



Aripiprazole, brexpiprazole, and cariprazine: Not all the same

Understanding the key differences among these agents can help inform treatment decisions

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Disclosure

In the past 12 months, Dr. Citrome has served as a consultant to Acadia, Alkermes, Allergan, Intra-Cellular Therapeutics, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, and Vanda; and a speaker for Acadia, Alkermes, Allergan, Janssen, Lundbeck, Merck, Neurocrine, Otsuka, Pfizer, Shire, Sunovion, Takeda, Teva, and Vanda.

Aripiprazole, brexpiprazole, and cariprazine are dopamine receptor partial agonists, and on the surface, they appear similar. However, there are key differences in terms of available indications, formulations, pharmacodynamics, pharmacokinetics, dosing, drug interactions, tolerability, and other factors related to successful use.¹ This review will cover the main points that the knowledgeable clinician will need to be mindful of when prescribing these agents.

Aripiprazole

Aripiprazole was launched in the United States in 2002² as the first dopamine receptor partial agonist approved for the treatment of schizophrenia; it later received additional indications for adults with manic or mixed episodes associated with bipolar I disorder and the maintenance treatment of bipolar I disorder, as well as for the adjunctive treatment of major depressive disorder (MDD). Pediatric indications include schizophrenia, acute treatment of manic or mixed episodes associated with bipolar I disorder, irritability associated with autistic disorder, and Tourette's disorder.

Several formulations also became available, including a short-acting injection indicated for agitation associated with schizophrenia or bipolar mania, and oral disintegrating tablets and an oral solution that could substitute for the regular tablet. Presently the medication has gone "generic," and not all formulations are being manufactured. The long-acting formulations of aripiprazole (aripiprazole monohydrate and aripiprazole lauroxil) are considered different products, each with its own product insert, with indications that are more limited in scope than for the oral forms.^{3,4}

continued





Dopamine receptor partial agonists

Clinical Point

Aripiprazole has very high binding affinities to dopamine D2, dopamine D3, and serotonin 5-HT2B receptors

Although dopamine D2 receptor partial agonism is a relevant mechanism of action, partial agonist activity at serotonin 5-HT1A receptors and antagonist activity at 5-HT2A receptors also play a role.² Actions at receptors other than dopamine D2, serotonin 5-HT1A, and serotonin 5-HT2A may explain some of the other clinical effects of aripiprazole. In terms of binding, aripiprazole has very high binding affinities (Ki) to dopamine D2 (0.34 nM), dopamine D3 (0.8 nM), and serotonin 5-HT2B (0.36 nM) receptors, and high binding affinities to serotonin 5-HT1A (1.7 nM) and serotonin 5-HT2A (3.4 nM) receptors.

Dosage recommendations for adults with schizophrenia suggest a starting and maintenance dose of 10 to 15 mg/d.² Although the maximum dose is 30 mg/d, there is no evidence that doses >15 mg/d are superior to lower doses.⁵ In adolescents with schizophrenia, the product label recommends a starting dose of 2 mg/d, a maintenance dose of 10 mg/d, and a maximum dose of 30 mg/d. Recommendations for dosing in bipolar mania are similar. Dosing for the other indications is lower.

Efficacy in schizophrenia can be quantified using number needed to treat (NNT) for response vs placebo. The NNT answers the question "How many patients need to be randomized to aripiprazole vs placebo before expecting to encounter one additional responder?"⁶ From the 4 positive pivotal short-term acute schizophrenia trials for aripiprazole in adults,⁷⁻¹⁰ using the definition of response as a $\geq 30\%$ decrease in the Positive and Negative Syndrome Scale (PANSS) total score or a Clinical Global Impressions-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved), and pooling the data for aripiprazole doses 10 to 30 mg/d, response rates were 38% for aripiprazole vs 24% for placebo, resulting in a NNT of 8 (95% confidence interval [CI] 6 to 13).

From the 4 positive pivotal short-term acute bipolar mania trials for aripiprazole monotherapy in adults¹¹⁻¹⁴ using the definition of response as a $\geq 50\%$ decrease in the Young Mania Rating Scale (YMRS) total score, and pooling the data for aripiprazole doses 15 to 30 mg/d, response rates were

47% for aripiprazole vs 31% for placebo, resulting in a NNT of 7 (95% CI 5 to 11).¹ Similar results were observed in the adjunctive aripiprazole acute bipolar mania trial¹⁵ where the NNT for response was also 7.¹

From the 2 positive pivotal short-term acute MDD trials for aripiprazole,^{16,17} using the definition of response as a $\geq 50\%$ decrease in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, and pooling the data (aripiprazole flexibly dosed 2 to 20 mg/d, with a median dose of 10 mg/d), response rates were 33% for aripiprazole vs 20% for placebo, resulting in a NNT of 8 (95% CI 6 to 17). After including a third trial not described in product labeling,¹⁸ the NNT became a more robust 7 (95% CI 5 to 11).¹

The most commonly encountered adverse events (incidence $\geq 5\%$ and at least twice the rate of placebo) in the pivotal trials were akathisia (schizophrenia); akathisia, sedation, restlessness, tremor, and extrapyramidal disorder (bipolar mania, monotherapy); akathisia, insomnia, and extrapyramidal disorder (bipolar mania, adjunctive therapy); akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision (MDD); and nausea (short-acting IM formulation). *Table 1*¹ (page 27) summarizes the tolerability information regarding rate of discontinuation due to adverse events (an overall indicator of tolerability), and the incidence of the most common adverse event, together with the calculated number needed to harm (NNH). Rates of discontinuation because of an adverse event were not higher for active medication vs placebo for the schizophrenia studies, suggesting excellent overall tolerability; for the other disease states, NNH values ranged from 17 (adjunctive use of aripiprazole for bipolar mania) to 100 (aripiprazole monotherapy for bipolar mania), representing reasonable overall tolerability for these indications.

Brexpiprazole

Brexpiprazole was launched in the United States in 2015 for 2 indications: schizophrenia and the adjunctive treatment of MDD, both in adults.¹⁹ In terms of binding, brexpiprazole has very high binding affinities



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Table 1

Safety and tolerability of aripiprazole, brexpiprazole, and cariprazine

	% of patients discontinuing because of an adverse event			% of patients with the most commonly encountered adverse event			
	Active medication	Placebo	NNH	Adverse event	Active medication	Placebo	NNH
Aripiprazole							
Schizophrenia	7%	9%	NA	Akathisia	8%	4%	25
Bipolar mania	11%	10%	100	Akathisia	13%	4%	12
Bipolar mania (adjunct)	12%	6%	17	Akathisia	19%	5%	8
Major depressive disorder (adjunct)	6%	2%	25	Akathisia	25%	4%	5
Brexpiprazole							
Schizophrenia	8%	15%	NA	Weight increased	4%	2%	50
Major depressive disorder (adjunct)	3%	1%	50	Akathisia	9%	2%	15
Cariprazine							
Schizophrenia (pooled 1.5 to 6 mg/d)	9%	12%	NA	Extrapyramidal	17%	8%	12
Bipolar mania (3 to 6 mg/d)	12%	7%	20	Extrapyramidal	26%	12%	8

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NA: not applicable as the rate observed with medication is lower than that observed with placebo; NNH: number needed to harm

Clinical Point

The rate of titration for brexpiprazole depends on the disease state being treated

to serotonin 5-HT_{1A} (0.12 nM), adrenergic α _{1B} (0.17 nM), dopamine D₂ (0.30 nM), serotonin 5-HT_{2A} (0.47 nM), and adrenergic α _{2C} (0.59 nM) receptors, and high binding affinities to dopamine D₃ (1.1 nM), serotonin 5-HT_{2B} (1.9 nM), adrenergic α _{1D} (2.6 nM), serotonin 5-HT₇ (3.7 nM), and adrenergic α _{1A} (3.8 nM) receptors.

The 1-mg/d starting dose for brexpiprazole is lower than the recommended dose range of 2 to 4 mg/d for schizophrenia or the recommended dose of 2 mg/d for MDD.¹⁹ Thus brexpiprazole requires titration. The recommended rate of titration depends on the disease state being treated. For schizophrenia, the recommended titration schedule is to increase the dose to 2 mg/d on Day 5 through Day 7, then to 4 mg/d (the maximum recommended dose) on Day 8 based on the patient's clinical response and tolerability. For MDD, there is the option of starting at 0.5 mg/d and the titration process is slower, with dosage increases occurring at

weekly intervals, and with a maximum dose of 3 mg/d.

Using the identical definition of response in persons with schizophrenia as for the aripiprazole data described above, pooling together all the available data for the recommended target dose of brexpiprazole for schizophrenia (2 to 4 mg/d) from the 2 studies listed in the product label,^{20,21} the percentage of responders was 46%, compared with 31% for the pooled placebo groups, yielding a NNT of 7 (95% CI 5 to 12).²²

For MDD, using the definition of response as a \geq 50% decrease in MADRS total score, and pooling the results for brexpiprazole 1, 2, and 3 mg/d from the 2 pivotal trials,^{23,24} 23.2% of the patients receiving brexpiprazole were responders, vs 14.5% for placebo, yielding a NNT of 12 (95% CI 8 to 26).²² Including the 1.5-mg/d dose arm and the placebo arm from the phase II study for which results are also available but not included in product labelling, the NNT becomes a slightly more



Dopamine receptor partial agonists

Clinical Point

The starting dose of cariprazine for schizophrenia can be therapeutic

Table 2

Number needed to harm vs placebo for weight gain, somnolence, and akathisia

Antipsychotic	NNH for weight gain $\geq 7\%$			NNH for somnolence adverse events		
	Schizophrenia	Bipolar mania	Adjunctive for MDD	Schizophrenia	Bipolar mania	Adjunctive for MDD
Aripiprazole	21	ND	22	20	20	50
Brexpiprazole	17		52	50		34
Cariprazine (to 6 mg/d)	34	ND		100	25	

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MDD: major depressive disorder; ND: no difference or rate with medication is lower than rate with placebo; NNH: number needed to harm

robust 11 (95% CI 8 to 20).²² Although the magnitude of the NNT effect size is stronger for aripiprazole than for brexpiprazole, the 95% CIs do overlap.

The most commonly encountered adverse event in the short-term trials in schizophrenia (incidence $\geq 4\%$ and at least twice the rate of placebo) was increased weight. The most commonly encountered adverse events in the short-term trials in MDD (incidence $\geq 5\%$ and at least twice the rate of placebo) were increased weight and akathisia. Rates of discontinuation because of an adverse event were not higher for active medication vs placebo for the schizophrenia studies, suggesting excellent overall tolerability, and for MDD the NNH vs placebo on discontinuation because of an adverse event was 50, representing reasonable overall tolerability for this indication as well (Table 1,¹ page 27).

Cariprazine

Cariprazine was launched in the United States in 2015 for 2 indications: schizophrenia, and the acute treatment of manic or mixed episodes associated with bipolar I disorder, both in adults.²⁵ In terms of binding, cariprazine has very high binding affinities to dopamine D3 (0.085 nM), dopamine D2L (0.49 nM), serotonin 5-HT2B (0.58 nM), and dopamine D2S (0.69 nM) receptors, and high binding affinity to serotonin 5-HT1A (2.6 nM) receptors. Cariprazine forms 2 major metabolites, desmethyl cariprazine and didesmethyl cariprazine, that have *in*

vitro receptor binding profiles similar to the parent drug. This latter metabolite, didesmethyl cariprazine, has a half-life of 1 to 3 weeks, and is the active moiety responsible for the majority of cariprazine's effect when in steady state. Thus, following discontinuation of cariprazine, the decline in plasma concentrations of active drug will be slow.

The starting dose for cariprazine for schizophrenia, 1.5 mg/d, can be therapeutic. The dosage can be increased to 3 mg/d on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5-mg or 3-mg increments to a maximum dose of 6 mg/d. For the treatment of bipolar mania, cariprazine will need to be titrated from the starting dose of 1.5 mg/d to the recommended target dose range of 3 to 6 mg/d; this can be done on Day 2. Cariprazine has been tested in clinical trials at higher doses; however, doses that exceed 6 mg/d did not confer significant additional benefit.²⁵

A more conservative definition of response was used in the reporting of the cariprazine acute schizophrenia studies. This was simply a $\geq 30\%$ decrease in the PANSS total score, and did not include the option of including patients who scored a 1 or 2 on the CGI-I. For pooled doses of cariprazine 1.5 to 6 mg/d,²⁶⁻²⁸ the percentage of responders was 31%, compared with 21% for the pooled placebo groups, yielding a NNT of 10 (95% CI 7 to 18).¹ Although the magnitude of the NNT effect size is weaker for cariprazine than the other dopamine receptor partial agonists, the 95%

NNH for akathisia adverse events

	Schizophrenia	Bipolar mania	Adjunctive for MDD
	25	12	5
	112		15
	15	7	

CI overlaps with that of aripiprazole and brexpiprazole. An appropriately designed head-to-head trial would be necessary to directly test noninferiority.

Pooling the data from the 3 pivotal short-term acute bipolar mania trials for cariprazine monotherapy in adults²⁹⁻³¹ and using the definition of response as a $\geq 50\%$ decrease in the YMRS total score for the recommended target dose of 3 to 6 mg/d, the percentage of responders was 57%, compared with 36% for the pooled placebo groups, yielding a NNT of 5 (95% CI 4 to 8).¹ The magnitude of the NNT effect size is stronger for cariprazine than for aripiprazole, but the 95% CIs overlap.

The most commonly encountered adverse events in the short-term trials (incidence $\geq 5\%$ and at least twice the rate of placebo) were extrapyramidal symptoms and akathisia (schizophrenia); and extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness (bipolar mania). In the schizophrenia studies, rates of discontinuation because of an adverse event were not higher for active medication vs placebo, suggesting excellent overall tolerability, and for bipolar disorder the NNH vs placebo on discontinuation because of an adverse event was 20, representing reasonable overall tolerability for this indication as well (Table 1,¹ page 27).

Differences to consider

Indications. Although all 3 medications are approved for the treatment of schizophrenia,

both aripiprazole and brexpiprazole are also approved for adjunctive treatment of MDD, and both aripiprazole and cariprazine are also approved for acute treatment of manic or mixed episodes associated with bipolar I disorder. In addition, aripiprazole is approved for a number of different disease states in pediatric patients. Aripiprazole has also been approved in a number of different formulations (oral and IM), but brexpiprazole and cariprazine are presently available only as oral pills (tablets for brexpiprazole, capsules for cariprazine).

Contraindications. All 3 agents are contraindicated in patients with a known hypersensitivity reaction to the product. All 3 also have a “black-box” warning for increased mortality in geriatric patients with dementia-related psychosis, a warning that is found in all antipsychotic medication labels. Additional black-box warnings are included regarding suicidality in the product labels of aripiprazole and brexpiprazole by virtue of their approval for the treatment of MDD.

Pharmacodynamics. All 3 agents describe a similar mechanism of action in their respective product labels: “efficacy ... could be mediated through a combination of partial agonist activity at central dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at serotonin 5-HT2A receptors.”^{2,19,25}

However, binding affinities differ substantially among the agents (for example, cariprazine has only moderate binding affinity at serotonin 5-HT2A receptors [18.8 nM]), and differences also exist in terms of intrinsic activity at the receptors where partial agonism is operative. Compared with aripiprazole, brexpiprazole has lower intrinsic activity at the dopamine D2 receptor (and thus is expected to cause less akathisia), and has an approximately 10-fold higher affinity for serotonin 5-HT1A and 5-HT2A receptors, also potentially enhancing tolerability and perhaps anxiolytic activity.^{32,33} When cariprazine was compared with aripiprazole in functional assays for dopamine D2 and D3 receptors, similar D2 and higher D3 antagonist-partial agonist affinity and

Clinical Point

In addition to schizophrenia, aripiprazole and brexpiprazole are also approved for adjunctive treatment of MDD



Dopamine receptor partial agonists

Clinical Point

Compared with aripiprazole, brexpiprazole has lower intrinsic activity at the dopamine D2 receptor

Table 3

Likelihood to be helped or harmed

Disease state/medication	NNT for response ^a	NNH for discontinuation because of an adverse event	LHH for response vs discontinuation because of an adverse event	NNH for weight gain ≥7%
Schizophrenia				
Aripiprazole	8	ND	NA	21
Brexpiprazole	7	ND	NA	17
Cariprazine (to 6 mg/d)	10	ND	NA	34
Bipolar mania				
Aripiprazole	7	100	14	ND
Cariprazine (to 6 mg/d)	5	20	4	ND
Major depressive disorder				
Aripiprazole	7	25	3.6	22
Brexpiprazole	11	50	4.5	52

^aResponse for schizophrenia defined as a ≥30% decrease in the Positive and Negative Syndrome Scale total score or a Clinical Global Impressions-Improvement score of 1 (very much improved) or 2 (much improved) for aripiprazole or brexpiprazole, or a ≥30% decrease in the Positive and Negative Syndrome Scale total score for cariprazine; response for bipolar mania or major depressive disorder defined as a ≥50% reduction in the Young Mania Rating Scale or Montgomery-Åsberg Depression Rating Scale, respectively.

a 3- to 10-fold greater D3 vs D2 selectivity was observed for cariprazine.³⁴ Whether specifically targeting the dopamine D3 receptor over the dopamine D2 receptor is clinically advantageous remains unknown, but in preclinical studies, dopamine D3-preferring agents may exert pro-cognitive effects.³⁵⁻³⁷ All 3 agents have only moderate binding affinities to histamine H1 receptors, thus sedation should not be prominent for any of them. None of the 3 agents have appreciable binding at muscarinic receptors, thus adverse effects related to antimuscarinic activity should not be present as well.

Schizophrenia is a heterogeneous disorder. We know from clinical practice that patients respond differently to specific antipsychotics. Having different pharmacodynamic “fingerprints” to choose from allows for flexibility in treatment. Moreover, dopamine receptor partial agonists provide an alternative to the array of dopamine receptor antagonists, such as the other second-generation antipsychotics and all first-generation antipsychotics.

Dosing. Although all 3 agents are dosed once daily, only for aripiprazole is the recommended starting dose the same as the

recommended maintenance dose in adults with schizophrenia or bipolar mania. Although the starting dose for cariprazine for schizophrenia can be therapeutic (1.5 mg/d), for the treatment of bipolar mania, cariprazine will need to be titrated from the starting dose of 1.5 mg/d to the recommended target dose range of 3 to 6 mg/d.

Half-life. Aripiprazole and brexpiprazole share a similar elimination half-life: approximately 75 hours and 94 hours for aripiprazole and its active metabolite dehydro-aripiprazole, respectively, and 91 hours and 86 hours for brexpiprazole and its major metabolite, DM-3411 (inactive), respectively. Cariprazine is strikingly different, with an elimination half-life of 2 to 4 days, and approximately 1 to 3 weeks for its active metabolite didesmethyl cariprazine.

Drug interactions. Both aripiprazole and brexpiprazole are metabolized via cytochrome P450 (CYP) 2D6 and CYP3A4, and thus the dose may need to be adjusted in the presence of CYP2D6 inhibitors or CYP3A4 inhibitors/inducers; with inhibitors, the dose is decreased by half or more, and with inducers, the dose is doubled. In

LHH for response vs weight gain $\geq 7\%$	NNH for somnolence adverse events	LHH for response vs somnolence adverse events	NNH for akathisia adverse events	LHH for response vs akathisia adverse events
2.6	20	2.5	25	3.1
2.4	50	7.1	112	16
3.4	100	10	15	1.5
NA	20	2.9	12	1.7
NA	25	5	7	1.4
3.1	50	7.1	5	0.7
4.7	34	3.1	15	1.4

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LHH: likelihood to be helped or harmed; NA: LHH not interpretable because the rate of the harm observed with medication is lower than that observed with placebo; ND: no difference or rate with medication is lower than rate with placebo; NNH: number needed to harm; NNT: number needed to treat

Clinical Point

In schizophrenia studies of all 3 agents, rates of discontinuation due to adverse events were not higher than for placebo

contrast, cariprazine is primarily metabolized by CYP3A4 and thus potential drug-drug interactions are primarily focused on CYP3A4 inhibitors (decrease cariprazine dose by half) and inducers (co-prescribing of cariprazine with a CYP3A4 inducer is not recommended).

Tolerability. For all 3 agents, rates of discontinuation because of an adverse event were not higher for active medication vs placebo for the schizophrenia studies, suggesting excellent overall tolerability.^{2,19,25} For the other disease states, NNH values ranged from 17 (adjunctive use of aripiprazole for bipolar mania) to 100 (aripiprazole monotherapy for bipolar mania), representing reasonable overall tolerability. For the most commonly encountered adverse event for each medication, the NNH values ranged from 5 (akathisia for aripiprazole for adjunctive use in MDD) to 50 (increased weight for brexpiprazole for schizophrenia). Of special interest are the adverse events of weight gain $\geq 7\%$ from baseline, somnolence adverse events, and akathisia adverse events; the NNH values vs placebo for these are listed in *Table 2*¹ (page 28). Pragmatically, NNH values < 10

are likely to be more clinically relevant. For aripiprazole, brexpiprazole, and cariprazine for the treatment of schizophrenia, none of the NNH values for weight gain, somnolence, or akathisia were < 10 ; however, this was not the case for the mood disorders, where in general, akathisia was more frequently observed for each of the agents. For the indication of schizophrenia, the rank order for propensity for weight gain appears to be brexpiprazole $>$ aripiprazole $>$ cariprazine, the propensity for somnolence aripiprazole $>$ brexpiprazole $>$ cariprazine, and the propensity for akathisia cariprazine $>$ aripiprazole $>$ brexpiprazole; however, this is by indirect comparison, and appropriately designed head-to-head clinical trials will be necessary in order to accurately assess these potential differences.

Because of the partial agonist activity at the dopamine D2 receptor, aripiprazole, brexpiprazole, and cariprazine are less likely to cause hyperprolactinemia than other first-line first- or second-generation antipsychotics. Other differentiating features of the dopamine receptor partial agonists compared with other choices include a relative lack of effect on the QT interval.³⁸

continued



Dopamine receptor partial agonists

Clinical Point

Aripiprazole, brexpiprazole, and cariprazine are less likely to cause hyperprolactinemia than other first-line antipsychotics

Related Resources

- Citrome L. A review of the pharmacology, efficacy and tolerability of recently approved and upcoming oral antipsychotics: an evidence-based medicine approach. *CNS Drugs*. 2013;27(11):879-911.
- Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract*. 2013;67(5):407-411.
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Drug Brand Names

Aripiprazole • Abilify	Brexpiprazole • Rexulti
Aripiprazole lauroxil	Cariprazine • Vraylar
• Aristada	
Aripiprazole monohydrate	
• Abilify Maintena	

In general, as predicted by their relatively lower binding affinities to histamine H1 receptors, the dopamine receptor partial agonists are not especially sedating.³⁹

Likelihood to be helped or harmed

The concept of likelihood to be helped or harmed (LHH) can be useful to assess benefit vs risk, provided you select a relevant harm to contrast with the expected benefit.⁴⁰ *Table 3¹ (page 30)* provides the NNT for response, NNH for discontinuation because of an adverse event (where applicable), the NNHs for weight gain $\geq 7\%$, somnolence adverse events, and akathisia adverse events, together with the calculated LHH (where applicable). With the exception of aripiprazole for the treatment of MDD when comparing response vs akathisia, all LHH values are >1.0 , and thus the benefit (response) would be encountered more often than the harm. When LHH values are ≥ 10 , this can be interpreted that one would

encounter a response at least 10 times more often than the adverse event of interest. This was observed for brexpiprazole for the treatment of schizophrenia when comparing response vs akathisia, for cariprazine for schizophrenia when comparing response vs somnolence, for aripiprazole for bipolar mania when comparing response vs discontinuation because of an adverse event, and for cariprazine for bipolar mania when comparing response vs somnolence.

Beyond acute studies

When treating patients with schizophrenia, delaying time to relapse is a main goal. In placebo-controlled randomized withdrawal studies of oral aripiprazole, brexpiprazole, and cariprazine in patients with schizophrenia, observed relapse rates vs placebo were reported, allowing the calculation of NNT vs placebo for the avoidance of relapse.⁴¹⁻⁴⁴ These NNT values were similar and ranged from 4 to 5. For aripiprazole, relapse rates vs placebo in the 26-week study were 34% vs 57%, resulting in a NNT of 5 (95% CI 3 to 9); brexpiprazole, 52-week study, 13.5% vs 38.5%, NNT of 4 (95% CI 3 to 8); and cariprazine, 72-week study, 25% vs 47.5%, NNT of 5 (95% CI 3 to 11). In addition, cariprazine, 4.5 mg/d, has been directly compared with risperidone, 4 mg/d, in a 26-week double-blind study in non-geriatric adult patients with schizophrenia and predominant negative symptoms for at least 6 months.⁴⁵ Cariprazine was superior to risperidone on the PANSS–Negative Factor Score, and response to treatment (decrease $\geq 20\%$ in PANSS–Negative Factor Score) was achieved by more patients treated with cariprazine by 26 weeks than those treated with risperidone (69% vs 58%, NNT 9 [95% CI 5 to 44]).

Bottom Line

Although aripiprazole, brexpiprazole, and cariprazine are all dopamine receptor partial agonists with demonstrated efficacy in psychiatric disorders, they differ in terms of available formulations, indications, pharmacodynamics, pharmacokinetics, titration requirements, and tolerability. Careful consideration of these factors can increase the likelihood of successful treatment.

Caveats

The harms discussed in this article are primarily from acute studies and do not reflect effects that can take time to develop, such as tardive dyskinesia, the long-term accumulation of body weight, and the development of insulin resistance/type 2 diabetes mellitus.⁴⁰ The data presented are from carefully conducted registration trials that enrolled subjects who fulfilled restrictive inclusion/exclusion criteria. Such patients may differ from those encountered in routine clinical practice. Keep in mind that adverse events may differ in terms of impact and may not be clinically relevant if the adverse event is mild, time-limited, or easily managed. Moreover, different patients carry different propensities to experience different adverse events or to achieve a therapeutic response.

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Clinical Point

The harms discussed in this article do not reflect effects that can take time to develop, such as insulin resistance



Dopamine receptor partial agonists

Clinical Point

Adverse effects that are mild, time-limited, or easily managed may not be clinically relevant

Dopamine receptor partial agonists continued from page 33

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