New Hope for Patients with Major Depressive Disorder?

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Major depressive disorder is a serious mental health condition that affects up to 16% of people in the United States during their lifetimes and about 7% of the U.S. population in a given year.[1] In addition, patients with major depressive disorder have an outsized risk of suicidal behavior. Approximately 60% of patients with major depressive disorder have a response to currently marketed antidepressant agents. However, many other patients do not have a response and are considered to have treatment-resistant depression. Reasons for treatment resistance include the clinical and biologic heterogeneity of the disorder and the likelihood that no single mechanism underlies responsiveness to antidepressants in all patients.[2]

Enhancement of various monoaminergic neurotransmitters such as norepinephrine, dopamine, and serotonin can alleviate the symptoms of major depressive disorder, but this effect is typically seen about 4 weeks after the start of treatment. The first generation of antidepressants (e.g., imipramine and amitriptyline) were thought to work by increasing central noradrenergic and serotonergic activity, but they have not been uniformly effective. Second-generation antidepressants, which putatively target a single neurochemical system (norepinephrine, dopamine, or serotonin) also have not been successful in all patients with major depressive disorder. Even different antidepressants in the same class (e.g., various selective serotonin-reuptake inhibitors) may not have similar effects in the same patient; for example, a patient may not have a response to fluoxetine but may have a response to escitalopram. Most important, the majority of antidepressants do not work quickly — a property that is critical in treating patients with suicidal ideation. Recently, glutamate modulators such as ketamine, which do not work directly on the canonical monoamine systems, have been found to bring about a rapid reduction in depressive symptoms, often within 24 hours, in some patients with treatment-resistant major depressive disorder,[3] but repeated administration is necessary for a sustained antidepressant effect.

In this issue of the *Journal*, Gunduz-Bruce et al. report the results of a trial of SAGE-217 in patients with major depressive disorder.[4] SAGE-217 is the latest example of an agent that is aimed at a new target in major depressive disorder. The authors make a case for why this orally administered positive allosteric modulator of γ-aminobutyric acid type A ($GABA_A$) receptors could have antidepressant activity, and they have provided preliminary evidence that this activity may be clinically relevant. The trial was designed to examine early antidepressant efficacy; the drug was administered for only 2 weeks, and the outcomes were measured for an additional 4 weeks — a period during which SAGE-217 levels in the blood, and presumably in the brain, would be declining and then become absent. Among patients with major depressive disorder, treatment with SAGE-217 resulted in a greater reduction in depressive symptoms, as assessed on a depression rating scale, than placebo over 2 weeks but not at 1 month. Although the magnitude of this effect is generally similar to that of other antidepressants, the clinical response appears to have occurred more rapidly than is typical of most antidepressants. The nonsignificant between-group difference in the change in depression scores from baseline to day 28 suggests that the drug should most likely be administered for longer than 14 days, because the early antidepressant effect dissipates once the drug has been discontinued. The fact that SAGE-217 targets a different central neurotransmitter system than most available antidepressants, is administered orally, appears to have a relatively benign side-effect profile (with headache, dizziness, and nausea as the most frequent adverse events), and appears to work quickly (though not as quickly as glutamate modulators such as ketamine[5]) make this an interesting compound for further study.

There are at least two caveats related to the current trial. First, it did not include patients with treatment-resistant depression, and whether SAGE-217 is efficacious in a large proportion of patients with major depressive disorder in a population that includes this group is not known. Enrolling treatment-resistant patients in a phase 2 trial might have obscured the observation of

an antidepressant effect. However, even if SAGE-217 is not found to be helpful in treatment-resistant depression, the availability of an agent that targets a central neurotransmitter system not previously targeted and that may produce a rapid antidepressant response is provocative. Second, several agents developed in the past to target non-monoamine neurotransmitter systems that had not previously been targeted have failed after promising phase 2 results such as the ones in the current trial. For example, the results of a phase 2 trial of a drug that targets the neurotransmitter substance P were positive,[6] but the agent was later found to be ineffective in a larger trial.[7] Although SAGE-217 represents an exciting conceptual development in new agents for major depressive disorder, only time will tell whether positive allosteric modulators of $GABA_A$ receptors will enter the pharmacopeia of agents that are effective for major depressive disorder.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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