

## Switching of Antipsychotics to Aripiprazole in the Treatment of Schizophrenia

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**Background:** A sudden change in antipsychotics in the pharmacotherapy of schizophrenia might worsen the clinical condition or induce a relapse of psychotic symptoms. This study reports on shifting from other antipsychotics to aripiprazole during the course of treatment, with further analysis of factors related to a successful switch.

**Methods:** An observational study was conducted. Study subjects included 45 patients with schizophrenia whose medication was changed from other antipsychotics to aripiprazole. The reasons for the change, course of illness, and types and dosage of antipsychotics previously used were collected. The clinical severity before and 12 weeks after switching or at termination were assessed using the Clinical Global Impression-Severity scale.

**Results:** The majority (71.1%) of the study subjects changed antipsychotics because of adverse effects from previous medications. About 70% successfully completed the switch. Patients who had been taking second-generation antipsychotics (SGAs), had less clinically severe disease, or had a shorter course of illness were able to make a smoother transition to aripiprazole. Reported adverse events related to the transition were mild and infrequent.

**Conclusion:** Not all antipsychotics can be successfully switched to aripiprazole, a novel antipsychotic. Apart from clinical factors, a successful change of antipsychotics also depends on the complexity and the pharmacological properties, as well as the duration of administration of previous antipsychotics.

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**Key words:** drug switching, antipsychotics, aripiprazole, schizophrenia

The serendipitous discovery of chlorpromazine with antipsychotic properties in 1952 opened a new era of psychopharmacology. Antipsychotic agents have thus become the mainstream treatment for schizophrenia, thereby reducing morbidity and relapse rates.<sup>(1)</sup> The conventional drugs or so-called

first generation antipsychotics (FGAs) were fairly effective in treating positive symptoms, but were not similarly effective for negative and cognitive symptoms, and sometimes even worsened the latter. In addition, adverse effects with extrapyramidal symptoms were commonly seen in patients treated with

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FGAs.<sup>(2)</sup> In recent years, atypical antipsychotics or second generation antipsychotics (SGAs) have been used. They target specific actions of neurotransmitters to overcome the above disadvantages of the FGAs with equal efficacy and better effectiveness, and have thus ensured a better quality of life for the patient.<sup>(3-5)</sup> SGAs have been replacing FGAs as the first drug of choice in the treatment of schizophrenia.<sup>(6)</sup> However, other adverse effects including weight gain, metabolic syndrome, and cardiac toxicity, have been found after long term use of SGAs.

Switching from one antipsychotic to another during the course of treatment is not an uncommon practice in the pharmacotherapy of schizophrenia.<sup>(7)</sup> Nevertheless, a sudden change from one drug to another during treatment might worsen the clinical symptoms or induce a relapse of psychosis. To prevent these consequences, it is not recommended that patients with an excellent response to the current antipsychotic change their drug regimen unless their clinical conditions have been stable for at least three to six months or other adverse effects from the current antipsychotic have been observed.<sup>(8)</sup> A partial or total lack of efficacy of a drug and adverse events related to patient compliance are the two most common reasons for switching drugs.<sup>(7,8)</sup> An additional common reason for switching is the preference for a new treatment option by the patient or family when a new drug is available on the market.<sup>(9)</sup>

In general, two strategies are commonly used when switching antipsychotics: abrupt withdrawal (abrupt cessation of the current drug with immediate introduction of the new one) and cross-tapering (gradual tapering off the current drug while introducing a new one).<sup>(7)</sup> In the cross-tapering strategy, the current drug is overlapped with the new one for a period of time before being completely tapered off, while the new drug can be started with or without gradual titration.<sup>(8)</sup> Each method has its own advantages as well as limitations. For instance, the overlapping method could prevent a relapse of illness, but increases the cost and the possibility of adverse events from interaction of the drugs. The appropriate method depends on the patient's clinical condition as well as the setting of treatment (in-patient versus out-patient).<sup>(7,8)</sup>

Aripiprazole is one of the SGAs with the lowest mean body weight gain and less effect on risk for

adverse metabolic changes.<sup>(10)</sup> It is a novel antipsychotic agent with unique mechanisms of partial agonism at dopamine D2 receptors and serotonin 5-HT1A receptors, and antagonism at serotonin 5-HT2A receptors.<sup>(11)</sup> Its efficacy and safety are well-documented and it is effective in the treatment of both the acute and relapse phases of chronic schizophrenia,<sup>(12,13)</sup> and prevention of relapse in maintenance therapy.<sup>(14)</sup> Its advantages which include simple administration once daily without any titration procedures have resulted in better compliance from patients.<sup>(11)</sup> Since weight gain and metabolic syndrome are the two main reasons for switching antipsychotics,<sup>(15)</sup> aripiprazole is considered an ideal candidate for switching. Although aripiprazole has been marketed for several years, to our knowledge, there are no consensus guidelines on a smooth transition from other antipsychotics, and what factors should be monitored during switching. This study aims to assess factors related to successful switching from other antipsychotics to aripiprazole in schizophrenic patients.

## METHODS

### Subjects and procedure

From July, 2004 to January, 2007, patients with a DSM-IV<sup>(16)</sup> diagnosis of schizophrenia who were switching from their current antipsychotic to aripiprazole were recruited from the outpatient and day-care units of a medical center to be included in this study. Reasons for switching were determined, and the overall clinical severity rating was assessed using the Clinical Global Impression-Severity of Illness Scale (CGI-S)<sup>(17)</sup> before and 12 weeks after switching, or at the time of early termination.

Patients who fulfilled the switching criteria and completed a 12-week course of treatment with aripiprazole were classified as completers. Those who dropped out, had an early termination of aripiprazole treatment during the follow-up period, or did not successfully switch to aripiprazole were considered non-completers. Informed consent was obtained from the patients.

### Antipsychotics and switching

The antipsychotics were classified into two groups, conventional or FGAs (such as haloperidol and trifluoperazine), and atypical or SGAs. For

further analysis, the SGAs were further grouped into 3 categories according to their pharmacological characteristics: (1) Pure dopamine antagonists (PDAs) with only simple actions on dopamine receptors, including amisulpride and sulpiride; (2) Serotonin dopamine antagonists (SDAs) with actions targeted on both dopamine and serotonin receptors, including risperidone and ziprasidone, and (3) Multi-acting receptor targeted agents (MARTAs) with complex binding portfolios on dopamine, serotonin, norepinephrine and other receptors, including olanzapine, quetiapine, and clozapine.<sup>(18)</sup>

Methods of switching from the current antipsychotic to aripiprazole fell into the 2 categories mentioned above: (1) abrupt withdrawal, i.e, abrupt withdrawal of the currently-used antipsychotics with immediate use of aripiprazole, and (2) cross-tapering, immediate initiation of aripiprazole while gradually tapering off the current antipsychotics.

The defined daily dosage (DDD), a technical unit of measurement by the Anatomical Therapeutic Chemical (ATC) classification of the World Health Organization for drug utilization, was used for analysis in this study.<sup>(19)</sup> According to the ATC, the DDD is the assumed average maintenance dose per day of a drug used for its main indication. Although the DDD does not necessarily reflect the recommended daily dose of a drug, it acts as a platform to perform comparisons between population groups. The DDDs of various antipsychotic drugs in this study were as follows: amisulpride, 400 mg; sulpiride, 800 mg; risperidone, 5 mg; ziprasidone, 80 mg; olanzapine, 10 mg; quetiapine, 400 mg; clozapine, 300 mg; haloperidol, 8 mg; and trifluoperazine, 20 mg. In order to compare the relevant dosage of drugs, a ratio with the prescribed daily dose (PDD) over the DDD was used. Higher or lower doses of antipsychotics used can thus be defined as a PDD/DDD ratio more or less than 1.

### Statistical analysis

Relevant factors related to the completion of the treatment course or early termination were compared and analyzed with *t*-tests or chi-square tests. Significant variables from univariate analysis were included in a binary logistic regression model to examine their interactions. SPSS 15.0 statistical software was applied for the data analysis. A *p*-value of < 0.05 was considered significant.

## RESULTS

Altogether, 45 patients were recruited for the study with a higher proportion of women (68.9%) and an overall mean age of 33.5 years ( $33.5 \pm 11.4$ ). The majority (71.1%) of them switched from their current antipsychotics to aripiprazole because of adverse effects, with metabolic problems of weight gain, hyperglycemia and dyslipidemia the most common, followed by abnormal endocrine function including hyperprolactinemia, galactorrhea and sexual dysfunction. Only 13.3% of the study subjects had a switch because of dissatisfaction over the efficacy of their current medications (Table 1).

Thirty-one patients (68.9%) successfully completed the switch (the completers), while their counterparts had early termination at an average duration of 3.39 ( $\pm 4.22$ ) weeks (median = 1.25). Slightly less than half of the non-completers (42.9%) terminated the switch in the first two weeks of treatment. There were no significant differences between the completers and non-completers in the distribution of sex ( $X^2 = 3.38$ ), present age ( $t = -0.7$ ), age at onset of illness ( $t = 0.51$ ), and method of switching ( $X^2 = 0.89$ ). The non-completers, however, had longer durations of illness ( $11.6 \pm 6.7$  vs  $7.4 \pm 6.5$  years,  $t = -1.97$ ,  $p = 0.05$ ), clinically more severe disease before switching ( $t = -3.15$ ,  $p < 0.01$ ), and a significantly higher proportion of FGA usage ( $X^2 = 14.44$ ,  $p < 0.001$ ) and were on higher doses of drugs in terms of PDD/DDD ( $X^2 = 6.13$ ,  $p < 0.05$ ) than the completers.

All significant variables in univariate analysis were further examined using logistic regression analysis. Two significant independent factors were demonstrated. They were the duration of illness (acute vs chronic, OR = 1.17, 95% CI: 1.02~1.35;  $p < 0.05$ ), and the type of antipsychotic discontinued (SGA vs FGA, OR = 17.54, 95% CI: 1.29~238.68;  $p < 0.05$ ).

Less than 30% of the patients reported adverse effects while switching to aripiprazole. The majority of these adverse effects were mild, with the most frequent being insomnia (17.8%), anxiety (8.9%), extrapyramidal syndromes including parkinsonian symptoms and akathisia (6.7%), and headache (4.4%). (Table 2)

**Table 1.** Data from 45 Patients who Switched to Aripiprazole from other Antipsychotics

	Completers (n = 31)	Non-Completers (n = 14)	Total	X <sup>2</sup> or <i>t</i> -test	<i>p</i> value
Sex: female, <i>N</i> (%)	24 (77.4)	7 (50.0)	31 (68.9)	3.38	n.s.
Age (years)	32.7 (10.0)	35.3 (14.1)		-0.7	n.s.
Course of illness					
Duration of illness (years)	7.4 (6.5)	11.6 (6.7)		-1.97	= 0.05
Age at onset of illness (years)	25.2 (8.4)	23.7 (10.6)		0.51	n.s.
Reasons for switching, <i>N</i> (%)					
Metabolic problems	18 (58.1)	6 (42.9)	24 (53.3)		
Hyperprolactinemia	7 (22.6)	2 (14.3)	9 (20.0)		
Drug efficacy	4 (12.9)	2 (14.3)	6 (13.3)		
EPS	3 (9.7)	2 (14.3)	5 (11.1)		
Others	5 (16.1)	2 (14.3)	7 (15.6)		
Method of switching, <i>N</i> (%)					
Abrupt discontinuation	11 (35.5)	3 (21.4)	14 (31)	0.89	n.s.
Cross-tapering	20 (64.5)	11 (78.6)	31 (69)		
Currently-used drug, <i>N</i> (%)					
FGA	1 (3.2)	7 (50.0)	8 (17.8)	14.44	< 0.001
SGA	30 (96.8)	7 (50.0)	37 (82.2)		
Dosage of current drug, <i>N</i> (%)					
PDD/ DDD ≥ 1	12 (38.7)	11 (78.6)	23 (51.1)	6.133	< 0.05
PDD/ DDD < 1	19 (61.3)	3 (21.4)	22 (48.9)		
CGI-S score					
Before switching	3.5 (1.1)	4.6 (1.1)		-3.15	< 0.05
At termination	2.4 (0.8)	5.6 (1.2)			
Average dose of Aripiprazole	11.1 (6.7)	10.4 (3.1)		-0.41	n.s.

Values reported are mean (S.D.) unless otherwise stated.

**Abbreviations:** EPS: Extrapyramidal symptoms; FGA: first generation antipsychotic; SGA: second generation antipsychotic; PDD: pre-scribed daily dose; DDD: defined daily dose; CGI-S: clinical global impression-severity of illness scale.

**Table 2.** Number of Reported Adverse Events during Switching to Aripiprazole

Currently-used drug	Insomnia	Anxiety	EPS	Headache	Others*
FGA	2	1	-	1	-
PDA	-	-	-	-	-
SDA	2	-	-	-	2
MARTA	4	3	3	1	2
Total (%)	8 (17.8)	4 (8.9)	3 (6.7)	2 (4.4)	4 (8.9)

\*: Others: including difficulty voiding, severe hand tremor, dry mouth, and tachycardia.

**Abbreviations:** FGA: first generation antipsychotic; PDA: pure dopamine antagonist; SDA: serotonin dopamine antagonist; MARTA: multi-acting receptor targeted agent; EPS: extrapyramidal symptoms.

## DISCUSSION

Despite the advances in pharmacotherapy for schizophrenia, there are still limitations in the effectiveness of antipsychotic drugs, the number of adverse events, and patient compliancy. Antipsychotic treatment for the same diagnosis can vary among individual patients, depending on their response to specific antipsychotic drugs, doses, duration of treatment, and combination with other psychotropic medications.<sup>(20,21)</sup> Problems related to drug efficacy and severe adverse effects are usually the main indicators for switching.<sup>(9)</sup>

In this clinical observational study, it was not surprising to see that more than half of the patients switched antipsychotics because of adverse events, especially metabolic syndrome. Switching of antipsychotics was requested by either the patient, psychiatrist, or both, with the awareness that long term use of their current drugs might lead to severe complications such as diabetes or coronary heart diseases.<sup>(22)</sup>

Although aripiprazole has a high affinity for dopamine receptors,<sup>(23)</sup> it also acts as a dopamine partial agonist. It has been found to be effective in the treatment of acute relapses of schizophrenia and prevention of relapse in randomized control trials.<sup>(11,14,24)</sup> Higher doses of the drug are generally needed in the acute phase than during maintenance therapy.<sup>(25)</sup> Contrary to the recommended dosage for initial treatment and switching,<sup>(26)</sup> the average dose of aripiprazole in this study was relatively low, and was similar to the target dose for maintenance therapy.<sup>(11)</sup> The doses may have been lower because of less severe or clinically more stable conditions among the completers.

Switching of antipsychotics however, may increase the risk of exacerbation of psychotic symptoms from a rebound effect of cholinergic activities in the brain,<sup>(7)</sup> a phenomenon labeled as discontinuation reaction or rebound syndrome. It is related to the different pharmacological properties of each drug and its effects on cholinergic receptors. In this study, about half of the non-completers (42.9%) terminated switching in the early phase of cross tapering, which might be related to this rebound syndrome. Among all antipsychotics, the FGAs and MARTAs have the strongest anti-cholinergic effect and could cause a severe rebound syndrome upon abrupt withdrawal.

Therefore, a longer duration is necessary for a smooth switch with gradual tapering of these drugs.

### Switching from FGAs

In this study, patients who had been taking FGAs had the lowest success rate in switching. FGAs have pharmacological properties with a high dopamine D<sub>2</sub>-receptor occupancy that totally blocks the transmission of dopamine, hence reducing positive symptoms of schizophrenia. With long term use, these properties are more likely to cause dopamine supersensitivity and tardive dyskinesia.<sup>(27)</sup> In addition, patients treated with FGAs in this study had a more chronic course and longer durations of illness. Therefore, switching from FGAs to aripiprazole could be more difficult than expected.

Antipsychotics cannot entirely prevent the ongoing pathological process of schizophrenia.<sup>(28)</sup> Early termination was commonly seen in unsuccessful switching from FGAs, and therefore, the duration of use of aripiprazole was insufficient. The success of a treatment very much depends not only on the severity, course and outcome of an illness, but also on the duration of treatment. In addition, most patients with FGAs were in a relapse psychotic episode rather than in a stable phase. Sedation is needed for the control of agitation and irritability in more severe cases, and aripiprazole has a low sedation potency. Benzodiazepines with sedative properties could be used as augmenting agents in this respect.

### Switching from SGAs

The SGAs are very different from FGAs in their pharmacological properties, and patients taking them had a higher success rate when switching to aripiprazole than patients taking FGAs. SGAs have an overall lower affinity for, as well as a faster dissociation rate from dopamine D<sub>2</sub> receptors.<sup>(29)</sup> Although an antipsychotic with faster dissociation from dopamine receptors might present higher risks for relapse when there is a discontinuation of treatment,<sup>(30)</sup> the overall lower affinity for dopamine D<sub>2</sub> receptors is also less likely to induce supersensitivity of the dopamine receptors, thereby reducing extra-pyramidal adverse effects.<sup>(31)</sup>

Among all the SGAs, MATRAs are the most difficult to replace successfully because of the complexity of their pharmacological properties.

Indications for switching in this group are mainly adverse events related to metabolic syndrome. In this study, however, patients using MATRAs as their current drug were generally in more stable clinical condition and were on low doses. Combination with a longer duration of cross-tapering allowed for a much smoother switching process with a high success rate.

Switching of antipsychotics is a safe and common procedure. Studies using meta-analysis have demonstrated that cross-switching of antipsychotics does not increase the number of adverse events.<sup>(32)</sup> In this study, mild adverse effects were noted during switching, notably insomnia, anxiety, restlessness, and headache; this was consistent with other reports with more stable patients.<sup>(14)</sup> However, during switching of antipsychotics, a careful evaluation is essential to differentiate between abrupt discontinuation symptoms from cholinergic rebound and similar manifestations that are adverse effects of the new drug.

Switching of antipsychotics in the treatment of schizophrenia is a common practice in clinical psychiatry. It has been suggested that the ideal candidates for switching are aripiprazole or ziprasidone with a low risk for metabolic syndrome.<sup>(33)</sup> There are to date, no reports on how and what factors influence the process of successful switching.<sup>(26)</sup> This clinical observation study has demonstrated that aripiprazole is a good candidate for switching, but a thorough examination of the course of illness and evaluation of the precedent drugs should be taken into consideration.

### Limitations

Based on clinical observations, this study restricted its generalization because of its design with a small sample and lack of a control group. In addition, no other standardized psychiatric clinical assessment tools except the CGI-S were used, and factors related to unsuccessful switching could not be satisfactorily explained.

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## 將抗精神病劑轉換至 Aripiprazole： 在治療精神分裂症中的臨床經驗

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**背景：** 在精神分裂症個案的藥物治療過程當中，不論任何因素突然將治療的藥物轉換至另一種抗精神病劑，可能會惡化臨床的症狀或引發精神症狀的復發。本研究主要是精神分裂症治療過程中將抗精神病劑轉換至 aripiprazole 的臨床經驗報告，並進一步分析可能影響順利轉換的因素。

**方法：** 本研究採取自然觀察法，以罹患精神分裂症，並經歷將當前治療的抗精神病劑轉換至 aripiprazole 者為收案研究對象。除了記錄個案轉換藥物的原因，罹病的時間，以及抗精神病劑的分類及劑量之外，並使用臨床綜合印象評估量表-嚴重程度次量表 (CGI-S)，來評量個案在抗精神病劑轉換當時、轉換至 aripiprazole 治療 12 週後或提早結束使用 aripiprazole 時的臨床症狀嚴重度。比較分析影響可以穩定轉換至 aripiprazole 治療達 12 週以上之因素。

**結果：** 45 位個案進入本研究當中，大部分的個案 (71.1%) 因為當前藥物的副作用而換藥。近 70% 個案可以穩定轉換至 aripiprazole 治療 12 週以上。當中使用第二代抗精神病劑，臨床症狀嚴重度較輕，發病時間較短者較能順利轉換至 aripiprazole 治療。轉換過程中發生相關的不良情況漸少且輕微。

**結論：** 並非所有的抗精神病藥物均可以成功轉換至 aripiprazole，除了臨床的因素之外，是否能成功地將當前治療的抗精神病劑轉換至另一種，端賴於該藥物之藥理學上的特性，作用複雜的程度以及藥物治療的時間。  
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**關鍵詞：** 藥物轉換，抗精神病劑，安立復，精神分裂症

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