ORIGINAL RESEARCH ARTICLE

Clin Drug Investig 2010; 30 (3): 187-193
1173-2563/10/0003-0187/$49.95/0

Predictors of Early Worsening after Switch to Aripiprazole

A Randomized, Controlled, Open-Label Study

Chi-Un Pae,[1,2] *Alberto Chiesa*,[3] *Laura Mandelli*,[3] *Ashwin A. Patkar*,[2] *Sara Gibiino*[3] and *Alessandro Serretti*[3]

1 Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, South Korea
2 Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA
3 Institute of Psychiatry, University of Bologna, Bologna, Italy

Abstract

Background: Despite the increasing evidence relating to strategies for switching between different antipsychotics, little evidence is available about predictors of improvement or worsening while switching. In a previous study, we compared different options for switching to aripiprazole and found that patients with schizophrenia switched to aripiprazole with immediate discontinuation of the previous antipsychotic showed an increase in symptom severity after 1 week.

Objective: To identify predictors of worsening in the first 4 weeks after the switch to aripiprazole in partial non-responders to previous treatments.

Methods: This was a 12-week randomized, controlled, open-label study that was carried out in the Department of Psychiatry of the Catholic University of Korea, Seoul, Korea. The study included 77 patients with schizophrenia whose symptoms were not optimally controlled and/or who did not tolerate their current antipsychotic medications well. Patients were randomly assigned to one of three different strategies for switching to aripiprazole 10 mg, i.e.: (i) simultaneous discontinuation of the current antipsychotic; (ii) tapering off the current antipsychotic over 4 weeks with half the dose after the first 2 weeks; or (iii) tapering off the current antipsychotic over 4 weeks after maintenance of the current dose for 2 weeks. The main outcome measure was the difference in Brief Psychiatric Rating Scale (BPRS) scores from baseline to weeks 1, 2 and 4.

Results: Baseline severity of disease, as measured by the Clinical Global Impression-Severity Scale, BPRS and Schedule for the Assessment of Negative Symptoms, significantly predicted worsening at weeks 1, 2 and 4. Specifically, lesser disease severity at baseline significantly predicted worsening after switching to aripiprazole.

Conclusion: Patients with relatively mild illness severity might be more susceptible to early worsening of symptoms when switched to aripiprazole. However, the limitations of the present study, including a small sample size,

absence of a control group designed to control for nonspecific factors such as regression to the mean, and implementation of a switching strategy that included only aripiprazole, mean the present findings should be considered with caution and further research is needed.

Background

New generation antipsychotics appear to offer better treatment options compared with conventional antipsychotics and are thus recommended as first-line agents in the treatment of schizophrenia and related psychotic disorders.[1]

Switching from previous antipsychotics to these new drugs is a relatively common practice.[2-4] Hence, in the last decade, some investigators have begun to investigate better strategies to switch from current antipsychotics to others.[5-8] In a recent study, we found that patients switched to aripiprazole with immediate discontinuation of the previous antipsychotic showed an increase in symptom severity in the first week after switching to aripiprazole; moreover, these patients were slightly more likely to discontinue the study prematurely, suggesting that a possible difference in symptom severity and exacerbation could exist within the first week after the switch.[8]

Despite increasing evidence about switching strategies, however, little evidence is available about predictors of improvement or worsening while switching. Indeed, to date, only a few studies have focused on this issue.[9,10] These studies have reported a longer period of treatment and higher doses of clozapine,[9] and previous or subsequent history of exposure to clozapine,[10] as negative predictors of response to subsequent treatment with olanzapine or aripiprazole, respectively. Additionally, no study has yet specifically investigated predictors of early worsening during the first weeks after the switch to a new antipsychotic drug, a critical issue in common clinical practice.

Aripiprazole is an antipsychotic with a unique mechanism of action. It provides significant advantages over typical and some atypical antipsychotics in terms of fewer extrapyramidal symptoms and less prolongation of the average corrected QT (QTc) interval.[11,12] Nonetheless, despite the favourable efficacy and adverse-effect profiles of aripiprazole, clinical management of patients with this medication has sometimes been challenging because of the lack of a comprehensive strategy for appropriate dosing with this drug while switching and the potential for adverse effects, including worsening of psychotic symptoms. Although the lack of significant affinity for muscarinic and histaminic receptors and the low affinity for α-adrenergic receptors may be linked to the low propensity of aripiprazole to cause several adverse effects, the pharmacological profile of aripiprazole may be related to difficulties and limitations in switching from other agents.[13] Indeed, in previous trials that focused on aripiprazole switch from other antipsychotics, the most common reason for early discontinuation of aripiprazole switch was psychotic worsening among early dropouts.[14-17]

Hence, there is a strong clinical need to find those clinical factors that predict early worsening in patients switched to aripiprazole from other antipsychotics so that the full benefit of the drug's favourable pharmacological profile can be maximized in the best interests of individual patients.[13] The aim of the present work was therefore to investigate the predictors of worsening in the first 4 weeks after switching to aripiprazole in patients with persisting symptoms and/or tolerability problems during their former antipsychotic treatment.

Patients and Methods

A detailed patient sample description has been reported in a previous paper.[8] Briefly, out of 177 screened inpatients or outpatients with schizophrenia according to Diagnostic and Statistical Manual (DSM)-IV criteria[18] who were seen at the Department of Psychiatry of the Catholic University of Korea, 77 patients (i.e. only those with at least one assessment after

baseline) were included in the intent-to-treat (ITT) sample. The sample was selected with the main aim of investigating aripiprazole switch and this is a further *post hoc* analysis of the same sample focusing on predictors.

Patients were eligible for inclusion if their symptoms were not optimally controlled, as measured by a Clinical Global Impression-Severity (CGI-S) scale[19] score at baseline >2 and <6, and/or if they did not tolerate their current antipsychotic medications well. Patients were randomly assigned to one of three different strategies for switching to aripiprazole 10 mg, i.e.: (i) simultaneous discontinuation of the current antipsychotic; (ii) tapering off the current antipsychotic over 4 weeks with half the dose after the first 2 weeks; or (iii) tapering off the current antipsychotic over 4 weeks after maintenance of the current dose for 2 weeks. Patients were then followed for 12 weeks in order to assess the safety and tolerability of the different switching strategies. The last observation carried forward (LOCF) method was employed in case of missing evaluations at follow-up.

Efficacy was assessed on the 18-item Brief Psychiatric Rating Scale (BPRS) with scores ranging from 0 to 6 points.[20] Other measures of outcome employed were the Schedule for the Assessment of Negative Symptoms (SANS)[21] and the CGI-S. Adverse effects were evaluated by means of the Simpson-Angus Scale (SAS) for extrapyramidal symptoms,[22] the Barnes Akathisia Scale (BAS)[23] and the Abnormal Involuntary Movement Scale (AIMS).[24] All evaluators were blind to the group allocation of patients. There was good reliability among evaluators ($k > 0.8$).

The study was approved by the local ethics committee. All patients provided written informed consent to participate in the original study.[8]

For the present investigation, subjects were compared with respect to changes in BPRS scores from baseline to weeks 1, 2 and 4 as this period (particularly week 1) was the period most associated with clinical worsening.[8] Predictors of worsening after the switch were analysed by multiple regression (general linear model) with BPRS at weeks 1, 2 and 4 after switch as dependent variables and baseline variables each in turn as independent variables. Age, sex and switching strategy were added as covariates in order to investigate possible stratification effects. Significance was set at a p-value <0.05, two-tailed. With these parameters we had sufficient power (0.80) to detect a medium effect size of 0.31, allowing detection, for example, of a difference of 4.2 points in BPRS scores at week 1 between males and females.

Results

For descriptive purposes, in table I, subjects were allocated to one of two groups: not worsened (stable or improved) or worsened, according to BPRS scores at weeks 1, 2 and 4, compared with baseline. Worsened patients were those with ≥10% increase in BPRS score from baseline. Baseline CGI-S, BPRS and SANS scores significantly predicted worsening at all timepoints, with patients with less severe disease at baseline showing higher BPRS scores at weeks 1, 2 and 4 (see table I). Sex, age, pre-switch medication, SAS, BAS and AIMS scores did not significantly predict improvement after switch to aripiprazole. Only switching strategy was marginally associated with worsening at week 1 ($p = 0.08$) but not in the following weeks. Four patients dropped out between the first and the second weeks and three patients dropped out between the second and the fourth weeks. Even when considering, where possible, sex, age, previous treatment and switching strategy as covariates, the results did not change significantly.

Discussion

The results of this investigation suggest that patients with milder persisting symptoms on their former antipsychotic treatment could show an early worsening in the first weeks after switch to aripiprazole. Thus, only patients who have shown little or no response to previous treatment should be considered as candidates for switching to aripiprazole, particularly when the previous treatment is discontinued immediately. Although this finding could appear paradoxical, as in clinical

Table I. Predictors of worsening (calculated as a ≥10% increase from baseline in Brief Psychiatric Rating Scale [BPRS] score) at weeks 1, 2 and 4 in patients switched to aripiprazole. Baseline scores of the two groups of patients (worsened and not worsened) at each timepoint are given[a]

Characteristics of the ITT sample (n = 77)	Group 1: not worsened	Group 2: worsened	F[b]	p-Value
Week 1				
n	66	11		
Sex [n (%)]				
males	27 (41)	6 (55)	0.15	0.69
females	39 (59)	5 (45)		
Age (y)	36.19 ± 9.02	40.18 ± 12.01	0.0006	0.97
Previous atypical antipsychotic [n (%)]				
risperidone	29 (45)	6 (55)	2.17	0.10
olanzapine	28 (42)	4 (36)		
amisulpride	6 (9)	1 (9)		
quetiapine	2 (3)	0 (0)		
missing data	1 (1)	0 (0)		
Switching strategy [n (%)]				
immediate	18 (27)	4 (36)	3.07	0.08
combination	48 (73)	7 (64)		
BMI (kg/m^2)	24.37 ± 4.05	26.56 ± 4.56	2.47	0.12
CGI-S	3.50 ± 1.19	3.18 ± 1.16	26.67	0.000002
BPRS	22.95 ± 14.46	17.36 ± 13.69	320.22	0.0000001
SANS	21.33 ± 18.79	20.00 ± 18.79	71.98	0.000001
SAS	10.29 ± 1.73	10.27 ± 0.91	0.01	0.94
BAS	0.31 ± 1.12	0.00 ± 0.00	0.29	0.59
AIMS	0.95 ± 3.54	0.54 ± 1.81	2.98	0.09
Week 2				
n	68	9		
Sex [n (%)]				
males	28 (41)	5 (55)	0.57	0.45
females	40 (59)	4 (45)		
Age (y)	36.73 ± 9.04	35.78 ± 10.45	0.45	0.49
Previous atypical antipsychotic [n (%)]				
risperidone	29 (43)	6 (67)	1.43	0.24
olanzapine	29 (43)	3 (33)		
amisulpride	7 (10)	0 (0)		
quetiapine	2 (3)	0 (0)		
missing data	1 (1)	0 (0)		
Switching strategy [n (%)]				
immediate	21 (31)	5 (56)	2.02	0.15
combination	47 (69)	4 (44)		
BMI (kg/m^2)	24.81 ± 4.35	23.80 ± 2.34	0.173	0.133
CGI-S	3.54 ± 1.17	2.77 ± 1.20	16.76	0.0001
BPRS	22.80 ± 14.65	17.33 ± 13.01	163.28	0.0000001
SANS	22.55 ± 18.84	20.67 ± 18.78	58.37	0.000001

Continued next page

Table I. Contd

Characteristics of the ITT sample (n = 77)	Group 1: not worsened	Group 2: worsened	F[b]	p-Value
SAS	10.39 ± 1.75	10.00 ± 1.10	0.03	0.86
BAS	0.27 ± 1.06	0.33 ± 1.00	0.34	0.56
AIMS	0.96 ± 3.55	0.55 ± 1.33	1.38	0.24
Week 4				
n	66	11		
Sex [n (%)]				
males	27 (41)	6 (55)	0.66	0.41
females	39 (59)	5 (45)		
Age (y)	36.73 ± 9.04	33.45 ± 7.39	0.36	0.55
Previous atypical antipsychotic [n (%)]				
risperidone	32 (48)	3 (27)	0.71	0.54
olanzapine	25 (39)	7 (64)		
amisulpride	7 (11)	1 (9)		
quetiapine	1 (1)	0 (0)		
missing data	1 (1)	0 (0)		
Switching strategy [n (%)]				
immediate	22 (33)	4 (36)	0.38	0.53
combination	44 (67)	7 (64)		
BMI (kg/m^2)	24.68 ± 4.14	25.32 ± 3.52	0.35	0.55
CGI-S	3.54 ± 1.17	2.90 ± 1.22	14.03	0.0003
BPRS	23.03 ± 14.44	16.81 ± 14.30	108.17	0.0000001
SANS	24.54 ± 19.54	20.27 ± 18.60	47.46	0.000001
SAS	10.35 ± 1.77	10.00 ± 1.10	0.18	0.67
BAS	0.27 ± 1.08	0.27 ± 0.90	0.04	0.84
AIMS	0.98 ± 3.60	0.45 ± 1.21	0.68	0.41

a Values are expressed as mean ± SD unless specified otherwise.

b Statistics refer to multivariate correlation analysis (see text for details).

AIMS = Abnormal Involuntary Movement Scale; **BAS** = Barnes Akathisia Scale; **BMI** = body mass index; **CGI-S** = Clinical Global Impression-Severity scale; **F** = statistical significance of the observed difference between the means of the two groups; **ITT** = intent-to-treat; **SANS** = Schedule for the Assessment of Negative Symptoms; **SAS** = Simpson-Angus Scale for extrapyramidal symptoms.

practice treatment-resistant patients very often do not display improvements when switched to a different compound, it is noteworthy that our finding could be related to the specific mechanism of action of aripiprazole; this differs from the majority of other antipsychotics in that it is characterized by a partial dopamine D_2-receptor agonism possibly related to a better regulation of dopaminergic transmission.[25]

Clinical experience suggests that an immediate switch to aripiprazole may worsen positive symptomatology, possibly because a relative increase in dopamine transmission mediated by the partial agonistic activity of the drug[15,26] could provoke acute changes in a prior equilibrium characterized by higher D_2-receptor blockade. Exacerbation of psychosis is considered a potential hazard when aripiprazole is substituted for other antipsychotics that have induced a functional hypodopaminergic state. Current evidence suggests, in fact, that careful cross-titration and monitoring is recommended when switching to aripiprazole.[6,27,28] In keeping with such findings, in our recent investigation[8] the best switching strategy was found to be tapering off previous antipsychotics gradually over 4 weeks while giving aripiprazole, a strategy that could facilitate a more gradual reduction of D_2-receptor blockade.

In addition, the findings of the present study could be clinically useful in showing that the choice of switching to aripiprazole only in patients with higher disease severity at baseline could avoid early worsening after aripiprazole switch.[8]

Study Limitations

Several limitations should be taken into account when interpreting our findings. The use of different switching strategies could represent a confounding factor in the interpretation of the results: this differential treatment meant that one group may have been undergoing withdrawal from the previous drug while the second group may have been exposed to an increase in antipsychotic medication for at least a brief period of time. Another important limitation was the absence of a control group not switched to aripiprazole, which would have helped determine whether the observed differences were specifically due to the switch to aripiprazole or, for instance, simply to a regression toward the mean. In addition, we did not control whether systematic differences in dosing habits (in higher vs lower residual symptom patients) could create pharmacodynamic group differences around the time of the switch. This could have influenced the results, given that a higher level of pre-switch dosing with D_2-receptor antagonists could have led to a more abrupt functional hyperdopaminergia after switching to a partial receptor agonist. While we did not record the dosage of prior antipsychotic at study entry, to be eligible for the present study, patients had to be treated with an antipsychotic at its therapeutic dosage. On the other hand, such an issue could be relevant to the present study given that there is some evidence suggesting that the dosage of the prior antipsychotic could predict worsening after aripiprazole switch.[29]

A further limitation was that the number of patients treated with quetiapine or amisulpride was too low to detect possible differences among previous treatments with different antipsychotics. In addition, although switching to aripiprazole can worsen psychotic symptoms, we did not control for discontinuation due to this specific adverse event. Another important limitation of the study was the lack of use of a scale to assess positive symptoms. As a consequence, we could have missed data indicating a possible worsening of positive symptoms after aripiprazole switch and future research is needed to address this issue. Furthermore, our sample of patients consisting only of partial responders to previous treatment or patients who did not tolerate previous treatment well could be characterized by many as yet undetermined differences from good responders. Also, we did not collect data about whether the included subjects were inpatients or outpatients. As a consequence, we could not evaluate a possible influence of in- versus outpatient status as a possible predictor of worsening after the switch.

Other possible limitations of the present study include the small sample size and the fact that the switching strategy included aripiprazole only; these limitations suggest our findings should be interpreted with caution and can not be generalized to other antipsychotics. Finally, we considered the response to previous drugs according to the BPRS scores at baseline; however, a formal assessment of improvement over time while taking the previous drug was not carried out.

Conclusion

Despite the limitations outlined in the previous section, our results suggest that patients with less severe persistent symptoms on a previous antipsychotic drug could be more prone to show early worsening in the first weeks after switching to aripiprazole. Further investigations are needed to confirm our findings in larger samples and to investigate switches to other antipsychotic medications.

Acknowledgements

This work was supported by a grant from the Medical Research Center, Korea Science and Engineering Foundation, Republic of Korea (R13-2002-005-04001-0). The authors have no conflicts of interest that are directly relevant to the content of the study.

References

1. National Institute for Clinical Excellence. Schizophrenia: core interventions in the treatment and management of

schizophrenia in primary and secondary care. National Collaborating Centre for Mental Health (NCCMH). London: NICE, 2003 Mar 25
2. Leslie DL, Rosenheck RA. From conventional to atypical antipsychotics and back: dynamic processes in the diffusion of new medications. Am J Psychiatry 2002; 159 (9): 1534-40
3. Covell NH, Jackson CT, Evans AC, et al. Antipsychotic prescribing practices in Connecticut's public mental health system: rates of changing medications and prescribing styles. Schizophrenia Bull 2002; 28 (1): 17-29
4. Rothbard AB, Kuno E, Foley K. Trends in the rate and type of antipsychotic medications prescribed to persons with schizophrenia. Schizophrenia Bull 2003; 29 (3): 531-40
5. Kinon BJ, Basson BR, Gilmore JA, et al. Strategies for switching from conventional antipsychotic drugs or risperidone to olanzapine. J Clin Psychiatry 2000; 61 (11): 833-40
6. Casey DE, Carson WH, Saha AR, et al. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. Psychopharmacology (Berlin) 2003; 166 (4): 391-9
7. Takeuchi H, Suzuki T, Uchida H, et al. A randomized, open-label comparison of 2 switching strategies to aripiprazole treatment in patients with schizophrenia: add-on, wait, and tapering of previous antipsychotics versus add-on and simultaneous tapering. J Clin Psychopharmacol 2008; 28 (5): 540-3
8. Pae CU, Serretti A, Chiesa A, et al. Immediate versus gradual suspension of previous treatments during switch to aripiprazole: results of a randomized, open label study. Eur Neuropsychopharmacol 2009; 19 (8): 562-70
9. Henderson DC, Nasrallah RA, Goff DC. Switching from clozapine to olanzapine in treatment-refractory schizophrenia: safety, clinical efficacy, and predictors of response. J Clin Psychiatry 1998; 59 (11): 585-8
10. Shajahan P, Macrae A, Bashir M, et al. Who responds to aripiprazole in clinical practice? An observational study of combination versus monotherapy. J Psychopharmacol 2008; 22 (7): 778-83
11. El-Sayeh HG, Morganti C, Adams CE. Aripiprazole for schizophrenia: systematic review. Br J Psychiatry 2006; 189: 102-8
12. Bhattacharjee J, El-Sayeh HG. Aripiprazole versus typical antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev 2008; (3): CD006617
13. Mago R. Proposed strategies for successful clinical management with aripiprazole. Expert Opin Pharmacother 2008; 9 (8): 1279-90
14. Casey D, Daniel D, Wassef A, et al. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 2003; 28 (1): 182-92
15. Ramaswamy S, Vijay D, William M, et al. Aripiprazole possibly worsens psychosis. Int Clin Psychopharmacol 2004; 19 (1): 45-8
16. Di Lorenzo R, Amoretti A, Forghieri M, et al. Aripiprazole: effectiveness and safety under naturalistic conditions. Exp Clin Psychopharmacol 2007; 15 (6): 569-75
17. Kerwin R, Millet B, Herman E, et al. A multicentre, randomized, naturalistic, open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients: Schizophrenia Trial of Aripiprazole (STAR) study. Eur Psychiatry 2007; 22 (7): 433-43
18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994
19. Guy W. Clinical Global Impression. In: Assessment manual for psychopharmacology. Washington, DC: Department of Health Education and Welfare, 1976: 217-22
20. Flemenbaum A, Zimmermann RL. Inter- and intra-rater reliability of the Brief Psychiatric Rating Scale. Psychol Rep 1973; 32 (3): 783-92
21. Andreasen N. Scale for the assessment of negative symptoms. Iowa City (IO): University of Iowa, 1983
22. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970; 21: 211-9
23. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989; 154: 672-6
24. Branch PR. Abnormal involuntary movement scale (AIMS). Early Clin Drug Eval Unit Intercom 1975; 4 (1): 3-6
25. Rivas-Vasquez RA. Aripiprazole: a novel antipsychotic with dopamine-stabilising properties. Professional Psychol: Res Pract 2003; 34: 108-11
26. Raja M. Improvement or worsening of psychotic symptoms after treatment with low doses of aripiprazole. Int J Neuropsychopharmacol 2007; 10: 107-10
27. Reeves RR, Mack JE. Worsening schizoaffective disorder with aripiprazole. Am J Psychiatry 2004; 161 (7): 1308
28. Travis MJ, Burns T, Dursun S, et al. Aripiprazole in schizophrenia: consensus guidelines. Int J Clin Pract 2005; 59 (4): 485-95
29. Takeuchi H, Uchida H, Suzuki T, et al. Predictors of clinical worsening after a switch to aripiprazole in patients with schizophrenia: a 1-year naturalistic follow-up study. J Clin Psychopharmacol 2009; 29 (4): 394-5

Correspondence: Dr *Alessandro Serretti*, Institute of Psychiatry, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy.
E-mail: alessandro.serretti@unibo.it
Dr *Chi-Un Pae*, Department of Psychiatry, Bucheon St Mary's Hospital, the Catholic University of Korea College of Medicine, Bucheon, Kyeonggi-Do 420-717, South Korea.
E-mail: pae@catholic.ac.kr