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*Research Article*

# Effect of Aripiprazole on Smoking Rate in Male Bipolar Mood Disorders I

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## Abstract

**Purpose:** Significant impairment in functioning of patients with mental disorders is created. Bipolar disorder is a common and debilitating mental illness that ranks the fifth for the burden of disease among all patients. It is hard to treat the disorder and stabilize patient's mood for a long-term due to lack of patient compliance, multiple recurrences and severity of the disease. The most common, costly and the deadliest addiction would belong to nicotine which is often neglected and involved people with bipolar disorder. Smoking and consequently mortality rate in psychiatric patients is higher than the population.

**Methods:** The interventional research studied all patients with Bipolar Disorder type I. Forty randomly selected patients were divided into two groups: Aripiprazole and placebo. The samples were examined two times; at the baseline and after 6 weeks, with Young Mania Rating Scale, and Fagerstrom Test for nicotine dependence. Data were analyzed using the software package SPSS 18 and p-value <0.05.

**Results:** Aripiprazole Group showed statistically significant difference in reduction in nicotine use between phases of before and after treatment, but it was not true in the placebo group. The intervention group decreased smoking significantly after 6 weeks of treatment, in contrast to the placebo group.

**Conclusion:** Aripiprazole reduces smoking in patients with Bipolar Disorder type I.



## Introduction

Bipolar disorder is a disabling psychiatric disorder [1]. In terms of burden of disease, it is ranked fifth by World Health Organization (WHO) [2]. It is hard to treat the disorder and stabilize patient's mood for a long-term due to lack of patient compliance, its recurrences, severity and various clinical forms. The lifetime prevalence of bipolar disorder is 0.6% and the prevalence of bipolar spectrum disorders is 4.8%.

The most common, costly and the deadliest addiction would belong to nicotine which is often neglected. Nicotine addicts are less likely to seek treatment because it does not cause behavioral problems [3]. Although about half of smokers have been able to quit smoking at some point in time, many of them have finally failed to quit. Drug and non-drug therapies can be helpful, regarding to the results of meta-analyses shown that drug therapy can make it successful in increasing the rate of smoking cessation [4]. Adults suffered from bipolar disorder are 2 to 3 times more likely to become smokers. Based on the related studies, the probability of commitment to quit smoking or lingering on the smoking cessation approach seems low among bipolar patients [5].

Nicotinic enhancement is attributed to dopamine neurons located in the ventral tegmental area [6]. Smoking affects the development of mental illnesses as well as the metabolism of prescribed drugs and they can be predicted by smoking cessation. Due to the important role of dopamine in the reward system, dopaminergic drugs for the treatment of nicotine dependence have been recently taken into account. In different studies, the more the patients use the first generation antipsychotics, the heavier they smoke. In contrary, a decrease in smoking was revealed among patients taking the second-generation anti-psychotic, according to some studies [7].

Several case reports have confirmed the efficacy of Aripiprazole as a relative dopamine agonist in smoking reduction in psychiatric patients [8]. The difference between aripiprazole and the rest of second-generation antipsychotics is that it is not an antagonist but a relative dopamine agonist that has stabilizing effect on dopaminergic system by increasing dopamine in

the hypo dopaminergic regions and lowering it in the hyper dopaminergic regions [9]. Aripiprazole are used as an effective drug in the acute phase of mania, as some studies examined its effect as a maintenance therapy[10,11,12]. Although there are case reports on smoking reduction by Aripiprazole, it is the lack of independent studies on nicotine dependency in mental patients that makes the current study a step forward in preventing smoking in such patients, and consequently, the risk of chronic illness caused by smoking.

## Methods

The study was a double-blind clinical trial. The study population was male patients with bipolar disorder type I who referred to Tabriz Medical Center of Razi and Bozorgmehr Clinic (affiliated to Tabriz University of Medical Sciences) in an outpatient department, or those hospitalized in male psychiatric departments of Tabriz Medical Center of Razi from 2016-2017. In each intervention group and control group, according to similar studies, 20 patients in their complete or partial recovery phase were randomly assigned by randomized blocking method. Blocking and randomization were performed by a nonexecutive person. A package including forty packs with enough Aripiprazole or placebo were got ready. Using the Microsoft Excel software package, label A or B (for medication and placebo respectively) was stuck on packs by the nonexecutive person.

First, a definitive diagnosis of BMD I was done by a psychiatrist using the structured interview of SCID-I. Then, the smoking rates among patients were determined via FTQ questionnaire. The intervention group was provided with aripiprazole 10 mg tablets/day for 6 weeks. During the intervention, the patients were not asked to quit smoking. In control group, the placebos were in the same shape, size and color as aripiprazole. In both groups, the drug was presented to the patients in a gradually increasing manner. After 6 weeks, the smoking rates of patients were measured by FTQ again. A checklist for the side effects of the drug was prepared based on the complications recorded by scientific studies. It was completed by interview with the sample in the first and fourth weeks. Those experienced the medication side effects were excluded, and another person was replaced.

## Inclusion criteria

1. Definitive diagnosis of bipolar disorder type I, according to DSM-IV-TR criteria
2. Being in the phase of partial or complete recovery based on YMRS
3. Having the necessary criteria for the diagnosis of nicotine dependence according to DSM-IV-TR criteria
4. The ages of 18 to 60 years
5. Male sex
6. Informed consent to participate in the study.

## Exclusion criteria

1. The history of drug allergy related to Aripiprazole or other antipsychotics
2. Other substance dependency (based on the patient's history, test of morphine and methamphetamine at the onset of the intervention)
3. Taking other drugs to quit nicotine
4. Taking drugs other than bipolar disorder drugs
5. History of physical disease
6. History of intellectual disability
7. History of cognitive impairment.

### Tools

Structured interview SCID-I was set out on Diagnostic and Statistical Manual of Psychiatric Disorders-Fourth Edition (DSM-IV) of the American Psychiatric Association. SCID-I. it was used to assess the underlying psychiatric disorders in axis I. In the study of Sharifi et al., the overall agreement of the Persian version for the current diagnosis and the lifetime diagnosis was 0.52 and 0.55, respectively. Most of diagnoses with specificity more than 0.85 and half of them with specificity more than 0.9 indicated a desirable specificity. The sensitivity was somehow lower. The Persian version of SCID is a valid tool for clinical and, in particular, educational and research purposes in diagnosis, so it is recommended for the above-mentioned purposes in clinical settings [13]. The Structured Clinical Interview (SCID) was utilized in a number of studies as a gold standard for clinical diagnosis [14,15].

### Young Mania Rating Scale (YMRS)

The questionnaire measures the severity of mania symptoms using [18] questions which are rated from 0 to 5 on a 6-point Likert scale. Its reliability was reasonable regarding the reliability tests among examiners as well as its internal consistency via its correlation with other tools measuring mania. The sensible sensitivity, specificity and validity of YMRS make it an appropriate tool to apply in clinical and research work. The study of Ebrahimi et al. verified desirable psychometric properties of the Persian version of YMRS [16].

### Nicotine dependence questionnaire

About 10 years ago, Karl Fagerstrom, a Swedish physician, developed the Fagerstrom Tolerance Test, which is currently verified as a standard tool by the World Health Organization. This six-question tool measures factors including time of smoking, the number of cigarettes, the best brand of cigarettes, early use in the morning, smoking during illness and in prohibited places. The total score fluctuates from zero to ten. In order to establish a smoking cessation clinic during 2005 and 2007, its reliability was confirmed by domestic studies of Heidari et al.[17,18].

Glasgow's antipsychotic drug scale was used to control the medication side effects. It takes five minutes to fill the questionnaire with 21 self-report items. The scale is utilized to assess the side effects in patients treated with second-generation antipsychotics [19].

Data were analyzed using the software package SPSS 18, considering p-value <0.05. the test of Kolmogorov-Sminorov was carried out for assessing the normality, kurtosis and skewness of data distribution in order to examine the statistical

difference between age, Yang Mania Score and the first and the second Fagerstrom Tolerance Tests among people with bipolar disorder type I in both groups of aripiprazole and placebo, the test showed the data without normal distribution, so nonparametric inferential tests were used. The significant difference between paired data in aripiprazole and placebo groups was analyzed via Wilcoxon test shown in Table 1.

From the ethical point of view, the confidentiality of the information was explained to the participants and written consent was obtained. This study was approved by International Registry of Clinical Trials in Iran under the registry code of IRCT2016121228173N3 IRCT2016121228173N3.

## Results

In the current study, 40 men were studied in two intervention and control groups. The mean age of intervention group and the placebo group was 34.55 years (SD: 10.88 years) and 35.05 years (SD: 7.23 years), respectively. There was no statistically significant difference between them. The mean age at which smoking initiated was 20.80 years (SD: 5.11) in the case group, and 20.05 years (SD: 4.01) in the placebo group. There was no statistically significant difference between them. The hospitalization history in the intervention group and the placebo group was 60% and 50% respectively. 35% of the intervention group and 30% of the control group were hospitalized at the time of study and the rest was outpatients.

The mean scores of YMRS before intervention in the study group and the control group were 7.80 (SD: 1.01) and 7.70 (SD: 0.99). Accordingly, there was no statistically significant difference between them.

Regarding the Fagerstrom tolerance test, the initial mean score (the score at the beginning of treatment) was 8.40 (SD: 1.10) in the intervention group and 7.80 (SD: 1.15) in the placebo group. There was no statistically significant difference between them. The final mean score (the score at the end of treatment) was 5.5 ppm (SD: 1.0) in the intervention group and 7.70 (SD: 1.17) in the placebo group. statistically, the difference between the final mean scores of two groups was significant (P <0.001).

According to the difference between scores of pretest and posttest for Fagerstrom Tolerance Test shown in Table 2, Aripiprazole was effective in reducing smoking in the case group, in spite of the placebo group.

## Discussion

Despite many studies on bipolar disorder as well as substance dependency, there was found no domestic research examining them simultaneously. Non-intervention approaches did not get much success in smoking cessation [2].

Consistent with the result demonstrating the effectiveness of aripiprazole in treating and reducing cigarette dependence in bipolar patients, Hughes study (2009) indicates that new generations of psychiatrics can be very useful in smoking cessation [2]. Also, meta-analyses conducted by Mills et al. (2009) showed that pharmacotherapy can make it successful to stop smoking [4]. A study by Zamir et al. in Qazvin province displayed that aripiprazole was successful in smoking cessation

**Table 1: Demographic variables**

| | Aripiprazole group | | Placebo group | |
|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent |
| Educational level | | | | |
| Illiterate | 0 | 0 | 1 | 5 |
| Primary | 0 | 0 | 5 | 25 |
| Guidance | 6 | 30 | 4 | 20 |
| High school/Diploma | 14 | 70 | 9 | 45 |
| Associate degree/Bachelor | 0 | 0 | 1 | 5 |
| Higher education | 0 | 0 | 0 | 0 |
| Marital status | | | | |
| Single | 12 | 60 | 8 | 40 |
| Married | 6 | 30 | 9 | 45 |
| Divorced | 2 | 10 | 3 | 15 |
| Widower | 0 | 0 | 0 | 0 |
| Single | 12 | 60 | 8 | 40 |
| Employment | | | | |
| Unemployed | 17 | 85 | 2 | 10 |
| Public and private sector employees | 1 | 5 | 2 | 10 |
| Retired | 1 | 5 | 1 | 5 |
| Out of service/disabled | 0 | 0 | 0 | 0 |
| Student | 1 | 5 | 0 | 0 |
| Self-employed | 0 | 0 | 15 | 75 |

**Table 2: The pre-test and post-test differences of Fagerstrom tolerance test by Wilcoxon test.**

| Variables | Phase | Mean | Standard deviation | P-value |
|---|---|---|---|---|
| Fagerstrom tolerance test | | | | |
| Aripiprazole group | Pre test | 40/8 | 10/1 | 001/0>0 |
| | Post test | 50/5 | 1 | |
| Fagerstrom tolerance test | | | | |
| Placebo group | Pre test | 80/7 | 15/1 | 62/0 |
| | Post test | 70/7 | 17/1 | |

as an adjunctive therapy among patients under methadone maintenance treatment, on the basis of (FTQ) scale [20]. Therefore, our findings were in line with available studies representing a positive effect of aripiprazole on reducing smoking, while placebo showed no significant effect.

According to recent findings by Lyon (1999), due to the important role of dopamine in the reward system, the dopaminergic drugs have been recently taken into consideration in order to treat nicotine dependency [3]. In various studies, the use of first-generation antipsychotics were associated with higher smoking among patients. However, it is not confirmed about the second-generation antipsychotics, and less smoking were seen in such patients, in some studies. A study by Arfaei et al., showed that aripiprazole acts better in smoking cessation in patients with schizophrenia rather than in the control group [21]. In in line with such findings, our study also verified the effect of aripiprazole as a relative dopamine agonist in reduction in smoking. The FTQ scale lessened by 1.53 units

after treatment in the study group and 0.42 units in the control group.

Ramaswamy and Bhatia revealed a causal relationship between aripiprazole and smoking cessation in their case study. They also reported that aripiprazole reduces the positive reward of nicotine and declines the desire to nicotine [8]. The current study also emphasizes the effect of aripiprazole on reducing smoking in patients with bipolar disorder type I, in consistent with other studies. Liu et al., found that prescription of aripiprazole ten mg tablets reduced the mental and psychological response due to smoking in heavy smokers [22]. Kim et al., reported the increment of nicotine dependency by haloperidol, but the second-generation antipsychotics did not do the same [23]. Aripiprazole reduced nicotine dependency and craving toward nicotine.

## Conclusion

The current study indicated that consistent with many of the above-mentioned studies, aripiprazole as a dopamine agonist, with few side effects, acts as an effective drug in reducing smoking in patients with bipolar disorder and it is possible to use it so as to reduction in injuries caused by excessive smoking in normal people and psychiatric patients.

### Limitations of study

Short term follow Up was most important limitation in this study.

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