

Identifying dopamine supersensitivity through a randomized controlled study of switching to aripiprazole from other antipsychotic agents in patients with schizophrenia

Chia-Hao Ma, Hung-Yu Chan , Ming H. Hsieh, Chen-Chung Liu, Chih-Min Liu, Hai-Gwo Hwu, Ching-Hua Kuo, Wei J. Chen and Tzung-Jeng Hwang 

Abstract

Background: Aripiprazole has been reported to worsen psychotic symptoms when switching from other antipsychotics, possibly due to dopamine supersensitivity psychosis.

Objective: This study aimed to explore the predictors and possible underlying mechanisms of aripiprazole-related psychotic exacerbation.

Methods: We conducted an 8-week, open-label, randomized controlled study from October 2007 to September 2009, assigning patients with a primary diagnosis of schizophrenia or schizoaffective disorder to switch from other antipsychotics to aripiprazole with 2-week dual administration, and then to taper off the original agents in fast ($n=38$, within 1 week) or slow ($n=41$, within 4 weeks) strategies. Positive and Negative Syndrome Scale (PANSS) was examined at day 0, 7, 14, 28, 56. Aripiprazole-related exacerbation (ARE) was defined positive as a 2-point increase in delusion/hallucination dimension score within 28 days compared with baseline. Baseline demographic, clinical and intervention-related variables were compared between the ARE+ and ARE- groups.

Results: Of the 79 randomized patients, 21 fulfilled the criteria of ARE+ , and 46 were classified as ARE-. Fourteen patients in the ARE+ group had worsening psychotic symptoms in the first and second weeks. Compared with the ARE- group, the ARE+ group had a higher baseline chlorpromazine equivalent dose (405.8 ± 225.8 mg vs 268.1 ± 165.4 mg, $p=0.007$) and was associated with prescription of first-generation antipsychotics ($p=0.038$).

Conclusions: A higher dose of original antipsychotics and prescription of first-generation antipsychotics may be associated with a higher risk of ARE. The underlying mechanism might be covert dopamine supersensitivity psychosis. These findings may help to identify high-risk patients and guide appropriate treatment strategies.

Trial Registration: ClinicalTrials.gov, identifier: NCT00545467

Keywords: aripiprazole, dopamine supersensitivity psychosis, switching

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Introduction

Aripiprazole is the first widely used D_2 receptor partial agonist, with a comparable therapeutic effect to other antipsychotics, better cognitive and negative symptom improvement, and fewer adverse

effects including metabolic syndrome and hyperprolactinemia.^{1,2} However, aripiprazole has been reported to worsen psychotic symptoms when added on to originally high-dose chronic antipsychotic treatment³ or when switching from other

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antipsychotics to aripiprazole.⁴⁻⁷ Previous studies have suggested that the innate partial D₂ receptor agonist property of aripiprazole and dopamine receptor supersensitivity of patients may play a role.

Past studies have reported behavioral changes after withdrawal from long-term antipsychotic therapy along with upregulated dopamine receptors in rats⁸⁻¹⁰ and patients with schizophrenia, termed dopamine supersensitivity psychosis (DSP).¹¹ The criteria for DSP were first proposed by Dr. Chouinard¹² in 1991, and have recently been revised.¹³ The core features of DSP include prolonged antipsychotic exposure, rapid relapse of psychotic symptoms upon a reduction in the dose of antipsychotic medication, and tolerance to previously effective antipsychotics. Tardive dyskinesia, low prolactin level and psychotic exacerbations caused by dopamine partial agonists have also been postulated.

Milder illness severity⁴ and higher original antipsychotic dose^{6,14} have been reported to be risk factors for psychotic exacerbations during/after switching from other antipsychotics to aripiprazole. However, several issues are still unclear. Most previous studies have been observational studies,^{6,14-16} and the dose of aripiprazole has not been controlled. Therefore, it is difficult to compare the equivalent dose before and after switching antipsychotics. In addition, some variables have seldom been analyzed, including tardive dyskinesia, switching strategies, and aripiprazole and prolactin serum concentrations. Moreover, the reported risk factors between studies have been inconsistent, probably due to methodological differences.

Previously, we reported an 8-week, open-label, randomized controlled study,¹⁷ and demonstrated no significant therapeutic difference between rapid and slow strategies of switching from other antipsychotics to aripiprazole. In the present study, we aimed to investigate demographic, clinical and intervention-related variables by using the data from the previous randomized controlled study to identify risk factors of aripiprazole-related psychotic exacerbations.

Methods

Study design and participants

This study was conducted at National Taiwan University Hospital, Taoyuan Psychiatric Center, and Ju-Shan Hospital from October 2007 to

September 2009. All patients were required to provide informed written consent. The study was approved by the Institutional Review Board of the participating hospitals and has been registered with ClinicalTrials.gov (number NCT00545467).

Details of the study sample were described in our previous work.¹⁷ Briefly, adult patients with a confirmed diagnosis of schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, were eligible for the study. The pre-switching antipsychotic doses were calculated as chlorpromazine equivalent doses (CPZeq).^{18,19} Long-acting injectable antipsychotics were not allowed. An adequate clinical reason was required for the patient to switch to aripiprazole, such as intolerance to adverse effects or inadequate therapeutic effect of the current medication. A fixed dose of 15 mg per day aripiprazole was given orally. The participants were randomly assigned to two different strategies: after initiating aripiprazole for 2 weeks, (a) fast tapering off the current medication within 1 week and (b) slow tapering off the current medication within 4 weeks. The initiation of aripiprazole was defined as day 1 of the study.

Measurements

Treatment efficacy was assessed using the Chinese version of the Positive and Negative Syndrome Scale (PANSS),²⁰ which included three extra supplementary excitation items (S1: anger, S2: difficulty in delaying gratification, S3: affective stability), and Clinical Global Impression (CGI) scale.²¹ Efficacy evaluations were performed at baseline and days 7, 14, 28 and 56 of the study. Adverse events were monitored at baseline and weekly.

Parkinsonism, akathisia, and dyskinesia were evaluated using the Simpson-Angus Scale (SAS),²² Barnes Akathisia Rating Scale (BAS)²³ and Abnormal Involuntary Movement Scale (AIMS),²⁴ respectively. Serum prolactin level was measured at baseline and on days 14 and 56. Serum aripiprazole level was measured on days 14 and 56.

In this study, aripiprazole-related exacerbation (ARE+) was defined as an increase in the summation of the delusion/hallucination dimensions of the PANSS (P1, P3, P6, G9)²⁵ by at least 2 points at any time point within 28 days of aripiprazole administration. Because a single occurrence of worsening was enough to fulfill this

criterion, earlier dropout (e.g. for psychiatric ward admission) or missing data (e.g. loss of one follow-up) was allowed. Participants without aripiprazole-related exacerbation (ARE-) were defined as those in whom the summation of delusion/hallucination dimension subscores worsened by less than 2 points at every measurement within 28 days. Those with symptoms that were maintained or improved were also counted in the ARE- group. No missing data were allowed to ensure a stable or improving state.

Statistical analysis

The model included baseline demographic, clinical variables and intervention-related variables. Baseline negative symptom dimensions including N1, N2, N3, N4, N5, N6, G7, G10, G13, disorganized thought dimensions including P2, N7, G11, G15, and hostility/excitement dimensions including P4, 7, G4, G8, G14, G16, S1, S2, S3²⁵ were also compared between groups. The Student's *t* test was used for continuous variables, and the chi-square test for categorical variables. Multiple logistic regression analysis was performed including sex, age and variables with significant differences between the two groups. We used van der Gaag's definition of positive (P1, P3, P5, P6, G9) factors of the PANSS²⁶ as a sensitivity test, while the negative factors were defined as N1, N2, N3, N4, N6, G7, G8, G16. All statistical analyses were performed using SPSS version 22 (SPSS Inc, Chicago, IL, USA/IBM, New York, USA).

Results

In our previous study, 79 participants were randomly assigned to the fast-switching ($n=38$) or slow-switching ($n=41$) groups. The basic demographic and clinical variables were comparable between the groups. Twenty-one (26.6%) of the randomized patients fulfilled the criteria of ARE+, and 46 were classified as ARE-. The other 12 patients dropped out within the first 4 weeks for reasons of poor medicine adherence or adverse effects (e.g. akathisia), rather than psychotic worsening. Based on the definitions mentioned above, these patients could not be classified into either ARE+ or ARE- group. Therefore, they were not included for analysis.

Thirteen of the ARE+ group had worsening psychotic symptoms in the first week, and one in the second week, when aripiprazole 15 mg had been added without tapering down the original antipsychotics.

The other seven of the ARE+ group worsened during the third and fourth weeks. Table 1 shows that compared with the ARE- group, the ARE+ group had significantly higher baseline CPZeq (405.8 ± 225.8 mg vs 268.1 ± 165.4 mg, $p=0.007$) and was significantly associated with first-generation antipsychotics (FGAs; 13/21 vs 16/46, $p=0.038$). There were no significant differences in the other baseline demographic, clinical and intervention-related variables between the two groups. Of note, none of those prescribed with risperidone and ziprasidone were in the ARE+ group.

Sex, age, CPZeq and categories of the original antipsychotics were entered into the multiple logistic regression model, in which the difference in CPZeq remained significant ($p=0.030$) and the category of original antipsychotics was marginally significant ($p=0.084$). The sensitivity test based on van der Gaag's definition revealed similar findings, and CPZeq remained the only significant variable ($p=0.002$) between the ARE+ and ARE- groups, while the category of original antipsychotics was not significantly different ($p=0.122$). When we define the outcome variable as the highest score for the positive symptom dimension within 4 weeks after switching, the only significant baseline predictor is still CPZeq in the 67 patients (stepwise multiple linear regression: $p=0.031$, $\beta = 0.338$, adjusted $R^2 = 0.092$).

Discussion

In this study, about one fourth of the schizophrenia patients had psychotic exacerbations within 4 weeks of switching to aripiprazole, and two thirds of the events occurred during the aripiprazole adding-on phase. A higher original antipsychotic dose was the most significant predictor, and original FGAs may have been a predictor. No other demographic, clinical and intervention-related variables were significantly related to psychotic exacerbations during/after switching.

Two thirds (14/21) of the ARE+ patients had psychotic exacerbations in the first 2 weeks of the trial, when aripiprazole 15 mg was being added on to the original medication (dose unchanged). The rapid exacerbation during/after switching to aripiprazole may be linked to DSP. Further, the ARE+ patients had significantly higher doses of the original antipsychotics, suggesting that they had more severe symptoms at baseline, leading to switching failure

Table 1. Baseline demographic, clinical and intervention-related variables in patients with and without aripiprazole-related exacerbation.

	ARE+ (N=21)		ARE- (N=46)		p value
Baseline demographic variables					
Age, mean (SD), year	38.1	(10.5)	39.5	(11.2)	0.65
Male, N (%)	7	(33.3)	21	(45.6)	0.34
Body weight, mean (SD), kg	63.2	(13.3)	68.1	(11.0)	0.12
Baseline clinical variables					
Onset of illness, mean (SD), year	25.3	(6.5)	28.3	(8.8)	0.17
Duration of illness, mean (SD), year	12.8	(8.7)	11.1	(8.9)	0.48
Category of original antipsychotic, FGA/SGA	13/8		16/30		0.038*
FGA, N (%)	13	(61.9)	16	(34.8)	
Chlorpromazine	0		1		
Flupentixol	1		1		
Haloperidol	2		3		
Loxapine	1		1		
Sulpiride	4		7		
Thioridazine	0		1		
Trifluoperazine	4		2		
Zuclopenthixol	1		0		
SGA, N (%)	8	(38.1)	30	(65.2)	
Amisulpride	3		4		
Olanzapine	2		10		
Quetiapine	2		1		
Risperidone	0		9		
Ziprasidone	0		2		
Zotepine	1		4		
Original antipsychotic dose in CPZeq, mean (SD), mg	405.8	(225.8)	268.1	(165.4)	0.007**
PANSS total score, mean (SD)	53.9	(14.0)	55.8	(12.9)	0.59
PANSS dimensional score, mean (SD)					
Delusion/ hallucination	9.14	(3.74)	8.07	(4.25)	0.32
Negative symptoms	15.95	(5.81)	17.89	(6.28)	0.24
Disorganized thought	6.43	(2.89)	6.48	(2.48)	0.94

(Continued)

Table 1. (Continued)

	ARE+ (N=21)		ARE- (N=46)		p value
Hostility/excitement	10.95	(3.26)	12.11	(4.08)	0.26
AIMS, mean (SD)	1.14	(3.15)	1.67	(4.49)	0.63
AIMS ≠ 0, N (%)	4	(19.4)	9	(19.6)	0.80
SAS, mean (SD)	8.90	(5.39)	9.59	(4.40)	0.59
BAS, mean (SD)	1.24	(2.43)	0.59	(1.20)	0.26
Prolactin serum level, mean (SD), ng/dL	57.2	(68.6)	51.3	(61.8)	0.73
Intervention-related variables					
Switching strategy (fast/slow)	12/9		24/22		0.71
Day 14 aripiprazole serum level, mean (SD), ng/dL	202.9	(99.5)	225.5	(75.6)	0.45
Day 14 prolactin serum level, mean (SD), ng/dL	20.5	(20.0)	26.7	(43.7)	0.57
AIMS, abnormal involuntary movement scale; ARE, aripiprazole-related exacerbation; BAS, Barnes Akathisia Rating Scale; CPZeq, chlorpromazine equivalent dose; FGA, first-generation antipsychotics; PANSS, positive and negative syndrome scale; SAS, Simpson-Angus Scale; SD, standard deviation; SGA, second-generation antipsychotics. * <i>p</i> < 0.05, ** <i>p</i> < 0.01.					

with a fixed dose of aripiprazole. However, all of the patients were chronic and stable in this study, and the baseline symptom severity, whether delusion/hallucination dimension or total PANSS, was not significantly different. Moreover, the original antipsychotic dose was not changed in the initial two weeks, and aripiprazole was added on. Therefore, the higher original antipsychotic dose may also be an independent variable and associated with DSP. A previous retrospective study also revealed that patients fulfilling the criteria of DSP and with psychotic exacerbations following switching to aripiprazole used a higher dose of antipsychotics prior to switching.⁶ This finding may suggest a dose-response relationship, that is, the chronic administration of a higher dose of antipsychotics may either stimulate overgrowth of dopamine D₂ receptors,^{27,28} elevate affinity of the receptors,²⁹ or both, and this is the core basis of DSP. This finding may also be a property of DSP itself. That is, because of tolerance to the effects of the original antipsychotic, a higher dose was needed to achieve an adequate clinical effect. In any case, switching to aripiprazole in patients with an originally higher dose of antipsychotics and subsequently covert DSP may result in competition with the original antipsychotics. Aripiprazole, a D₂ receptor partial agonist, may stimulate overgrowing/high-affinity D₂ receptors, and lead to psychotic

exacerbation even without tapering down the original antipsychotics.

The influence of categories of original antipsychotics has been inconsistent in different settings. Animal studies have reported that haloperidol provoked dopamine receptor supersensitivity, whereas clozapine, sulpiride, olanzapine and ziprasidone did not.^{30–33} On the other hand, both FGAs and second-generation antipsychotics (SGAs) have been reported to provoke DSP, with a prevalence of DSP-related symptoms of around 30%–40%.^{6,34–38} The prevalence of DSP for individual antipsychotics is unclear. The D₂ receptor binding affinity is generally high in FGAs but varies in SGAs, with a gap of almost 100 times between risperidone and quetiapine.³⁹ The binding profile has also been reported to vary among SGAs. Quetiapine has been reported to have a higher risk of rebound psychosis due to its loose binding profile and affinity.^{40,41} An observational study showed that patients using FGAs were more likely to fail in switching to aripiprazole.¹⁵ In this study, we found that FGAs were potentially linked with psychotic exacerbations after switching to aripiprazole. The patients prescribed with SGAs, and especially risperidone, seemed to have a lower risk. As the sample size was limited, we could not evaluate specific risks of individual

antipsychotics. Taken together, these findings suggest that FGAs may be more likely to provoke D₂ receptor supersensitivity and induce psychotic exacerbations during/after switching to aripiprazole, while SGAs may have diverse effects due to various binding profiles.

D₂ receptor occupancy by antipsychotics above a threshold of 72–78% may provoke movement disorders and hyperprolactinemia,⁴² and prolonged exposure may lead to tardive dyskinesia,⁴³ while 65%–72% occupancy is optimal for psychosis treatment.⁴² Tardive dyskinesia⁴⁴ and hypoprolactinemia⁴⁵ have been suggested to be features of DSP, although this is controversial.^{46,47} In this study, we found no significant differences in baseline movement disorder scale scores or prolactin serum level at baseline and Day 14 between the ARE + and ARE- groups. However, in a previous publication based on the same sample, we found an ‘abnormally low prolactin level’ (defined as < 3.7 ng/mL) were associated with a psychotic rebound after switching to aripiprazole.⁴⁸ In that study, compared to the group without psychotic rebound, the psychotic rebound group has a significantly higher proportion of subjects with ‘abnormally low prolactin level’ during the follow-up phase till Day 56.

Since the participants in this study were essentially chronic stable patients, some of them would be likely to develop dopamine supersensitivity under a higher dose of antipsychotic treatment. After switching to aripiprazole, those patients with dopamine supersensitivity might experience abnormally low prolactin level through the tuberoinfundibular pathway and psychotic rebound through the mesolimbic system. The concomitant action of dopamine on the two pathways has been demonstrated in the action of apomorphine, also a DRD2 agonist.⁴⁹ Putting together, the findings of the 2 studies suggest patients with a pre-switching high dose of antipsychotics plus post-switching abnormally low level of prolactin may be at greater risk of psychotic rebound.

Two observational studies suggested that a longer duration of illness was associated with failure to switch to aripiprazole,^{15,50} however, we found no significant difference between the ARE + and ARE- groups. This may be due to different study designs and sample homogeneity. Negative symptoms have been reported to be more severe in treatment-refractory schizophrenia patients with DSP,^{34,35} but we did not find a significant

difference between the ARE + and ARE- groups. Negative symptoms have been associated with hypoactive mesocortical projection.⁵¹ Therefore, the underlying mechanism may be irrelevant to DSP. Although recent guidelines suggested a stepwise cross-titration method for switching to aripiprazole,⁵² different switching strategies seemed to be equally effective in different study designs.^{4,15,17,53} In this study, we also found that the switching strategy did not predict subsequent exacerbations.

A higher original antipsychotic dose and FGAs might predict psychotic exacerbation during/after switching to not only aripiprazole but also other antipsychotics, such as quetiapine. The common underlying mechanism may be dopamine supersensitivity, which is caused by upregulation of post-synaptic dopamine receptors after a higher degree of antipsychotic blockade (via higher antipsychotic dose or tighter binding of FGAs) for an adequate duration.^{29,54} When patients with dopamine supersensitivity undergo antipsychotic switching to aripiprazole or other antipsychotics (especially those with loose binding of dopamine receptors such as quetiapine),⁵⁵ psychotic exacerbation may occur because of inadequate inhibition of mesolimbic dopamine activity during/after switching. In addition, since different antipsychotics have different receptor-binding profiles besides dopamine, clinical exacerbation during/after switching may also be related to withdrawal symptoms originating from other receptors, for example, cholinergic rebound when switching from olanzapine to aripiprazole.⁵⁶

There are several limitations in this study. First, the sample size was small. Further studies with a larger sample size are needed to evaluate the significance of variables other than the original antipsychotic dose, and especially the potential induction of DSP with different antipsychotics. Second, the aripiprazole dose was fixed at 15 mg, so we could not observe the effect of dose adjustments. Third, traditionally, DSP is defined as psychotic exacerbations within 6 weeks after drug adjustment. We did not collect several parameters on the sixth week, so we chose psychotic exacerbations within 4 weeks as a proxy. That is a more restrictive definition than the original criteria, and we assumed that the risk factors of this group might be more representative. On the other hand, we may have missed patients whose symptoms exacerbated during the fifth and sixth weeks. Fourth, most of our patients were clinically stable with mild symptoms, and the original

antipsychotic dose was not high. Thus, our results may not be generalizable to patients with more severe symptoms or higher antipsychotic doses. Finally, this was an open-label study, and bias may have existed. However, in our preliminary evaluation, the inter-rater reliability was acceptable, and each patient was rated by the same rater, thereby minimizing rating bias.

In conclusion, our findings suggest that a higher original antipsychotic dose and FGAs may predict psychotic exacerbations during/after switching to aripiprazole, and that the underlying mechanism may be D₂ receptor supersensitivity. These findings should raise clinical awareness of the potential consequences when switching antipsychotics. Future research is needed to investigate the underlying pathophysiological mechanisms and appropriate management if switching fails.

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Conflict of interest statement

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