The ABC’s of dopamine receptor partial agonists – aripiprazole, brexpiprazole and cariprazine: the 15-min challenge to sort these agents out

In prior 15-min challenges, we tackled the three new anorectic agents (1) and three new antidepressant medications (2). This time we will sort out three dopamine receptor partial agonists, one old (aripiprazole, commercialised in 2002, and now available as a generic medication) and two new (brexpiprazole and cariprazine, both commercialised in 2015) that have been approved for the treatment of schizophrenia as well as other disorders. How are they similar? How are they different?

Table 1 is a list of pertinent information regarding indications, contraindications, bolded boxed warnings, dosage recommendations, drug interactions and most commonly encountered adverse effects, taken directly from the product labels for each of these agents (3–5).

The approved indications differ. Although all three are approved for the treatment of schizophrenia, both aripiprazole and brexpiprazole are also approved for adjunctive treatment of major depressive disorder, 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 improved for a number of different disease states in the paediatric population. Aripiprazole is also available as a short-acting intramuscular injection for the management of agitation associated with schizophrenia or bipolar mania. A long-acting injectable formulation of aripiprazole for the treatment of schizophrenia is also marketed, using a different product label (6).

Although the mechanisms of action as listed are similar, the three agents differ in terms of their pharmacodynamic profiles (Table 2). Compared with aripiprazole, brexpiprazole has lower intrinsic activity at the dopamine D2 receptor and has an approximately 10-fold higher affinity for serotonin 5-HT1A and 5-HT2A receptors, potentially enhancing tolerability (7–9). 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 a 3- to 10-fold greater D3 vs. D2 selectivity was observed for cariprazine (10). As noted in an earlier review (11), whether targeting the dopamine D3 receptor over the dopamine D2 receptor is clinically advantageous remains unknown but theoretically dopamine D3 preferring agents may exert pro-cognitive effects.

Contraindications are similar, as are the bolded boxed warnings as generally found in all antipsychotic drug labels. Additional warnings are included regarding suicidality in the product labels of aripiprazole and brexpiprazole by virtue of their approval for the treatment of major depressive disorder.

Although all three agents are dosed once daily, the starting dose for brexpiprazole (1 mg/day) is lower than the recommended dose range of 2–4 mg/day for schizophrenia or the recommended dose of 2 mg/day for major depressive disorder. Thus, brexpiprazole will require titration. The recommended rate of titration depends on the disease state being treated and for schizophrenia the recommended titration schedule is to increase to 2 mg/day on Day 5 to Day 7, then to 4 mg/day on Day 8 based on the patient’s clinical response and tolerability. For major depressive disorder, titration of brexpiprazole is slower, with dosage increases occurring at weekly intervals. In contrast, the starting dose for aripiprazole can be therapeutic, as can the starting dose for cariprazine for schizophrenia (1.5 mg/day). For the treatment of bipolar mania, cariprazine will need to be titrated from the starting dose of 1.5 mg/day to the recommended target dose range of 3–6 mg/day; this can be done on Day 2. Cariprazine has been tested in clinical trials at higher doses; however, doses that exceed 6 mg/day did not confer significant additional benefit (5). Of note, an important metabolite of cariprazine, didesmethyl cariprazine, has a half-life of 1–3 weeks, thus following discontinuation of cariprazine the decline in plasma concentrations of active drug and metabolites will be slow.

Table 3 outlines the efficacy information from the pivotal acute short-term trials as extracted from product labelling (3–5) for the different indications (schizophrenia, bipolar mania and adjunctive use in major depressive disorder). Additional information can be found in the corresponding published or presented studies for aripiprazole (12–22), brexpiprazole (23–26) and cariprazine (27–32).

More intuitive than the comparisons of effect size using placebo-subtracted differences in least mean squares is the number needed to treat (NNT) vs. placebo for the outcome of response (33). From the four positive pivotal short-term acute schizophrenia trials for aripiprazole in adults (12–15), using the
Table 1 Overview and indications, contraindications, bolded boxed warnings, adult dosage recommendations, drug interactions and most commonly encountered adverse effects in adults, taken from the highlights of prescribing information and section 12.1 (Mechanism of Action) from the product label (3–5)

| Generic name | Aripiprazole | Brexpiprazole | Cariprazine |
|--------------|--------------|---------------|-------------|
| US brand name | Abilify | Rexulti | Vraylar |
| Initial US approval | 2002 | 2015 | 2015 |
| Formulations available | Tablets, oral disintegrating tablets, oral solution, short-acting intramuscular injection. There is a long-acting intramuscular injection for schizophrenia that has its own product label. | Tablets | Capsules |
| Mechanism of action | The mechanism of action of aripiprazole in schizophrenia or bipolar mania is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors. Actions at receptors other than D2, 5-HT1A, and 5-HT2A may explain some of the other clinical effects of aripiprazole (e.g. the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic α1 receptors). | The mechanism of action of brexpiprazole in the treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors. | The mechanism of action of cariprazine in schizophrenia and bipolar I disorder is unknown. However, the efficacy of cariprazine 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. Cariprazine forms two major metabolites, desmethyl cariprazine and didesmethyl cariprazine that have in vitro receptor binding profiles similar to the parent drug. |
| Indications (with data included in Section 14. Clinical Studies) | Treatment of schizophrenia (adults and paediatrics); as monotherapy or as an adjunct to lithium or valproate in both the acute treatment of manic or mixed episodes associated with bipolar I disorder (adults and paediatrics) and the maintenance treatment of bipolar I disorder (adults); for the adjunctive treatment of major depressive disorder (adults); to treat irritability associated with autistic disorder (paediatrics); and for the treatment of Tourette’s disorder (paediatrics). The short-acting injection (9.75 mg) is indicated for agitation associated with schizophrenia or bipolar mania. | Treatment of schizophrenia (adults); acute treatment of manic or mixed episodes associated with bipolar I disorder (adults). | Treatment of schizophrenia (adults); acute treatment of manic or mixed episodes associated with bipolar I disorder (adults). |
| Contraindications | History of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis. | Known hypersensitivity to brexpiprazole or any of its components. Reactions have included rash, facial swelling, urticaria and anaphylaxis. | Known hypersensitivity to cariprazine. Reactions have ranged from rash, pruritus, urticaria and events suggestive of angioedema (e.g. swollen tongue, lip swelling, face oedema, pharyngeal oedema and swelling face). |
| Bolded boxed warnings | Increased mortality in elderly patients with dementia related psychosis. Suicidal thoughts and behaviours. | Increased mortality in elderly patients with dementia related psychosis. Suicidal thoughts and behaviours. | Increased mortality in elderly patients with dementia related psychosis. |
| Dosage: adults with schizophrenia | Starting dose 10–15 mg/day, recommended dose 10–15 mg/day, maximum dose 30 mg/day | Starting dose 1 mg/day, recommended dose range 2–4 mg/day, maximum dose 4 mg/day | Starting dose 1.5 mg/day, recommended dose range 1.5–6 mg/day |
The definition of response as a 30% or greater 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 10–30 mg/day, response rates were 38% for aripiprazole vs. 24% for placebo, resulting in a NNT of 8 (95% CI 6–13). Using the identical definition of response, pooling together all the available data for the recommended target dose of brexpiprazole for schizophrenia (2–4 mg/day) from the two studies listed in the product label (23,24), the percentage of responders was 46%, compared with 31% for the pooled placebo groups, yielding a NNT of 7 (95% CI 5–12) (34). A more conservative definition of response was used in the reporting for the cariprazine studies and was simply a 30% or greater decrease in the PANSS total score and did not include the option of including persons who scored a 1 or 2 on the CGI-I. For pooled doses of cariprazine 1.5–6 mg/day (27–29), the percentage of responders was 31%, compared with 21% for the pooled placebo groups, yielding a NNT of 10 (95% CI 7–18). Although the magnitude of the NNT effect size is weaker for cariprazine, the 95% CIs overlap with that for aripiprazole and brexpiprazole (Figure 1). An appropriately designed head-to-head trial would be necessary to directly test non-inferiority.

From the four positive pivotal short-term acute bipolar mania trials for aripiprazole monotherapy in adults (16–19), using the definition of response as a 50% or greater decrease in the Young Mania Rating Scale (YMRS) total score, and pooling the data for aripiprazole doses 15–30 mg/day, response rates were 47% for aripiprazole vs. 31% for placebo, resulting in a NNT of 7 (95% CI 5–11). Similar results are observed in the adjunctive aripiprazole acute bipolar mania trial (20) where the NNT for response was also 7. Using the identical definition of response, pooling together all the available data for the recommended target dose of cariprazine for bipolar mania (3–6 mg/day) from the three studies listed in product labelling (30–32), the percentage of responders was 57%, compared with 36% for the pooled placebo groups, yielding a NNT of 5 (95% CI 4–8). The magnitude of the NNT effect size is stronger for cariprazine; however, the 95% CI overlaps with that for aripiprazole.
From the two positive pivotal short-term acute major depressive disorder trials for aripiprazole (21,22), using the definition of response as a 50% or greater decrease in the Montgomery–Asberg Depression Rating Scale (MADRS) total score, and pooling the data (aripiprazole flexibly dosed 2–20 mg/day, with a median dose of 10 mg/day), response rates were 33% for aripiprazole vs. 20% for placebo, resulting in a NNT of 8 (95% CI 6–17). When including a third trial not described in product labelling (35), the NNT is strengthened to a more robust 7 (95% CI 5–11). When the results for brexpiprazole 1, 2 and 3 mg from the two pivotal trials are pooled together (25,26), 23.2% of the patients receiving brexpiprazole were responders, vs. 14.5% for placebo, yielding a NNT of 12 (95% CI 8–26) (34). Inclusion of the 1.5 mg 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 robust 11 (95% CI 8–20) (34). Although the magnitude of the NNT effect size is stronger for aripiprazole than for brexpiprazole, the 95% CIs do overlap.

Table 1 includes a summary of the most commonly encountered adverse effects in adults. Table 4 summarises the safety and tolerability information regarding rate of discontinuation because of adverse events, 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; however, for the other disease states, NNH vs. placebo for discontinuation because of an adverse event ranged from 17 (adjunctive use of aripiprazole for

| Table 2 Pharmacodynamic profiles: in vitro binding affinities for human receptors (3–5, 7–9) |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Very high binding affinities (subnanomolar – Ki < 1 nM) | Very high binding affinities (subnanomolar – Ki < 1 nM) | Very high binding affinities (subnanomolar – Ki < 1 nM) |
| Very high binding affinities (subnanomolar – Ki < 1 nM) | Very high binding affinities (subnanomolar – Ki < 1 nM) | Very high binding affinities (subnanomolar – Ki < 1 nM) |
| Moderate binding affinities (Ki values between 5 and 100 nM) | Moderate binding affinities (Ki values between 5 and 100 nM) | Moderate binding affinities (Ki values between 5 and 100 nM) |
| Weak binding affinities | Weak binding affinities | Weak binding affinities |

In case of conflicting information for aripiprazole, Ki values taken preferentially from the most current information: product labelling (3), then from (8). *Partial agonist at these receptors.
### Table 3  Acute efficacy in adults in placebo-controlled randomised trials as extracted from product labelling (3–5)

| Condition                        | Aripiprazole vs. placebo | Brexpiprazole vs. placebo | Cariprazine vs. placebo |
|----------------------------------|--------------------------|---------------------------|-------------------------|
| **Schizophrenia**; placebo-subtracted differences in least-squares mean change from baseline (95% CI) on the PANSS | Four positive short-term (4-week and 6-week) trials: | Two short-term (6-week) trials: | Three short-term (6-week) trials: |
| (1) 15 mg/day:                  | −12.6 (−18.9, −6.2)     | 2 mg/day: −8.7 (−13.1, −4.4) | 1.5 mg/day: −7.6 (−11.8, −3.3) |
| 30 mg/day:                     | −8.5 (−14.8, −2.1)      | 4 mg/day: −7.6 (−12.0, −3.1) | 3 mg/day: −8.8 (−13.1, −4.6) |
| (2) 20 mg/day:                  | −9.6 (−15.4, −3.8)      | 2 mg/day: −3.1 (−7.2, 1.1)   | 4.5 mg/day: −10.4 (−14.6, −6.2) |
| 30 mg/day:                     | −9.0 (−14.8, −3.1)      | 4 mg/day: −6.5 (−10.6, −2.4) | 3 mg/day: −6.0 (−10.1, −1.9) |
| (3) 10 mg/day:                  | −12.7 (−19.0, −6.4)     |                         | 6 mg/day: −8.8 (−12.9, −4.7) |
| 15 mg/day:                     | −9.4 (−15.7, −3.1)      |                         | (3) 3–6 mg/day: −6.8 (−11.3, −2.4) |
| 20 mg/day:                     | −12.1 (−18.5, −5.7)     |                         | 6–9 mg/day: −9.9 (−14.5, −5.3) |
| (4) 2 mg/day:                   | −2.9 (−8.3, 2.5)        |                         |                         |
| 5 mg/day:                      | −5.2 (−10.7, 0.2)       |                         |                         |
| 10 mg/day:                     | −5.9 (−11.3, −0.6)      |                         |                         |
| **Bipolar mania**; placebo-subtracted differences in least-squares mean change from baseline (95% CI) on the YMRS | Four positive short-term (3-week) trials: | Not applicable | Three short-term (3-week) trials: |
| (1) 30–15 mg/day:              | −5.3 (−7.9, −2.8)       |                         | (1) 3–6 mg/day: −6.1 (−8.4, −3.8) |
| (2) 30–15 mg/day:              | −4.8 (−7.8, −1.8)       |                         | 6–12 mg/day: −5.9 (−8.2, −3.6) |
| (3) 15–30 mg/day:              | −3.6 (−5.8, −1.5)       |                         | (2) 3–12 mg/day: −6.1 (−8.9, −3.3) |
| (4) 15–30 mg/day:              | −2.3 (−4.4, −0.1)       |                         | (3) 3–12 mg/day: −4.3 (−6.7, −1.9) |
| Adjunctive 6-week study with 15–30 mg/day plus lithium or valproate: | −2.6 (−4.3, −1.0)      |                         |                         |
| **Major depressive disorder (adjunct); placebo-subtracted differences in least-squares mean change from baseline (95% CI) on the MADRS** | Two positive short-term (6-week) trials: | Two positive short-term (6-week) trials: | Not applicable |
| (1) 5–20 mg/day:               | −2.6 (−4.5, −1.2)       | 2 mg/day: −3.2 (−4.9, −1.5) |                         |
| (2) 5–20 mg/day:               | −3.0 (−4.7, −1.4)       | 1 mg/day: −1.3 (−2.7, 0.1)  |                         |
|                                |                         | 3 mg/day: −2.0 (−3.4, −0.5) |                         |

CI, confidence interval; MADRS, Montgomery–Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale.
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 major depressive disorder) to 50 (weight increased for brexpiprazole for schizophrenia). Pragmatically, NNH values less than 10 are likely to be more clinically relevant (33). Placing these agents into perspective within the context of other available first-line oral second-generation antipsychotics is Table 5, outlining the NNH for clinically relevant weight gain, somnolence and akathisia. For aripiprazole, brexpiprazole and cariprazine for the treatment of schizophrenia.

Table 5 | Outline of the number needed to harm (NNH) for clinically relevant weight gain, somnolence and akathisia

| Active Medication | Placebo | NNH |
|-------------------|---------|-----|
| Schizophrenia     | 7%      | 9%  | NA  |
| Bipolar mania     | 11%     | 10% | 100 |
| Bipolar mania (adjunct) | 12% | 6%  | 17  |
| Major depressive disorder (adjunct) | 6%  | 2%  | 25  |
| Brexpiprazole     | 6%      | 2%  | 12  |
| Schizophrenia     | 8%      | 15% | NA  |
| Major depressive disorder (adjunct) | 3%  | 1%  | 50  |
| Cariprazine (pooled 1.5–6 mg/day) | 9%   | 12% | NA  |
| Bipolar mania (3–6 mg/day) | 12% | 7%  | 20  |

The % of patients discontinuing because of an adverse event is not currently listed in product labelling if rates for the active drug are similar to or lower than with placebo. For aripiprazole, this information was contained in prior versions of product labelling. For brexpiprazole, the information was taken from a prior review (34). For cariprazine, data were extracted from four 6-week trials that in addition to the positive trials noted in product labelling (27–29), also included a Phase II proof-of-concept study (Litman RE, Papadakis K, Bose A, Xie J. Use of cariprazine in the treatment of schizophrenia: a proof-of-concept trial. Poster presentation. American Psychiatric Association-Institute on Psychiatric Services, Chicago, Illinois, October 2–5, 2008). CI, confidence interval; NA, not applicable as the rate observed with medication is lower than that observed with placebo; NNH, number needed to harm.
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 to accurately assess these potential differences.

As we compare and contrast, the concept of likelihood to be helped or harmed (LHH) can be helpful, provided that you select a relevant harm to contrast with the expected benefit (33). Table 6 provides the NNT for response, NNH for discontinuation because of an adverse event (where applicable), the NNHs for weight gain ≥7%, somnolence adverse events and akathisia adverse events, together with the calculated LHH (where applicable). With the exception of aripiprazole for the treatment of major depressive disorder 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, and for aripiprazole for bipolar mania when comparing response vs. discontinuation because of an adverse event.

Additional work has been done with both brexpiprazole and cariprazine for the maintenance treatment of schizophrenia (36,37). In addition, cariprazine has been directly compared with risperidone in a 26-week double-blind study in patients with schizophrenia with predominant negative symptoms (38). Cariprazine is also in Phase III of clinical development for the treatment of posttraumatic stress disorder (NCT01838876, NCT01715063). Brexpiprazole is also in Phase III of clinical development for the treatment of posttraumatic stress disorder and for agitation associated with dementia of the Alzheimer type (39).

There are several important caveats. The harms discussed are primarily from acute studies and do not reflect effects that can take time to become manifest, such as tardive dyskinesia, the long-term accumulation of body weight, or the development of insulin resistance/type 2 diabetes mellitus (40). The

| Antipsychotic       | Schizophrenia | Bipolar mania | Adjunctive for MDD |
|---------------------|---------------|---------------|--------------------|
| Aripiprazole        | 21            | ND            | 22                 |
| Brexpiprazole       | 17            | 52            |                    |
| Cariprazine (to 6 mg/d) | 34        | ND            |                    |
| Risperidone         | 18 (for SCZ and BM) | 3 |                    |
| Olanzapine          | 6 (for SCZ and BM) | 8 | 15                 |
| Quetiapine IR       | 6             | 3             | 11                 |
| Paliperidone        | 35            | 15            | 4                  |
| Iloperidone         | 10            | 16            | 6                  |
| Asenapine           | 36            | 29            | 20                 |
| Lurasidone          | 67            | 58            | 3                  |

*Adapted and updated from (34) and 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: 879–911. Data for risperidone are for doses ≤8 mg/day. For adjunctive use for MDD, data for olanzapine are for the combination of olanzapine with fluoxetine. Data for somnolence for aripiprazole for schizophrenia and bipolar mania are taken from the section regarding potential for cognitive and motor impairment and include sedation. Data for somnolence for brexpiprazole and cariprazine (includes all doses tested) are taken from the section regarding potential for cognitive and motor impairment and include sedation and hyperactivity. BM, bipolar mania; IR, immediate release; MDD, major depressive disorder; NA, not available, presumably because the incidence did not meet the reporting threshold; ND, no difference or rate with medication is lower than rate with placebo; NNH, number needed to harm; SCZ, schizophrenia; XR, extended release.
Table 6  Likelihood to be helped or harmed: response vs. discontinuation because of an adverse event, and response vs. weight gain ≥ 7%, somnolence adverse events or akathisia adverse events

| Disease state/medication | NNT for response* | NNH for discontinuation because of an adverse event | LHH for response vs. discontinuation because of an adverse event | NNH for weight gain ≥ 7% | LHH for response vs. weight gain ≥ 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 |
|--------------------------|-------------------|------------------------------------------------------|----------------------------------------------------------------|-----------------------|--------------------------------------|-----------------------------------|--------------------------------------|---------------------------------|----------------------------------------|
| Schizophrenia             |                   |                                                      |                                                                |                       |                                      |                                   |                                      |                                 |                                         |
| Aripiprazole              | 8                 | ND                                                   | NA                                                              | 21                    | 2.6                                  | 20                                | 2.5                                  | 25                             | 3.1                                    |
| Brexpiprazole             | 7                 | ND                                                   | NA                                                              | 17                    | 2.4                                  | 50                                | 7.1                                  | 112                            | 16                                    |
| Cariprazine (to 6 mg/day) | 10                | ND                                                   | NA                                                              | 34                    | 3.4                                  | 100                               | 10                                  | 15                             | 1.5                                    |
| Bipolar mania             |                   |                                                      |                                                                |                       |                                      |                                   |                                      |                                 |                                         |
| Aripiprazole              | 7                 | ND                                                   | NA                                                              | ND                    | NA                                   | 20                                | 2.9                                  | 12                             | 1.7                                    |
| Cariprazine (to 6 mg/day) | 5                 | ND                                                   | NA                                                              | 25                    | 5                                    | 7                                 | 7                                   | 1.4                             |                                         |
| Major depressive disorder |                   |                                                      |                                                                |                       |                                      |                                   |                                      |                                 |                                         |
| Aripiprazole              | 7                 | ND                                                   | NA                                                              | 3.6                   | 3.1                                  | 50                                | 7.1                                  | 5                              | 0.7                                    |
| Brexpiprazole             | 11                | ND                                                   | NA                                                              | 4.5                   | 4.7                                  | 34                                | 3.1                                  | 15                             | 1.4                                    |

*Response for schizophrenia defined as a 30% or greater 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% or greater decrease in the Positive and Negative Syndrome Scale total score for cariprazine; response for bipolar mania or major depressive disorder defined as a 50% or greater reduction in the Young Mania Rating Scale or Montgomery–Asberg Depression Rating Scale, respectively. 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.
data presented are from carefully conducted registration trials that enrolled subjects who fulfilled restrictive inclusion/exclusion criteria. Such patients may differ from persons encountered in routine clinical practice. Thus, pragmatic clinical trials that are more generalizable will help place these antipsychotic medications into clinical perspective for their use in the ‘real world’. However, schizophrenia, bipolar disorder and major depressive disorder are heterogeneous disorders and medication response (and tolerability) in an individual patient can vary. As always, having additional choices can offer greater opportunities for success.

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