Rersearch Article

Effect of Aripiprazole on Smoking Rate in Schizophrenic Patients

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Abstract

Purpose: Ventral Tegmental Area dopaminergic neurons consist of the pathway strengthening the use of psychoactive substances including nicotine. Dopamine over activity in this pathway could be the underlying cause of using substances. As a second-generation antipsychotic with a dopamine partial agonistic activity, it seems that aripiprazole could reduce substance use by adjusting dopamine in the mentioned pathway. Among schizophrenic patients, smoking and consequent cardiovascular diseases are more common compared with general population. The purpose of this study is to evaluate the effect of aripiprazole on smoking rate of schizophrenic patients.

Methods: This is a randomized triple blind parallel clinical trial in which 40 schizophrenic patients were allocated in two intervention and control groups. The intervention group received 10 mg aripiprazole on daily basis while the control group received placebo. In both groups, smoking rate was measured before and after the study using a standard instrument (Fagerstrom Tolerance Questionnaire) and the obtained data was compared and statistically analyzed by SPSS.

Results: There was no significant difference between the groups regarding age, duration of illness, duration of nicotine dependency and other demographic variables. The average FTQ score of the intervention group was 8 and 6.47 before and after taking aripiprazole, respectively, indicating a significant decrease; but in the control group, these values were 7.57 and 7.15 before and after receiving placebo, respectively indicating no significant decrease. The average decline in FTQ score during the study was 1.53 and 0.42 in the intervention and control groups, respectively, which is statistically significant.

Conclusion: According to this study, aripiprazole decreases the rate of nicotine dependency in male schizophrenic patients.

Introduction

Substance dependency is a behavioral pattern syndrome in which consuming a psycho-active or another substance is preferred to important behaviors. It has been asserted that addiction is a "brain disease," that the critical processes that transform voluntary drug-using behavior to compulsive drug use are changes in the structure and neurochemistry of the brain of the drug user. The pathway and structure which strengthen the consumption of a number of dependence inducing drugs, including nicotine, are associated with dopaminergic neurons in Ventral Tegmental Area (VTA). Studies suggest that dealing with addictive substances results in the hyperactivity of dopaminergic reward system in Meso-Accumbens pathway and generates an abnormal neuronal activity [1-3].

Smoking doubles cardiovascular disease mortality and nicotine dependency is the most prevalent, deadly and costly substance dependency which is generally ignored [4,5].

Mesolimbic dopaminergic neurons have multiple nicotinic cholinergic receptors; When activated, these receptors increase dopamine release. On the other hand, a number of the unpleasant effects induced by nicotine abstinence result in dysphoria and reinforce smoking; These effects are also associated with the dopaminergic system. Evidence now indicates that when one stops substance use, even when

there are no obvious and dramatic withdrawal symptoms, reward system is exposed to changes due to a relative hypodopaminergic state occurring in nucleus accumbens which, encourages reuse of substances [1].

Just a minority of smokers could quit smoking permanently. According to meta-analyses, pharmacological treatments (nicotinic or non-nicotinic treatments) have increased the rate of quitting smoking [2,6].

Bupropion (Zyban) and Varenicline (Chantix) are FDA approved non-nicotinic treatments for smoking cessation [7].

Since dopamine plays a pivotal role in reward and reinforcement systems, attention have been recently drawn to dopaminergic drugs for treating nicotine dependence disorders. The use of the first generation antipsychotics in different studies resulted in the rise of smoking rate among patients. This point is completely different regarding the second generation antipsychotics so that some studies reported a decline in smoking rate among patients [4]. Meanwhile, a number of case reports have confirmed the effectiveness of aripiprazole in decreasing smoking rate in schizophrenic patients [8,9]. It is used both as a treatment for acute phase and maintenance therapy in schizophrenia. It differs from other anti-psychotic drugs in that it is a dopamine partial agonist rather than being an antagonist [10,11].

Different studies have reported smoking rate among schizophrenic patients as 62%-90% [12-14]. Ziaaddini study also showed that smoking rate is higher in schizophrenic patients compared with general population in Iran and also cardiovascular diseases are more prevalent in these patients [15].

Although case reports have justified the use of aripiprazole for decreasing smoking rate, there are not sufficient independent studies especially in psychiatric patients with nicotine dependence. The present study, in case of obtaining positive results can be an important step in decreasing smoking rate in schizophrenic patients – who are less inclined to quite voluntarily – and subsequently lead to a decrease in the associated mortality and morbidity.

Materials and Methods

This was a randomized triple blind parallel clinical trial. As no similar study was available, a pilot sample size of 20 subjects was determined for each of the intervention and control groups. Samples were collected through convenience sampling method among schizophrenic patients who referred to Tabriz psychiatry clinics. The samples were selected in accordance with inclusion and exclusion criteria and were divided in intervention and control group according to blocking method. Diagnosis was approved by structured psychiatric interview.

Inclusion criteria

- Definitive diagnosis of schizophrenia based on SCID-I (Structured Clinical Interview for DSM Disorders).
- Meeting diagnostic criteria for nicotine dependence according to DSM IV TR.
- Age: 18-60 years.
- Male gender.
- Informed consent.

Exclusion criteria

- Hospitalized or getting hospitalized during intervention.
- Any sensitivity to aripiprazole or other antipsychotics or history of related side effects.
- Having any comorbidity.
- Dependency to other substances based on the patient's history, as well as morphine and methamphetamine tests conducted at the start of the study.
- Receiving other drugs with indication in smoking cessation.

None of the psychiatrist, patients and the evaluator knew the type of the prescribed (aripiprazole or placebo). To blind the study, a person who played no role in none of the study's steps helped us. All patients continued their standard treatments during the study. In order to monitor the changes in the natural inclination of the cases to smoking more accurately, they were not asked to try to lower smoking rate or to stop it completely. Hospitalized patients were not allowed to participate in the study due to the fact that hospitalization affects smoking rate. (In our inpatient departments for the mentally ill, smoking is generally limited and this is a serious confounding factor for the measurement of smoking inclination).

Since the number of cigarettes smoked per day is not a perfect scale for measuring the severity of smoking dependency and other factors like cigarette type in terms of nicotine concentration, smoking pattern (the quality of inhaling and exhaling the smoke), time of smoking the first cigarette in the morning (the closer to get up time the more the severity) and inclination to smoking in mornings or late in the day influence the determination of nicotine dependency severity, in this study, FTQ (Fagerstrom Tolerance Questionnaire) questionnaire was used to determine severity of nicotine dependency.

FTQ is one of the most commonly used instruments in determination of severity of nicotine dependency and its validity and reliability have been approved frequently [16-22]. WHO and GARD (global alliance against chronic respiratory diseases) have introduced it as a standard instrument. The Persian version of it has been previously validated by Heydari et al [23] and it has multiple studies as a standard scale [15, 23-26]. The last version of the questionnaire contains 8 questions about numbers of smoked cigarettes per day, nicotine percentage of cigarettes, dominant temporal pattern of smoking, quality of inhaling and exhaling cigarette smoke and smoking during illness and in forbidden places. The more the scores of the questions, ranged from 0 to 15, the more nicotine dependency severity.

In the beginning of the study smoking rate of all subjects was determined using FTQ questionnaire. Then, the intervention group received aripiprazole 10 mg once daily for 6 weeks. Regarding the comparison (control) group, they received placebo with the same appearance. In order to increase treatment compliance as well as to decrease probable future side effects, in the first week a quarter of a 10 mg aripiprazole tablet was prescribed. This rose to half of a tablet in the second week and from the third week on a 10 mg tablet per day was prescribed for 6 weeks. The control group, also, received a quarter and half of a tablet of placebo in the first and second weeks, respectively. When intervention steps were completed, again smoking rate of all subjects was measured by FTQ questionnaire.

The drug used in this study was aripiprazole under commercial name of Abilizol produced by Sobhan Factory.

To respect patients' rights, all the subjects participated in this study voluntarily and they were allowed to abandon it whenever they wanted. However, written consent of their authorities was collected. All information was treated as confidential and will be. In order to continue their standard treatment, the subjects were allowed to receive their standard medication during the study. Ethical terms were observed in employing other sources of information. This study has received ethical approval No. 91197 from medical ethics committee of Tabriz University of Medical Sciences and it has been registered in IR of Iran clinical trial website under the registration code of IRCT2013010512018N1.

Statistical analysis

The obtained data were statistically analyzed using SPSS 19. Discrete variables were presented as frequency percent; Continuous variables were expressed as mean ± standard deviation. Wilcoxon test was used to compare severity of nicotine dependency (FTQ scores), before and after receiving aripiprazole or placebo in intervention and control groups and Mann-Whitney U test was used to compare effect of aripiprazole and placebo in modifying severity of dependency (FTQ changing during intervention). X^2 test was used to compare qualitative variables. For all analyses, statistical significance was considered 0.05 (2-tailed).

Results

The average age of the intervention and control groups was 38.85 and 43.57, respectively indicating no statistically significant difference. Average duration of disorder was 12.57 years and 15.52 years in the intervention and control groups, respectively. Again, there was no significant difference between the groups in this regard. Duration of smoking dependency was 15.47 years and 16.26 years in the intervention and control groups, respectively which was not statistically significant. Table 1 shows demographic information of both groups including age, duration of disease and duration of smoking dependency.

There was no difference between the intervention and control groups in the occupational status variable (considering the fact that the cases were divided in two employed and unemployed groups). Regarding marital status, the subjects were single, married or divorced and their distribution in the intervention and control groups was not significantly different. Regarding education level, the subjects were divided in two under and over high school diploma groups. Again, their distribution in the intervention and control groups was not significantly different. The subjects were divided in three groups in terms of the received antipsychotic type: a) those who received only second generation antipsychotic, b) those who received both the first and second generation antipsychotics and c) those who received clozapine either alone or along with another antipsychotic. Again, there was no significant difference between the groups in this regard (Table 2).

The subjects in both groups were compared in terms of schizophrenia subtype and no significant difference was seen between them.

There was a significant difference between the groups in the average number of received antipsychotics (p=0.017) where the average of antipsychotic items was 1.85 and 2.47 in the intervention and control groups, respectively. Figure 1 illustrates number of antipsychotics received by the subjects of both groups.

None of the subjects in both groups experienced medication induced movement side effects as measured by AIMS (Abnormal Involuntary Movement Scale).

In response to the first question of FTQ (number of cigarettes smoked per day) the intervention group got 1.71 and 1.33 points before and after intervention, respectively and the emerged difference was significant. Regarding the control group, it was 2.00 and 1.84 in the beginning of the study and after receiving placebo, respectively and the difference was not significant. Regarding the fourth question (time of smoking the first cigarette in the morning), although the control group showed no significant change before and after the intervention (decline from 2.15 to 2.05) the intervention group, however, showed a significant change (decline from 2.04 to 1.66). The scores of other 6 questions implied no significant change in both groups. It could be summarized that after receiving the medication or placebo both groups showed no change in the following
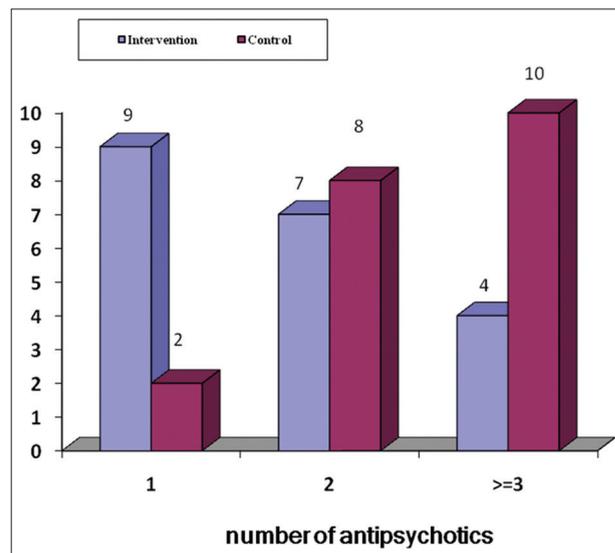

Figure 1. Bar chart of number of the received antipsychotics in two groups.

Table 1. Comparison of age, duration of disorder and duration of dependency between two groups.

	Intervention group			Control group			P value
	Mean	Standard deviation	Confidence interval	Mean	Standard deviation	Confidence interval	
Age (years)	38.85	8.65	35.09-42.61	43.57	9.36	39.29-47.85	0.106
Duration of disorder (years)	12.57	7.98	9.09-16.05	15.52	10.44	10.74-20.30	0.318
Duration of dependency (years)	15.47	9.24	11.45-19.49	16.26	8.17	12.52-20	0.778

variables: nicotine percentage of cigarette, inhaling smoke, inclination to smoking in the morning compared with late in the day, smoking during illness and smoking in forbidden places.

In the intervention group the average final score in FTQ test was 8.00 and 6.47 before and after the intervention, respectively. The difference was statistically significant. Regarding the control group it was 7.57 and 7.15 in the beginning of the study and after the intervention, respectively and the difference was not statistically significant. In other words, the drop of FTQ score was 1.53 and 0.42 in the intervention and control groups, respectively and there is a significant difference between these values (p=0.009). Table 3 and Figure 2 show statistical analysis of FTQ test considering the eight questions.

Discussion

The results revealed that there was no significant difference between the intervention and control groups in age, duration of illness, duration of dependency, educational, marital and occupational status variables. Therefore, these variables had no significant influence on the results. The only different variable was the average number of antipsychotics received by the subjects. Regarding the fact that the subjects were distributed equally in terms of antipsychotic types i.e. the second generation only, both the first and second generation and clozapine with/without other drugs, the influence of this variable is minimized and the obtained results could be interpreted.

According to data analysis, aripiprazole is effective in the mitigation of smoking dependency in schizophrenic patients and it has a significant superiority to placebo. The effect was tangible in the number of cigarettes smoked per day as well as the final score in FTQ test. Unlike Placebo, aripiprazole caused some subjects to smoke their first morning cigarette within a longer interval after awaking. FTQ test designers view this too, as an indicator of nicotine dependence decline.

Since dopamine partial agonists have attracted the attention of researchers recently, as efficient drug on addiction neural pathway, there are only a few studies in this field and all of them have a different methodology compared with the present study.

Our findings agree with Ramaswamy and et al case study. In that study a depressed smoker stopped smoking completely after receiving aripiprazole (10 mg per day for 1 week) and his FTQ score dropped from 7 to zero [8].

In a randomized clinical trial, Yu Liua prescribed aripiprazole 10 mg daily and found that this reduces subjective signs of nicotine withdrawal in heavy smokers, but this decline was not seen in persons with mild cigarette use on one hand and on the other hand objective signs including blood pressure and heart rate had not been decreased in the subjects [27]. Since our study instrument (FTQ questionnaire) is self-report and does not measure objective signs, it is impossible to statistically compare the two studies and it could be summarized briefly, that both studies have confirmed aripiprazole efficacy on reduction of smoking rate and the results agree with each other in this regard.

In Kim et al study, 139 schizophrenic patients were treated, in a clinical trial, with haloperidol, olanzapine, risperidone and aripiprazole. In the study after 8 weeks of treatment, FTQ score as well as craving to smoking was increased, remained unchanged and decreased in haloperidol, olanzapine, risperidone

Table 2. Occupational, marital and educational status and received antipsychotics in two groups.

	Intervention group		Control group		P value
	Frequency	%	Frequency	%	
Occupation					
Employed	6	30	6	30	1.00*
Unemployed	14	70	14	70	
Marriage					
Single	8	40	7	35	0.637
Married	9	45	11	55	
Divorce	3	15	2	10	
Education					
Under diploma	11	55	13	65	0.596
Diploma and higher	9	45	7	35	
Type of antipsychotics					
only SGA	8	40	4	20	0.211
FGA & SGA	10	50	15	75	
Clozapine	2	10	2	10	

*Two groups are exactly similar

Table 3. Comparing changes in FTQ scores between two groups.

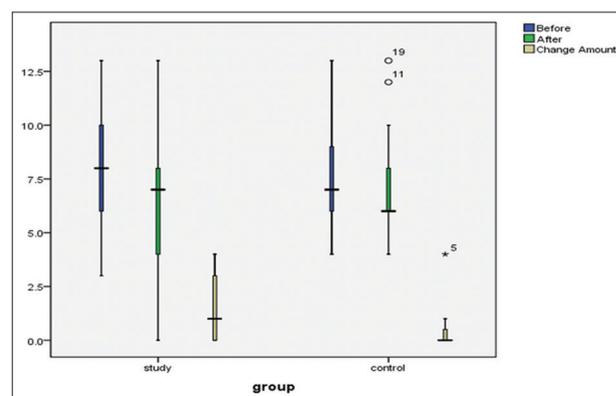| FTQ questions	Intervention group (mean)	Control group (mean)	P value
Q1	0.38	0.16	0.046
Q2	0.14	0	<0.001
Q3	0.14	0.05	0.057
Q4	0.38	0.10	<0.001
Q5	0.15	0	<0.001
Q6	0.14	0	<0.001
Q7	0.05	0.05	0/888
Q8	0.14	0.06	0.057
FTQ score	1.53	0.42	0.009

Figure 2. Box plot of the FTQ scores before, after and FTQ changes in each group.

and aripiprazole groups, respectively. These findings are also in concordance with the results of our study [28].

The study of Brunetti et al, which is actually a review on a few studies performed in recent years, admits new papers' approach in

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the use of dopamine partial agonist as a treatment for dependency to different substances and confirms the potential of them in the modulation of dopaminergic activity contributing in addiction reinforcing system. It reminds that, at this point, there is no definite evidence confirming the effectiveness of aripiprazole in the treatment of alcohol, cocaine, and nicotine and amphetamine dependency, due to no sufficient studies in this field, lack of randomization of studies and statistical weakness of most of them [29]. The mentioned study in fact, is not incompatible with ours and it simply proposes that more studies and controlled research and stronger statistical approaches are necessary to confirm the results of past studies. Since our study employed control group and used a placebo and on the other hand it was a blind study, it could be argued that it is a step that could make the previous studies more decisive and put the suggestions of Brunetti's study in to practice.

Other studies focusing on the effect of aripiprazole on other addictive substances dependency had remarkable results which agree with the theoretical basis of our study. For example, in the case study by Desseilles et al, a schizophrenic patient who was addicted to cannabis stopped its use and had no inclination to it just three months after changing his drug from olanzapine to aripiprazole [30]. Other interesting results were obtained by Haney et al in study of 8 cocaine dependent patients. The patients in that study received aripiprazole with a dosage of 15 mg exactly after smoking cocaine. They reported fewer positive mental effects on one hand and on the other hand they experienced fewer cocaine induced cardiovascular effects. Therefore, they were less eager to pay money to buy cocaine on one hand and on the other hand when cocaine was available they wanted to use more in order to achieve previous positive effects [31]!

Conclusion

The results of this study confirmed the effect of aripiprazole in decreasing the inclination of schizophrenic patients to smoking. By adding aripiprazole to patients' treatment they smoked fewer cigarettes on one hand and on the other hand they were less inclined to smoke immediately after getting out of bed; and according to FTQ test result their nicotine dependency severity was decreased. It is expected that the choice of aripiprazole as the main treatment of schizophrenic patients or adding it to their primary treatment could decrease their smoking tendency which in turn reduces cardiovascular and other smoking associated problems and enables us to reduce the related mortality.

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