Dosage windows could be difficult to understand pharmacologically, but for a partial agonist the presumed mechanism could be more evident. Clinicians should be aware that more is not always better, meaning that with partial agonist drugs a higher dosage might not lead to greater patient response. With brexpiprazole, a dopamine D2 partial agonist FDA-approved for schizophrenia and an adjunct for major depressive disorder (MDD), moderation is best because of the drug’s known dosage window of efficacy in the treatment of MDD. It is important to note that studies examine populations and not individuals. Specific patients could have genetic variations or be taking agents that may alter metabolism of brexpiprazole, and therefore may benefit from lower or higher doses.

Recommended dosage
Two placebo-controlled studies2,3 examined brexpiprazole dosages of 1, 2, and 3 mg/d. The recommended dosage of 2 mg/d for MDD was determined by changes in Montgomery-Åsberg Depression Rating Scale scores (Figure).4 Lower dosages of 1 mg/d did not reach statistical significance, and 3 mg/d were less effective than the intermediate dosage of 2 mg/d. This result suggests a window of efficacy for brexpiprazole for MDD. This therapeutic window likely applies to most patients; however, patient-specific variables could alter the optimum dosage.

Dosage window
Brexpiprazole has high affinity for dopamine D2, D3, serotonin 5-HT1A, 5-HT2A, norepinephrine α1B, and α2C receptors. At relatively low drug concentrations, brexpiprazole achieves high receptor occupancy. At receptors for which brexpiprazole is a partial agonist (5-HT1A, D2, D3) the drug blocks the receptor and stimulates it at a fraction of the endogenous neurotransmitter. With a very high affinity agent, the endogenous neurotransmitter could be completely excluded from interacting with these receptors if brexpiprazole occupancy is high. At lower dosages, the drug occupies only a fraction of the receptors, allowing the endogenous neurotransmitters to continue interacting with their receptors, thereby magnifying the signal of that receptor above baseline.

**Figure**

Brexpiprazole dosage window of efficacy

<table>
<thead>
<tr>
<th>Brexpiprazole dosage window is visible when placebo-subtracted improvement is graphed as a function of dose in the 2 regulatory placebo-controlled studies. The error bars represent the 95% confidence intervals. A dosage of 2 mg was associated with the greatest improvement, and 1 mg did not reach statistical significance.</th>
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<tr>
<td>MADRS: Montgomery-Åsberg Depression Rating Scale</td>
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<td>Source: Adapted from reference 4</td>
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References