Clinical Predictors of Extrapyramidal Symptoms Associated With Aripiprazole Augmentation for the Treatment of Late-Life Depression in a Randomized Controlled Trial

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ABSTRACT

Objective: Augmentation with aripiprazole is an effective pharmacotherapy for treatment-resistant late-life depression (LLD). However, aripiprazole can cause extrapyramidal symptoms (EPS) such as akathisia and parkinsonism; these symptoms are distressing and can contribute to treatment discontinuation. We investigated the clinical trajectories and predictors of akathisia and parkinsonism in older patients receiving aripiprazole augmentation for treatment-resistant LLD.

Methods: Between 2009 and 2013, depressed older adults who did not remit with venlafaxine were randomized to aripiprazole or placebo in a 12-week trial. Participants were 60 years or older and met *DSM-IV-TR* criteria for major depressive episode with at least moderate symptoms. The presence of akathisia and parkinsonism was measured at each visit using the Barnes Akathisia Scale (BAS) and Simpson-Angus Scale (SAS), respectively. In an exploratory analysis, we examined a broad set of potential clinical predictors and correlates: age, sex, ethnicity, weight, medical comorbidity, baseline anxiety severity, depression severity, concomitant medications including rescue medications, and aripiprazole dosage.

Results: Twenty-four (26.7%) of 90 participants randomized to aripiprazole and who had akathisia scores available developed akathisia compared to 11 (12.2%) of 90 randomized to placebo. Greater depression severity was the main predictor of treatment-emergent akathisia. Most participants who developed akathisia improved over time, especially with reductions in dosage. Fifteen (16.5%) of 91 participants taking aripiprazole and who had parkinsonism scores available developed parkinsonism, but no clinical predictors or correlates were identified.

Conclusions: Akathisia is a common side effect of aripiprazole, but it is typically mild and responds to dose reduction. Patients with greater baseline depression may warrant closer monitoring for akathisia. More research is needed to understand the course and predictors of treatment-emergent EPS with antipsychotic augmentation for treatment-resistant LLD.

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Aripiprazole augmentation is an evidence-based pharmacotherapeutic option for treatment-resistant depression with increasing evidence in late-life depression (LLD).[1–3] Extrapyramidal symptoms (EPS) such as akathisia and parkinsonism are common adverse side effects from antipsychotic augmentation treatment of mood disorders.[4,5] Both akathisia and parkinsonism may limit adequate dosing and lead to premature treatment discontinuation.[6] Thus, it is important to understand the risk factors of developing these adverse effects. In general, there is a paucity of data with regard to clinical predictors and trajectories of treatment-emergent akathisia and parkinsonism with aripiprazole. There are even fewer data on aripiprazole as an augmentation strategy in late-life depression LLD.

Akathisia is characterized by a subjective feeling of restlessness and an objective movement component.[7] In studies of adults treated with antipsychotics mainly for primary psychotic disorders, clinical correlates associated with akathisia include higher antipsychotic dosages, polypharmacy, depression, female sex, and older age.[4,8–10] However, the clinical profiles have been inconsistent across studies,[4,8–10] and studies investigating risk factors associated with antipsychotic-induced akathisia in late-life depression are limited.[4]

Parkinsonism is defined as the presence of coarse tremor, rigidity, and bradykinesia.[4] Risk factors have been clearly identified for the development of antipsychotic-induced parkinsonism in older adults receiving antipsychotics for the treatment of psychotic symptoms or agitation associated with dementia.[4] They include older age, female sex, higher antipsychotic dosages, higher antipsychotic potency, and preexisting EPS. Predictors of parkinsonism in depressed older adults receiving augmentation pharmacotherapy with an atypical antipsychotic, however, have not been described.

Given that parkinsonism may contribute to falls[11] and akathisia may have a negative impact on treatment response[9,12] and an association

Clinical Points

- Akathisia and parkinsonism are common side effects with aripiprazole augmentation in late-life depression but are difficult to predict.
- Patients with more severe depressive symptoms may have a higher likelihood of developing akathisia, warranting close monitoring.
- In patients who develop treatment-emergent akathisia, the clinical trajectories indicate that symptoms are likely to resolve over time with dose reductions.

with treatment-emergent suicidality,[13] further investigation is necessary to elucidate the clinical correlates and course of these common and distressing adverse effects. Identifying patients at high risk of developing EPS may personalize care and minimize this potential negative effect on both tolerability and treatment outcomes.

We previously reported on the prevalence of EPS with aripiprazole augmentation in patients with LLD, finding that akathisia and parkinsonism were among the most common adverse effects in a randomized controlled trial.[1] The present study is a comprehensive examination of these EPS syndromes and was conducted to provide clinicians with useful information regarding their course and predictors when aripiprazole is used as an augmentation strategy for incomplete response in LLD.

METHODS

The data are from the Incomplete Response in Late-Life Depression: Getting to Remission (IRL-Gray) study; methods of this randomized controlled trial are described in detail elsewhere.[1] Participants were recruited in 3 academic medical centers (University of Pittsburgh, Pittsburgh, Pennsylvania; Centre for Addiction and Mental Health/University of Toronto, Toronto, Ontario, Canada; and Washington University, St. Louis, Missouri) between 2009 and 2013. Approval was obtained from the 3 institutional review boards, and all participants provided written informed consent. Main eligibility criteria included age 60 years or older, diagnosis of a major depressive disorder (*DSM-IV-TR* criteria), and a Montgomery-Asberg Depression Rating Scale (MADRS)[14] score ≥ 15 at recruitment. This trial is registered with ClinicalTrials.gov (identifier NCT00892047).

Patients who did not achieve remission after approximately 12 weeks of open treatment with venlafaxine extended release up to 300 mg/d continued it at the same dose and were randomized under double-blind conditions to the addition of either aripiprazole or placebo for 12 weeks. Remission was defined as a MADRS score of 10 or less at both of the final 2 study visits. Aripiprazole was started at 2 mg daily and titrated weekly based on clinical response and tolerability to a maximum of 15 mg/d. For management of treatment-emergent EPS, there were no rescue medications as part of the study protocol; rather, a dose reduction strategy was employed. Participants were allowed lorazepam or other, non-benzodiazepine sedative medications such as zopiclone for anxiety or insomnia. In addition, trazodone up to 50 mg was allowed for insomnia. We tracked medications prescribed to the participants outside of the study medications and report specifically on medications commonly used to manage EPS including β-blockers, benzodiazepines, and sedative/hypnotics.

The outcomes of interest for this analysis include the development of treatment-emergent akathisia or parkinsonism. Akathisia was assessed with the Barnes Akathisia Scale (BAS)[7] and parkinsonism with the Simpson-Angus Scale (SAS).[15] For the SAS, item 7 related to "head dropping" was not assessed due to participant discomfort with the procedure.

Treatment-emergent akathisia was defined as a score of 2 ("mild akathisia") or higher on the BAS global item (range, 0–5).[7] Treatment-emergent parkinsonism was defined liberally as an increase from baseline in the total SAS score by 2 points or more. Reliability was fair for both syndromes (intraclass correlation coefficient was 0.57 for the SAS and 0.58 for the BAS). The calculated internal reliability of the BAS and SAS using the Cronbach α is 0.84 and 0.66, respectively, in keeping with previous reports in other populations.[16]

We analyzed the following variables: age, sex, ethnicity, baseline depression severity as measured by the MADRS, baseline anxiety as measured by the Brief Symptom Inventory (BSI),[17] baseline EPS scores, weight, burden of comorbid physical illness as measured by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)[18,19] (for which we report total score and number of categories endorsed), number of coprescribed non-psychotropic medications, aripiprazole dosage, and treatment response as defined by a MADRS score of 10 or lower for 2 consecutive assessments. We also analyzed the use of common rescue medications such as β-blockers, benzodiazepines, and sedative/hypnotics prescribed outside of the study.

Among the participants randomized to aripiprazole (n = 91), we compared these variables between those with and without treatment-emergent EPS using the Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. We used logistic regression to identify potential correlates for each outcome. Initially, all variables were included followed by backward elimination of the least significant predictors until only significant predictions remained in the model. The significance level was set at .05 as this is primarily an exploratory analysis. Statistical analyses were conducted using statistical software (R version 3.3.1[20]).

Finally, we performed a growth mixture model in the aripiprazole group to investigate the trajectories of developing akathisia. We used the global clinical assessment variable of the BAS at each time point. The model used a negative binomial model as the global scores assumed integer values from 0 to 4. Intercept, linear, and quadratic random slopes were specified since initial descriptive analysis showed that the trajectories were not well represented by a linear

Table 1. Characteristics of Participants Randomized to Aripiprazole With and Without Treatment-Emergent Akathisia and Parkinsonism[a]

Variable	No Akathisia	Akathisia	*P* Value[b]	No Parkinsonism	Parkinsonism	*P* Value[b]
Total, n	66	24	…	76	15	…
Male, n (%)	27 (40.9)	12 (50.0)	.48	31 (40.8)	8 (53.3)	.40
Age, y	68.4 (7.0)	65.3 (4.5)	.07	67.9 (6.5)	66.4 (7.0)	.21
White, n (%)	60 (90.9)	20 (83.3)	.45	66 (86.8)	14 (93.3)	.68
Remission, n (%)	41 (62.1)	11 (45.8)	.23	46 (60.5)	6 (40)	.16
CIRS-G total score	10.1 (4.5)	9.8 (5.2)	.91	10.0 (4.6)	10.0 (5.0)	.88
CIRS-G count	6.2 (2.4)	5.8 (2.7)	.55	6.2 (2.4)	5.8 (2.9)	.51
No. of prescribed non-psychotropic medications	6.6 (5.0)	7.4 (5.6)	.62	7.0 (5.2)	5.8 (4.8)	.52
BAS global item score at baseline	0.38 (0.7)	0.38 (0.49)	.53	…	…	…
SAS score at baseline	…	…	…	0.33 (0.57)	0.60 (0.91)	.28
MADRS score at baseline	22.7 (6.4)	25.9 (6.1)	**.03**	23.1 (6.4)	25.7 (6.4)	.24
BSI score at baseline	1.8 (0.95)	1.6 (0.96)	.32	1.7 (0.9)	2.0 (1.0)	.28
Weight at baseline, lb	183 (43)	193 (50)	.49	186 (45)	188 (41)	.62
Highest aripiprazole dosage, mg/d	10.3 (3.8)	10.29 (3.3)	.99	10.0 (3.7)	11.4 (3.9)	.18
Mean aripiprazole dosage, mg/d	7.6 (2.6)	6.8 (2.8)	.25	7.1 (2.6)	8.3 (3.0)	.12

[a]Values shown as mean (SD) unless otherwise noted.
[b]Fisher test for categorical variables; Mann-Whitney *U* test for continuous variables. Statistical significance is indicated in boldface.
Abbreviations: BAS = Barnes Akathisia Scale, BSI = Brief Symptom Inventory, CIRS-G = Cumulative Illness Rating Scale for Geriatrics, MADRS = Montgomery-Asberg Depression Rating Scale, SAS = Simpson-Angus Scale.
Symbol: … = not applicable.

function. We selected the number of classes with the Akaike information criterion,[21] Bayesian information criterion, and Vuong-Lo-Mendell-Rubin likelihood ratio tests.[22,23] The analysis was conducted with statistical software (Mplus version 7.11[24]).

RESULTS

In the IRL-Gray trial, 468 participants were recruited from July 20, 2009, to December 30, 2013. A total of 181 (39%) did not achieve remission and were randomized to aripiprazole (n = 91) or placebo (n = 90). A greater proportion of participants achieved remission in the aripiprazole group compared to the placebo group (40 [44%] vs 26 [29%] participants; OR = 2.0; 95% CI, 1.1–3.7; *P* = .03). As reported, the most common adverse effects were akathisia and parkinsonism.

Akathisia

Of the 91 participants randomized to aripiprazole, 1 had missing akathisia scores; 24 (26.7%) of 90 developed akathisia compared to 11 (12.2%) of 90 randomized to placebo. In the aripiprazole group, 1 (1.1%) of 90 participants dropped out due to akathisia and 3 (3.3%) reported a temporary increase in suicidal thoughts due to akathisia. Table 1 shows the characteristics of the participants who developed akathisia versus those who did not. The only variable that differed significantly between those who developed akathisia and those who did not was baseline depression severity: participants who developed akathisia had higher depression severity with a mean (SD) MADRS score of 25.9 (6.1) versus 22.7 (6.4) (Mann Whitney *U* test, *P* = .03). Next, we used a multivariable model including the identified variables[4,10,25,26] that have been reported to be associated with the development of akathisia. Using logistic regression for predictive modeling in which nonsignificant variables were excluded with backward selection, only MADRS score remained significant (OR = 1.09; 95% CI, 1.01–1.18). Of note, mean and maximum aripiprazole doses were not associated with the development of akathisia. We analyzed the effect of β-blockers, benzodiazepines, and sedative/hypnotics taken by participants before and after starting aripiprazole and found no clinically meaningful associations with akathisia.

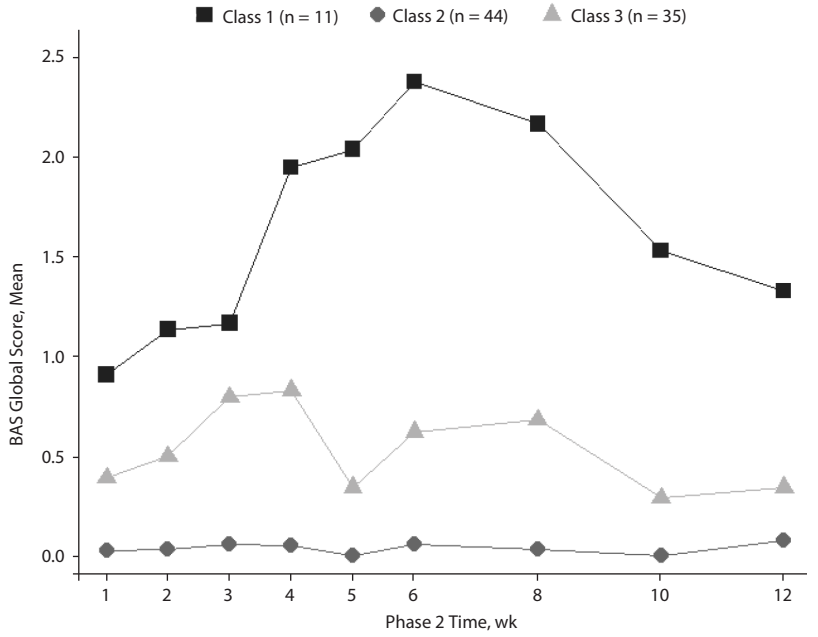
Akathisia Trajectories

Clinical trajectories were modeled only for akathisia as there were insufficient data points to model parkinsonism (Figure 1). Based on fit indices from mixture models, a 3-class model showed a better fit as compared to 4- and 2-class models. In particular, the model did not improve significantly when going from 3 to 4 classes, and the 4-class model added a group with only 2 participants, which is too small for analysis. Class 1 (n = 11) has participants with akathisia peaking and subsiding, defined by lower BAS global scores at the beginning and end of the study period, with peak scores associated with initial dosage titration. With time, akathisia seemed to resolve in this group. Class 2 (n = 44) is the largest group and describes participants without akathisia who had BAS global scores of mostly zero throughout the study period. Class 3 (n = 35) describes participants with time-varying akathisia and comprises participants who, in general, have some BAS global scores higher than zero occurring at various times during the study period but overall low global scores (mean BAS global score is below 1 at all time points). However, some participants in Class 3 met criteria for akathisia at certain study visits. We found no participant clinical characteristics associated with the trajectories.

Parkinsonism

In the aripiprazole group, 15 (16.5%) of 91 participants developed parkinsonism compared to 2 (2.2%) of 90 in

Figure 1. Trajectory for the Development of Akathisia in Participants Randomized to Aripiprazole



Abbreviation: BAS = Barnes Akathisia Scale.

the placebo group, and 1 (1.1%) of 91 and 1 (1.1%) of 90 participants dropped out due to worsening parkinsonism in these respective groups. Table 1 shows the characteristics of the participants who developed parkinsonism compared to those who did not. No statistically significant clinical predictors of the development of parkinsonism were identified in our bivariate comparison or multivariate logistic regression. There was no clinically meaningful association found with any rescue medication use.

DISCUSSION

The IRL-Gray study showed that both akathisia and parkinsonism are relatively common adverse effects with aripiprazole augmentation in late-life depression. Consistent with previous literature, it was difficult to predict the development of treatment-induced EPS. Our novel finding is that higher baseline depression severity was associated with a higher risk of akathisia. As this is an exploratory analysis, further studies are needed to confirm this finding. We identified no characteristics associated with the development of parkinsonism.

These findings may help clinicians to identify some older depressed patients who are at higher risk of developing akathisia when treated with aripiprazole and to understand their clinical trajectory. Previous studies investigating the clinical correlates of antipsychotic-induced akathisia have focused on younger patients with psychotic disorders. A recent study[27] of 372 patients (mean [SD] age = 32.9 [9.9] years) with schizophrenia or schizoaffective disorder investigated the clinical variables associated with antipsychotic-induced akathisia. The authors were unable to elucidate clear risk factors such as demographic characteristics such as age and sex. However, as in previous studies,[26,28] negative symptoms were significantly associated with an increased risk of akathisia. Similarly, in our sample of older adults with treatment-resistant depression, we could not identify demographic characteristics associated with akathisia, but more severe depression at baseline was identified as a risk factor. Thus, clinicians would be prudent to closely monitor depressed older patients with greater depression symptom severity for the development of akathisia when starting aripiprazole.

Finally, we identified 3 distinct akathisia trajectories: (1) akathisia peaking and subsiding, (2) no akathisia, and (3) time-varying akathisia. The second and third trajectories correspond to more than 88% of patients (79/90) with no or low and transient akathisia, reflecting the overall good tolerability of aripiprazole augmentation in late-life depression. The first trajectory corresponds to akathisia that is very likely associated with dose titration. As indicated by this trajectory, akathisia can be expected to improve with dosage reductions or the passing of time. The trajectory is congruent with several published reports[8,10,25] of the occurrence of akathisia associated with increases in antipsychotic dosages followed by resolution of symptoms.

A strength of our study was the rigor in which we measured EPS and our inclusion of interrater reliability, which has been rare among clinical trials in psychiatry.[29] The analyses came from a prospective randomized placebo-controlled trial with frequent monitoring for akathisia and parkinsonism using validated scales. It is limited by the relatively small number of participants who developed EPS. In particular, there were few participants who developed parkinsonism, which

may have limited our ability to identify its correlates. Given our sample of 90 participants and 1 significant association related to depression severity, there is 80% power to detect medium to large effect sizes; thus, it is unlikely that there was a type 2 error. With regard to type 1 error, based on our number of predictors, a Bonferroni correction would yield a cutoff *P* value for significance of .003. We did not use this cutoff given that this is an exploratory analysis and the cutoff would significantly impact the power of our investigation. Further study is warranted with larger sample sizes to elucidate clinical predictors of developing parkinsonism with aripiprazole augmentation. In addition, there may be an interaction with aripiprazole and venlafaxine as all participants were on 300 mg of the latter medication at randomization. This possible interaction may impact the generalizability of the findings.

Nevertheless, our analysis addresses the limited data on EPS when aripiprazole is used as augmentation pharmacotherapy for late-life depression, an increasingly common treatment strategy in this population. In general, it is challenging for clinicians to predict which patients will develop EPS; we found no predictors for parkinsonism. The severity of depression may be an important risk factor when assessing and monitoring akathisia in these patients. The occurrence of suicidal ideation in association with akathisia is an important clinical phenomenon to which clinicians must pay close attention. Thus, clinicians may want to closely monitor patients with more severe depression using clinical measures such as the BAS. Fortunately, most older depressed patients who are prescribed aripiprazole will not develop akathisia, yet the emergence of these symptoms should be assessed carefully, particularly during initial dosage titration.

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