Original Investigation

Predictors and Moderators of Remission With Aripiprazole Augmentation in Treatment-Resistant Late-Life Depression
An Analysis of the IRL-GRey Randomized Clinical Trial

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IMPORTANCE Safe, efficacious, second-line pharmacological treatment options exist for the large portion of older adults with major depressive disorder who do not respond to first-line pharmacotherapy. However, limited evidence exists to aid clinical decision making regarding which patients will benefit from which second-line treatments.

OBJECTIVE To test the moderating role of pretreatment executive function, severity of anxiety, and severity of medical comorbidity in remission of treatment-resistant late-life depression after aripiprazole augmentation.

DESIGN, SETTING, AND PARTICIPANTS As follow-up to a 12-week randomized clinical trial of aripiprazole augmentation for first-line treatment-resistant late-life depression (Incomplete Response in Late-Life Depression: Getting to Remission [IRL-GRey]), we evaluated the effects of the following potential moderators and their interactions with treatment: baseline assessments of executive function (set shifting measured by the Trail Making Test) and response inhibition control (measured by a Color-Word Interference task), anxiety symptoms, and medical comorbidity. Analyses were conducted in May and June 2015.

INTERVENTIONS Aripiprazole or placebo tablets were started at 2 mg daily and titrated as tolerated, to a maximal dose of 15 mg daily.

MAIN OUTCOMES AND MEASURES Remission of treatment-resistant late-life depression (defined as a Montgomery-Åsberg Depression Rating Scale score of ≤10 at both of the last 2 consecutive visits).

RESULTS Of 181 trial participants (103 female [56.9%]) who were 60 years of age or older and whose major depression had failed to remit with venlafaxine hydrochloride monotherapy, 91 received aripiprazole and 90 received placebo. Remission occurred in 40 (43%) who received aripiprazole and 26 (29%) who received placebo. Baseline set shifting moderated the efficacy of aripiprazole augmentation (odds ratio [OR], 1.66 [95% CI, 1.05-2.62]; $P = .03$ for interaction with treatment). Among participants with a Trail Making Test scaled score of 7 or higher, the odds of remission were significantly higher with aripiprazole than with placebo (53% vs 28%; number needed to treat, 4; OR, 4.11 [95% CI, 1.83-9.20]). Among participants with a Trail Making Test scaled score of less than 7, aripiprazole and placebo were equally efficacious (OR, 0.64 [95% CI, 0.15-2.80]). Greater severity of anxiety at baseline predicted a lower remission rate but did not moderate aripiprazole efficacy; each standard deviation greater anxiety severity was associated with 50% reduced odds of remission in both aripiprazole and placebo arms. Medical comorbidity and Color-Word Interference test performance were neither general predictors nor treatment-moderating factors.

CONCLUSIONS AND RELEVANCE Set-shifting performance indicates which older adults with treatment-resistant depression may respond favorably to augmentation with aripiprazole and thus may help to personalize treatment.

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Editorial

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Over half of older adults with major depressive disorder fail to respond adequately to first-line pharmacotherapy with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors.[1] Persistent depression in this population heightens the risk for disability, nonadherence to treatment of other medical disorders, cognitive impairment leading to dementia, low quality of life, caregiver burden, suicidality, and early mortality.[2-6] Data from randomized controlled clinical trials to guide second-line treatment for older adults are sparse.[7]

Recently, we reported the results of a randomized controlled clinical trial testing the efficacy and safety of aripiprazole for late-life depression that is resistant to first-line treatment.[8] Aripiprazole is an atypical antipsychotic approved by the US Food and Drug Administration for second-line treatment of major depressive disorder. Its pharmacodynamic actions involve partial agonism at the dopamine receptors D_2 and D_3 and antagonism at the serotonin $5HT_{1A}$ and $5HT_{2A}$ receptors.[9,10] Aripiprazole is not an anticholinergic drug, and aripiprazole's partial agonism at the dopamine receptors may have favorable effects in late-life depression wherein the mesolimbic dopamine system may be disrupted.[11,12] Indeed, the addition of aripiprazole to venlafaxine hydrochloride was well tolerated and effective in inducing and maintaining remission for up to 12 weeks; 44% of participants treated with aripiprazole and 29% of placebo-randomized participants had late-life depression that was in remission.

While our initial report[8] focused on the safety and efficacy of aripiprazole for treatment-resistant late-life depression (the first 2 aims of our study), the present report focuses on our third aim, which was to examine the roles of prespecified variables as moderators of response to aripiprazole. The importance of identifying treatment moderators has been highlighted previously.[13] In brief, it is important to determine whether specific clinical characteristics are general prognostic variables (ie, that predict the course of depression regardless of treatment) or treatment-moderating factors (ie, that predict the effect size of active treatment vs placebo). Identifying moderators of aripiprazole response could help clinicians tailor treatment to individual patients, thereby minimizing exposure to inefficacious trial-and-error pharmacotherapy.

Evidence regarding moderators of response to first-line treatment of late-life depression has advanced to the level of meta-analysis.[14] This literature has found that cognitive impairment,[15] anxiety,[16] and medical comorbidity[17] may moderate response to first-line treatments of late-life depression. However, to our knowledge, no such data exist regarding the moderators of response to second-line treatments such as aripiprazole. Because more than half of older adults do not adequately respond to first-line pharmacological therapy for major depressive disorder,[1] it is important to identify for whom such second-line pharmacotherapy is likely to be efficacious.

We therefore evaluated the potential moderating roles of 3 factors, specified a priori in the trial protocol (executive dysfunction, anxiety severity, and medical burden), in remission of treatment-resistant late-life depression after 12 weeks of aripiprazole augmentation. We selected these factors based on prior literature regarding their role as moderators of first-line treatments,[15-17] as well as the fact that these factors are highly but variably prevalent among older adults with depression. We hypothesized that pretreatment executive function, severity of anxiety, and severity of medical comorbidity would moderate the efficacy of aripiprazole augmentation.

Key Points

Question: How do executive dysfunction, anxiety, and medical burden relate to the remission of symptoms among older adults whose major depressive disorder is resistant to venlafaxine monotherapy and who were subsequently randomized to adjunctive aripiprazole or placebo?

Findings: In this 12-week, randomized, placebo-controlled clinical trial, set-shifting performance (an aspect of executive function) moderated the efficacy of adjunctive aripiprazole. Anxiety severity was a prognostic factor (unrelated to aripiprazole efficacy but associated with worse remission rates overall), and medical burden was not a prognostic factor or treatment moderator.

Meaning: Set-shifting performance may mark a subgroup of patients resistant to first-line treatment who are unlikely to benefit from adjunctive aripiprazole treatment.

Methods

Data from the 12-week, multisite, randomized, placebo-controlled, double-blind clinical trial of aripiprazole augmentation for first-line treatment-resistant late-life depression (Incomplete Response in Late-Life Depression: Getting to Remission [IRL-GRey]) were used for this analysis. This trial was conducted to test the efficacy, safety, and tolerability of aripiprazole augmentation for older adults whose depression had not remitted with venlafaxine.[8] The methods of IRL-GRey trial have been described in Lenze et al[8] and are summarized here.

Participants

Participants were 60 years of age or older with a current major depressive episode (diagnosed using *DSM-IV* criteria in the Structured Clinical Interview for *DSM-IV*) and a Montgomery-Åsberg Depression Rating Scale (MADRS)[8] score of 15 or higher. Individuals who received a diagnosis of bipolar disorder, dementia, schizophrenia, current psychotic symptoms, alcohol abuse, or substance abuse during the last 6 months were excluded from the study. All participants provided written informed consent. The conduct of the study was overseen by a data safety and monitoring board. Ethical approval was obtained from the institutional review board at each site (Washington University, the University of Pittsburgh, and the University of Toronto).

Interventions

After open treatment with venlafaxine extended release (up to 300 mg/d) for 12 weeks to establish treatment resistance, the 181 participants who did not achieve remission (defined as an MADRS score of ≤10 for 2 sequential assessments) were randomly assigned, using permuted block randomization, to

the addition of aripiprazole or placebo for 12 weeks, while maintaining the dose of venlafaxine achieved during initial monotherapy. This randomized augmentation phase was conducted under double-blind conditions with outcomes assessed by independent evaluators. In terms of allocation concealment, no member of the research team other than the pharmacist was aware of treatment assignment. Aripiprazole or placebo tablets were started at 2 mg daily and titrated as tolerated, to a maximal dose of 15 mg daily.

Assessments

Outcome

The primary outcome of the treatment trial and present analysis was remission of symptoms, defined as an MADRS score of 10 or lower, at the last 2 consecutive visits (week 10 and 12 of the augmentation phase). Symptoms of depression were measured over time, with the total MADRS score assessed at each weekly or biweekly visit. Assessments were administered by an independent evaluator, and regular intersite sessions were conducted to maintain interrater reliability (with an intraclass correlation coefficient of 0.997).

Baseline Clinical Factors

We administered a neuropsychological test battery (supervised by a senior neuropsychologist [M.A.B.]) before starting venlafaxine extended-release open treatment. Executive function was evaluated using 2 tests from the Delis-Kaplan Executive Function System—the Color-Word Interference task (measuring response inhibition) and 2 Trail Making Test tasks (measuring set shifting).[18] Color-Word Interference condition 3, called *inhibition*, assesses the ability to inhibit an automatic response (ie, reading words); instead, participants must produce a response that requires more effort (ie, naming the colors of words). The Trail Making Test condition 4 (also known as *the Number-Letter Switching condition*) requires that examinees switch back and forth between connecting numbers and letters (ie, 1, A, 2, B, etc, to 16, P). Condition 5 is a motor speed condition in which examinees trace over a dotted line connecting circles on the page as quickly as possible to gauge their motor drawing speed. Comparing performance on condition 4 (which assesses cognitive flexibility) with performance on condition 5 (which assesses motor speed) removes the motor speed element from the test score to ascertain cognitive flexibility[19]; we used the Delis-Kaplan Executive Function System normed scaled score (with a mean [SD] of 10 [3]) based on the difference in speeds between condition 4 and condition 5, representing set-shifting performance.[20]

The Brief Symptom Inventory (BSI), a self-report scale with strong construct validity, internal consistency, and test-retest reliability,[21] was used as a continuous score to assess anxiety symptoms. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G),[22] expressed as a total score, was used to assess medical comorbidity. The BSI and CIRS-G were administered at the start of aripiprazole/placebo augmentation.

Statistical Analysis

All continuous variables, including executive function measures, were standardized before analysis. In our primary analyses, the hypothesized moderators were expressed as continuous predictors using separate logistic regression models of remission status. We defined general prognostic factors as main effects that were statistically significant (at $P < .05$) and associated with the odds of remission without demonstrating an interaction with treatment assignment. Moderating factors were defined as those baseline variables that interacted with treatment in predicting remission. To illustrate moderating effects, we present the odds of remission associated with each hypothesized moderator stratified by treatment assignment. All models were adjusted for age, sex, study site, and treatment assignment; models including executive function variables were further adjusted for educational attainment.

To test whether the associations detected in separate models were independent of each other, we constructed a final multivariable model including the significant main effects and interactions identified. (The main effects of variables comprising the selected interactions were also included, as required for properly interpreting the regression analysis.) To increase interpretability and clinical relevance, when interactions were detected between treatment and continuously expressed executive function performance, we also examined the effect of impairment in the executive function domain. We defined executive impairment as a score of more than 1 SD below age-normed performance, and we present the odds of remission associated with aripiprazole (vs placebo) among patients with or without impaired executive function. Clinical effect sizes are expressed in numbers needed to treat.

Results

The demographic and clinical characteristics of the participants are presented in **Table 1**, stratified by treatment arm and remission status. In the initial trial, of 181 participants who had failed to remit with venlafaxine, 91 were randomized to receive aripiprazole and 90 to placebo. Forty (43%) of those who received aripiprazole and 26 (29%) of those who received placebo were determined to be remitters. The mean (SD) MADRS scores were 21.45 (6.42) in the aripiprazole remitters vs 19.78 (5.99) in the placebo remitters.

Examining the potential moderators separately (**Table 2**) indicated that better baseline performance on the Trail Making Test task (condition 4 vs 5; set shifting) was associated with higher odds of remission among patients treated with aripiprazole but not placebo ($P = .03$ for interaction with treatment); this interaction was significant with (Table 2) and without ($P = .03$) adjustments for age and sex. Performance on the Color-Word Interference task (response inhibition) was not a significant predictor of remission (ie, the 95% CIs overlapped with 1; Table 2), and there was no moderating effect ($P = .38$ for interaction with treatment).

For each standard deviation (overall BSI SD = 0.77) higher pretreatment anxiety severity, the odds of remission were reduced by 54% (Table 2). Note that this association was consistent within both aripiprazole and placebo arms, indicating that pretreatment anxiety was a general prognostic factor but not a moderating factor. Medical comorbidity was not a sig-

Table 1. Descriptive Information By Treatment Arm and Remission Status

Variable	Aripiprazole Arm		Placebo Arm	
	Remitters (n = 40)	Nonremitters (n = 51)	Remitters (n = 26)	Nonremitters (n = 64)
Age, mean (SD), y	68.08 (4.53)	67.34 (7.42)	66.59 (4.90)	67.25 (5.87)
Female sex, No. (%)	22 (55.0)	30 (58.8)	10 (38.5)	41 (64.1)
White, No. (%)	38 (95.0)	42 (82.4)	22 (84.6)	57 (89.1)
Education, mean (SD), y	15.03 (2.75)	13.51 (2.96)	14.19 (2.88)	14.14 (2.62)
Test score, mean (SD)				
Depression (MADRS)	21.45 (6.42)	25.09 (5.99)	19.78 (5.36)	24.34 (6.60)
Anxiety (BSI)	0.81 (0.57)	1.27 (0.81)	0.51 (0.60)	0.99 (0.81)
Physical health (CIRS)	10.48 (9.59)	9.59 (4.39)	9.42 (3.43)	9.30 (4.49)
Color-Word Interference (condition 3)[a]	10.98 (2.57)	9.90 (3.53)	10.24 (2.67)	10.08 (3.14)
Trail Making Test (condition 4 vs 5, scaled score)	9.18 (3.18)	7.55 (4.04)	8.50 (3.44)	8.98 (3.58)

Abbreviations: BSI, Brief Symptom Inventory; CIRS, Cumulative Illness Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.

[a] Used with permission from Pearson.

Table 2. Association of Remission With Potential Moderators Within Aripiprazole and Placebo Arms

Moderator[a]	OR (95% CI)	*P* Value[b]
Anxiety (BSI)		
Aripiprazole (n = 91)	0.54 (0.32-0.93)	.64
Placebo (n = 90)	0.44 (0.22-0.87)	
Physical health (CIRS total)		
Aripiprazole (n = 91)	1.13 (0.74-1.70)	.57
Placebo (n = 90)	0.93 (0.56-1.56)	
Color-Word Interference (condition 3)		
Aripiprazole (n = 89)	1.43 (0.90-2.26)	.38
Placebo (n = 86)	1.05 (0.63-1.74)	
Trail Making Test (condition 4 vs 5, scaled score)		
Aripiprazole (n = 89)	1.66 (1.05-2.62)	.03
Placebo (n = 84)	0.75 (0.44-1.27)	

Abbreviations: BSI, Brief Symptom Inventory; CIRS, Cumulative Illness Rating Scale; OR, odds ratio.

[a] Moderators are separately modeled (per standard deviation) and adjusted for age, sex, and study site.

[b] For interaction between treatment and moderator.

nificant predictor of remission, and we detected no interaction between medical comorbidity and treatment arm (Table 2).

A final multivariable model including the detected crude associations indicated that both the general prognostic role of anxiety and the moderating effect of Trail Making Test task performance were independent (**Table 3**). We did not detect significant interactions of age or sex with treatment (P = .33 and .11, respectively), and further adjusting the multivariable model (Table 3) for these interaction terms did not alter the associations of anxiety with remission or the interaction of Trail Making Test task performance with treatment.

Table 4 further highlights the treatment moderating effect of Trail Making Test performance. Among participants with a Trail Making Test baseline score equal to or greater than 7 (within 1 SD of age-normed performance or better[19]), the odds of remitting were more than 4 times higher with aripiprazole treatment than with placebo (odds ratio, 4.11 [95% CI, 1.83-9.20]). However, among patients with Trail Making Test (condition 4 vs condition 5) scores less than 7, there was no statistically significant difference between the treatment arms (Table 4).

Remission rates also illustrate this moderating effect (**Figure**, A); among patients with Trail Making Test (condition 4 vs condition 5) scores of 7 or higher, aripiprazole was associated with higher remission rates compared with placebo (53.3% remission rate with aripiprazole and 28.1% remission rate with placebo). Thus, among participants with intact set-shifting performance, the number needed to treat with aripiprazole was 4. However, among patients with Trail Making Test (condition 4 vs condition 5) scores of less than 7, remission rates were low in both treatment arms (21.7% remission rate with aripiprazole and 30.0% remission rate with placebo).

To illustrate the general prognostic role of baseline anxiety symptoms, we present remission rates stratified by treatment arm and the presence BSI-measured anxiety symptoms more than 1 SD of the sample's mean (Figure, B); remission rates are reduced in the groups of participants with higher levels of baseline anxiety severity, but the difference in remission rates between aripiprazole and placebo arms was similar across groups of participants with lower or higher levels of anxiety severity. We also performed a post hoc descriptive analysis of the basic characteristics of patients with set-shifting impairment and patients without set-shifting impairment (eTable in the Supplement). The patients with and the patients without set-shifting impairment did not differ in the clinical characteristics examined, including the rate of treatment-emergent akathisia (the most common adverse effect that we previously identified[8]). Patients with set-shifting impairment were somewhat older and were less often white.

Table 3. Parameter Estimates From the Final Multivariable Model Predicting Remission[a]

Factor	β (SE)	*P* Value
Aripiprazole (main effect vs placebo)	0.50 (0.18)	.01
Anxiety (BSI main effect per SD)	−0.70 (0.22)	.002
Trails Making Test condition 4 vs 5 (main effect per SD)	0.11 (0.20)	.59
Treatment × Trail Making Test (condition 4 vs 5) interaction	0.44 (0.19)	.02

Abbreviation: BSI, Brief Symptom Inventory.

[a] Adjusted for all factors given, plus age, sex, study site, and education (for 173 participants).

Table 4. Remission Illustrating the Interaction Between Trail Making Test Impairment and Treatment[a]

Effect of Aripiprazole vs Placebo	Adjusted OR (95% CI)
Trail Making Test condition 4 vs 5 scaled scores	
≥−1 SD	4.11 (1.83-9.20)
<−1 SD	0.64 (0.15-2.80)

Abbreviation: OR, odds ratio.

[a] Adjusted for age, sex, study site, education, anxiety, and the main effects of treatment and Trail Making Test condition 4 vs 5 comparing patients with scaled scores less than −1 SD below the norm vs the rest.

Discussion

Given the high rate of treatment resistance in late-life depression, clinicians, patients, and family caregivers need data from randomized controlled clinical trials to inform treatment decisions. The IRL-GRey trial demonstrated that aripiprazole is efficacious and well tolerated for inducing and maintaining remission in older adults.[8] However, this prior work did not address which patients might benefit from aripiprazole. Based on prespecified moderator analyses, the present study now adds that pretreatment performance on the Trail Making Test task condition 4 vs condition 5 (set shifting) moderated the efficacy of aripiprazole response. Aripiprazole was associated with higher odds of remission (compared with placebo) only among participants without set-shifting impairment.

The observed moderating effect of set-shifting performance is consistent with previous studies[23,24] showing that cognitive dysfunction, in general, and executive impairment, in particular, correlate with (predict) poor treatment outcomes in late-life depression. To our knowledge, the present study provides the first test of these moderators (including 2 measures of executive function) in a large randomized clinical trial of second-line treatment. Our findings make clear the distinction between the general prognostic and moderating effects in treatment-resistant late-life depression. We found that pretreatment performance on the Color-Word Interference task (response inhibition) showed neither a prognostic nor moderating effect over the trial. The 2 subdomains of executive function examined (set shifting and response inhibition) may therefore be dissociable in their ability to moderate the efficacy of aripiprazole for venlafaxine-resistant late-life depression. Specificity of executive function deficits may indicate differences in the neurobiological basis of resistance to particular treatments (eg, first- and second-line moderators).

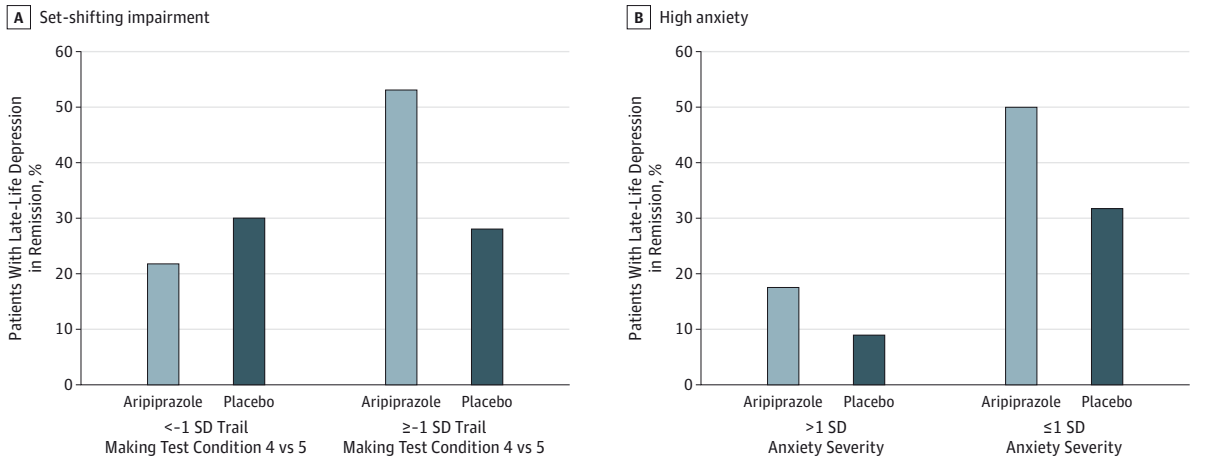
We also found that a higher level of anxiety severity was associated with lower odds of remission but did not influence the strength of (moderate) aripiprazole efficacy. The absence of treatment moderation associated with anxiety severity suggests that aripiprazole is efficacious regardless of pretreatment anxiety levels. Nevertheless, the observed evidence for a general prognostic role of pretreatment anxiety is useful information for determining which patients are likely to have a more challenging treatment course. Medical comorbidity as assessed with the CIRS-G was neither a moderating factor nor a general prognostic factor. We previously reported that a higher medical burden undermines the stability of remission over 2 years, placing patients at higher risk for recurrence of major depressive episodes.[17] In light of these findings, it will be important for future studies to determine whether pretreatment medical comorbidity has a differential effect on the clinical outcomes of short- and long-term aripiprazole treatment.

The strengths of our study include the placebo-controlled design following open-label venlafaxine treatment that prospectively established treatment resistance. Identifying set-shifting performance as a moderator of aripiprazole efficacy could be an important step toward personalizing intervention strategies for older adults with major depressive disorder. Our initial report from the IRL-GRey trial found that aripiprazole was associated with a number needed to treat of 6.6.[8] The present study now adds that, among patients with normal set-shifting functioning, aripiprazole is associated with a number needed to treat of 4.0. Equally important, our current findings suggest that aripiprazole may not be efficacious for treatment-resistant late-life depression occurring in the presence of set-shifting impairment. Because set-shifting tests, including a version of the Trail Making Test, are fairly easily administered and available in the public domain,[19] clinicians may find such tests useful for objectively evaluating who is likely or not likely to respond to aripiprazole augmentation.

Executive dysfunction, including impaired set shifting, is also present in teenagers and young adults with major depression,[25] even during the first major depressive episode.[26] Given the relatively "young" older adults included in the IRL-GRey trial (with a mean age of 68 years), we can hypothesize that executive dysfunction might also be a moderator of treatment response in younger age patients as well. Future research is needed to investigate whether executive dysfunction is a moderator of antidepressant treatment response in other age groups.

Although our study focused on clinical rather than biological factors, the observed moderating effect of set-shifting impairment suggests a possible neurobiological basis for aripiprazole resistance among older adults with treatment-resistant depression. Set shifting is plausibly related to aripiprazole's known mechanisms of action because set shifting involves the cooperative interaction between D_1 and D_2 receptors in the prefrontal cortex.[27] A recent small study[10] of

Figure. Remission Rates in the Aripiprazole Arm vs the Placebo Arm Stratified by the Presence of Set-Shifting Impairment (A) and High Anxiety (B)



High anxiety is associated with lower remission rates but no difference in aripiprazole-placebo separation (anxiety is a general prognostic factor that does not moderate the efficacy of aripiprazole). In contrast, set-shifting impairment is a treatment moderator. In the absence of set-shifting impairment, aripiprazole is clearly superior to placebo; however, in the presence of set-shifting impairment, there is no difference between the 2 treatment arms (Table 4).

treatment-resistant depression found that response to aripiprazole treatment is associated with enhanced dopaminergic activity in the striatum. Set-shifting impairment and aripiprazole nonresponse may therefore share a common substrate in dopamine receptor imbalance and/or loss of structural integrity of the frontostriatal connections (potentially due to cerebrovascular, neurodegenerative, or other pathological processes). These changes may lead to reduced aripiprazole target engagement and therapeutic success by preventing effective activation of the relevant dopaminergic circuits. Although plausible, the biological basis of aripiprazole's antidepressant effect and the moderating role of set-shifting impairment must be confirmed in future research.

The other limitations of our study should also be noted. Most participants in the IRL-GRey trial could be characterized as being "young-old," with a mean age of 68 years. As a result of this somewhat truncated distribution of participants' ages, our results may not be generalizable to the "older-old" patient population. Future research is needed to generalize our findings beyond groups of predominately older white patients because we did not have sufficient representation of participants self-identifying as persons from nonwhite ethnic and racial groups; future research is needed to test the potential moderating effect of race and ethnicity on achieving remission with aripiprazole vs placebo. In addition, although a significant interaction between treatment and set-shifting performance was detected, the confidence intervals of the association between set shifting and remission within the aripiprazole and placebo treatment arms did somewhat overlap (Table 2); this may be a result of the relatively restricted sample size, the large variability in these estimates, and/or a relatively small moderator effect size.

Future research is needed to characterize more thoroughly the patients who benefit from aripiprazole augmentation. The present study focused on only 3 a priori–specified potential response predictors. The observed moderating effect of Trail Making Test performance suggests that set-shifting abilities are relevant to the capacity for aripiprazole response; nevertheless, it remains possible that other aspects of neuropsychological function (not specified for moderator analyses a priori) may also moderate aripiprazole efficacy. Our finding that set-shifting impairment marks a subgroup of patients who are not likely to remit following aripiprazole treatment may help health care professionals avoid prescribing aripiprazole to patients who are unlikely to benefit. However, even though aripiprazole was efficacious (compared with placebo) in the absence of set-shifting impairments, the remission rate in this group remained modest (53.4%). Identifying additional moderators of aripiprazole's effect could lead to greater precision in determining which patients will remit following aripiprazole treatment. Future exploratory analyses using a wider range of clinical data to create combined moderators[28] may be necessary to accomplish this goal.

Conclusions

In conclusion, our study extends published observations of executive impairment, anxiety, and medical burden as correlates or predictors of poorer outcomes in late-life depression. Our findings support set-shifting performance as a moderator of short-term remission (ie, influencing the efficacy of aripiprazole) and distinguish anxiety as a general short-term prognostic variable (predictor). Further examining a wider range of pretreatment factors, including other aspects of cognition, as well as the neurobiological basis of these observed effects, will continue to improve our understanding of how treatments work and for whom they do or do not work.

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