

# Do Dopamine Partial Agonists Have Partial Efficacy as Antipsychotics?

By Stephen M. Stahl, MD, PhD

## NEW TREND IN PSYCHOPHARMACOLOGY

Dopamine (D)<sub>2</sub> partial agonists (DPAs) activate D<sub>2</sub> receptors in a manner that is less than the full agonist dopamine yet more than full antagonists (eg, most known antipsychotics). Various DPAs span the spectrum between full agonist at one end and antagonists at the other, with the antipsychotic aripiprazole close to the antagonist end of this spectrum, and with the antiparkinsonian/restless legs syndrome agents pramipaxole and ropinirole close to the full agonist end of this spectrum (Figure). Numerous DPAs have been tested as antipsychotics, but most have proven to have limited efficacy as antipsychotics or even to be psychotomimetic. Recent experience with a number of DPAs now suggests that although these agents may have less efficacy as antipsychotics than D<sub>2</sub> antagonists, their novel pharmacologic actions may have important clinical utility in mood disorders and as augmenting agents to reduce the side effects of D<sub>2</sub> antagonists (Table).

## WHAT IS A DOPAMINE (D)<sub>2</sub> PARTIAL AGONIST?

Dopamine (D)<sub>2</sub> receptors are linked to G-protein second messenger systems, and can be activated along a spectrum from full agonists at one end, to inverse agonists at the other

(Figure). When occupied by a full agonist, the D<sub>2</sub> receptor is fully activated, and thus the G-protein second messenger system coupled to the D<sub>2</sub> receptor, also called a signal transduction cascade, is activated to the maximum extent.<sup>1</sup> Antagonists, on the other hand, occupy D<sub>2</sub> receptors, but do not activate the second messenger system, and are thus sometimes called "silent."<sup>1</sup> Antagonists will block or reverse ago-

### TABLE. Some Potential Novel Therapeutic Uses for DPAs

First-line treatment of unipolar or bipolar depression
Augmenting SSRIs/SNRIs for treatment-resistant unipolar depression
Augmenting mood stabilizers for bipolar depression
Augmenting D <sub>2</sub> antagonists to reduce hyperprolactinemia
Augmenting D <sub>2</sub> antagonists to reduce weight gain and metabolic abnormalities
Combination with D <sub>2</sub> antagonists to reduce nausea, vomiting, and activation
Substance abuse

DPAs=dopamine (D)<sub>2</sub> partial agonists; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin-norepinephrine reuptake inhibitors.

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nists, but, by themselves do not show activation of the second messenger system.<sup>1</sup>

Partial agonists have actions on D<sub>2</sub> receptors between these two extremes, and thus partially activate the D<sub>2</sub> receptor's second messenger system, but in a manner that is less than the activation of the D<sub>2</sub> receptor's second messenger system by a full agonist.<sup>1</sup> Inverse agonists are at the far end of the agonist spectrum, beyond antagonists. They are the pharmacologic opposites of full agonists, and can reduce baseline activation of the G-protein second messenger system.<sup>1</sup>

The amount of partial agonist action that results from a given DPA is intrinsic to the conformational change caused by the specific partial agonist molecule and cannot be increased by dose.<sup>1</sup> Sometimes partial agonists are called "stabilizers" because they tend to find an intermediate position between the extremes of agonist and antagonist action.<sup>1-3</sup> Thus, DPAs *reduce* signal transduction in the D<sub>2</sub> receptor signal transduction system in the presence of excessive agonist action by dopamine, yet *increase* D<sub>2</sub> receptor signal transduction when the full agonist dopamine is deficient.<sup>1-3</sup>

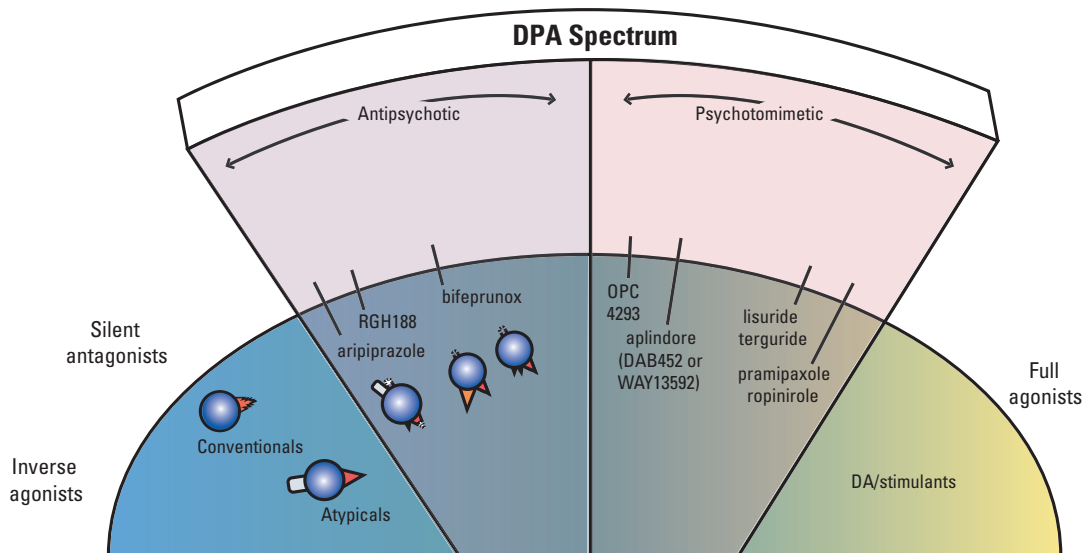
## HOW EFFECTIVE ARE DOPAMINE D<sub>2</sub> PARTIAL AGONISTS AS ANTIPSYCHOTICS?

Although one D<sub>2</sub> partial agonist (aripiprazole) is approved as an antipsychotic, all other proven antipsychotics are D<sub>2</sub> antagonists or inverse agonists.<sup>1</sup> Clinical experience with DPAs<sup>1,4-7</sup> suggests that only those close to the antagonist end of the spectrum may have antipsychotic efficacy, and the closer the partial agonist is to the full agonist end of the spectrum, the less effective it becomes as an antipsychotic, the more difficult it is to find the optimal dose, and the more activating and psychotomimetic it becomes (Figure).<sup>1</sup>

For example, the partial agonist OPC 4293 was developed in the same laboratory as aripiprazole, but was found to be too activating, improving negative symptoms of schizophrenia but worsening positive symptoms. It was "too full" of a partial agonist (Figure).<sup>1</sup> In response, a "less full" partial agonist, OPC 14597, now known as aripiprazole, was tested in schizophrenia and found to be an effective antipsychotic.<sup>1-5</sup> Actions at serotonin receptors may also contribute to aripiprazole's clinical properties, especially to its tolerability profile, yet are not as potent as

### FIGURE.

The spectrum of DPAs: less antipsychotic efficacy with increasing agonist actions?<sup>1</sup>



DPAs=dopamine D<sub>2</sub> receptor partial agonists; DA=dopamine.

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aripiprazole's actions at dopamine receptors, and may only be relevant at higher doses.<sup>1,8,9</sup>

Aripiprazole improves psychosis and acute mania, and is not known for worsening the positive symptoms of psychosis, properties consistent with antagonist actions at D<sub>2</sub> receptors.<sup>4,5</sup> On the other hand, aripiprazole can be activating in some patients, and, unlike D<sub>2</sub> antagonists, aripiprazole can show an inverted U-shaped dose response for its antipsychotic actions, consistent with partial agonist actions at D<sub>2</sub> receptors.<sup>4,5</sup>

Dosing of aripiprazole for use in augmenting antidepressants in major depression may be even lower than the ideal dose of aripiprazole for use as an antipsychotic, possibly optimizing its agonist rather than its antagonist actions.<sup>10-13</sup> Finally, whereas D<sub>2</sub> antagonists are classically antiemetics and raise plasma prolactin levels, aripiprazole's partial agonist properties can be seen by its ability to do the opposite: namely, to cause nausea and even vomiting and also to lower plasma prolactin levels.<sup>1-5</sup>

Although clearly effective as an antipsychotic, some head-to-head studies<sup>4,5</sup> suggest that aripiprazole may be a less effective antipsychotic than some D<sub>2</sub> antagonists, such as olanzapine.<sup>4,5</sup> The fact that aripiprazole is an effective antipsychotic at all may be due to the fact that it is close to the silent antagonist section of the agonist spectrum (Figure),<sup>1</sup> and that it is also metabolized to an active metabolite that is a D<sub>2</sub> antagonist (known as DM1451) that may contribute to aripiprazole's clinical actions at steady state.<sup>9</sup>

Studies with several other DPAs<sup>1,6,7,14-16</sup> also suggest that these compounds may have less efficacy as antipsychotics than D<sub>2</sub> antagonists. This includes bifeprunox, a DPA that is probably even closer to the full agonist end of the spectrum than aripiprazole (Figure).<sup>1</sup> This compound was given a non-approval by the Food and Drug Administration, since it has a slow onset of action due to activating side effects, nausea and vomiting, no significant efficacy at high doses (eg, 40 mg/day), greater antipsychotic efficacy at lower doses (eg, ≤30 mg/day), but the efficacy at such doses is inferior to a D<sub>2</sub> antagonist (risperidone).<sup>6</sup>

Other DPAs that have proven to be too close to the full agonist end of the spectrum to be useful as antipsychotics include aplindore (DAB452 or WAY13592), lisuride, terguride, and others. A novel DPA with D<sub>2</sub> and D<sub>3</sub> receptor partial agonist actions,<sup>1</sup> RGH188,<sup>14</sup> has reported

antipsychotic actions at low doses but not at high doses, consistent with the antipsychotic properties of other DPAs.<sup>7</sup>

Thus, DPAs can have antipsychotic efficacy, can be psychotomimetic and activating, or both, consistent with an intermediate position between silent antagonist and full agonist. While demonstrating antipsychotic actions, DPAs may exhibit an inverted U-shaped dose-response curve and somewhat less antipsychotic efficacy than D<sub>2</sub> antagonists.

## WHITHER THE DOPAMINE D<sub>2</sub> PARTIAL AGONISTS?

The unique pharmacologic properties of partial agonism may not be limited to antipsychotic actions. In fact, the best therapeutic targets for DPAs may not be as antipsychotics, given some limits to their antipsychotic actions, and unusual inverted U-shaped dosing in the antipsychotic range. Thus, aripiprazole has already been approved as adjunctive treatment for major depression, albeit at lower doses than used for schizophrenia or mania.<sup>10,11</sup> Although aripiprazole failed to show convincing efficacy in bipolar depression,<sup>12,13</sup> this may have been due to utilizing too high dosing in the trials, and to use as monotherapy rather than as augmentation of mood stabilizers.<sup>12,13</sup>

RGH188 also shows preclinical evidence of antidepressant action,<sup>15</sup> and may prove a useful adjunct or even first-line treatment for major depression, bipolar depression, and treatment-resistant depression. RGH188 also has an active metabolite with a long half-life, and thus has the potential of being developed into an oral "depot" biweekly treatment.<sup>16</sup>

Other potential novel clinical uses for DPAs include their potential for modifying the dopamine system in various forms of substance abuse, or combining them with D<sub>2</sub> antagonists to reduce side effects. The latter has been reported for aripiprazole augmentation of risperidone to reduce hyperprolactinemia,<sup>17</sup> and for aripiprazole augmentation of clozapine to reduce weight gain and metabolic side effects.<sup>18</sup> Also, for bifeprunox and other DPAs, such as SLV 313 and 314, with similar high degrees of "fullness" to their partial D<sub>2</sub> agonism, combination with a D<sub>2</sub> antagonist, such as risperidone, may not only reduce the hyperprolactinemia of risperidone, but simultaneously reduce the activation, nausea, and vomiting of bifeprunox, rendering dosing of the combination faster and more tolerable.

## CONCLUSION

DPA's represent an important therapeutic innovation in psychopharmacology, and are distinct from D<sub>2</sub> antagonists. The most promising clinical applications of these agents may not be as antipsychotics, but in mood disorders and other novel clinical applications. **CNS**

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