Pilot Study of Augmentation With Aripiprazole for Incomplete Response in Late-Life Depression: Getting to Remission

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Objective: To determine the feasibility and safety of aripiprazole augmentation for incomplete response to sequential selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) pharmacotherapy in late-life depression.

Method: This study was a 12-week, open-label pilot study of 24 patients (recruited from June 1, 2006, to June 1, 2007) aged 65 years and above (mean, 73.9 years) diagnosed with major depressive disorder (MDD) (according to DSM-IV) who responded partially (17-item Hamilton Rating Scale for Depression [HAM-D-17] score of 11 to 15) or not at all (HAM-D score > 15) to a 16-week trial of escitalopram (up to 20 mg/day), followed by either duloxetine (up to 120 mg/day) or venlafaxine (up to 225 mg/day) for 12 weeks. Subjects received 2.5 to 15 mg per day of adjunctive aripiprazole (mean dose, 9.0 mg/day) for 12 weeks. The criterion for remission during treatment with aripiprazole was a HAM-D score ≤ 10 for 2 consecutive weeks.

Results: Of 24 subjects in the intent-to-treat study group, 19 completed 12 weeks of augmentation with aripiprazole, 12 of 24 (50%) met criteria for remission, and 2 of 24 discontinued due to side effects (sedation, akathisia). The mean (SD) HAM-D score decreased significantly by 6.4 (5.8) points (paired t test for means, $p < .01$, $df = 16$). There were no relapses among the 12 subjects who participated in continuation treatment over a median period of 27.6 weeks.

Conclusions: In older adults with MDD with incomplete response to SSRI and SNRI pharmacotherapy, aripiprazole was well tolerated, and symptoms of depression improved significantly during treatment with aripiprazole. A randomized, double-blind, placebo-controlled trial of adjunctive aripiprazole for incomplete response in late-life depression is warranted to further evaluate benefit and risk.

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Major depressive disorder (MDD) is common in older adults, with estimates of point prevalence ranging from 6% to 10% in primary care clinic populations.[1] Although pharmacotherapy is effective for late-life nonpsychotic MDD, approximately 50% of older adults with MDD do not respond completely to initial treatment with antidepressant pharmacotherapy, as seen in 2 large-scale studies, Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT)[1] and IMPACT (a collaborative-care program for late-life depression).[2] Incomplete or partial responders show impaired psychosocial functioning, a guarded prognosis with heightened risk for relapse, and increased mortality.[3] The high rate of incomplete response in older adults, together with the absence of data on the management of incomplete response, is both a clinical and public health concern.

Recently, atypical antipsychotic agents have been studied as adjunctive or augmentation pharmacotherapy for incomplete response in young and middle-aged adults with major depression. The use of atypical antipsychotics is based upon their effects on serotonergic and dopaminergic neurotransmitter systems, both of which may have a role in anxiety and depression.[4,5] A recent meta-analysis[6] found 10 double-blind, placebo-controlled studies of augmentation of an antidepressant with an atypical antipsychotic agent. Augmentation with olanzapine, risperidone,

or quetiapine was found to have utility for difficult-to-treat depression. However, the use of atypical antipsychotic agents in late-life depression has not been studied with respect to efficacy, durability of response, tolerability, or acceptability. We present preliminary information in this report.

The addition of aripiprazole to standard antidepressant pharmacotherapy has been examined in young and mid-life patients with MDD. A double-blind, controlled study[7] of 358 young and middle-aged adults showed that adjunctive aripiprazole therapy may help patients with MDD who respond incompletely to initial antidepressant pharmacotherapy. Patients who had an incomplete response to 6 weeks of a selective serotonin reuptake inhibitor (SSRI) were randomly assigned to receive placebo or 2 to 20 mg per day of aripiprazole, aiming for an overall target dose of 10 mg per day aripiprazole. Patients taking adjunctive aripiprazole reported significantly greater remission rates compared to those receiving placebo: 26.0% vs. 15.7%, respectively. Aripiprazole was generally well tolerated, with commonly reported adverse events of akathisia (23.1% for aripiprazole vs. 4.5% for placebo), restlessness (14.3% for aripiprazole vs. 3.4% for placebo), and headache (10.8% for aripiprazole vs. 6.0% for placebo). Patients taking aripiprazole had a significantly greater mean weight change compared to those receiving placebo.[7]

Evaluating the use of atypical antipsychotics such as aripiprazole in late life is still in its early stages. An open trial of aripiprazole augmentation in 20 older adults with MDD that had not remitted after 6 weeks of treatment with an SSRI was associated with improvement in 50% of the patients.[8] The most frequent side effects were dry mouth, agitation/anxiety, drowsiness, nausea, headaches, and blurred vision. These side effects were experienced by 9 patients (45%), 5 of whom described them as moderate to severe. Three patients (15%) discontinued aripiprazole due to side effects.[8]

We hypothesized that combined pharmacotherapy using an antidepressant with aripiprazole would be an effective, tolerable, and acceptable treatment strategy for older adults with incomplete response to sequential treatment with both an SSRI and a serotonin-norepinephrine reuptake inhibitor (SNRI). We chose aripiprazole for several reasons. Relative to other atypical antipsychotics, it has lower anticholinergicity and less tendency to promote weight gain.[9] Data from controlled evaluations in nongeriatric adults show efficacy, utility, and acceptability as adjunctive pharmacotherapy in incomplete responders.[7]

METHOD

Subjects

From June 1, 2006, to June 1, 2007, 24 subjects aged 65 years and above were recruited for aripiprazole augmentation therapy as part of an open-label pilot study nested in a larger, 5-year study of maintenance therapies in late-life depression (MTLD-III; supported by NIH grant MH43832; principal investigator, C.F.R.). Altogether, a total of 268 patients began treatment in the parent MTLD-III study, and 130 remitted and were able to be randomly assigned to experimental maintenance treatment cells. The 24 participants in the aripiprazole pilot study were a subgroup of the 268 who began MTLD-III. Recruitment occurred by word of mouth, referrals from clinicians, advertisements, and presentations to lay groups of older adults and their families. All subjects were currently experiencing a nonpsychotic, unipolar major depressive episode as established by the Structured Clinical Interview for DSM-IV (SCID), had a baseline rating of 15 or higher on the 17-item Hamilton Rating Scale for Depression (HAM-D-17),[10] and scored at least 18 on the Folstein Mini-Mental State Examination (MMSE).[11] Participants were excluded from enrollment in the MTLD-III if they had a SCID lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective or other psychotic disorders, a history of alcohol/drug abuse within the past 12 months, or a diagnosis of dementia. The study was approved by the University of Pittsburgh Institutional Review Board, and all subjects provided written informed consent.

Enrollment Criteria for the Open-Label Pilot Study

The current study was an open-label pilot study of aripiprazole augmentation in patients who responded partially (score of 11–15 on the HAM-D) or not at all (score > 15 on the HAM-D) to first-line antidepressant pharmacotherapy with escitalopram (up to 20 mg/day for 16 weeks), followed by either duloxetine (up to 120 mg/day) or venlafaxine (up to 225 mg/day) for 12 weeks.

Measures and Assessments

Subjects' demographic information and history of depression were assessed and a physical examination was performed before study entry. Key assessments at baseline and at weekly follow-ups included depression severity (HAM-D-17),[10] anxiety severity (Brief Symptom Inventory [BSI][12] anxiety subscale), the UKU Side Effect Rating Scale (UKU),[13] and weight. Since akathisia is a common side effect of atypical antipsychotics, including aripiprazole, we also examined the item in the UKU scale that is specific for akathisia complaints. We defined akathisia as a side effect if a subject experienced a 1-point increase at any 1 time point during aripiprazole exposure. Similarly, we monitored restlessness as a side effect, using an item from the BSI anxiety subscale. Restlessness was scored as no restlessness (0 points), mild restlessness (1 point), significant but transient restlessness (2 points), or significant and persistent restlessness (3 points).

Demographic and Clinical Characteristics of Participants

The subjects who received augmentation therapy with aripiprazole had a mean age of 73.9 years (SD = 6.6 years; range, 65–91 years). Of the participants, 58.3% were female, 8.3% were black, and 75.0% had a history of an anxiety disorder; 70.8% had HAM-D scores of 15 or higher at the start of aripiprazole administration, and 29.1% had HAM-D scores of 11 to 14 at the beginning of aripiprazole administration. The fact that 29% could be considered partially remitted at entry into the augmentation phase could have decreased the likelihood of demonstrating significant improvement over the next 12 weeks, thus providing a useful preliminary test of aripiprazole's value. At the start of aripiprazole treatment, the mean baseline HAM-D score was 18.0 (SD = 5.7). Furthermore, the mean baseline BSI anxiety subscale score was 1.4 (SD = 0.8), and the mean baseline UKU side effects score was 13.4 (SD = 5.4). All subjects except 1 had pretreatment MMSE scores of ≥ 26; 1 subject had a score of 21.

Intervention With Aripiprazole

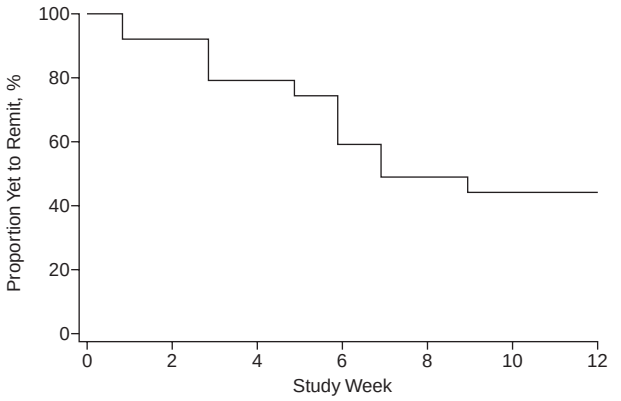
Once the patients began aripiprazole treatment, the dose of the current antidepressant medication was held constant as the aripiprazole dose was titrated according to tolerability and clinical improvement. The starting dose was 2.5 mg per day, and the maximal dose was 15 mg per day. We increased the dose in 2.5-mg/day increments weekly. The mean dose of aripiprazole at 12 weeks was 9.0 mg per day (SD = 4.5 mg). Because treatment nonadherence or self-medication with alcohol could each be a confounding factor in determining the clinical benefit of adjunctive aripiprazole, we addressed these issues by asking at each clinic visit whether participants had finished the antidepressant medication and aripiprazole allotment for the given week. Similarly, we asked at each weekly visit about the number of alcoholic beverages consumed, reasoning that self-medication with alcohol can be associated with difficult-to-treat depression.

An intent-to-treat mixed-effects analysis examined weekly depression scores over 12 weeks of treatment in all 24 subjects. Changes in depression, anxiety, and side-effect scores from week 0 to week 12 were tested with paired t tests. At baseline, severity of depression (HAM-D) and anxiety (BSI) were correlated with one another ($r = 0.60$, $N = 23$, $p = .003$).

RESULTS

Nineteen of 24 (79%) patients completed all 12 weeks of augmentation with aripiprazole, and 12 of 24 patients (50%) met criteria for remission (Figure 1). HAM-D scores showed a significant decrease during exposure to aripiprazole (mixed-effects analysis, $F = 21.20$, $df = 1,23$; $p < .0001$); Figure 2 shows changes in mean HAM-D score during initiation and titration of aripiprazole.

Figure 1. Aripiprazole Augmentation of Serotonin-Norepinephrine Reuptake Inhibitors in Treatment-Resistant Late-Life Depression: Survival Curve of Time to Remission

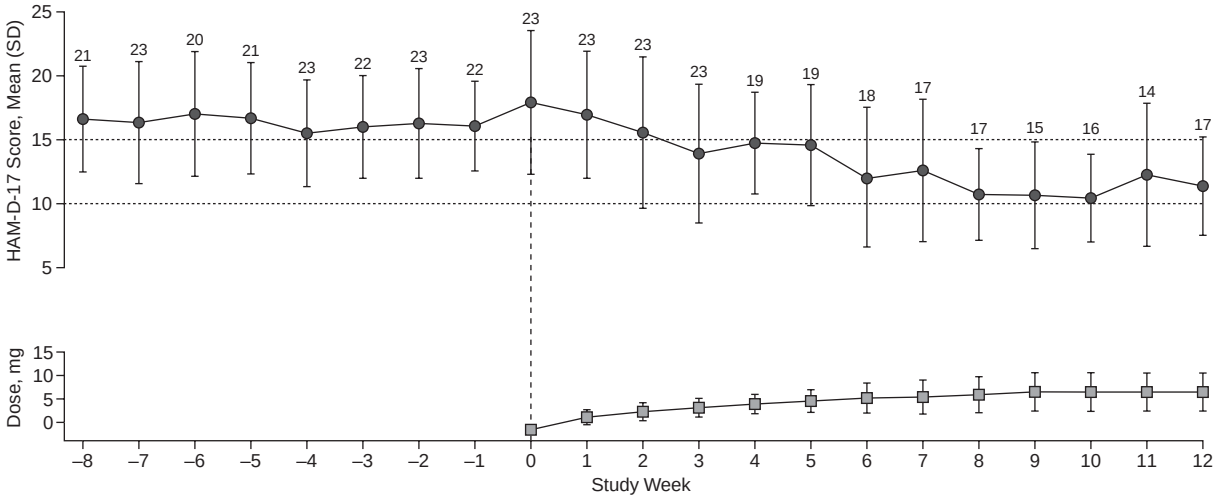


Three of 24 patients (13%) dropped out by week 12 due to failure to improve or withdrawal of consent, and 2 of 24 patients (8%) discontinued due to side effects (1 each for sedation and akathisia). Side effects were also examined via the UKU side effects scale.[13] Overall UKU scores showed a decline (indicating fewer reports of somatic complaints than before use of aripiprazole). However, the mean score of the UKU neurologic subscale increased (it includes a specific akathisia item) (Table 1).

We examined akathisia and restlessness in more detail, given the association of aripiprazole with these side effects in studies of young adults. Six of 24 subjects (25%) had a positive score on the UKU akathisia item during at least 1 time point; however, in all but 1 case, these were mild and/or transient. On the other hand, 18 of 24 subjects (75%) reported at least a mild increase in the BSI restlessness item for at least 1 time point during the 12-week trial.

In the absence of a placebo, and given overall decreases in anxiety, these data are difficult to interpret; however, clinically, we observed that most of these subjects had an initial decrease in restlessness from baseline (representing improved anxiety) during the initial portion of the 12-week trial, with a subsequent increase in restlessness as the aripiprazole dose approached 15 mg per day. Akathisia was typically mild and transient, only infrequently resulting in medication discontinuation. However, restlessness may reflect a common and dose-related side effect that could counteract aripiprazole's therapeutic effect. Our preliminary results are in agreement with studies of aripiprazole in younger adults with treatment-resistant depression,[7,14] which found that restlessness at higher doses of aripiprazole typically resolved promptly with a lowering of the dose. Our results

Figure 2. Improvement in Depressive Symptoms (according to HAM-D-17 score) Following Initiation of Aripiprazole Augmentation[a]



[a]Numbers above the SD bars refer to the number of observations taken at each time point.
Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Table 1. Measures of Clinical Change During Exposure to 12 Weeks of Aripiprazole

		Rating Scale Score, Mean (SD)						
Measure	N	Week 0	Week 12	Change	Effect Size[a]	t Statistic	p Value[b]	df
HAM-D-17	17	17.9 (5.7)	11.5 (3.9)	–6.4 (5.1)	1.26	5.20	< .01	16
BSI anxiety	14	1.5 (0.9)	0.8 (1.0)	–0.8 (1.2)	0.64	2.41	.03	13
UKU total	17	13.7 (5.8)	10.0 (4.0)	–3.7 (4.9)	0.76	3.13	< .01	16
UKU psychological	17	7.7 (2.7)	5.6 (2.2)	–2.1 (2.3)	0.90	3.73	< .01	16
UKU neurologic	17	0.8 (0.9)	1.1 (1.5)	0.4 (1.1)	0.32	–1.31	.21	16
UKU autonomic	17	4.4 (2.8)	2.5 (1.6)	–1.9 (3.0)	0.64	2.62	.02	16
UKU other[c]	17	0.9 (1.1)	0.8 (1.1)	–0.1 (1.4)	0.09	0.36	.73	16

[a]Cohen d effect size.
[b]Paired t test for means.
[c]Symptoms in the UKU-other subscale include rash, skin changes, weight loss or gain, and problems with sexual desire and dysfunction.
Abbreviations: BSI = Brief Symptom Inventory, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, UKU = UKU Side Effect Rating Scale.

are also comparable to a small study of aripiprazole augmentation in elderly depressed patients (mean age, 63) who had responded incompletely to 6 weeks of escitalopram.[8] That 12-week study had similar completion rates (75%) and remission rates (50% reached a HAM-D score of ≤ 10), and similar adverse events were observed (mainly restlessness).[8]

We also examined metabolic changes and weight gain. One subject had a significant increase in lipids, and none had a significant increase in blood sugar, suggesting that metabolic effects were infrequent with aripiprazole. Weight gain was highly variable: 9 of 15 patients (60%) for whom weight data were available gained < 2.0 kg (mean [range] = 0.8 [–0.7 to 1.8] kg), while 6 of 15 patients (40%) gained > 3.0 kg (mean [range] = 4.7 [3.2 to 6.4] kg), suggesting that an examination of sources of weight gain variability would be useful. We were not able to determine whether weight gain represented an increase in adiposity versus an increase in lean body mass with remission from depression.

Finally, we examined continuation treatment outcomes: the 12 remitted subjects continued treatment over a median period of 27.6 weeks. None of these participants experienced relapse of a major depressive episode. One of 12 participants was noncompliant with study procedures (due to respondent burden and other treatment preferences) and exited the study. UKU side effect scores remained stable, and body mass index was also stable over 6 months of continuation phase pharmacotherapy. One participant each had a spike in glucose, triglycerides, and low-density lipoprotein cholesterol. In general, glucose and triglycerides showed minimal change, suggesting that aripiprazole does not cause insulin resistance as do some other atypical antipsychotics. These pilot data support the feasibility and acceptability of continuation treatment with aripiprazole.

Adherence

The mean percentage of medication doses taken was 91.6% (SD = 17.8%), and the median percentage of doses taken was 98.1%. Eighteen subjects (75%) reported missing at least 1 dose of aripiprazole. Three patients (13%) reported a mean of greater than 1 missed dose per week; 2 of these 3 patients subsequently discontinued aripiprazole.

Alcohol Use

Nine subjects (38%) reported no alcohol use while in the study, while 15 subjects (63%) reported at least 1 instance of alcohol use. One subject, who reported a mean of 57.5 drinks per week, dropped out of the study after 2 weeks.

DISCUSSION

In older adults with MDD showing incomplete response to sequential SSRI and SNRI pharmacotherapy, remission was achieved in 50% of patients during aripiprazole augmentation. In subjects who remitted, improvements in depression were stable throughout continuation treatment (median, 6 months). Aripiprazole was well tolerated, with a low rate of dropout due to side effects (8%) and a high completion rate (79%), but restlessness and weight gain were not uncommon. A larger, placebo-controlled study is needed to test hypotheses related to remission, stability of remission, tolerability, safety, and outcome predictors.

We established incomplete response to SSRI and SNRI pharmacotherapy before exposing patients to aripiprazole. Even in this difficult-to-treat group, the use of aripiprazole was associated with clinically meaningful reductions in symptom burden. Two of 24 patients left the study because of apparent side effects (sedation, akathisia). Thus, overall, aripiprazole was well tolerated. Future placebo-controlled studies of adjunctive aripiprazole are needed to evaluate metabolic, neurologic, and electrocardiographic effects of aripiprazole systematically. This approach will allow simultaneous estimates of both potential benefit and risk.

Other data have suggested that sequential treatment of incomplete response in late-life depression leads to a cumulative overall response rate of about 75%. That is, whether we augment with antidepressants[15] or switch to a different class of antidepressant,[16] about 50% of incomplete responders show meaningful clinical improvement. In this context, adjunctive use of aripiprazole seems to be a promising strategy to evaluate. It has been shown in a placebo-controlled trial to be an effective adjunctive therapy in young and middle-aged adults with incomplete antidepressant response,[7] and our pilot data suggest but do not prove that it may be efficacious and well tolerated in older adults who have failed sequential pharmacotherapy with SSRI and SNRI agents.

Regarding the necessity of a geriatric trial, older patients with depression usually have a high burden of medical illness, are subject to extensive medication regimens, and often experience adverse drug effects.[17] In general, pharmacokinetic changes associated with aging result in higher and more variable drug concentrations in older patients. Nonetheless, available information on pharmacokinetics of antidepressants is inadequate, particularly with regard to medical subgroups and potential drug interactions.[18] Because geriatric patients have been excluded from randomized controlled trials, a placebo-controlled geriatric study is needed to determine specifically whether aging-related pharmacokinetic and pharmacodynamic factors influence treatment response or tolerability.

In future controlled evaluation of aripiprazole, the role of potential predictors and moderators of treatment response variability should be systematically evaluated. These include symptoms of anxiety,[19] coexisting medical burden,[20] and pharmacogenetic polymorphisms.[21]

Finally, developing treatment strategies that are practicable in general medical settings, where most older Americans receive treatment for depression (if they receive it at all), is of great public health significance.[1,2] A proven pharmacologic augmentation strategy, with a well-documented benefit-to-risk ratio, would be amenable to dissemination and uptake in primary care medicine.

Drug names: aripiprazole (Abilify), duloxetine (Cymbalta), escitalopram (Lexapro and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), venlafaxine (Effexor and others).

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