occur in patients with PD when treated with rasagiline. Here, we report a case of some compulsive behaviors arising from rasagiline treatment in a patient with PD.

CASE

A 70-year-old married man experiencing counting compulsions and ritualistic behaviors was admitted in the psychiatric ward. He was given 12 mg/d of ropinirole and 1 mg/d of rasagiline with a diagnosis of PD 1.5 years ago. Despite partial remission in his symptoms and functionality, the patient did not use rasagiline because of an erectile dysfunction for 1 year. Two months ago, 1 mg/d of rasagiline was added again to his ongoing dose of 12 mg/d of ropinirole because his symptoms of PD worsened. A few days later, he began to repeatedly count the number set of 3, 13, and 23 before performing specific actions throughout the day. He also reported an illness anxiety just on the 23rd day of the consecutive months. He had no personal or family history of any psychiatric disorder. The brain magnetic resonance imaging revealed no significant abnormalities. His Mini-Mental State Examination score was 30. The results of all laboratory tests were normal.

At admission, the Hoehn and Yahr scale revealed a stage 1.5 score for PD. He scored 18 on the Yale-Brown Obsessive-Compulsive scale. The neurologists decided to maintain the rasagiline treatment at a dose of 1 mg/d because significant improvement was observed in the symptoms of PD. For his compulsive symptoms, sertraline was started at a dose of 25 mg/d and titrated up to 75 mg daily. At the end of the fourth week, his Yale-Brown Obsessive-Compulsive scale score was decreased to 13.

To our knowledge, this is the first patient with PD in the literature presenting compulsive behaviors induced by rasagiline treatment. We suggest that the onset of compulsive symptoms in our patient seemed to be related to the rasagiline adjunctive therapy. Indeed, he has been under a regular treatment of ropinirole and rasagiline for at least 1 year without any obsessive-compulsive or impulsive symptoms. The occurrence of compulsive symptoms during the second trial of rasagiline at the same doses in our patient should alert the clinicians about the potential effects of these kinds of drugs.

The dysfunctions of the mesocorticollimbic pathways may cause repetitive, compulsive behaviors in humans. The basis for drug-induced pathologic behaviors might be related to alterations in dopamine neurotransmission along these pathways. The dopamine replacement therapy leading to changes in dopamine levels and frontal lobe dysfunctions may precipitate the occurrence of these abnormal behaviors. Rasagiline increases the concentration of catecholamines and dopamine at the synaptic space by blocking the MAO-B enzyme. Possibly, in stimulating postsynaptic dopamine receptors at dysfunctional corticostriato-thalamocortical circuits, rasagiline may account for the compulsive behaviors developed in our patient. Because rasagiline is an effective and widely used drug in PD, clinicians should also be aware of various compulsive symptoms.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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widely reported 65% threshold proposed for clinical response, yet they are effective antipsychotics. Clozapine and quetiapine may exert their activity on other neuroreceptors, and evaluating them only as D2 receptor–occupying agents could be unfair and even invalid.

Another possible explanation for the reported low D2 receptor occupancies of clozapine and quetiapine could lie in the PET imaging protocol adopted in the reviewed studies. In the measurement of D2 receptor occupancies, the affinity of the compound for the D2 receptor is 1 of the key determining factors. The rates of drug-receptor complex association (Kon) for clozapine and quetiapine have been reported to be similar to haloperidol, but these 2 antipsychotics have very high dissociation rates (Koff). Both clozapine and quetiapine have been shown to transiently occupy more than 60% of D2 receptors, and this occupancy might not have been detected on routine PET and single-photon emission computed tomographic imaging protocols. This leaves yet another unanswered question: what is the required duration of D2 receptor antagonism to exert a clinical effect?

It has been widely accepted that 65% and 80% of D2 receptor occupancies represent the thresholds required for antipsychotic effectiveness and development of extrapyramidal adverse effects, respectively. In Table 1, we calculated the doses for the 8 antipsychotics at 65% and 80% of D2 receptor occupancies from the functions derived by the authors. In addition, we computed the D2 receptor occupancies at the recommended dose ranges and at maximum doses of the antipsychotics. What is immediately apparent is the considerable discrepancy between recommended dose range and dose required for up to 80% of D2 receptor occupancy for aripiprazole. Aripiprazole has a unique pharmacologic profile, being a D2 receptor partial agonist, and measured D2 receptor occupancies do not capture this. Although 3 mg of aripiprazole may occupy more than 80% of D2 receptors, in clinical practice, much higher doses are required for clinical efficacy, perhaps the higher D2 receptor occupancy rates for aripiprazole are required to counterbalance the agonistic properties.

The antipsychotic doses at 80% of D2 receptor occupancy for less potent antipsychotics such as ziprasidone and amisulpride are considerably above their respective recommended dose range and maximal doses. This again highlights the limitations of an approach focused solely on D2 receptor occupancy in establishing equipotent doses with the different antipsychotics currently available. A typical clinical scenario that occurs daily in clinical practice would be the switching of antipsychotics. A patient on 8 mg of risperidone should not be switched to 1150 mg of ziprasidone or 3 mg of aripiprazole, computed purely on D2 receptor occupancies. It would also be pertinent to emphasize that there could be other sources of variations in ascertaining pharmacologic doses, such as pharmacogenetics, drug-drug interactions, and even nonadherence.

In conclusion, we are of the opinion that the assumptions made may not be applicable for all antipsychotics. Therefore, comparing all antipsychotics for their D2 receptor occupancies might not be valid, a point that has been emphasized before. It might be more appropriate if this approach was used in antipsychotics with known pharmacologic profiles and activity at the D2 receptor (eg, a highly selective D2 receptor antagonist). It remains though that caution should be exercised when comparing doses of antipsychotics that are based on D2 receptor occupancies.

### Table 1. Calculated Antipsychotic Doses at 65% and 80% of D2 Receptor Occupancies, Recommended Antipsychotic Dose Ranges, and Maximum Doses

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>65% D2 Receptor Occupancies</th>
<th>80% D2 Receptor Occupancies</th>
<th>Recommended Antipsychotic Dose Range (D2 Receptor Occupancies), %</th>
<th>Maximum Antipsychotic Dose (D2 Receptor Occupancies), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>1.6</td>
<td>4.4</td>
<td>5–10 (81.3–86.3)</td>
<td>20 (89.0)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2.5</td>
<td>6.9</td>
<td>4–6 (72.9–78.4)</td>
<td>8.5 (82.1)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>13.3</td>
<td>31.3</td>
<td>10–20 (58.6–72.9)</td>
<td>30 (79.4)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Exceeded E&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Exceeded E&lt;sub&gt;max&lt;/sub&gt;</td>
<td>200–500 (34.0–49.4)</td>
<td>800 (53.4)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Exceeded E&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Exceeded E&lt;sub&gt;max&lt;/sub&gt;</td>
<td>400–800 (26.1–34.1)</td>
<td>950 (35.8)</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.7</td>
<td>2.9</td>
<td>15–30 (85.5–86.2)</td>
<td>30 (86.2)</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>151.4</td>
<td>1150.3</td>
<td>120–160 (61.6–65.8)</td>
<td>200 (68.6)</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>445.3</td>
<td>2192</td>
<td>400–800 (63.3–72.6)</td>
<td>1000 (74.8)</td>
</tr>
</tbody>
</table>

*Antipsychotic doses (s) were calculated from the function x = O<sub>02</sub> × EC<sub>50</sub>/(Emax – O<sub>02</sub>), which was derived from the meta-analysis.
†Dose range obtained from expert consensus recommendations.

### AUTHOR DISCLOSURE

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Letters to the Editors

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7. Kapur S, Zipursky RB, Remington G. Aripiprazole, a novel antipsychotic, is a dopamine D2 receptor occupancy agent, much as clozapine, risperidone, olanzapine, and quetiapine, aripiprazole, ziprasidone, and amisulpride from imaging studies. The main point of concern expressed by Lee et al is that this method may only be used for antipsychotics for which the effect is primarily mediated by the D2 receptor. We included less potent antipsychotics, such as ziprasidone and amisulpride, as well as antipsychotics with very rapid dissociation rate (koff), such as clozapine and quetiapine, to provide a complete overview of all the antipsychotics for which sufficient D2 receptor occupancy data were available. Our curves are intended to investigate the (adverse) effects mediated by the D2 receptor, including extrapyramidal symptoms (EPS), cognitive symptoms, and altered emotional experiences. In future studies, our approach may be used for other receptors and these findings could be integrated to create a complete model of the relationship between receptor occupancy and antipsychotic-mediated (adverse) effects. We thank Lee et al for their detailed comments on our study. Lee et al have described that our dose-occupancy functions can help to translate between D2 receptor occupancies and antipsychotic dose ranges. Their overview demonstrates that 65% (clinical effect) and 80% (occurrence of EPS) of the D2 receptor occupancy indeed translate to recommended doses for most antipsychotics. This approach is, on the one hand, limited because some antipsychotics are weak D2 antagonists and will never reach 80% occupancy; hence, such conversions result in unrealistic doses.

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Estimating Dopamine D2 Receptor Occupancy for Doses of 8 Antipsychotics: A Meta-Analysis

A Reply

To the Editors:

We would like to reply to the comments of Lee et al on our recent study “Estimating Dopamine D2 Receptor Occupancy for Doses of 8 Antipsychotics: A Meta-analysis.” In this study, we derived formulas for the relationship between receptor occupancy and antipsychotic-mediated (adverse) effects. Imaging studies have shown that antipsychotics with weak affinity for the D2 receptor result in a transient peak level of approximately 60% of the D2 receptor occupancy that drops quickly to 30%. Antipsychotics with a high binding affinity are likely to have a prolonged and high (60%–80%) occupancy of the D2 receptors. This continuous D2 receptor occupancy may reduce the sensitivity to dopamine blockade because of tolerance as well as receptor up-regulation and is associated with high risks for EPS as well as altered emotional experiences. Discontinuous (transient) occupancy by antipsychotics with D2 receptor affinity such as clozapine and quetiapine may be more sensitive to endogenous dopamine responses than that by antipsychotics with very high affinity/continuous occupancy. Generally, discontinuous occupancy (“fast off”) is likely to be represented by lower D2 receptor occupancy values measured by positron emission tomography, whereas continuous occupancy may be represented by high occupancy of the D2 receptor. Our curves can thus help to visualize such differences between antipsychotics and give insight into the contribution of the D2 receptor occupancy to the clinical effects.

As an important addition to previous meta-analyses, we were the first to separate interindividual variability from intrastudy variation in the D2 receptor occupancy, using a non–linear mixed