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Impact of Prior Treatment on Remission of Late-Life Depression with Venlafaxine and Subsequent Aripiprazole or Placebo Augmentation

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Abstract

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Declaration of Interests:

JHH reports no conflicts of interest.

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Objectives—Prior treatment history can inform clinical decisions about subsequent treatment choices. We examined the impact of prior antidepressant treatment on outcome of treatment with venlafaxine only and then with augmentation with aripiprazole or placebo in depressed older adults.

Methods—We analyzed outcome data from a randomized, placebo-controlled clinical trial of aripiprazole augmentation in depressed older adults. The study consisted of an open-label lead-in phase with venlafaxine XR, followed by a placebo-controlled phase of aripiprazole augmentation. Prior treatment history was assessed with the Antidepressant Treatment History Form.

Results—Documented prior treatment failure predicted a reduced remission rate with venlafaxine. However, aripiprazole augmentation was efficacious in those with prior treatment failure (42.6% remission with aripiprazole vs 25.8% with placebo; $\chi^2 = 3.87$ df = 1, p = 0.049).

Conclusions—Aripiprazole augmentation is an efficacious strategy in older depressed adults who fail to remit with two or more adequate antidepressant trials, including a course of venlafaxine.

Keywords

geriatric depression; antidepressant; treatment resistance; augmentation; venlafaxine; aripiprazole; randomized controlled trial

Introduction

Clinicians treating older adults for depression are often faced with treatment resistant cases, as late-life depression (LLD) often does not respond to first-line pharmacotherapy (1). Failure to respond to an adequate antidepressant pharmacotherapy trial has been associated with lower remission rates in depressed patients across the lifespan with various treatment modalities(2–6). Interestingly, patients who have been treated with an inadequate dose or duration of antidepressant (e.g., “pseudo-treatment resistance”) and those that are treatment naïve respond at equally higher rates than those with adequate prior treatment failures(2–5).

However, it is not clear whether this negative effect on remission rates with prior antidepressant treatment failure also applies to atypical antipsychotic augmentation of an antidepressant. A recent meta-analysis(7) of randomized controlled trials (RCTs) in younger adults did not find suppression of remission rates with atypical antipsychotic augmentation of antidepressants among patients with no previous failure compared to those with two or more antidepressant failures. The efficacy of antipsychotic augmentation after multiple antidepressant failures has not been studied in patients with LLD.

Given the paucity of data to guide treatment in LLD after one or two antidepressant failures, we assessed the impact of prior antidepressant treatment, first on open label treatment with venlafaxine, and then on augmentation with aripiprazole or placebo, using data from the Incomplete Response in Late-Life Depression: Getting to Remission (IRL-GRey) study(8). First, we hypothesized that patients with a history of non-response to adequate pharmacotherapy would have lower remission rates with venlafaxine. Second, as little data exist on pharmacotherapy after two failed treatment trials, we assessed whether aripiprazole

augmentation is an efficacious strategy in this group. We evaluated the efficacy of aripiprazole augmentation in patients who had failed to respond to venlafaxine only compared to those who had failed at least one antidepressant prior to entering the study (thus having at least two treatment failures at the time of randomization for augmentation).

Methods

The methods of IRL-GRey are described elsewhere (8). In brief, this was a multi-phase clinical trial for older adults with major depression; it consisted of an open-label trial of venlafaxine, followed by a placebo-controlled trial of aripiprazole augmentation in venlafaxine nonresponders. Participants were recruited in three academic centers (University of Pittsburgh; Centre for Addiction and Mental Health/University of Toronto; Washington University in St. Louis) between 2009 and 2013. Approval was obtained from the three institutional review boards. Inclusion criteria included age 60 years or older, diagnosis of a major depressive disorder, and a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 15.

The primary outcome was remission defined as a MADRS score of 10 or lower for two consecutive assessments. The first phase was treatment with open-label venlafaxine extended-release (XR) for approximately 12 weeks. Venlafaxine was titrated initially to 150 mg/day. Then, patients who did not remit on this dose by week 6 had the dose titrated to 300 mg/day. Patients who did not remit at the end of this phase were randomized to continue venlafaxine XR at the same dose, plus they received augmentation under double-blind conditions with either aripiprazole (2 – 15 mg/day) or placebo. Participants who already had an adequate trial of venlafaxine XR (150 mg/day or higher for > 4weeks) prior to entering the study were excluded from this analysis to ensure that these individuals were not erroneously categorized as having failed two different antidepressant trials.

We used the Antidepressant Treatment History Form (ATHF) (9)to describe the adequacy of each individual antidepressant trial in the current depressive episode. Based on dose and duration criteria, an ATHF score of 0 indicates no previous pharmacotherapy; 1: a definitely inadequate trial; 2: a probably inadequate trial; 3: a probably adequate trial, 4: a definitely adequate trial; and 5: a definitely adequate trial that included augmentation pharmacotherapy. Thus, at the start of the open-label venlafaxine phase, those with ATHF scores of 0 were treatment naïve; those with scores of 1 or 2 had received inadequate treatment; those with scores of 3–5 had received previous adequate treatment. Participants were only randomized to augmentation with aripiprazole or placebo if they had failed to remit after achieving an adequate dose of venlafaxine XR (minimum of 150 mg/day) during the first phase of the study. Thus, those who had an ATHF score ≥ 3 prior to starting venlafaxine (i.e., they had already failed one adequate antidepressant trial prior to participating) constituted a group with at least two adequate antidepressant treatment failures prior to randomization with aripiprazole or placebo augmentation.

We used Pearson's chi-square tests to compare remission rates in the groups of interest, first, after treatment with venlafaxine; second, after augmentation with aripiprazole/placebo. Because we have reported in two independent samples that outcomes do not differ between

those who are treatment naïve and those who have had an inadequate treatment trial (pseudo-treatment resistant)(2, 5), we considered these participants as one group. All statistical analyses were conducted using statistical software (SPSS for Mac 22.0; IBM Inc.).

Results

As summarized in Table 1, 446 participants met the inclusion criteria for our analysis and were treated openly with venlafaxine. 186/446 (41.7%) achieved remission and completed the study. Of the 272 with a previous antidepressant failure, 169 were non-remitters (62.1%). Of the 174 with no previous adequate treatment failure, 91 (52.3%) were non-remitters. 92 subjects were not randomized for various reasons(8).

Thus, 168/446 (37.7%) non-remitters were randomized to augmentation with aripiprazole or placebo, of whom 45/168 (26.8%) had failed only venlafaxine and 123/168 (73.2%) had failed venlafaxine and at least one other previous antidepressant trial. Specifically, they had failed to achieve remission with antidepressants from other classes than serotonin-norepinephrine reuptake inhibitors including selective serotonin reuptake inhibitors: 82/123 (66.7%); bupropion: 31/123 (25.2%); mirtazapine 9/123 (7.3%); tricyclic antidepressants: 3/123 (2.4%); mono-amine oxidase inhibitors: 3/123 (2.4%).

Lead-In Venlafaxine Phase

The 272/446 participants with a previous adequate treatment trial were significantly less likely to achieve remission with venlafaxine than the 174/446 participants with no previous adequate treatment trial or an inadequate treatment trial (37.9% vs 47.7%; χ^2= 4.22; df =1; p = 0.04). Of the 272 with a previous adequate treatment failure, 94 (34.6%) had two or more treatment failures and 178 (65.4%) had one previous adequate treatment failure. The remission rate on venlafaxine was 22.3% (21/94) for those with two or more treatment failures versus one treatment failure 46.1% (82/178), (χ^2= 14.72; df =1; p < 0.0001). There was also a significant difference in remission rates on venlafaxine comparing those with at least two treatment failures versus those with no previous adequate treatment 47.7% (83/174) (χ^2= 16.53; df =1; p < 0.0001).

Aripiprazole of Placebo Phase

When restricting the sample to those who had failed venlafaxine and at least one other adequate treatment trial, the remission rates were higher with aripiprazole (26/61) than with placebo (16/62) (42.6% vs 25.8%; χ^2= 3.87, df =1, p = 0.049), yielding a number needed to treat of 6 (95% CI 3.0–311.8). In contrast, in those who were treatment naïve at baseline and were only exposed to and failed venlafaxine during the first phase, the remission rates with aripiprazole (11/23) and placebo (10/22) did not differ significantly (47.8% vs 45.5%; χ^2= 0.25; df =1; p = 0.873). Overall, the remission rates with aripiprazole in those who were naïve at baseline (11/23) compared to those with previous adequate treatment (26/61) was similar (47.8% vs 42.6%).

Discussion

This analysis confirmed our hypothesis that older depressed patients who have failed one or more previous adequate antidepressant treatment trials have lower remission rates when they are treated with venlafaxine than those patients who are treatment naïve or have been treated inadequately. After having failed to remit with venlafaxine, the patients who had failed one or more other adequate antidepressant treatment trials are more likely to benefit from aripiprazole augmentation than from placebo. In contrast, those with no previous adequate treatment may benefit similarly from aripiprazole or placebo.

Our first finding that previous antidepressant treatment failure is a robust clinical predictor of poor outcome with subsequent antidepressant monotherapy confirms several published reports(5, 10). Our other main finding addresses an important issue: identifying subgroups of depressed patients who require augmentation with an atypical antipsychotic such as aripiprazole. The superior efficacy of aripiprazole vs. placebo in the subgroup with multiple prior antidepressant failures is consistent with a recent meta-analysis of antipsychotic augmentation trials in younger adults that found no loss of efficacy with increasing levels of antidepressant failures(7). In our sample, the remission rates with aripiprazole augmentation were similar in those with one failed antidepressant trial (i.e., venlafaxine) and in those with two or more failed trials (i.e., venlafaxine and at least one other trial): 47.8% vs. 42.6%. However, those who had failed two or more trials benefitted more from augmentation with aripiprazole than with placebo (remission rates: 42.6% vs. 25.8%), while those who had failed only one treatment trial did not (47.8% vs. 45.5%). Thus, the variation in effect size may be attributed to the difference in response to placebo, rather than difference in response to augmentation. Indeed, a recent study has shown lower placebo response rates in patients who have failed more prior active treatments(4). There may be biological differences in those who are nonresponsive to 2 or more antidepressants where a multi-receptor approach is required and achieved by combination of 2 different drugs classes.

The strengths of this study include its design as a prospective randomized placebo-controlled trial. It is limited by the retrospective evaluation of previous medication trials. In addition, the efficacy of aripiprazole in those with two or more failures is limited by a marginal level of statistical significance.

Nevertheless, these findings have potentially important clinical implications for the approach to antidepressant therapy for treatment resistant LLD. When starting an initial antidepressant trial, it is important that clinicians take detailed information about the adequacy of prior treatment as it can guide future treatment decisions. First, those who were treatment naïve before being treated with venlafaxine appeared to have similar and relatively robust remission rates when treated with aripiprazole or placebo, yet the sample size of this analysis was quite small. Clinicians, may consider a longer treatment trial with venlafaxine to see if patients remit before considering augmentation with aripiprazole. Second, our results support that patients with two or more prior treatment failures can benefit from aripiprazole augmentation and provide evidence for an augmentation rather than switching strategy in such patients. Prospective comparative effectiveness trials in depressed older

adults that test augmentation versus switching strategies in patients with treatment resistance are warranted.

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