A Review of Differences in Clinical Characteristics between Tardive Syndrome Induced or Improved by Aripiprazole Treatment

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Abstract-

Introduction: Tardive syndrome is a troublesome complication secondary to the long-term usage of antipsychotic medication. At present, there is a lack of effective treatment for tardive syndrome. Aripiprazole has been used in the treatment of tardive syndrome, with some reports of a good response. However, other reports have suggested that tardive syndrome can actually be induced by aripiprazole. The aim of current study was to investigate whether aripiprazole is beneficial or harmful for the treatment of tardive syndrome in specific patients.

Method: We performed a thorough literature search via PubMed. We included all of the studies discussing the relationship between tardive syndrome and aripiprazole, either with regards to "inducing" or "improving" the disease.

Result: None of the included studies were well-designed clinical trials, and all were case reports or case series. A total of 26 articles were included in which aripiprazole induced tardive syndrome, and another 24 in which tardive syndrome was improved by aripiprazole treatment. In the "improved" group, there were significantly more cases of schizophrenia than in the "induced" group (p=0.002). However, there were significantly more cases with other miscellaneous diagnoses in the "induced" group than in the "improved" group (p=0.003). In addition, the cases in the "induced" group had a significantly longer duration of aripiprazole usage than those in the "improved" group (p=0.001).

Conclusion: Current study is important for clinicians to pay attention to the risk of tardive syndrome when prescribing aripiprazole in patients with a diagnosis other than a psychiatric illness or in the long-term administration of aripiprazole.

Key Words: antipsychotics, tardive dyskinesia, tardive dystonia, tardive parkinsonism, complication, risk factor

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INTRODUCTION

Tardive syndrome, including tardive dyskinesia, tardive dystonia, and tardive parkinsonism, is a troublesome complication which occurs after long-term exposure to psychotropic agents[(1)] including antipsychotics

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and other forms of dopamine receptor blocking agents[2]. There are several hypotheses with regards to its etiology. Some studies suggest that hypersensitivity and up-regulation of the D2 receptor may play a role[3], where D2 hypersensitivity results in hyperkinesia[2]. Other researchers have focused on free radicals and consequent oxidative stress resulting from an increased dopamine turnover rate followed by long-term blocking of dopamine [4]. In addition, interactions between neurotransmitters is believed to play an important role in the pathophysiology of tardive syndrome. For example, the activation of specific serotonin receptors has been reported to inhibit the activity of dopamine[2,3]. At present, there are no guidelines for the treatment of tardive syndrome. Several medications and procedures have been suggested, such as amantadine, benzodiazepine, muscle relaxants, botulinum toxin injections and deep brain stimulation, however most lack acceptable effectiveness or strong evidence of a beneficial effect[1,2].

Unlike other antipsychotics, aripiprazole has a unique pharmacologic mechanism, and it is believed to act as a dopamine D2, D3 and 5HT1A partial agonist, as an antagonist over the 5HT2A receptor, and to modulate the activity of dopamine[5]. Through this modulating pharmacologic mechanism, an increasing number of studies have reported the benefits of aripiprazole in the treatment of movement disorders such as Tourette's syndrome[6] and tardive syndrome[7-9]. However, an increasing number of studies have also reported that the use of aripiprazole is actually associated with the occurrence of tardive syndrome[10-12]. These conflicting results raise the important question of whether aripiprazole therapy is beneficial or harmful with regards to tardive syndrome, and no previous studies have investigated risk factors or predictive variables that may be able to answer this question. Therefore, the aim of the current study was to investigate possible predictive or risk factors which may help clinicians to predict the benefits or harmful effects of aripiprazole treatment with regards to tardive syndrome in specific patients.

METHODS

The design of this study was based on a previous report conducted by Atsariyasing and colleagues[13], who conducted a thorough review of case reports and case series of hyponatremia in schizophrenia. We searched the PubMed database using the keywords (aripiprazole) AND (tardive) without any "Limitations" in order to obtain the maximum number of search results. The search was performed by two independent authors, Tseng PT and Chen YW. The search included available studies up to October 17th 2015, and the search process is shown in Figure 1. Initially, we excluded articles that were not related to tardive syndrome, either in forms of tardive dyskinesia, tardive dystonia, or tardive parkinsonism, and aripiprazole. The inclusion criteria were: (1) articles that discussed aripiprazole-induced tardive syndrome or tardive syndrome ameliorated by aripiprazole; and (2) case reports or case series. We then divided the pooled cases into two groups: (a) cases involving aripiprazole-induced tardive syndrome; and (b) cases of tardive syndrome ameliorated by aripiprazole.

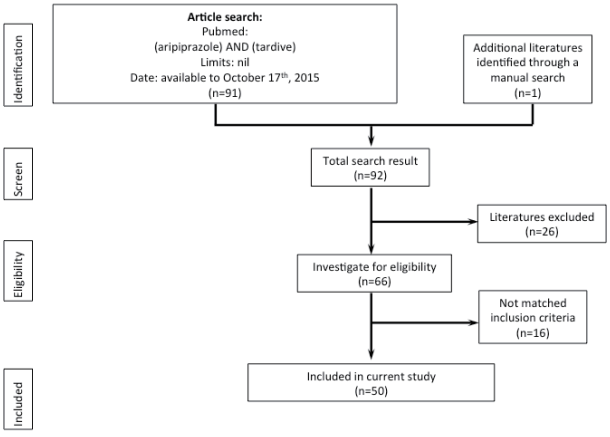

Figure 1. Flowchart of selection strategy of the current study

We next extracted all of the clinical variables and clinical characteristics of the included studies. Continuous variables are presented as mean ± standard deviation (SD). All statistical analyses were performed using Statistical Package for the Social Sciences(SPSS) software version 11.0 for Windows. Statistical significance was defined as a p-value of less than 0.05. The chi-squared test was used to compare categorical data, and the two tailed t-test was used to compare continuous variables between the two groups. We also performed correlation analysis to

investigate the relationship between each clinical variable. The age at major disease onset was defined as the age when the major symptoms of the disease first occurred, and the duration of aripiprazole therapy was defined as the total duration that aripiprazole was prescribed to the patients in both the "induced" and "improved" groups.

RESULTS

Main results of the search

Using our search strategy, we initially identified 92 articles, of which 26 were excluded because of their irrelevance to tardive syndrome and aripiprazole. We screened the remaining 66 articles using the inclusion criteria. None of these 66 articles were case-controlled trials or cohort studies related to aripiprazole and tardive syndrome. A total of 50 articles were finally included in the current study, with 26 articles with 41 cases in the induced group [10-12, 14-36] and 24 articles with 31 cases in the improved group [7-9, 37-57].

Differences in demographic data

The demographic data of the included studies are listed in Table 1. With regards to diagnosis, the cases

Table 1. The demographic data in current study

	Induced group	Improved group	p value
Case numbers (N)	41	31	
Age (years)[a]	45.3±17.0	51.7±16.7	0.117
Gender (N)[b]			0.381
female	25	22	
male	16	9	
AIMS initial [a]	11.9±8.0	16.3±7.3	0.197
AIMS later [a]	1.5±2.1	3.9±2.9	0.272
Diagnosis [b]			*0.004
schizophrenia (%)	17.1	51.6	*0.002
bipolar disorder (%)	22.0	9.7	0.169
major depressive disorder (%)	12.2	9.7	0.738
schizoaffective disorder (%)	9.8	19.4	0.247
delusional disorder (%)	0.0	3.2	0.250
miscellaneous diagnosis (%)	24.4	0.0	*0.003
unknown (%)	14.6	6.5	0.277
Major disease onset age (years old) [a]	31.7±16.5	33.7±13.3	0.736
Aripiprazole dosage (mg/day) [a]	15.2± 6.3	15.8± 8.3	0.742
Aripiprazole period (weeks) [a]	53.6±64.6	14.1±20.5	*0.001
Duration of tardive syndrome (weeks) [a]	16.9±28.0	146.2±184.2	*0.034
Tardive dyskinesia (%)[b]	70.7	80.6	0.339
oro-linguo-buccal dyskinesia (%)	70.7	61.3	0.403
limb dyskinesia (%)	4.9	3.2	0.730
trunk dyskinesia (%)	0.0	3.2	0.250
Tardive dystonia (%)[b]	41.5	48.4	0.561
limbs dystonia (%)	17.1	29.0	0.230
occulogyric dystonia (%)	4.9	3.2	0.730
trunk dystonia (%)	22.0	25.8	0.705
other tardive dystonia (%)	4.9	0.0	0.216
Tardive parkinsonism (%)[b]	19.5	6.5	0.115
tardive akathesia (%)	17.1	3.2	0.066
other tardive parkinsonism (%)	7.3	3.2	0.456

Value: mean ± standard deviation

Abbreviation: AIMS: abnormal involuntary movement scale

a: two-tailed independent t test

b: chi-square test

*: $p<0.05$

with a diagnosis other than schizophrenia, bipolar disorder, major depressive disorder, schizoaffective disorder, or delusional disorder were defined as having a "miscellaneous diagnosis". These included neurological diseases such as Lewy body dementia [22], motor tics, and Parkinson's disease [31], and the others included childhood onset fragile X syndrome, post-traumatic stress disorder [18], stress-induced anxiety, anger and irritability [19], and otherwise specified psychotic disorders [29]. There were no significant differences between the two groups in age, gender, age at major disease onset, aripiprazole dosage, and initial and final Abnormal Involuntary Movement Scales (AIMS) scores. However, there was a significant difference in the diagnosis between the two groups (p=0.004). The improved group had significantly more cases of schizophrenia than the induced group (p=0.002), whereas there were significantly more cases with other miscellaneous diagnoses in the induced group than in the improved group (p=0.003).

Different patterns of tardive syndrome

There were no significant differences in the three main categories of tardive syndrome, namely tardive dyskinesia, tardive dystonia, and tardive parkinsonism, between the two groups (p=0.339, 0.561 and 0.115, respectively). Furthermore, when we further investigated the distribution of each symptom of tardive syndrome, there were still no significant differences between the two groups, except for a trend in tardive akathesia (p=0.066).

Differences in the usage of medication

The cases in the induced group had a significantly longer duration of aripiprazole usage than those in the improved group (p=0.001). In contrast, the cases in the improved group had a significantly longer duration of tardive syndrome than those in the induced group (p= 0.034, respectively).

The main results of correlation analysis for the clinical variables

We performed correlation analysis of the continuous variables, including age, age at major disease onset, aripiprazole dosage, duration of aripiprazole usage, duration of tardive syndrome, and initial and final AIMS scores. Among them, we found a significantly inverse association between age and final AIMS score (r=-0.483, p=0.031). This significance disappeared when we subdivided the cases into induced and improved groups.

DISCUSSION

To the best of our knowledge, this is the first report to summarize and compare the characteristics of patients with tardive syndrome induced by aripiprazole and tardive syndrome improved by aripiprazole. The main findings of this study are the significant differences in clinical variables between those who experienced a beneficial effect and those who experienced a harmful effect with regards to tardive syndrome and aripiprazole treatment.

There were no significant differences in demographic data between the two groups except for the distribution of diagnosis. We found a significantly higher prevalence rate of schizophrenia in the improved group and a higher prevalence rate of other miscellaneous diagnoses in the induced group. This indicated that the use of aripiprazole in patients with schizophrenia was more beneficial in ameliorating tardive syndrome than in inducing tardive syndrome. In fact, the prescription of aripirazole in patients with diagnosis rather than schizophrenia, bipolar disorder, major depressive disorder, or delusional disorder is so-called "off-labeled use". This result should alert clinicians to the potential risk of tardive syndrome being induced by aripiprazole when prescribing aripiprazole for patients with a diagnosis other than the indicated diagnosis (schizophrenia, bipolar disorder, major depressive disorder, or delusional disorder). For example, even though aripiprazole has been proven to be beneficial in the treatment of motor tics and Tourette's syndrome [6], clinicians still need to pay attention to the risk of tardive syndrome induced by the long-term use of aripiprazole [31] and need to make comprehensive explanation the benefit and risk of this "off-labeled use".

We also found significant differences in the duration of aripiprazole usage, and the duration of tardive syndrome between the two groups. This may be due to difficulties in treating tardive syndrome, as it is difficult to manage tardive dyskinesia, tardive dystonia, and tardive parkinsonism, and it takes time to resolve the problems [1]. Tardive syndrome responds poorly to shifting medication, so in general the duration of tardive syndrome are long. However, the duration of aripiprazole usage was

significantly shorter in the improved group than in the induced group in this study. This may indicate that the administration of aripiprazole in patients with existing tardive syndrome leads to a quick response, but that this may incur the potential risk of developing tardive syndrome under long-term usage.

LIMITATIONS

There are several limitations to the current study. First, although we tried our best to perform a thorough literature search by setting "no limitations" and using simple keywords, we did not find any case-controlled trials or well designed trials discussing this topic, and all of the pooled cases were extracted from case reports or case series, and this may have led to publication bias. Second, although we included as many clinical variables as possible to investigate whether there were any differences in them between the two groups, most of the studies still lacked detailed data. This limitation may weaken the strength of the statistical results. Furthermore, we could not perform further investigations about the possible confounding effect of concurrent medications such as benzodiazepine, antipsychotics, antidepressants, anticholinergics, and any other psychotropic agents. These medications may confound the inducing or improving effects of aripiprazole. Finally, we found that the follow-up duration in most of the cases in the "improving" group was significantly shorter than that in the "inducing" group. This may suggest that patients in the "improving" group receiving aripiprazole may develop another one episode of tardive syndrome induced by aripiprazole with long-term usage.

CONCLUSION

The significantly higher prevalence rate of other miscellaneous diagnoses in the "induced" group should alert clinicians to the risk of tardive syndrome when prescribing aripiprazole for such patients, especially in situation of "off-labeled use". In addition, the significantly longer duration of aripiprazole usage in the induced group suggests that the administration of aripiprazole in patients with existing tardive syndrome would lead to a quick response, but that the long-term administration of aripiprazole may incur the risk of developing of another one episode of tardive syndrome.

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Contributors:

Chen Y.W., the first author, took the responsibility of information collection and wrote down the whole manuscript.

Tseng P.T., the corresponding author, took the responsibility of statistics procedure, literature searching, and revision of manuscript written by Yen-Wen, Chen.

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