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# An open trial of aripiprazole augmentation for SSRI non-remitters with late-life depression

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## SUMMARY

**Objective** To evaluate the efficacy and tolerability of aripiprazole augmentation in elderly depressed patients who did not reach remission after treatment with an SSRI.

**Method** Outpatients 50 years and older with major depressive disorder not remitting after adequate treatment with an SSRI were eligible for the study. In the 6-week long augmentation phase, antidepressants were continued without change and aripiprazole was titrated if needed to a maximum dose of 15 mg per day. Patients were evaluated at the study endpoint on an intent to treat basis, and the primary outcome measure was remission of depression as measured by Hamilton Rating Scale for Depression (HRSD)  $\leq 10$ .

**Results** Twenty patients having mean age  $63.0 \pm 9.6$  years old, HRSD  $20.0 \pm 4.2$ , Beck Depression Inventory (BDI)  $21.0 \pm 9.8$ , Clinical Global Impression—Severity (CGI—S)  $3.7 \pm 0.9$ , and Mini Mental State Examination (MMSE)  $29.2 \pm 1.0$  entered the study. At the study endpoint, mean HRSD was  $7.6 \pm 5.9$ , BDI  $9.1 \pm 9.3$ , and CGI—S  $1.9 \pm 1.1$ . A 50% remission rate of depression was observed after six weeks of augmentation with aripiprazole. Twenty five percent of subjects did not complete the study. The most frequent side effects observed were dry mouth (25%), agitation/anxiety (20%), and drowsiness (15%).

**Conclusion** In this study 50% of depressed patients not remitting after an adequate trial of an SSRI achieved a final HRSD  $\leq 10$  when given aripiprazole augmentation. Open trials such as this require follow up in a randomized, placebo-controlled trial. Copyright © 2007 John Wiley & Sons, Ltd.

**KEY WORDS**—aripiprazole; selective serotonin reuptake inhibitor; augmentation; geriatric depression; remission; open study

## INTRODUCTION

Untreated or partially treated depression in older patients is associated with high mortality due to comorbid medical conditions and suicide (Zubenko *et al.*, 1997). Failure of the depression to remit with antidepressant treatment is a common problem, since only 40–50% of elderly patients respond to a first medication trial (Baldwin and Simpson, 1997).

Recently, the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) study provided important information about treating patients whose depressions do not remit with antidepressants (Rush

*et al.*, 2006). However, this study did not enroll patients older than 60 years old. While augmentation strategies such as combining antidepressant medications and adding lithium to an antidepressant have been studied in elderly patients, clear evidence of efficacy for these treatments is lacking (Lotruch and Pollock, 2005). Therefore, clinicians are faced with uncertainty regarding what is the most appropriate next step for elderly patients whose depressions do not remit after treatment with an antidepressant.

Atypical antipsychotics in combination with antidepressants are recommended as the treatment of choice for psychotic major depression (Alexopoulos *et al.*, 2004) and have been increasingly studied for partially or non-responsive patients with non-psychotic depression (Nemeroff, 2005). In one open

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series of 36 outpatients with major depressive disorder (seven of whom were older than 60 years), 76% of those treated with risperidone and fluvoxamine for 6 weeks experienced remission of their depression (Hirose and Ashby, 2002). A study of risperidone augmentation for SSRI non-responders aged 18–85 found significantly greater improvement compared to continued administration of citalopram alone (Nemeroff *et al.*, 2004).

Although these reports suggest augmentation with atypical antipsychotics may be an effective treatment strategy, few systematic data exist on the efficacy and tolerability of these medications in older patients. Given recent concerns about increased cardiovascular mortality among elderly patients with dementia who were prescribed atypical antipsychotics (Schneider *et al.*, 2006), it is critical to investigate the safety of these medications in non-demented elderly patients with depression.

This study openly administered aripiprazole to depressed patients over 50 whose depression did not remit after adequate treatment with an SSRI. Aripiprazole was selected because of its decreased propensity to cause metabolic and cardiac side effects. The primary hypothesis was that aripiprazole augmentation would result in at least a 50% remission rate of depression as measured by HRSD  $\leq 10$ .

## METHODS

### *Subjects*

Depressed outpatients were recruited through physician referral and media advertisements to the Late Life Depression Clinic of the New York State Psychiatric Institute. A psychiatrist conducted a medical and psychiatric history on each patient. Patients with a clinical diagnosis of major depressive disorder were interviewed by a research rater, who completed the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) axis I disorders—Patient edition (SCID-P) (Ventura *et al.*, 1998) and a Hamilton Rating Scale for Depression (HRSD) 24-item questionnaire (Hamilton, 1960). In addition, a physical examination, routine blood tests (complete blood count and SMAC-20), and an electrocardiogram were completed for eligible candidates.

Inclusion criteria were: (1) age  $\geq 50$  years; (2) unipolar, non-psychotic Major Depressive Disorder; (3) HRSD score of  $\geq 13$  after at least six weeks treatment with an SSRI at an adequate dose (citalopram 20 mg per day, paroxetine 20 mg per

day, fluoxetine 20 mg per day, escitalopram 10 mg per day, or sertraline 100 mg per day); (3) English speaking; and (4) willing to and capable of giving informed consent. Exclusion criteria were: (1) severe or unstable medical illness; (2) stroke, dementia, or other major neurologic disorders; (3) Mini Mental State Exam (MMSE) score  $\leq 24$ ; (4) previous exposure to aripiprazole with significant side effects; (5) acute suicidal intent; (6) history or current evidence of a psychotic or bipolar illness; or (7) substance abuse or dependence other than nicotine in the past 6 months.

### *Non-remission to SSRI*

Patients with major depressive disorder who were not currently taking an antidepressant were started on escitalopram at a dose of 10 mg per day. If the HRSD was not  $\leq 10$  at the end of 3 weeks, the dose was raised to 20 mg for an additional 3 weeks. Patients with an HRSD  $\geq 13$  at the end of 6 weeks of treatment with escitalopram became eligible for the augmentation phase of the study. For patients presenting with an HRSD  $\geq 13$  who were currently taking an SSRI, the duration and dose of the antidepressant trial were determined through patient and family interview or report of the prior psychiatrist to see if the patient met inclusion criteria.

### *Aripiprazole augmentation*

Antidepressants were continued without dosage change during the 6-week trial. Aripiprazole was started at 5 mg daily, then increased by 5 mg every two weeks if the HRSD score was not  $\leq 10$ , to a maximum potential dose of 15 mg. Patients returned weekly for follow-up evaluations and clinical management. Compliance with medications was measured by a pill count at each visit. If this count indicated the subject had not received all the prescribed drug, the subject was counseled on the importance of compliance and how to take study medication. Clinicians filled out the Treatment Emergent Symptom Scale (TESS) weekly to monitor for the presence of side effects.

### *Statistical analyses*

The intent to treat sample comprised all patients in the study. Descriptive statistics are expressed as means and standard deviations or percentages. Change over time in depression scores was modeled using growth curve procedures in SPSS (version 14). Only the fixed effects (i.e. average effects of predictors on depression across participants) of the final growth curve are

reported, as the focus of this study was quantifying mean level change over time. The primary outcome measure was treatment remission defined by HRSD  $\leq 10$ . Chi-square analyses and independent samples *t*-tests, respectively, were used to compare remitters and non-remitters in demographic and clinical features.

## RESULTS

### Descriptive statistics

Twenty patients who were  $63.0 \pm 9.6$  years old, 75% women, 75% college-educated, and 90% white entered the study (Table 1). Baseline measures showed HRSD  $20.0 \pm 4.2$ , BDI  $21.0 \pm 9.8$ , CGI—Severity

(CGI—S)  $3.7 \pm 0.9$ , MMSE  $29.2 \pm 1.0$ , and Cumulative Illness Rating Scale—Geriatrics (CIRS-G)  $6.2 \pm 2.9$  (Table 2). Mean scores on all measures decreased by the study endpoint—final HRSD was  $7.6 \pm 5.9$ , BDI  $9.1 \pm 9.3$ , and CGI—S  $1.9 \pm 1.1$ .

Figure 1 represents each individual's trajectory of change. All but one participant's depression scores decreased over time. These individual decreases were reflected in a decreasing HRSD trajectory for the average study participant. As can be seen in Figure 2, the average person began the study with an HRSD score of approximately 20 and decreased over the 6-week study to approximately 7.5. To quantify this, we fit a growth curve model (Table 3) that included statistically significant decreases (linear and quadratic) in HRSD scores over time (Figure 3).

Table 1. Clinical and demographic characteristics of included patients

| Characteristic                  | Total ( <i>n</i> = 20) |     |
|---------------------------------|------------------------|-----|
|                                 | Mean                   | SD  |
| Age                             | 63.0                   | 9.6 |
| Baseline HRSD                   | 20.0                   | 4.2 |
| Baseline BDI                    | 21.0                   | 9.8 |
| Baseline CGI—Severity           | 3.7                    | 0.9 |
| Baseline CIRS-G                 | 6.2                    | 2.9 |
| MMSE                            | 29.2                   | 1.0 |
|                                 | <i>N</i>               | %   |
| Male gender                     | 5                      | 25  |
| Married                         | 4                      | 20  |
| Employed                        | 9                      | 45  |
| Ethnicity                       |                        |     |
| White                           | 18                     | 90  |
| Hispanic                        | 1                      | 5   |
| Indian                          | 1                      | 5   |
| Education                       |                        |     |
| High school graduate            | 3                      | 15  |
| Some college                    | 2                      | 10  |
| College graduate                | 4                      | 20  |
| Graduate degree                 | 11                     | 55  |
| Depressive Subtype              |                        |     |
| Non-Melancholic                 | 14                     | 70  |
| Melancholic                     | 2                      | 10  |
| Atypical                        | 4                      | 20  |
| Age of Onset                    |                        |     |
| <25                             | 5                      | 25  |
| 25–49                           | 6                      | 30  |
| 50–74                           | 7                      | 35  |
| $\geq 75$                       | 2                      | 10  |
| Number of prior episodes        |                        |     |
| 0                               | 4                      | 20  |
| 1–2                             | 9                      | 45  |
| $\geq 3$                        | 7                      | 35  |
| Number of antidepressant trials |                        |     |
| 0                               | 2                      | 10  |
| 1                               | 4                      | 20  |
| 2                               | 8                      | 40  |
| $\geq 3$                        | 6                      | 30  |

### Side effects and patient attrition

Fifteen patients (75%) completed the study. Two patients discontinued due to intolerable anxiety, and

Table 2. Outcome of augmentation with aripiprazole in patients whose depression did not remit to adequate treatment with an SSRI

|                                   | Baseline ( <i>n</i> = 20) |     | End point ( <i>n</i> = 15) |     |
|-----------------------------------|---------------------------|-----|----------------------------|-----|
|                                   | Mean                      | SD  | Mean                       | SD  |
| HRSD                              | 20.0                      | 4.2 | 7.6                        | 5.9 |
| BDI                               | 21.0                      | 9.8 | 9.1                        | 9.3 |
| CGI                               |                           |     |                            |     |
| Severity                          | 3.7                       | 0.9 | 1.9                        | 1.1 |
| Improvement                       |                           |     | 1.9                        | 1.1 |
|                                   |                           |     | <i>N</i>                   | %   |
| Remission (Final HRSD $\leq 10$ ) |                           |     | 10                         | 50  |
| Dropouts                          |                           |     | 5                          | 25  |
| CGI Remission                     |                           |     |                            |     |
| Very Much Improved                |                           |     | 7                          | 35  |
| Much Improved                     |                           |     | 5                          | 25  |
| Final Aripiprazole Dose           |                           |     |                            |     |
| 5 mg                              |                           |     | 7                          | 35  |
| 10 mg                             |                           |     | 9                          | 55  |
| 15 mg                             |                           |     | 4                          | 20  |
| Side Effects                      |                           |     |                            |     |
| Dry Mouth                         |                           |     | 5                          | 25  |
| Agitation/Anxiety                 |                           |     | 4                          | 20  |
| Constipation                      |                           |     | 3                          | 15  |
| Blurred Vision                    |                           |     | 2                          | 10  |
| Nausea                            |                           |     | 2                          | 10  |
| Headaches                         |                           |     | 2                          | 10  |
| Sweating                          |                           |     | 1                          | 5   |
| Hypotension                       |                           |     | 1                          | 5   |
| Drowsiness                        |                           |     | 1                          | 5   |
| Dizziness                         |                           |     | 1                          | 5   |
| Rash                              |                           |     | 1                          | 5   |

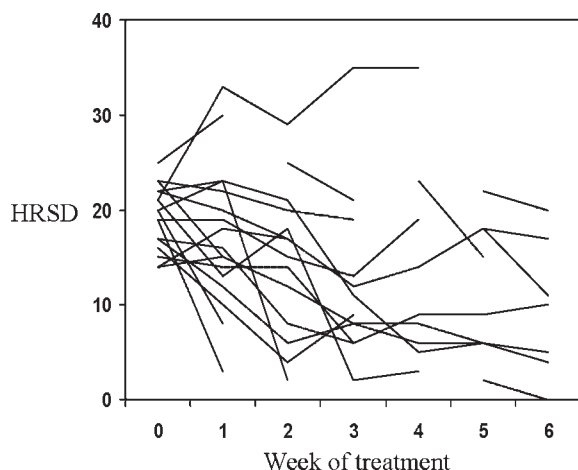


Figure 1. Individual outcomes of augmentation with aripiprazole on HRSD scores over time.

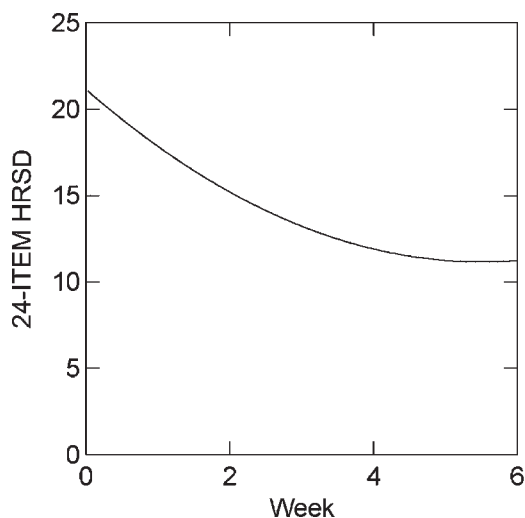


Figure 3. Mixed model of change over time in HRSD scores.

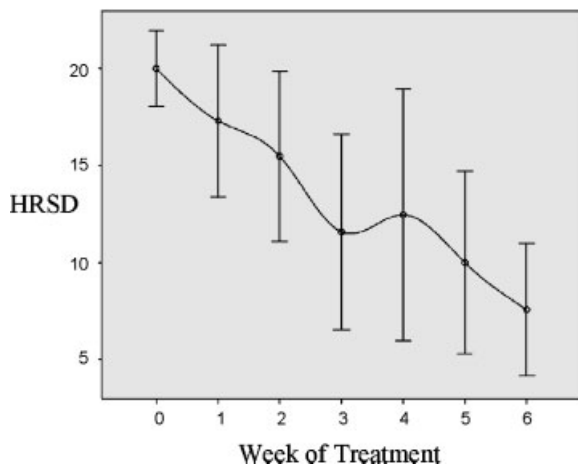


Figure 2. Mean HRSD score (SD) by week of treatment.

Table 3. Final growth curve model estimates for HRSD scores

| Parameter         | Estimate | SE   | t     | df    | p     | 95% CI       |
|-------------------|----------|------|-------|-------|-------|--------------|
| Intercept         | 12.51    | 1.67 | 7.48  | 21.22 | 0.001 | 9.03, 15.98  |
| Time              | -1.28    | 0.32 | -3.98 | 14.05 | 0.001 | -1.97, -0.59 |
| Time <sup>2</sup> | 0.34     | 0.15 | 2.27  | 48.43 | 0.028 | 0.039, 0.64  |
| -2 Log Likelihood | 491.687  |      |       |       |       |              |
| Parameters        | 8        |      |       |       |       |              |

Dependent variable = Hamilton Rating Scale for Depression. Time is centered to correspond to the study midpoint. The final model covaried for baseline HRSD. Estimate = unstandardized regression weight; CI = Confidence Interval; SE = standard error.

one patient's medication was stopped due to a rash. One additional patient dropped out due to lack of efficacy, and one was dropped from the protocol due to noncompliance. Overall, 9/20 patients (45%) experienced side effects of treatment as measured by the TESS. Four of these patients described mild side effects, while 5/9 patients described moderate or severe side effects. The most frequent side effects noted were dry mouth (25% of total sample), agitation/anxiety (20%), drowsiness (15%), nausea (10%), headaches (10%), and blurred vision (10%). At their last study visit, seven patients were taking 5 mg of aripiprazole, nine patients were receiving 10 mg, and four patients 15 mg.

*Primary Outcome (HRSD ≤ 10)*

Ten of the 20 patients entering the study (50%) met criteria for remission in this study (HRSD ≤ 10).

Five patients (25%) were treated with an SSRI prior to coming to the Late Life Depression Clinic (three fluoxetine, two sertraline), while all others (n = 15) received escitalopram as described in the study methods. Of the patients who presented to the study taking an SSRI, 2/5 (40%) was classified a remitter after aripiprazole augmentation, while 8/15 (53%) patients not remitting after 6 weeks of open treatment with escitalopram remitted after aripiprazole augmentation ( $\chi^2 = 0.267$ , df 1,  $p = 0.61$ ).

Post hoc analyses compared the remitter group (n = 10) to the non-remitter group (n = 10) (Table 4). Compared to non-remitters, remitters had significantly

Table 4. Comparison of demographic and clinical data between augmentation remitters (HRSD  $\leq 10$ ) and non-remitters

|                               | Remitters<br>( <i>n</i> = 10) |                 | Non-remitters<br>( <i>N</i> = 10) |     | <i>p</i> |
|-------------------------------|-------------------------------|-----------------|-----------------------------------|-----|----------|
|                               | Mean                          | SD              | Mean                              | SD  |          |
| Baseline HRSD                 | 18.3                          | 2.7             | 22.2                              | 4.8 | 0.03     |
| Endpoint HRSD                 | 5.1                           | 3.2             | 19.7                              | 8.1 | <0.001   |
| Baseline BDI                  | 21.0                          | 5.8             | 26.4                              | 9.2 | 0.123    |
| Endpoint BDI                  | 6.6                           | 4.8             | 19.9                              | 9.1 | <0.001   |
| Baseline CGI-Severity         | 3.4                           | 1.0             | 4.0                               | 0.7 | 0.108    |
| Endpoint CGI-Severity         | 1.5                           | 0.7             | 3.5                               | 1.4 | <0.001   |
| Endpoint CGI-Improvement      | 1.4                           | 0.7             | 3.3                               | 1.0 | <0.001   |
|                               | % Remitters                   | % Non-remitters |                                   |     | <i>p</i> |
| Male gender                   | 10                            | 40              |                                   |     | 0.606    |
| Married                       | 20                            | 20              |                                   |     | 0.379    |
| Employed                      | 50                            | 40              |                                   |     | 0.931    |
| Completed trial               | 100                           | 50              |                                   |     | 0.004    |
| Depressive Subtype            |                               |                 |                                   |     |          |
| Non-Melancholic               | 80                            | 60              |                                   |     | 0.526    |
| Melancholic                   | 10                            | 10              |                                   |     |          |
| Atypical                      | 20                            | 20              |                                   |     |          |
| Ethnicity                     |                               |                 |                                   |     |          |
| White                         | 100                           | 70              |                                   |     | 0.329    |
| Hispanic                      | 0                             | 10              |                                   |     |          |
| Indian                        | 0                             | 10              |                                   |     |          |
| Age of Onset of MDD $\leq 50$ | 70                            | 60              |                                   |     | 0.157    |
| Number prior episodes         |                               |                 |                                   |     |          |
| 0                             | 10                            | 30              |                                   |     | 0.83     |
| 1–2                           | 80                            | 10              |                                   |     |          |
| $\geq 3$                      | 20                            | 50              |                                   |     |          |
| Number anti depressant trials |                               |                 |                                   |     |          |
| 0                             | 0                             | 20              |                                   |     | 0.48     |
| 1                             | 30                            | 10              |                                   |     |          |
| 2                             | 50                            | 30              |                                   |     |          |
| $\geq 3$                      | 30                            | 30              |                                   |     |          |

lower baseline HRSD score ( $t = 2.313$ ,  $df = 18$ ,  $p = 0.033$ ) and lower final aripiprazole dose ( $t = 2.33$ ,  $df = 18$ ,  $p = 0.031$ ). Both groups had similar mean baseline BDI ( $t = 1.620$ ,  $df = 18$ ,  $p = 0.123$ ), CGI—S ( $t = 1.690$ ,  $df = 18$ ,  $p = 0.108$ ), age ( $t = -0.927$ ,  $df = 18$ ,  $p = 0.37$ ), CIRS-G ( $t = 0.11$ ,  $df = 3$ ,  $p = 0.92$ ), MMSE ( $t = -1.450$ ,  $df = 18$ ,  $p = 0.16$ ), gender ( $\chi^2 = 0.267$ ,  $df = 1$ ,  $p = 0.606$ ), marital status ( $\chi^2 = 3.086$ ,  $df = 3$ ,  $p = 0.379$ ), employment ( $\chi^2 = 0.444$ ,  $df = 3$ ,  $p = 0.931$ ), ethnicity ( $\chi^2 = 2.222$ ,  $df = 2$ ,  $p = 0.329$ ), depressive subtype ( $\chi^2 = 1.286$ ,  $df = 2$ ,  $p = 0.526$ ), number of prior depressive episodes ( $t = 0.216$ ,  $df = 16$ ,  $p = 0.83$ ), duration of the current depressive episode ( $t = -0.047$ ,  $df = 18$ ,  $p = 0.96$ ), and number of past antidepressant trials ( $\chi^2 = 2.50$ ,  $df = 3$ ,  $p = 0.48$ ).

## DISCUSSION

All outcome results must be interpreted with caution, since medication administration was not blinded or randomized. The major finding was that aripiprazole augmentation in older patients whose depressions did not remit with adequate SSRI treatment resulted in a 50% remission rate. Patients completing the study had a 12.4 point reduction in mean HRSD score (endpoint score of  $7.6 \pm 5.9$ ), 11.9 point reduction in mean BDI scores (endpoint  $9.1 \pm 9.3$ ), and 1.9 point reduction in mean CGI—Severity scores (endpoint  $1.5 \pm 0.7$ ). Aripiprazole was generally well tolerated in this sample. Three patients discontinued due to intolerable side effects. Side effects observed in the study were generally consistent with those found in larger trials of aripiprazole for schizophrenia and bipolar disorder. These included agitation, anxiety, drowsiness, blurred vision, dry mouth, and headache.

In addition to the open label administration of medication, results must be interpreted with a number of other limitations in mind. First, remitters in this study were primarily patients who were not taking medication at the time of presenting to our clinic. It is possible that extending the escitalopram trial to 8 or 12 weeks might have resulted in the same rate of remission observed with the aripiprazole augmentation. It has been demonstrated within a single 12 week clinical trial that medication response rates are greater at the end of a trial than after eight weeks (Georgotas and McCue, 1989). However, in comparisons between different trials, other investigators have shown that longer antidepressant trials for patients with late-life depression do not increase response rate (Roose and Sackeim, 2004). In addition, no significant difference in response rates was observed between patients presenting to the clinic while taking medications and those who received escitalopram in the study.

Second, the study included subjects  $\geq 50$  years old, while most studies of late life depression use a higher age cutoff (typically 65 or 70 years old). In fact, most patients in this study were elderly, since the median age was 61 years, the mean was 63 years, and only six patients in the study were younger than 59 years old. At the time of their entry into the study, patients took from 0–4 non-psychiatric prescription medications for ongoing medical problems (mean  $1.5 \pm 1.5$  medications). Seventeen of 20 patients reported chronic medical issues requiring ongoing treatment. This medical burden is comparable to that reported for the elderly population in general (Mulsant and Pollock, 1998).



Given the high prevalence of late-life depression, its associated morbidity and mortality, the limited remission rate to an antidepressant alone, and the findings of this study, there are compelling reasons to do a randomized, placebo-controlled trial of atypical antipsychotic augmentation of antidepressants in patients with late-life depression.

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