptors and the subsequent increase in acetylcholine. Haloperidol reduces the need for sedatives and analgesics, especially in patients connected to a ventilator, and also has potentially beneficial effects on the immune system. According to the guidelines, haloperidol is the drug of choice and is recommended to treat delirium in ICU patients. (8) However, the most significant limitation in using this drug is the presence of extrapyramidal symptoms, which second-generation antipsychotic drugs can be used as a side choice for them. The role of these drugs in treating delirium has been studied, and some positive findings have been reported. (10)

Olanzapine is a second-generation antipsychotic drug with a very low affinity for dopamine receptors but a very high affinity for serotonin receptors. It also has a high affinity for histamine and alpha one adrenergic receptors but is shallow for the M1 muscarinic receptor.

These characteristics make it effective in treating delirium and provide sedation without extrapyramidal side effects. Olanzapine is rapidly absorbed and has a short half-life of 3 to 6 hours, immediately affecting the body. Drowsiness, hypotension, and dizziness are some of its typical side effects. It also prolongs QTc in patients on ECG. (11) Quetiapine is a second-generation antipsychotic drug from benzothiazepines, effective in treating schizophrenia, major depression, and the depressive phase of bipolar disorder and mania. This drug also treats the positive and negative symptoms of psychotic disorders by antagonizing various neurotransmitters in the brain, including receptors for dopamine (D1 and D2), histamine (H1), adrenergic (alpha one and alpha 2), and a variety of serotonin 1 and 2 receptors (5HT1A and 5HT2). It does not affect benzodiazepines and cholinergic muscarinic receptors (12,13). Quetiapine, however, has a very low affinity for dopamine receptors and a very high affinity for serotonin receptors. It also has a high affinity for histamine and alpha one adrenergic receptors but is shallow for the M1 muscarinic receptor. These aspects of quetiapine make it potent in treating delirium and help sedate patients without extrapyramidal side effects. It is rapidly absorbed in the body and has a short half-life of 3 to 6 hours, making it effective in the body. Common side effects of this drug include drowsiness, hypotension, and dizziness. It also prolongs QT in patients on ECG. This atypical and typical antipsychotic drug is used as a monotherapy to treat mania in bipolar disorder. In studies about the effect of quetiapine in treating bipolar disorder, the drug is started at a dose of 100 mg/day and reaches 600 to 800 mg/day on days 5 to 6. The average adequate amount to respond to the treatment is 600 mg/day (12). The Richmond Agitation Sedation Scale (RASS) is an instrument designed to assess the level of alertness and agitated behavior in ICU patients. this is a 10 point scale ranging from -5 to +4. Levels -1 to -5 denote five levels of sedation, starting with "awakens to voice" and ending with "unarousable." Levels +1 to +4 describe increasing levels of agitation. The lowest level of agitation starts with apprehension and anxiety and peaks at combative and violent. RASS level 0 is "alert and calm." This standard has been used many times in research. Most of these scales for measuring delirium are based on DMS criteria. Like DRS-R-98, MDSA, and CAM. The DRS-R-98 is a valid measure of delirium severity over a broad range of symptoms that includes 16 criteria Which would be checked within 24 hours. This scale is helpful for repeated measurements during research when delirium is diagnosed and also can detect delirium from dementia, depression, and schizophrenia with a sensitivity of nearly 91%. [14] Haloperidol as a first-generation antipsychotic drug is the primary treatment for delirium. Still, it causes extrapyramidal side effects, while olanzapine and quetiapine as second-generation antipsychotic drugs cause no extrapyramidal side effects. Concerning this, we decided to evaluate the effects of olanzapine, quetiapine, and haloperidol in treating individual delirium symptoms in this study.

Based on this study, suppose it is proved that olanzapine and quetiapine have similar effects to haloperidol, considering their less extrapyramidal side effects. In that case, these drugs could be used as an excellent alternative to haloperidol in treating this disorder.

## Materials and Methods

This is a double-blind clinical trial study performed on patients in a delirious state. and the diagnosis of delirium was based on the criteria set out in the Diagnostic and Statistical Manual of DSM V. the requirements are as follow:

1. Disorders of attention and awareness
2. Delirium typically increases from a few hours to a day over a short period (initial awareness changes throughout the day)
3. There are other cognitive impairments such as memory, language, and comprehension impairment
4. The presence of a neurological disorder increases the level of delirium.
5. There must also be some evidence to determine the causes of delirium (for example, physiological causes, toxins, etc.) (15)

After obtaining informed consent, 90 patients admitted to the intensive care unit of selected hospitals were randomly selected by envelope method and divided into three groups. They were in a delirium condition and were being treated during the completion of the research sample. The study was a double-blind clinical trial. As much as possible, the drugs were prepared in one color and one size and prescribed according to the protocols. In the first group, haloperidol (Sobhan Daru Company - Iran) with a dose of 2.5 mg per day and in the second group, olanzapine (Sobhan Daru Company - Iran) with a dose of 2.5 - 10.5mg per day (16) and in the third, quetiapine (Bakhtar Shimi company - Iran) with a 12.5 to 75 mg per day dosage were administrated and were given to patients through the NG tube. In order to track sedation scores, all patients in the three study groups were initially in a state of agitation. During the 15 (8-hour) work shifts on the first, second, third, seventh, and tenth day the sedation score was being recorded in each group. We selected several envelopes as the first group and the same number for the second and third groups in the envelope method. The envelopes were chosen randomly and then merged with one card, it was extracted, and its allocation was recorded, and this process continued until the sample size was completed. In the end, patients were divided into three groups based on the letters on the envelopes. Patients' sedation status was checked in each working shift according to RASS scoring criteria (The Richmond Agitation Sedation Scale). (17)

According to APACHE II (Acute Physiology and Chronic Health Evaluation II), disease severity was assessed.

## RESULTS

This study aimed to evaluate the effects of three drugs, olanzapine, haloperidol, and quetiapine, on delirium symptoms of 90 ICU patients with a mean age of 59.57 years and 61.1% of the patients were male.

Recording the initial vital signs of the patients (including mean systolic blood pressure, heart rate, respiration, body temperature, and oxygen saturation status) at the beginning of the study, we found no significant differences. Therefore, it can be concluded that the initial vital signs of patients as an underlying confounding factor in the three groups were almost the same and may have inconsiderable effects on the results of this study.

We evaluated patients' level of consciousness considering the Glasgow Coma Scale. We found that the average GCS of the patients in the range of 3 to 15 was 11.58, and the level of consciousness of patients in the three groups was statistically significant. The level of consciousness of patients of all three groups at the beginning of the study was almost the same, and the possible effects of this variable on the final results could be almost negligible. The sedation status of study patients was evaluated based on RASS criteria and was nearly the same in all three groups.

Assessing the severity of the disease showed the same results in all three groups. Therefore, it can be concluded that all patients in the three groups were almost identical in terms of sedation status and disease severity.

The results demonstrate that in terms of sedation, all patients in three study groups were initially in the state of agitation and checking during the 15 (8 hours) work shifts on the first, second, third, seventh, and tenth day the sedation score decreased significantly in all groups. All three administered drugs effectively improved patients' agitation in 10 days. During the evening and night of the first study day, the sedation score in the quetiapine group was higher than the other two groups; however, after the treatment period and in the work shifts of the seventh and tenth days, the patients in the quetiapine group had the lowest sedation score ~~on~~ according to the RASS scale. Also, on the last day of treatment (day 10), the sedation rate of patients in the olanzapine group was less than the haloperidol group (Figure 1). Therefore, it can be concluded that after ten days, quetiapine and olanzapine, and haloperidol, respectively, had the most significant effect on the resolution of the patients' sedation. As in the results, changes in the level of the disease severity were also investigated, and it had a decreasing trend in all three groups studied in the first, third, seventh, and tenth days. Also, after starting drugs as a treatment in study cases, the mean disease severity in the three groups was significantly different. On the third and seventh days, the olanzapine group had the lowest, and the haloperidol group had the highest disease severity. However, on the tenth day, the severity of the disease was most lacking in patients in the quetiapine group (Figure 2). Therefore, it can be concluded that the treatment of delirium with all three drugs, haloperidol, olanzapine, and quetiapine, effectively reduced the severity of the disease over ten days. Olanzapine also had a faster effect on treating the severity of the illness, but quetiapine had the most significant impact on the severity. However, various factors could have been

intervening with the mechanism of action of the above drugs, which can therefore affect the severity of the disease over ten days, and the improvement of the severity of the disease can not be attributed exclusively to the treatment of delirium with the administration of above drugs.

## **Discussion**

In the study of Grover et al., There was no significant difference in the response rate of the two groups treated with quetiapine and haloperidol. In this study, the researchers concluded that quetiapine, like haloperidol, could effectively control the patient's symptoms. (18)

Lee YJ and Benchalak Maneeton obtained similar results in two separate studies. They concluded that the effects of haloperidol and quetiapine on the treatment of delirium were the same (19, 20)in Our research on the other hand, not only quetiapine aren't as effective as haloperidol in treating delirium, but even within ten days of investigation, quetiapine has been shown more effective.

Kiberd et al. also demonstrated the equal effect of olanzapine and haloperidol in treating delirium. [16] (21, 22) As is evident, the results of the above studies could be a good conformation of ours; In our study, olanzapine and quetiapine (atypical antipsychotic drugs) were more effective than haloperidol in treating delirium, but unlike our previous studies, atypical antipsychotic drugs were even more effective than haloperidol on patient's sedation and the disease severity. The use of atypical antipsychotic drugs had a more favorable impact on patients' delirium than the typical ones.

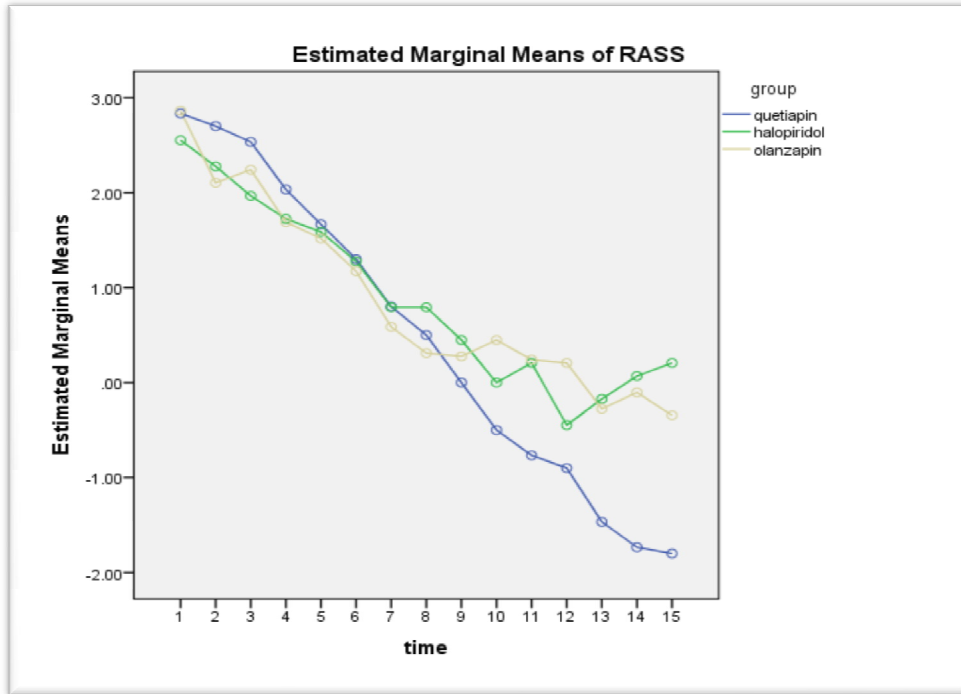
## **Conclusion**

As a result of this study, quetiapine, olanzapine, and haloperidol had the most significant effect on improving sedation in patients with delirium according to RASS criteria. The use of atypical antipsychotic drugs had a more favorable impact on patients' delirium than the typical ones.

**Ethical Approval:** The project was found to be following the ethical principles and the national norms and standards for conducting Medical Research in Iran.

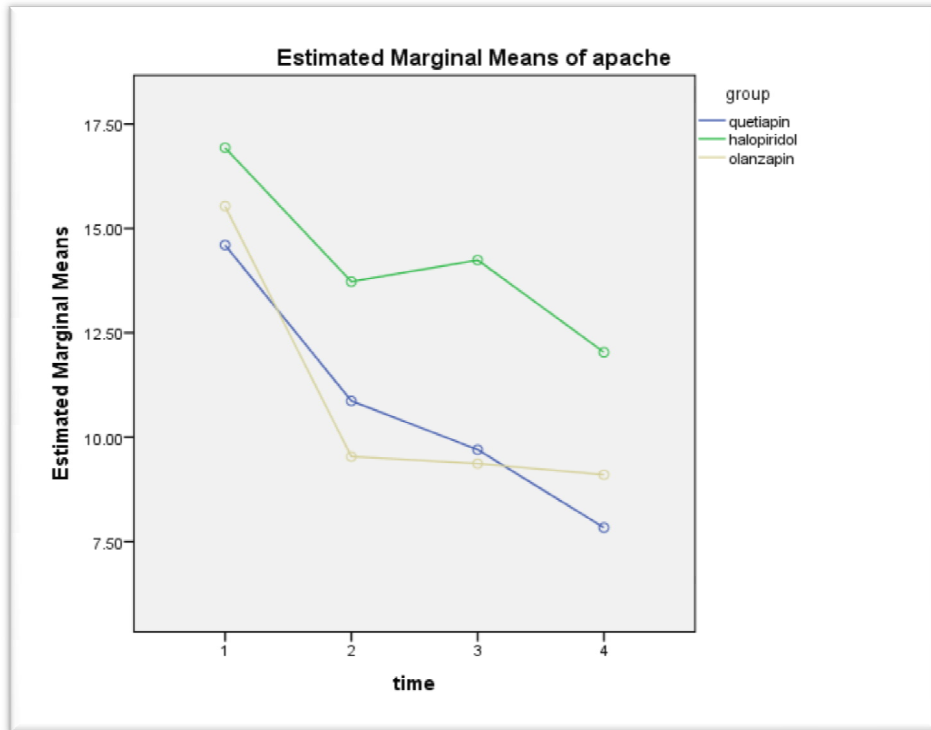
## **Consent**

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).



**Figure number 1**

Time on the figure is on the basis of the work shifts in table 1 that patients were under observation.



**Figure number 2**

The 1st time on the figure demonstrates 1st day of observation of patients

The 2nd time on the figure demonstrates 3rd day of observation of patients

The 3rd time on the figure demonstrates the 7th day of observation of patients

The 4th time on the figure demonstrates the 10<sup>th</sup> day of observation of patients

**Table 1 . Changes in patients' sedation status in different work shifts by groups.**

**p-value	*p-value	groups			Working shifts	
		Quetiapine	Haloperidol	Olanzapine	Average	Standard deviation
0.00	0.119	2.83	2.50	2.86	Average	<b>Morning Shift 1st day</b>
		0.69	0.82	0.73	Standard deviation	
	0.005	2.70	2.26	2.10	Average	<b>Evening Shift 1st day</b>
		0.95	0.69	0.40	Standard deviation	
	0.010	2.53	1.93	2.23	Average	<b>Night shift 1st day</b>
		0.73	0.86	0.62	Standard deviation	
	0.113	2.03	1.66	1.70	Average	<b>Morning Shift 2nd day</b>
		0.80	0.80	0.59	Standard deviation	
	0.750	1.66	1.53	1.53	Average	<b>Evening shift 2nd day</b>
		0.60	0.97	0.73	Standard deviation	
	0.780	1.30	1.26	1.16	Average	<b>Night shift 2nd day</b>
		0.74	0.86	0.64	Standard deviation	
	0.607	0.80	0.73	0.53	Average	<b>Morning Shift 3rd day</b>
		0.80	1.28	1.07	Standard deviation	
	0.180	0.50	0.73	0.26	Average	<b>3rd day Evening shift</b>
		0.86	0.94	1.08	Standard deviation	
	0.340	0.00	0.40	0.23	Average	<b>3rd day Night shift</b>
		0.83	1.13	1.16	Standard deviation	
0.004	-0.50	0.00	0.43	Average	<b>7th day Morning Shift</b>	
	0.97	1.05	1.10	Standard deviation		

	0.00	-0.76	0.20	0.23	Average	<b>7th day Evening shift</b>
		0.89	1.21	0.97	Standard deviation	
	0.00	-0.90	-0.43	0.20	Average	<b>7th day night shift</b>
		0.80	0.89	0.96	Standard deviation	
	0.00	-1.46	-0.17	-0.27	Average	<b>10th day Morning shift</b>
		1.07	1.00	0.99	Standard deviation	
	0.00	-1.73	0.06	-0.10	Average	<b>10th day Evening shift</b>
		1.43	1.03	0.77	Standard deviation	
	0.00	-1.80	0.20	-0.34	Average	<b>10th-day night shift</b>
		1.15	0.97	0.81	Standard deviation	

\*One way ANOVA

\*\* Repeated measure test

Table 2. Changes in disease severity according to APACHE II criteria in patients by groups

	**p-value	*p-value			Workdays
		groups			
		Quetiapine	Haloperidol	Olanzapine	
	<b>0.178</b>	<b>14.60</b>	<b>16.96</b>	<b>15.53</b>	Average <b>1st day</b>
		4.51	4.83	5.38	Standard deviation
<b>0.00</b>	<b>0.008</b>	<b>10.86</b>	<b>13.86</b>	<b>9.53</b>	Average <b>3rd day</b>

	5.69	5.50	4.93	Standard deviation	
<b>0.002</b>	<b>9.70</b>	<b>14.20</b>	<b>9.36</b>	Average	<b>7<sup>th</sup> day</b>
	5.21	7.15	4.58	Standard deviation	
<b>0.006</b>	<b>7.83</b>	<b>12.03</b>	<b>9.10</b>	Average	<b>10<sup>th</sup> day</b>
	4.28	5.81	4.77	Standard deviation	

\*One way ANOVA

\*\* Repeated measure test

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Comparison of the effect of Olanzapine and Haloperidol and quetiapine on the treatment of delirium in Intensive care unit (ICU) patients

has been approved in the Iranian Registry of Clinical Trials on 2020-10-13.

Your registration reference is IRCT20200927048852N1.

Best Regards

Iranian Registry of Clinical Trials (IRCT)

Evaluated by: ARAK UNIVERSITY OF MEDICAL SCIENCES

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Conflict of interest: The authors state that there is no contradiction of interests in the current study.

#### Data Availability

All relevant data are within the manuscript and its Supporting Information files.

Conflict of interest: The authors state no contradiction or conflict of interest in the current study.

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## References

1. Kanova M, Sklienka P, Kula R, Burda M, Janoutova J. Incidence and risk factors for delirium development in ICU patients-a prospective observational study. *Biomedical Papers of the Medical Faculty of Palacky University in Olomouc.* 2017;161(2).
2. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. *New England Journal of Medicine.* 2013;369(14):1306-16.
3. Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU. *Critical care medicine.* 2015;43(1):40-7.
4. Ryan DJ, O'Regan NA, Caoimh RÓ, Clare J, O'Connor M, Leonard M, et al. Delirium in an adult acute hospital population: predictors, prevalence, and detection. *BMJ Open.* 2013;3(1).
5. Shadvar K, Baastani F, Mahmoodpoor A, Bilehjani E. Evaluation of the prevalence and risk factors of delirium in cardiac surgery ICU. *Journal of cardiovascular and thoracic research.* 2013;5(4):157.
6. González M, Martínez G, Calderón J, Villarroel L, Yuri F, Rojas C, et al. Impact of delirium on short-term mortality in elderly inpatients: a prospective cohort study. *Psychosomatics.* 2009;50(3):234-8.
7. McCoy Jr TH, Hart KL, Perlis RH. Characterizing and predicting rates of delirium across general hospital settings. *General Hospital Psychiatry.* 2017;46:1-6.
8. Santos E, Cardoso D, Neves H, Cunha M, Rodrigues M, Apóstolo J. Effectiveness of haloperidol prophylaxis in critically ill patients with a high risk of delirium: a systematic review. *JBPI database of systematic reviews and implementation reports.* 2017;15(5):1440-72.
9. Grover S, Kumar V, Chakrabarti S. Comparative efficacy study of haloperidol, olanzapine and risperidone in delirium. *Journal of psychosomatic research.* 2011;71(4):277-81.

10. Devlin JW, Skrobik Y, Riker RR, Hinderleider E, Roberts RJ, Fong JJ, et al. Impact of quetiapine on resolution of individual delirium symptoms in critically ill patients with delirium: a post-hoc analysis of a double-blind, randomized, placebo-controlled study. *Critical care*. 2011;15(5):R215.
11. Hawkins SB, Bucklin M, Muzyk AJ. Quetiapine for the treatment of delirium. *Journal of hospital medicine*. 2013;8(4):215-20.
12. Vieta E. Mood stabilization in the treatment of bipolar disorder: focus on quetiapine. *Human Psychopharmacology: Clinical and Experimental*. 2005;20(4):225-36.
13. Vieta E, Calabrese J, Goikolea J, Raines S, Macfadden W, Group BS. Quetiapine monotherapy in the treatment of patients with bipolar I or II depression and a rapid-cycling disease course: a randomized, double-blind, placebo-controlled study. *Bipolar disorders*. 2007;9(4):413-25.
14. Grover S, Kate N. Assessment scales for delirium: a review. *World journal of psychiatry*. 2012;2(4):58.
15. Komossa K, Depping AM, Gaudchau A, Kissling W, Leucht S. Second-generation antipsychotics for major depressive disorder and dysthymia. *Cochrane Database of Systematic Reviews*. 2010(12).
16. Kiberd M, Hall R. Does haloperidol cause delirium? *Critical Care Medicine*. 2015;43(5):1143-4.
17. Keegan J, Wira III CR. Early Identification and Management of Patients with Severe Sepsis and Septic Shock in the Emergency. *Critical Care Emergencies, An Issue of Emergency Medicine Clinics of North America, E-Book*. 2014;32(4):759.
18. Grover S, Mahajan S, Chakrabarti S, Avasthi A. Comparative effectiveness of quetiapine and haloperidol in delirium: A double-blind randomized controlled study. *World journal of psychiatry*. 2016;6(3):365.
19. Maneeton B, Maneeton N, Srisurapanont M, Chittawatanaarat K. Quetiapine versus haloperidol in the treatment of delirium: a double-blind, randomized, controlled trial. *Drug design, development and therapy*. 2013;7:657.
20. Lee Y-J, Jung H-Y, Lee SI, Kim SG, Park JH. Comparison on the efficacy of quetiapine versus haloperidol in the treatment of delirium: prospective, randomized trial. *Korean Journal of Biological Psychiatry*. 2009;16(1):15-24.
21. Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: a comparison of efficacy, safety, and side effects. *Palliative & supportive care*. 2015;13(4):1079.
22. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive care medicine*. 2004;30(3):444-9.

