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Moderators of Remission in Patients With Late-Life Depression:

Where Do We Go Next?

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The article by Kaneriya and colleagues¹ in this issue of *JAMA Psychiatry* reports on a randomized double-blind clinical trial examining the moderating factors that influence remission with aripiprazole treatment in an elderly population of participants with treatment-resistant late-life depression. The participants initially received extended-release venlafaxine hydrochloride to establish treatment resistance, and then they were randomly assigned to 12 weeks of augmentation with aripiprazole or placebo.² Pursuing their a priori hypotheses, the investigators tested for the moderating effects of executive dysfunction (specifically, measures of set shifting and response inhibition), comorbid anxiety, and medical burden. All of these factors have been implicated in contributing to poor antidepressant responses in late-life depression,^{3,4} but they have not previously been examined in second-line therapies and often not in the context of placebo-controlled trials. The study team found that neither medical morbidity nor response inhibition was related to remission. A higher severity of anxiety predicted an overall lower remission rate but did not specifically moderate aripiprazole efficacy. In contrast, set-shifting performance measured with the Trail Making Test moderated aripiprazole efficacy; participants who performed better were more likely to remit with aripiprazole than with placebo. For participants performing poorly, aripiprazole did not demonstrate a benefit over placebo. These findings have several implications and raise many questions.

The observed relationship between a poor response to aripiprazole and poor set-shifting performance may be related to a common underlying factor: dopaminergic dysfunction. As observed by Kaneriya and colleagues,¹ aripiprazole acts as a partial agonist across several dopamine receptors, while set shifting involves cooperative interactions between the D₁ and D₂ receptors. Hypothetically, dysfunction or an imbalance of dopamine receptors may contribute to set-shifting deficits, altered aripiprazole dopamine receptor binding, and poorer clinical response. Although it needs to be tested, such a theory of a common underlying biological substrate is appealing. Certainly other groups have implicated dopaminergic dysfunction in the pathogenesis of depression, anhedonia, and deficits in reward processing.

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Dopaminergic dysfunction may also contribute to the cognitive deficits that are commonly seen in patients with late-life depression.⁴ Despite work demonstrating that the density of dopamine receptors changes with aging and that such changes may parallel cognitive decline,⁵ the role of dopaminergic dysfunction as it contributes to the development or course of late-life depression has not been widely studied.

Intriguingly, as set-shifting performance moderates aripiprazole response, can we use standardized neuropsychological tests of this cognitive process to guide therapeutic decisions? This could lead to earlier clinical decisions to proceed with aripiprazole augmentation for individuals who do not remit with a first-line antidepressant. Knowing the likelihood of a response could also ensure that patients less likely to respond would avoid starting aripiprazole augmentation treatment, thus reducing the rate of unsuccessful trials. These patients could be steered toward other treatments that hopefully provide better chances of remission. However, several questions arise: What is this “next step” treatment? How can we improve outcomes in this population of patients with executive dysfunction? Would evidence-based psychotherapy provide a benefit for this pharmacologically resistant population, or should patients be guided toward brain stimulation therapies?

Although the current state of the literature does not provide a clear answer about the optimal next step, the theoretical framework of dopaminergic dysfunction leading to a shared vulnerability to set-shifting deficits and poor aripiprazole response may be informative. Beyond aripiprazole and other second-generation antipsychotic medications, augmentation strategies that engage dopaminergic systems include both bupropion hydrochloride and methylphenidate hydrochloride.⁶ In contrast to aripiprazole’s activity at dopamine receptors, these agents work via a different mechanism by inhibiting dopamine reuptake. It is currently unclear whether individuals with set-shifting deficits, possibly related to alterations in density or function of dopaminergic receptors, would receive any differential benefit from these other agents. Do set-shifting deficits also predict poor responses to other dopaminergic agents used to augment antidepressant responses?

A limitation of such agents is that while augmentation with bupropion or methylphenidate may result in greater clinical improvement over antidepressant monotherapy, they do not necessarily result in a greater improvement in cognitive performance.⁶ As an alternative strategy, could a therapeutic focus on the cognitive deficits result in clinical improvement in depressive symptoms? One possibility may be cognitive training, an approach based on the theory that increased cognitive activity results in neuroplastic changes in the brain. As reviewed elsewhere,⁷ recent work in older adults demonstrates that neuroplasticity-based computerized cognitive remediation (nCCR) can improve in vivo measures of neuroplasticity and performance across a range of cognitive domains and is also generalizable and sustainable. A recent preliminary study examined nCCR in geriatric depression (nCCR-GD),⁷ using a training approach that specifically focused on executive functions, including set shifting. This preliminary study⁷ found that 30 hours of nCCR-GD over 4 weeks was as effective as 12 weeks of escitalopram oxalate in treating depressive symptoms, but with a faster reduction in depressive symptoms and a greater improvement in the targeted executive functions. Although a definitive trial is needed, such an approach

could be beneficial to patients with set-shifting deficits who have poorer odds of responding to antidepressant medications.

This study¹ also highlights the need to incorporate broader, hypothesis-driven dimensional measures into clinical trials. The design of the study by Kaneriya and colleagues¹ was developed from past literature examining how clinical, cognitive, and medical heterogeneity in late-life depression may be related to variability in treatment outcomes. As exemplified by the decision to examine anxiety and executive function, such measures may inherently be transdiagnostic and may not obviously fit within the *DSM-5* conceptualization of a major depressive disorder diagnosis. Consideration of such comorbid dimensional symptomatology can thus be clinically relevant and can help us to identify clinical phenotypes that put patients at higher risk of poor treatment responses. These findings can also inform future studies examining alternative interventions or probing the underlying neurobiology. This study¹ thus supports the integration of transdiagnostic psychiatric formulations into traditional clinical efficacy trials, such as those proposed by the National Institute of Mental Health's Research Domain Criteria program. However, this endorsement comes with a note of caution. The decision to incorporate such dimensional measures should be made carefully, building from established literature, because the examination of moderating effects has implications for statistical power. Before testing for a moderating effect, one should feel confident in the study's power to detect such an effect, should it exist.

Although this study's findings require replication, the potential for using a common, easy-to-administer neuropsychological test to personalize antidepressant treatment decisions for older adults is appealing. However, even with this approach, remission rates continue to be lower than we would like. Overall, the authors report that aripiprazole is superior to placebo in achieving remission in older patient with treatment-resistant late-life depression (44% of participants treated with aripiprazole and 29% of placebo-randomized participants had late-life depression that was in remission, with a number needed to treat of 6.6).² When targeting individuals with an intact set-shifting performance, these numbers improve (53.3% remission rate with aripiprazole and 28.1% remission rate with placebo), with a number needed to treat of 4,¹ potentially allowing us to better target aripiprazole's use. Thus, half of the individuals with an intact set-shifting performance still do not remit with aripiprazole. The picture is even more dire when considering individuals with high levels of anxiety, a population where less than 20% of participants remitted.¹ This study's findings are thus a step forward, but it also highlights the need for more effective interventions, particularly for individuals with executive dysfunction or substantial comorbid anxiety.

In summary, this study¹ has important implications for clinical treatment and clinical trial methodology. Moreover, it provides important clues about neurobiological mechanisms that may underlie both cognitive deficits and poor clinical response.

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