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ADJUNCT ALLOPURINOL TO SODIUM VALPROATE AND HALOPERIDOL IN TREATMENT OF IN-PATIENTS WITH ACUTE BIPOLAR MANIA

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ABSTRACT

Objectives: There is only limited previous evidence for the management of mania to shorten the in-patient phase of treatment, reduce costs and prevent recurrence of the episodes, as well as causing fewer side effects and enhance patient's compliance. The main objective of the present study was to investigate effectiveness of Allopurinol adjunct treatment for the acute mania episode of bipolar disorder and determine whether this treatment is effective in relieving acute mania symptoms. **Methods:** This study was a double-blind randomized clinical trial, 70 bipolar patients in manic episode were treated with Allopurinol and Sodium valproate and Haloperidol versus Sodium valproate and Haloperidol plus placebo, and treatment responses were assessed on a weekly basis for 4 weeks, by Young Mania Rating Scale (YMRS). **Results:** YMRS score did not have statistically significant difference between intervention and control groups at the baseline. In both groups, YMRS score had significant decrease within 4 weeks ($p<0.001$), and a statistically significant difference was obtained between the two groups($p<0.001$). The most decline in YMRS score was observed within 4 weeks of treatment. **Conclusion:** In the light of reported findings, it is

conceivable that combination of Sodium Valproate and adjunct Allopurinol added to the routine pharmacotherapy regimen of acute mania treatment, could significantly improve most patient's symptoms, since Allopurinol reduced the severity and duration of acute mania symptoms. On the other hand, these findings confirm the role of purinergic system malfunction in developing Mania.

KEYWORDS: Bipolar Disorder, Allopurinol, Sodium Valproate, Mania, Haloperidol, Young Mania Rating Scale (YMRS).

INTRODUCTION

Mental disorders arise challenging problems by provoking direct costs (i.e. diagnosis, treatment, rehabilitation and prevention) and indirect costs (i.e. increased function and productivity, family burden), and cause the highest rate of disabilities in Iran.[1] Bipolar disorder is a prevalent, chronic, severe and recurrent psychiatric condition, also known as a general health problem in the society.[2,3] A series of recent studies has indicated that almost 90% of patients with one episode of mania will experience another one. Also, up to 30% of patients referred to primary health centers with chief complain of depression, suffer from bipolar disorder.[3,6] Previous studies have emphasized that mania is typically comorbid with behavioral disorders and may cause numerous issues for the patient and his relatives. In addition, experiencing recurrent episodes of mania dramatically affect patient's function and quality of life, after remained asymptomatic for a while.[7,8] According to the World Health Organization (WHO), bipolar disorder is rated as the sixth disabling disease in people aged 15 to 44 years, globally. It has been also reported that 25-50% of patients with bipolar disorder attempt suicide.[9,10]

Various medications are effective in reducing symptoms of the acute mania phase of bipolar disorder. However, many patients do not respond to conventional pharmacotherapy during the manic phase and remain symptomatic. Lithium, Sodium Valproate and Carbamazepine are widely accepted as the first-line treatment for mania. Lithium can still be considered as the gold standard in treatment of the manic episodes. Old researches estimated that, Lithium could be effective up to 70% in controlling symptoms of acute mania, this is whilst most recent investigations documented that Lithium could only be effective in 50% of the patients and not all cases respond well to Lithium therapy.[11]

This contrast requires further explorations to recognize the most effective pharmaceuticals for treatment of mania. Prior studies have suggested that co-prescription of benzodiazepines and antipsychotics can enhance the therapeutic results.[12] The FDA, has approved Lithium, Sodium Valproate and Carbamazepine for treatment of acute mania.[13]

On the other hand, all effective medications in schizophrenia, including typical and atypical antipsychotics could be effective in treatment of mania with even more effectiveness in treatment of mania, in comparison with schizophrenia disorder.[9]

There seems to be a tendency toward co-prescribing two or even more medications for treating acute mania episodes, but one primary problem with this idea is that, it is yet unknown which drug combination would be the most effective in each particular patient. However, the most commonly prescribed medications fail to reach optimal rate of effectiveness in treatment of acute mania. In spite of great improvements in pharmacological therapy of patients with mania, drug resistance remains an open problem, which necessitates focus on extensive research in this area. At the present time, there is no absolute consensus on the most effective treatment for mania. Although Lithium, Sodium Valproate and Olanzapine are considered as, well-recognized medications for treatment of the acute mania and according to the findings of prior research have similar effects on most patients; still patient's poor response to the above mentioned medications and drug resistance in the acute mania has been reported up to 50%.[14,15]

Considering the prevalence of bipolar disorder and its negative consequences on patient's function and quality of life, investigating better pharmacotherapy seems necessary. Currently, the accepted treatment for mania consists of mood stabilizers (Lithium, Sodium Valproate, Carbamazepine) besides second generation antipsychotics (atypical antipsychotics). Prior research has emphasized that such prescription accelerates the therapeutic effect and could enhance the therapeutic response up to 60 to 80 percent, compared to prescribed mood stabilizer solely (50%) or antipsychotics alone (50%).[16]

As has been previously reported in the literature, Allopurinol had anti-manic effects in patients with bipolar disorder under treatment of Lithium, combined with Allopurinol.[17]

A study conducted on 59 outpatients with schizophrenia who were randomly assigned into two groups to receive Allopurinol 300 mg (31 subjects) or placebo alone (28 subjects),

showed a 20% reduction in total PANSS score among 4 participants of the experimental group, but none of the control group members showed any reduction in the above mentioned score. Therefore, the researchers concluded that patients under Allopurinol treatment well-tolerated the drug and did not show any side effects. They have even recommended Allopurinol as an adjunct pharmacotherapy for the patients with chronic schizophrenia disorder.[18] Machado-vieria et al., conducted a study during 2003 to 2006 in Brazil aiming to investigate effectiveness and tolerability of adding purinergic drugs for treatment of patients during acute mania phase and concluded that Allopurinol was clinically effective and well-tolerated in patients with acute mania.[9]

There exists a considerable body of literature on effectiveness of Allopurinol as an adjunct to various antipsychotics in treatment-resistant schizophrenia, mania and aggressive behaviors.[16] There is only limited previous evidence for the management of mania to shorten the in-patient phase of treatment, reduce costs and prevent recurrence of the episodes, as well as causing fewer side effects and enhances patient's compliance. The main objective of the present study was to investigate effectiveness of Allopurinol adjunct treatment for the acute mania episode of bipolar disorder and determine whether this treatment is effective in relieving acute mania symptoms.

MATERIALS AND METHODS

The present randomized clinical trial study was conducted on patients diagnosed with Bipolar I disorder in the mania episode admitted to Razi Psychiatric Center of Tehran. The convenient sampling method was applied and a total sample size of 70 individuals (males and females) was calculated in accordance with prior similar investigations, which as a result, 35 patients who met the inclusion criteria of our study were enrolled into the setting of our study. All participants provided a written informed consent prior to the onset of conducting the research. The study was also approved by the Ethics Committee of the University of Social Welfare and Rehabilitation Sciences.

We have randomly placed all 70 participants into two experimental and control groups using Random allocation software. The experimental group consisted of 35 patients under treatment of 5-15 mg daily Haloperidol + 600-1200 mg daily Sodium Valproate + 300 mg (100 mg three times per day) Allopurinol. The control groups (35 patients) received 5-15 mg daily Haloperidol + 600-1200 mg daily Sodium Valproate + placebo (1 capsule three times per day).

Patients received benzodiazepines as per their course of treatment and in accordance with the ethical guideline for medicinal drug promotion. Patient's course of treatment was 4 weeks during which a psychiatrist resident who was trained for this purpose and not informed about the study groups and their medication types visited the subjects regularly. The subjects were evaluated in respect of the study variables at the time of referral, and once a week (4 times in total). In each visit, patients were evaluated in terms of drug tolerance, appetite changes, side effects of drugs, suicidal ideation (considering the probability of suicidal ideation while consuming anticonvulsants). In addition, their demographic data and information regarding their symptoms were collected in details. The Young Mania Rating Scale (YMRS) was also applied to evaluate patients at every week of the intervention plan.

The Young Mania Rating Scale (YMRS) is an assessment tool that consists of 11 items and scoring is on the basis of patient's report on their past 48 hours and the supplementary information is gathered through clinical observation and interviewing. The scores might range between 0 to 60. Meanwhile, validity and reliability of this inventory was measured in 2009 on the Iranian population and got proved reliable by the researcher. It was also confirmed that sensitivity and specificity of this scale is reliable for both clinical settings and research work.[18]

The data was analyzed using SPSS software version 20. Our quantitative data were reported through Mean score, Standard Deviation and Median Score [IQR]. The qualitative data was also demonstrated in frequency (percentage) format. Data obtained from the Young Mania Rating Scale (YMRS) in different times of the study was compared using a T-Student Test. Also, to assess the effect of Allopurinol on decreasing trend of the Young Mania Rating Scale (YMRS) through 4 weeks of treatment, Repeated Measure Analysis of Variance (ANOVA) was used. Meanwhile, T-Student test, Chi-square and Mann-Whitney Test were applied to compare the demographic characteristics of the two groups of our study.

RESULTS

In the current study, a total 70 patients were assigned into two groups receiving either Allopurinol or placebo in addition to their conventional medications regimen through a four-week intervention plan. Analysis of our results showed that mean age of the subjects was 38.7±10.1 and majority of the participants were female. In addition, most participants (34.4%) were married and 70% were unemployed.

Table one demonstrates results of patient's demographic data. As shown, mean age comparison of Allopurinol receivers was higher than the placebo group, but the mean age of groups was not significantly different. Also no statistical significant difference is observed between the two groups in terms of gender composition as per the results of Chi-square test. Table 1 also shows findings regarding comparing marital status among the study groups on the basis of Chi-square test. We observed that most patients were female and the marital status variable was not significantly different between the Allopurinol receivers and placebo group. Results of Chi-square test for comparing occupational status of the participants revealed that most patients of both groups were unemployed and no significant difference was seen between the two groups in terms of employment. According to the results of Chi-square test, most patients of each group have finished high-school. Patents with bachelor's degree had the lowest rate among all participants. Our analysis revealed no statistically significant difference between the two groups in terms of level of education. our findings of Mann-Whitney test analysis demonstrated no significant difference between the Allopurinol receivers and placebo receivers in terms of in-patient treatment histories.

Table 1: Demographic Data of Groups of Allopurinol and Placebo Receivers.

Variable	**Allopurinol Receivers**		**Placebo Receivers**		**P-value**
Age	***Mean Score***	***SD***	***Mean Score***	***SD***	0.31
	39.97	10.7	37.43	10	
Gender	*Frequency*	*Percentage*	*Frequency*	*Percentage*	1
Male	23	65.7	23	65.7	
Female	12	34.3	12	34.3	
Marital Status	*Frequency*	*Percentage*	*Frequency*	*Percentage*	0.79
Single	9	25.7	8	22.9	
Married	11	31.4	13	37.1	
Divorced	11	31.4	8	22.9	
Widowed	4	11.4	6	17.1	
Employment Status	*Frequency*	*Percentage*	*Frequency*	*Percentage*	0.96
Employed	8	22.9	7	20	
Housewife	3	8.6	3	8.6	
Unemployed	24	68.6	25	71.4	
Level of education	*Frequency*	*Percentage*	*Frequency*	*Percentage*	0.76
Illiterate	3	8.6	5	14.3	
Primary School	5	14.3	7	20	
Up to the 9th Grade	8	22.9	5	14.3	
High-school	9	27.5	8	22.9	
High-school Diploma	10	28.6	9	27.5	
Bachelor's Degree	0	0	1	2.9	
History of In-patient Treatment	*Median*	*Interquartile range*	*Median*	*Interquartile range*	0.21
	2	3-1	2	3-1	

Results of T-student test for comparing the mean rate of prescribed Sodium Valproate and Haloperidol between the two groups of study are presented in table2. Based on our results, no statistically significant difference was seen in terms of mean dosage of consumed Valproate and Haloperidol between the experimental and control groups.

Table 2: Comparison of Mean Dosage of Consumed Valproate Sodium and Haloperidol between the experimental and control groups.

Medication	Allopurinol Group		Placebo Group		P-Value
	Mean Score	*SD*	*Mean Score*	*SD*	
Sodium Valproate	856.15	191.41	857.14	197.46	0.99
Haloperidol	11	3.39	11.29	3.05	0.71

We have evaluated patients based on the Young Mania Rating Scale (YMRS) in aim of exploring the effect of adjunct Allopurinol to the participant's conventional prescribed medications. Results of comparing subject's YMRS mean scores are provided in table 3. According to our findings, mean score of YMRS was higher in the experimental group, prior to the onset of intervention. Also, compared to the control group, YMRS mean score significantly decreased within two weeks after initiation of the treatment among members of the experimental group. Same results were obtained after completion of the fourth week of intervention, in which the YMRS mean score was significantly lower in the group of Allopurinol receivers, compared to the placebo group.

Table 3: Comparing Mean Score of the YMRS among the Study Groups at Different Intervals.

Intervals	Allopurinol Group		Placebo Group		P-Value
	Mean Score	*SD*	*Mean Score*	*SD*	
Pre-test	43.86	4.9	40.94	5.5	0.022
2nd Week of the Treatment	33.26	5.55	37.97	4.74	*<0.001*
4th Week of the Treatment	11.47	8.7	28.06	3.76	*<0.001*

DISCUSSION

Discussions regarding bipolar disorder pharmacotherapy have dominated research in the recent years, as issues like high prevalence of bipolar disorder, disabilities consequence to episodes of this disorder, lack of optimal response to conventional therapies and medicine-related side effects and weight gain that could affect patient's compliance with treatment plan, have made a number of significant contributions to explore medications that not only could increase patient's therapeutic response, but also improves their compliance with the treatment plan.[10]

This paper explored how combination of Sodium Valproate and Allopurinol impacts treatment procedure of patients affected by bipolar I disorder who are experiencing a manic episode. For this aim, we applied two groups of experimental and control subjects (whom received Sodium Valproate and placebo) for 4 weeks and assessed the study participants using YMRS inventory tool. In accordance with our findings, the mean score of YMRS significantly decreased in the experimental group within two weeks from the initiation of our intervention plan; compared to the control one. Our results also revealed a significant decrease in the group who received Sodium Valproate and Allopurinol, compared to the group members who only received Sodium Valproate and placebo.

Analyzing data obtained from YMRS showed that compared to the control group; mean score of this tool was lower in the group who received Allopurinol in the second and fourth week of intervention, which reflects effectiveness of Allopurinol in controlling symptoms of acute mania. Furthermore, the rate of remission was much higher in the experimental group (reduction of YMRS scores for more than 50%) was 86.4% at the completion of intervention process, compared to the onset of study in the Allopurinol group, while none of the placebo group members showed a 50% reduction in YMRS score which indicates that combined pharmacotherapy with Allopurinol delivers significantly better results during the acute mania episode of Bipolar I disorder.

The findings are directly in line with the previous eight-week experimental research of Akhoondzadeh et al., conducted on patients with bipolar disorder who were divided into two groups including adjunct Allopurinol receivers and placebo receivers. They observed a decreased rate of scores for YMRS in the experimental group at the completion of their eight-week program, compared to the baseline scores.[19]

Limitations & Future Work

A limitation of the present study naturally includes short-term follow-up (4 weeks). Benzodiazepines are clearly effective in remission of Mania symptoms and not all subjects received equal dosage of Benzodiazepines, therefore, another concern about the findings was that both experimental and control groups of our study received Benzodiazepines as required and due to medical ethics.

Future studies could fruitfully explore this issue further by a longer-term follow-up procedure, as well as administrating prescription of Benzodiazepines on the basis of a fixed

protocol with similar directions for the therapeutic groups of research. Further research could also delimitate comparing combination of Allopurinol with other Anticonvulsants, as well as comparing therapeutic effect of Allopurinol in Antipsychotics recipients with those who do not receive Antipsychotic medications.

CONCLUSION

In the light of reported findings, it is conceivable that combination of Sodium Valproate and adjunct Allopurinol added to the routine pharmacotherapy regimen of acute mania treatment, could significantly improve most patient's symptoms, since Allopurinol reduced the severity and duration of acute mania symptoms. On the other hand, these findings confirm the role of purinergic system malfunction in developing Mania.

Conflict of interests

The authors declare no conflict of interests regarding the publication of this paper.

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REFERENCES

1. Shirazi E, Shahrivar Z. Diagnostic debates of childhood bipolar disorder: From the formal diagnostic criteria to the severe mood dysregulation. Iranian Journal of Psychiatry and Clinical Psychology, 2009; 15(2): 128-46.
2. Shirazi E, Zarei M, Shahrivar Z. Sub threshold signs and symptoms of mania in the premorbid phase of the first manic episode: A retrograde study. Journal of Affective Disorders, 2008; 107: S101.
3. Amini H, Sharifi V, Nejatisafa A, Arbabi M, Tabatabaie M, Alimadadi Z, et al. One year follow-up of patients with bipolar disorder admitted to Roozbeh Hospital. Iran J Psychiatr Clin Psychol., 2009; 15(2): 168-74.
4. Mohammadi M-R, Davidian H, Noorbala AA, Malekafzali H, Naghavi HR, Pouretemad HR, et al. An epidemiological survey of psychiatric disorders in Iran. Clinical practice and epidemiology in mental health, 2005; 1(1): 16.
5. Leclerc E, Mansur RB, Brietzke E. Determinants of adherence to treatment in bipolar disorder: a comprehensive review. Journal of affective disorders, 2013; 149(1): 247-52.
6. Gajwani P, Kemp DE, Muzina DJ, Xia G, Gao K, Calabrese JR. Acute treatment of mania: an update on new medications. Current psychiatry reports, 2006; 8(6): 504-9.

7. Montes J, Saiz J, De Dios C, Ezquiaga E, Garcia A, Argudo I, et al. Profile of bipolar disorder outpatients: a cross-sectional study in the Madrid Community. Actas espanolas de psiquiatria, 2008; 36(5): 277-84.
8. Rosa AR, Reinares M, Franco C, Comes M, Torrent C, Sánchez-Moreno J, et al. Clinical predictors of functional outcome of bipolar patients in remission. Bipolar Disorders, 2009; 11(4): 401-9.
9. Machado-Vieira R, Lara DR, Souza DO, Kapczinski F. Therapeutic efficacy of allopurinol in mania associated with hyperuricemia. Journal of clinical psychopharmacology, 2001; 21(6): 621-2.
10. Fan A, Berg A, Bresee C, Glassman LH, Rapaport MH. Allopurinol augmentation in the outpatient treatment of bipolar mania: a pilot study. Bipolar disorders, 2012; 14(2): 206-10.
11. Salvi V, Cat AB, Bechon E, Bogetto F, Maina G. Lithium and anticonvulsants in the treatment of mania and in the prophylaxis of recurrences. Rivista di psichiatria, 2011; 46(3): 172-81.
12. Machado-Vieira R, Lara D, Souza D, Kapczinski F. Purinergic dysfunction in mania: an integrative model. Medical hypotheses, 2002; 58(4): 297-304.
13. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Azorin J-M, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long-term treatment of mixed states in bipolar disorder. The World Journal of Biological Psychiatry, 2018; 19(1): 2-58.
14. Marro PJ, Mishra OP, Delivoria-Papadopoulos M. Effect of allopurinol on brain adenosine levels during hypoxia in newborn piglets. Brain research, 2006; 1073: 444-50.
15. Brunstein MG, Ghisolfi ES, Ramos F, Lara DR. A clinical trial of adjuvant allopurinol therapy for moderately refractory schizophrenia. The Journal of clinical psychiatry, 2005; 66(2): 213-9.
16. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. The Journal of Clinical Psychiatry, 2007.
17. Yatham LN, Kennedy SH, O'donovan C, Parikh S, MacQueen G, McIntyre R, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar disorders, 2005; 7(s3): 5-69.
18. Barekatain M, Tavakoli M, Molavi H, Maroufi M, Salehi M. Standardization, reliability and validity of the Young Mania Rating Scale. Psychology, 2007; 11(2): 150-66.

19. Akhondzadeh S, Safarcherati A, Amini H. Beneficial antipsychotic effects of allopurinol as add-on therapy for schizophrenia: a double blind, randomized and placebo controlled trial. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2005; 29(2): 253-9.