Predictors of Aripiprazole Treatment Continuation in Hospitalized Patients

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Objective: Aripiprazole is a second-generation antipsychotic that is increasingly prescribed in a variety of psychiatric disorders. The goal of this study was to investigate patient and treatment factors associated with aripiprazole treatment continuation on hospital discharge in psychiatric inpatients.

Method: This was a retrospective cohort analysis of patients admitted to a psychiatric hospital between January 1, 2003, and June 30, 2006, and treated with aripiprazole. The goal was to determine factors associated with continuation of aripiprazole throughout the hospital stay and on discharge from the hospital. Covariates assessed included patient demographics, prior psychiatric hospitalizations, diagnoses, prior antipsychotic use, and concomitant psychotropic medications. Aripiprazole-specific covariates were starting and maximum dose and dose titration pattern. Diagnoses were identified using ICD-9-CM codes.

Results: There were 1957 aripiprazole-treated patients included in this study, and 1573 (80%) continued aripiprazole treatment at the time of hospital discharge. Median starting doses were lower (5 mg/day) for younger and older patients, and patients with psychotic disorders received higher doses than other patients. Approximately 58% of patients had at least 1 aripiprazole dose titration while hospitalized, and most (73%) of those patients had a dose titration within 3 days of admission. Predictors of treatment continuation in this broad patient population were younger age, a diagnosis of bipolar or major depressive disorder, higher maximum aripiprazole doses, and upward dose titration within 3 days of admission. Patients receiving concomitant anticholinergics or antipsychotics were less likely to continue treatment as were those receiving aripiprazole at the time of hospitalization.

Conclusion: In this acute inpatient psychiatric setting, continuation of aripiprazole treatment on discharge was achieved in most patients. Demographic, diagnostic, and treatment factors predicting aripiprazole treatment effectiveness were identified.

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Aripiprazole is a second generation (atypical) antipsychotic with partial dopamine D_2 and 5-HT_{1A} agonist activity and potent antagonist activity at the 5-HT_{2A} receptor.[1–5] It also displays low affinity for H_1-histaminergic, muscarinic, and cholinergic receptors. This pharmacologic profile has been associated with a lower potential for extrapyramidal side effects, weight gain, and sedation.[6–8]

Aripiprazole has been studied in a variety of patient populations including those with schizophrenia/schizoaffective disorder, affective disorders, and anxiety disorders.[7,9–12] It has also been investigated on a limited basis in elderly patients and in children and adolescents.[13–16] While clinical trials provide important efficacy and safety data, dosing strategies are often restricted by preset study methodology. Data obtained from naturalistic studies offer additional insights into actual practice as drug doses and titration schemes may vary across patient populations. Additional advantages of naturalistic studies in-

clude the ability to evaluate a large number of subjects and to investigate effectiveness in a more diverse patient population. A pilot study of patients at our institution revealed treatment with aripiprazole across the spectrum of clinical indications with variability in dosing and continuation rates.[17] Therefore, we set out to conduct a larger naturalistic study to investigate factors such as dosing and titration methods associated with aripiprazole treatment continuation in psychiatric inpatients.

METHOD

Study Design

Using a retrospective cohort study design, we evaluated 2277 inpatients admitted to Western Psychiatric Institute and Clinic between January 1, 2003, and June 30, 2006, who were treated with aripiprazole. Western Psychiatric Institute and Clinic is a 280-bed psychiatric hospital that is part of the University of Pittsburgh Medical Center (UPMC). Patients were identified through the institution's medical record data repository. This repository contains whole-text medical records and integrates information from central transcription, laboratory, pharmacy, finance, administrative, and other departmental databases throughout the UPMC.[18,19] To meet Health Insurance Portability and Accountability Act guidelines and insure patient confidentiality, all data were de-identified using an honest broker system. This study met the criteria for exemption of informed consent by the University of Pittsburgh Institutional Review Board.

The study sample consisted of inpatients of all ages treated with aripiprazole during their hospitalization. Patients were excluded if the discharge medication list was not recorded in the patient's chart. Patients taken off all antipsychotics at discharge from the hospital were also excluded. The primary outcome of interest was aripiprazole treatment continuation throughout the hospital stay and as a prescribed medication at hospital discharge. Patients whose aripiprazole treatment was discontinued and a different antipsychotic was prescribed during the hospital stay were classified as treatment failure. Treatment continuation is an accepted surrogate for treatment effectiveness as it integrates an assessment of efficacy, safety, and tolerability by both the clinician and patient.

Patient- and treatment-level covariates were collected that were deemed to have the potential to affect treatment continuation. Patient variables included age, race, gender, prior number of psychiatric hospitalizations, primary psychiatric diagnosis, and history of substance abuse. Diagnoses, including substance abuse, were identified using the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Prior antipsychotic use and specific antipsychotic agents prescribed were also collected as were psychotropic medications such as antidepressants, mood stabilizers, and benzodiazepines prescribed concomitantly with aripiprazole during the inpatient hospitalization. Aripiprazole-specific treatment level covariates included starting inpatient doses, maximum dose, and dose titration, either upwards or downwards, within the first 3 days of hospital admission. Aripiprazole use as a current medication at the time of admission was also recorded and evaluated.

Statistical Analysis

The unit of analysis was treatment episode. Characteristics of patients continuing aripiprazole treatment were compared to those in the treatment failure group using 2-tailed t tests for normally distributed parameters, Mann-Whitney U test for nonparametric data, and χ^2 tests for categorical data. The relationship between patient and treatment level covariates and aripiprazole treatment continuation was assessed using multivariate logistic regression modeling. Each covariate was first entered into a univariate model to determine its relationship to the dependent variable of aripiprazole treatment continuation. Tests of collinearity were conducted to assess independence of covariates. Additionally, we performed tests for interactions between diagnosis and concomitant psychotropic use. All covariates with $p < .1$ were subsequently entered into a multivariate model using the backward conditional approach with maximum likelihood tests of model fit. Because diagnosis was significantly associated with treatment continuation, we subsequently stratified the sample across 3 broad diagnostic categories, psychotic disorders (i.e., schizophrenia or schizoaffective disorder), major depressive disorder, and bipolar disorder, for separate multivariate analysis. All analyses were conducted using SPSS Version 15.0 (SPSS Inc., Chicago, Ill.). p Values less than .05 were considered significant.

RESULTS

Study Population

Of the 2277 patients treated with aripiprazole during hospitalization, 192 (8%) did not have pharmacy discharge records recorded in the chart and were excluded from the analysis. Of the remaining 2085 patients, an additional 128 (6%) were excluded from the study because they did not receive any antipsychotic agents as part of their discharge regimen. Therefore, 1957 aripiprazole-treated patients met the study inclusion criteria, and of these, 1573 (80%) continued aripiprazole treatment at the time of hospital discharge. Table 1 provides the demographic characteristics of the cohort. Mean ± SD age for the cohort was 31 ± 16 years (range, 4–92 years), 54% were female, and 63% were white. Although there were no differences in race and gender between patients continuing aripiprazole treatment or those with treatment failure, patients continuing treatment were significantly younger, with a median age of 24 compared to 33 years

Table 1. Demographic Information of Inpatients Treated With Aripiprazole

Characteristic	Total Sample (N = 1957)
Age, y	
Mean ± SD	30.8 ± 16.2
Median	25.6
Range	4–92
Age groups, N (%)	
< 18	593 (30.3)
18–64	1309 (66.9)
≥ 65	55 (2.8)
Sex, N (%)	
Female	1058 (54.1)
Male	899 (45.9)
Race, N (%)	
White	1236 (63.2)
Non-white	721 (36.8)
Length of stay, d	
Median	10
Range	1–145
1-year prior hospitalizations, N (%)	
None	985 (50.3)
1	454 (23.2)
2	234 (12.0)
3 or more	284 (14.5)

Table 2. Aripiprazole Dosing Patterns by Age and Diagnosis[a]

Group	Median Starting Daily Dose, mg[b]	Median Maximum Daily Dose, mg	Median Last Daily Dose, mg
Age group			
< 18	5	10	10
18–64	10	20	15
≥ 65	5	12.5	10
Diagnosis group			
Psychotic disorder	10	20	15
Bipolar disorder	5	15	15
MDD	5	15	10
Conduct disorder	7.5	15	15

[a]Dosing information available on 1935 patients.
[b]Includes aripiprazole-naive patients only.
Abbreviation: MDD = major depressive disorder.

($p < .001$) in the treatment failure group. The most common diagnosis in the cohort was bipolar disorder (N = 640, 32.7%), followed by psychotic disorders (N = 612, 31.3%), and major depressive disorder (MDD) (N = 470, 24.0%). Psychotic behavior was coded in 82% of patients with bipolar disorder and 23% of those with MDD. Approximately half (50.3%) of the cohort had no prior psychiatric hospitalizations in the year prior to the aripiprazole admission. Patients continuing aripiprazole treatment had similar prior hospitalization patterns compared to those with treatment failure.

Aripiprazole Dosing and Titration

Inpatient dosing information was available on 1935 patients. We evaluated aripiprazole dosing and titration patterns in patients by age group and diagnosis (Table 2). When evaluating starting dose, only aripiprazole naive patients (N = 1082) were included in the data in order to provide a better understanding of starting doses utilized in actual practice. Median doses were lower for younger and older patients compared to those aged 18–64 years. The majority of pediatric patients < 18 years old were initiated at 5 mg of aripiprazole and achieved maximum and final doses of 10 mg/day. The elderly followed a similar pattern, although their median maximum dose was slightly higher at 12.5 mg/day. In general, patients with a diagnosis of psychotic disorder were treated with higher doses than other diagnoses. Starting median daily doses were 10 mg/day in these patients compared to 5 mg/day in those with bipolar disorder or MDD. Additionally, maximum doses were highest at 20 mg/day in patients with psychotic disorders compared to 15 mg/day in all other diagnosis groups.

Over half (1119 or 57.8%) of patients had at least 1 aripiprazole dose titration (upward or downward) while hospitalized. Of these patients, 576 (51.5%) had 1 dose titration, 276 (24.7%) had 2 dose titrations, and 267 (23.9%) had 3 or more dose titrations. Most patients receiving dose titrations (814/1119 or 72.7%) were titrated within 3 days of admission. The vast majority of these dose titrations were upward titrations (720/814 or 88.5%).

Table 3. Multivariate Model for Predictors of Treatment Continuation

Variable	β	SE	p Value	OR	95.0% CI
Age	–0.010	0.004	.014	0.990	0.983 to 0.998
Bipolar disorder	0.631	0.153	< .001	1.880	1.391 to 2.593
MDD	0.906	0.172	< .001	2.475	1.766 to 3.466
Concomitant anticholinergics	–0.531	0.155	.001	0.588	0.434 to 0.798
Concomitant antipsychotics	–1.434	0.146	< .001	0.238	0.179 to 0.317
Maximum aripiprazole dose	0.028	0.007	< .001	1.028	1.014 to 1.043
Upward aripiprazole dose titration within 3 d	0.825	0.149	< .001	2.281	1.703 to 3.056
Aripiprazole use at the time of admission	–0.449	0.136	.001	0.638	0.489 to 0.833

Abbreviations: MDD = major depressive disorder, OR = odds ratio.

Predictors of Aripiprazole Treatment Continuation: Global Model

For each patient variable and treatment variable, a univariate regression model was developed to assess its impact on aripiprazole treatment continuation. The following were independent predictors, either positive or negative, of treatment continuation: age, concomitant use of anticholinergics, concomitant use of benzodiazepines, concomitant use of antipsychotics, diagnosis, prior use of atypical antipsychotics, prior use of typical antipsychotics, aripiprazole as a medication on admission, maximum inpatient aripiprazole dose, and upward titration of aripiprazole within 3 days of admission. These variables were then entered into a multivariable model (Table 3). Factors asso-

ciated with treatment continuation in this global model included younger age, a diagnosis of bipolar disorder or MDD, higher maximum aripiprazole doses, and upward titration of aripiprazole within 3 days of hospital admission. Notably, those patients titrated up within 3 days of admission were 2.3 times more likely to continue aripiprazole treatment. Patients receiving concomitant anticholinergics and antipsychotics were less likely to continue aripiprazole treatment as were those who were receiving aripiprazole at the time of hospitalization.

Predictors of Aripiprazole Treatment Continuation: Diagnosis Models

Because diagnosis was a significant predictor of treatment continuation, we stratified the analysis by diagnostic category. Similar to the global model, univariate analyses were conducted first and significant variables were entered into the multivariate analysis. The first model included patients (N = 612) with psychotic disorders. Factors positively associated with aripiprazole treatment continuation in this patient subset were concomitant use of antidepressants (OR = 1.7, 95% CI = 1.2 to 2.6) and upward titration of aripiprazole within 3 days of admission (OR = 1.8, 95% CI = 1.2 to 2.7). Patients requiring anticholinergics (OR = 0.4, 95% CI = 0.3 to 0.5) and those on aripiprazole treatment at the time of admission (OR = 0.5, 95% CI = 0.3 to 0.7) were less likely to continue aripiprazole treatment. Patients with a history of olanzapine use prior to hospitalization (OR = 0.6, 95% CI = 0.4 to 0.9) were also less likely to continue aripiprazole.

In patients with bipolar disorder (N = 640), positive predictors of treatment continuation were black race (OR = 1.8, 95% CI = 1.02 to 3.2) and upward titration of aripiprazole within 3 days of admission (OR = 2.8, 95% CI = 1.6 to 4.7), while use of concomitant anticholinergics (OR = 0.4, 95% CI = 0.2 to 0.8) was a negative predictor.

In the MDD model (N = 470), the only factor associated with treatment continuation was female sex (OR = 1.9, 95% CI = 1.05 to 3.6). An increasing number of antipsychotics prescribed prior to admission (OR = 0.6, 95% CI = 0.4 to 0.9) was associated with treatment failure.

DISCUSSION

The findings of this retrospective cohort study suggest that a high proportion (80%) of inpatients treated with aripiprazole continue treatment throughout the hospital stay and are prescribed aripiprazole at hospital discharge. This is similar to the rate reported by Centorrino and colleagues,[20] who investigated 142 hospitalized patients treated with aripiprazole and found that 83.8% continued treatment upon discharge. In that study, aripiprazole was also used in a broad range of psychiatric disorders.

To identify the characteristics of patients most likely to maintain treatment with aripiprazole, we analyzed patient and treatment variables using multivariate logistic regression modeling. The results indicate that patients with affective disorders, patients who were aripiprazole-naive at the time of admission, and those titrated upward within 3 days of admission had the highest likelihood of continuing treatment. Increasing maximum aripiprazole dose was also associated with treatment continuation. However, it is important to note that the median maximum aripiprazole dose in our study was 15 mg, which is well within the recommended dosing for most indications. In contrast, patients who received concomitant antipsychotic or anticholinergic medications were less likely to continue treatment with aripiprazole.

It is difficult to interpret the relatively strong association between mood disorders and aripiprazole treatment continuation. However, the unique receptor-affinity profile of aripiprazole may impart important anxiolytic and antidepressant activity in addition to its efficacy against the symptoms of schizophrenia.[7,12,21] These findings may also be attributed to differences in the severity of illness among the major diagnostic categories, or perhaps characterized as an apples-to-oranges comparison. To address this possibility, we conducted subanalyses among the major diagnostic groups. One factor that was consistently significant across most diagnoses as well as the global model was upward titration of aripiprazole within 3 days of hospital admission. Increasing pressure to shorten lengths of stay compels many practitioners in the acute care setting to titrate drugs more rapidly than established by clinical trials or recommended in the product labeling. Mago[22] recently reported 2 general dosing strategies, rapid titration/high dose or slow titration/low dose, for successful clinical management of patients with schizophrenia or bipolar disorder using aripiprazole. For the rapid titration strategy, dosage adjustment may be considered after 2–3 days. Clinical factors that may support a rapid titration/high-dose strategy included younger patients, hospitalized patients, and those with an acute exacerbation. Due to the retrospective nature of this study, we cannot determine a true cause-effect relationship with respect to a relatively rapid upward titration and treatment continuation. However, this is an intriguing epidemiologic inference that should be examined further. Irrespective, it is evident from these findings that rapid upward titration is practiced, that many of these patients tolerate such protocol as evidenced by the association with treatment continuation.

We did not find an association between starting dose and treatment continuation. In general, aripiprazole naive patients received initial doses within the product labeling recommendations. The young and elderly were most often initiated at 5 mg/day. In studies involving children and adolescents, 5 mg/day is commonly employed as a starting dose, and lower doses have been investigated in elderly populations as well.[13,15,16,23] The median maximum

doses observed in our study of 10–20 mg are also consistent with the product labeling for aripiprazole.

The racial and gender effects identified in the bipolar disorder and MDD models, respectively, are intriguing. Of the 640 patients with bipolar disorder, 183 (28.6%) were African American. It is possible that the side effect profile for aripiprazole makes it an attractive choice for African American patients in which weight gain and lipid abnormalities are of particular concern.[24,25] Berman and colleagues[21] recently reported a statistically significant interaction between response and gender when aripiprazole was used as adjunctive therapy in MDD. Treatment differences in the Montgomery-Asberg Depression Rating Scale mean change scores favored aripiprazole in women. Although our outcome endpoint of treatment continuation at discharge was different from Berman's methodology, our findings provide additional insight and suggest that the potential for a gender effect should be investigated further.

Limitations of this study include its retrospective design and its restriction to a single acute academic inpatient setting. Generalizing these findings to nonacademic, long-term inpatient or outpatient settings may not be appropriate. Since we were limited to information captured in the patient chart, we were unable to examine reasons, such as intolerance or patient preference, for aripiprazole discontinuation. Finally, this study did not adjust for confounding related to clinical preferences or channeling bias. For example, we cannot fully interpret whether higher maximum dose was a cause for treatment continuation or a consequence of the patient tolerating aripiprazole.

In summary, most patients in this acute inpatient psychiatric setting were able to continue aripiprazole treatment throughout their hospital stay and at discharge. Patient- and treatment-specific factors such as younger age and rapid upward dose titration were identified as important contributors to treatment effectiveness.

Drug names: aripiprazole (Abilify), olanzapine (Zyprexa).

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