

## Class Update with New Drug Evaluations: Antipsychotics

**Date of Review:** May 2016

**End Date of Literature Search:** February 2016

**New Drugs:** brexpiprazole  
cariprazine

**Brand Names (Manufacturer):** Rexulti® (Otsuka)  
Vraylar™ (Actavis)

**Dossiers Received:** yes

**PDL Classes:** Antipsychotics, First generation  
Antipsychotics, Second generation  
Antipsychotics, Parenteral

### Current Status of PDL Class:

See **Appendix 1**.

### Purpose for Class Update:

Several new antipsychotic drug products have been approved by the U.S. Food and Drug Administration since these drug classes were last reviewed by the Oregon Health Plan (OHP) Pharmacy and Therapeutics Committee.

### Research Questions:

1. Is there new comparative evidence of meaningful difference in efficacy or effectiveness outcomes for schizophrenia, bipolar mania or major depressive disorders (MDD) between oral antipsychotic agents (first- or second-generation) or between parenteral antipsychotic agents (first- or second-generation)?
2. Is there new comparative evidence of meaningful difference in harms between oral antipsychotic agents (first- or second-generation) or between parenteral antipsychotic agents (first- or second-generation)?
3. Is there new comparative evidence of meaningful difference in effectiveness or harms in certain subpopulations based on demographic characteristics?

### Conclusions:

- There is insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms between antipsychotic agents for schizophrenia, bipolar mania or MDD.
- There is insufficient evidence to determine if brexpiprazole and cariprazine offer superior efficacy or safety to other antipsychotic agents for schizophrenia.
- There is insufficient evidence to determine if brexpiprazole offers superior efficacy or safety to other antipsychotic agents for MDD.
- There is insufficient evidence to determine if cariprazine offers superior efficacy or safety to other antipsychotic agents for bipolar mania.

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- There is insufficient evidence to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents generally.

**Recommendations:**

- Designate Rexulti (brexpiprazole), Vraylar (cariprazine), and new formulations of aripiprazole (Aristada) and paliperidone (Invega Trinza) voluntary non-preferred (no PA required) based on limited data.
- After executive session, make Latuda (lurasidone), Saphris (asenapine) and Abilify Maintenna (aripiprazole) preferred and make chlorpromazine voluntary non-preferred (no PA required).

**Previous Conclusions:**

- There continues to be no consistent differences in the efficacy between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole or asenapine in shorter-term trials. There is moderate quality evidence for aripiprazole, clozapine, olanzapine, quetiapine and risperidone. The comparative evidence is insufficient or very low for aripiprazole long-acting injection, loperidone, olanzapine long-acting injection, olanzapine ODT, extended-release paliperidone and lurasidone.
- There is new moderate quality evidence that the risk of relapse may be lower with olanzapine and risperidone than immediate-release quetiapine and with risperidone long-acting injection than with oral risperidone in patients with first-episode schizophrenia.
- There is new moderate quality evidence of no difference in response or remission rates between extended-release paliperidone and either olanzapine or immediate-release quetiapine for manic and mixed episodes of bipolar disorder.
- There continues to be insufficient comparative evidence of efficacy and effectiveness of second generation antipsychotics in the treatment of Major Depressive Disorder, Bipolar Disorder in children and adolescents, Pervasive Developmental Disorders and Disruptive Behavior Disorders.
- There is moderate quality evidence that the rate of clinically important weight gain (> 7% increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), quetiapine (RR 1.82), risperidone (RR 1.81) and particularly ziprasidone (RR 5.76) across 3.7 to 24 months. Single studies of olanzapine and olanzapine long-acting injection, olanzapine ODT, and paliperidone palmitate did not find statistically significant differences in risk of weight gain. Data for other second generation antipsychotics was insufficient to assess the risk of clinically important weight gain compared with olanzapine.
- There is limited comparative effectiveness data available for this class in regards to mortality and serious harms.
- High rates of attrition and small sample sizes in randomized clinical trials make it difficult to draw strong conclusions for this class in systematic review.
- There continues to be insufficient comparative evidence of a meaningful difference in efficacy or harms of second generation antipsychotics in any subgroup population.
- There is low quality evidence that aripiprazole long-acting injection improves time to relapse compared to placebo; there are no head-to-head trials comparing aripiprazole long-acting injection to other second generation antipsychotics.
- There is insufficient evidence to determine the long-term safety and comparative efficacy of aripiprazole long-acting injection.

**Previous Recommendations:**

- Based on the lack of long-term effectiveness and safety data, recommend listing aripiprazole long-acting injection as non-preferred on the voluntary PDL.
- No changes are recommended for the second generation antipsychotic preferred drug class list based on safety and efficacy. Costs should be reviewed in executive session.

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**Background:**

Schizophrenia is the ninth most debilitating disease in North America<sup>1</sup> and treatment with second-generation antipsychotics (SGAs) is associated with substantial cost (estimated US \$14.5 billion globally in 2014).<sup>2</sup> Schizophrenia not only affects mental health; patients with schizophrenia die 12-15 years earlier than the average population, a trend that appears to be increasing.<sup>3</sup> Persons with schizophrenia experience positive symptoms (hallucinations, delusions, thought disorders) but also typically experience negative symptoms (social withdrawal, loss of motivation, emotional blunting, self-neglect), alterations in cognition (memory, attention, executive functioning), and affective dysregulation giving rise to depressive and manic (bipolar) symptoms.<sup>3,4</sup> Schizophrenia is characterized by long duration, bizarre delusions, negative symptoms, and few affective symptoms (non-affective psychosis).<sup>3</sup> Patients who present with a psychotic disorder with fewer negative symptoms, but whose psychosis is preceded by a high level of affective symptoms (depression and mania) are usually diagnosed with psychotic depression or bipolar disorder (affective psychosis).<sup>3</sup>

Lifetime prevalence of schizophrenia, schizophrenic disorders and schizophreniform disorders are commonly reported as less than 0.5%, with men affected more severely with earlier age of onset and higher rates of negative symptoms than women.<sup>4</sup> Perinatal and early childhood factors might account for a small proportion of incidence of schizophrenia: hypoxia to the fetus, maternal infection, maternal stress, and maternal nutrition have shown to be risk factors.<sup>3</sup> Environmental factors may also play a role. Children who grow up in more urban areas, or children of immigrant ethnic groups, particularly if they live in a low ethnic density area, are more likely to be diagnosed with schizophrenia later in life than children in less urbanized area or native-born children.<sup>3</sup> Cannabis use is also associated with increased risk for psychotic disorder and symptoms (odds ratio [OR] 1.5-2.0). Vulnerability for schizophrenia is partly genetic. Twin studies have demonstrated that schizophrenia has heritability estimates of around 80% (compared to 60% for osteoporosis of the hip and 30-50% for hypertension), though the high heritability may also be partly due to environmental effects that are moderated by genes.<sup>3</sup> Management of negative and cognitive symptoms have

Schizophrenia, in its acute psychotic state, is associated with an increase in dopamine synthesis and dopamine release. Functional MRI results show these abnormal neurochemical compositions lead to abnormal function, with both hyperactivity and hypoactivity in different brain regions compared to healthy control groups. Once the diagnosis is made, antipsychotic drugs, which block dopamine D2 receptors, are used in the context of other psychological and social supports, as the main treatment of schizophrenia. First-generation antipsychotics such as haloperidol and chlorpromazine effectively managed psychotic symptoms of schizophrenia since the 1950s, but often lead to adverse extrapyramidal motor symptoms. The SGAs generally cause less motor effects and remain effective treatment for positive symptoms, but are associated with a high incidence of adverse metabolic effects (weight gain, hyperglycemia, hypercholesterolemia).<sup>3</sup> With a combination of medications and community-case management, remission of about 80% of patients can be achieved if treatment is initiated early during the first episode of the illness.<sup>3</sup> However, during the course of the disease, about one third of patients with schizophrenia remain symptomatic despite medications, psychological and vocational interventions.<sup>3</sup> In such patients, an attempt is often made to use a different antipsychotic, or add an anxiolytic, antidepressant and antiepileptic drug.<sup>3</sup> Other than switching to clozapine, additional treatments are of low proven value and may result in unnecessary polypharmacy.<sup>3</sup> Substance abuse is common in this population: more than half of patients with schizophrenia smoke and a significant higher number abuse cannabis and alcohol relative to the general population.<sup>3</sup>

New SGA drugs such as asenapine, iloperidone, lurasidone and paliperidone continue to be marketed as earlier second-generation drugs come off patent. In addition, several new SGA drugs have been recently approved by the U.S. Food and Drug Administration. Marketing of these new agents focuses not on comparative safety and efficacy but the slightly different pharmacological profiles of these agents with respect to affinity for dopamine or serotonin receptor subtypes, and adrenergic, histamine or muscarinic receptors. Many of these antipsychotics have not been directly compared in clinical trials so it has not been possible to generate clear hierarchies for the efficacy and safety of available regimens. However, drugs for mental health conditions, including antipsychotic

agents, are by Oregon rule exempt from the traditional Preferred Drug List (PDL) and prior authorization (PA) requirements. However, specific clinical PA criteria may be placed to restrict medically inappropriate use or to address specific safety risks.<sup>5</sup>

Trials that assess antipsychotics routinely have high numbers of participant withdrawals (average is 35%). The reasons for patients discontinuing antipsychotic treatment are similar to those in other chronic illnesses except for 2 issues specific to schizophrenia: the stigma of being labeled as psychotic and the fact the dopamine-blocking medications inhibit motivational drive.<sup>3</sup> Unfortunately, high withdrawals in clinical trials frequently lead to poor quality evidence for antipsychotic agents.

Two common scales used to assess the efficacy of antipsychotic agents are the Positive and Negative Syndrome Scale (PANSS) and the Montgomery-Asberg Depression Rating Scale (MADRS). The PANSS is a widely used tool in clinical research to assess symptoms associated with schizophrenia.<sup>6</sup> The PANSS is a 30-item, 7-point rating instrument that uses a positive scale (7 items) to assess positive symptoms, a negative scale (7 items) to assess negative symptoms, and a 16-item General Psychopathology scale.<sup>6</sup> The 7-point rating scale represents increasing levels of psychopathology: 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate-severe, 6 = severe; and 7 = extreme.<sup>6</sup> Therefore, a minimum score of 30 points to a maximum score of 210 points can be achieved. The instrument was validated in 101 patients with schizophrenia with mean scores of 18.20 in the positive scale, 21.01 in the negative scale, and 37.74 in the general psychopathology scale.<sup>6</sup> The minimum clinically important difference (MCID) for PANSS scores is 50%,<sup>7</sup> though lesser differences (34%) have also been deemed relevant.<sup>8</sup> The MADRS is a 10-item diagnostic questionnaire used to measure severity of depressive episodes in patients with mood disorders.<sup>9</sup> Higher MADRS score indications more severe depression, and each item yields a score of 0 to 6 (total score range 0 to 60).<sup>9</sup> The questionnaire addresses the following items: 1) apparent depression; 2) reported depression; 3) inner tension; 4) insomnia; 5) reduced appetite; 6) concentration difficulties; 7) loss of interest; 8) difficulty in activities; 9) pessimism; and 10) suicidal ideation.<sup>9</sup> MCID estimates for MADRS range from 1.6 to 1.9.<sup>10</sup>

### **Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence for this review is on high quality systematic reviews and evidence-based guidelines.

### **Systematic Reviews:**

A network meta-analysis (i.e., multiple-treatments meta-analysis) was performed to integrate all the evidence from available antipsychotics in treatment-resistant schizophrenia.<sup>11</sup> This technique was utilized to compare relative effect estimates between all antipsychotics that may or may not have been directly compared in any trial, but are part of a connected network through intermediate comparators (i.e., placebo, other antipsychotics) which allows statistical analyses between the agents and a more precise effect estimate. The analysis included all published and unpublished single- and double-blind RCTs (minimum 3 weeks duration) of adult patients with a treatment-resistant form of schizophrenia, schizophreniform disorder, or schizoaffective disorder. Open-label trials were excluded because they systematically favored SGAs. All antipsychotics, at any dose and in any formulation that were compared with another antipsychotic

or placebo, were included if the antipsychotics were used as monotherapy. The primary outcome was the mean change from baseline to end point in overall symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale, or any other validated scale for the assessment of overall schizophrenia symptoms. A clinically significant response to treatment, defined primarily as at least a 20% reduction of PANSS or Brief Psychiatric Rating Scale score, or at least minimum improvement on the Clinical Global Impressions Scale, was used as a secondary outcome. Forty unique RCTs were identified (n=5172; 71.5% male; mean age 38.8 years). Median trial duration was 11 weeks. The mean dropout rate was 32.0%, and 45% of the studies had evidence of selective reporting. The drug involved with the most comparisons was clozapine (20 of 40 trials), followed by haloperidol (15 of 40 trials), olanzapine (14 of 40 trials), and risperidone (12 of 40 trials). Few trials were available for the other drugs. Aripiprazole, perphenazine and thiothixene were included in the systematic review but were not included in the meta-analysis due to network limitations of the studies. Results from the meta-analysis found severe inconsistency between direct and indirect evidence due to older studies published before 1990 and so these studies had to be removed. Standardized mean differences (SMD) of -0.20 are considered small, -0.50 are considered medium, and -0.80 are considered large. Few statistically significant differences were found. Olanzapine was significantly more effective than quetiapine fumarate (SMD, -0.29, corresponding to -6.08 PANSS points; 95% confidence interval [CI], -0.56 to -0.02) and haloperidol (SMD, -0.29, corresponding to -6.08 PANSS points; 95% CI, -0.44 to -0.13); and clozapine was significantly more effective than haloperidol (SMD, -0.22, corresponding to -4.61 PANSS points; 95% CI, -0.38 to -0.07). A pattern of superiority was seen for olanzapine, clozapine and risperidone in other efficacy outcomes, but results were inconsistent and effect sizes were usually small. Overall, there is insufficient evidence to determine whether one antipsychotic is more efficacious than another for patients with treatment-resistant schizophrenia. In addition, there is little evidence to show that clozapine is superior to other SGAs in this population despite its FDA-approved indication for treatment-resistant schizophrenia. Few significant differences were found in terms of adverse effects.<sup>11</sup>

A systematic review of literature was performed to determine the efficacy of antipsychotics for the management of hostility and aggression in patients with schizophrenia spectrum disorders (SSDs).<sup>12</sup> SSDs are associated with an elevated risk of committing violent acts such as assault or other violent crimes, and has been related to premorbid conduct disorders, positive symptoms of schizophrenia, especially paranoia, or concomitant antisocial or psychopathic traits. A total of 186 studies were identified that evaluated improvement in hostility or overt interpersonal aggression as primary or secondary outcomes. The studies showed considerable and problematic differences in quality (i.e., risk of bias) and research study design. Heterogeneity limitations included: diagnoses of the patient populations, which varied between populations confined to schizophrenia and mixed populations; clinical sites (inpatients vs. outpatients); adjunctive treatments (monotherapy with an antipsychotic vs. allowance for adjunctive treatments); and differing definitions for aggression. Given the diversity of research, the investigators sought to determine 1) if there is evidence that any medication will reduce overt aggression in patients with SSDs; 2) if there is evidence that any medication will reduce hostility in patients with SSDs; and 3) if there is evidence that one antipsychotic is more effective than another antipsychotic at reducing overt aggression or hostility in patients with SSDs. Of the original 186 studies, 92 studies provided sufficient methodological information to grade the evidence, which was classified according to the Academy of Neurology's recommendations for levels of evidence. Study durations ranged from 3 weeks to 3 years and included mostly inpatients. For reduction in overt aggression, there was insufficient placebo-controlled evidence. However, low quality evidence was found to suggest clozapine may be significantly superior to haloperidol at reducing over aggression among inpatients with SSDs on concomitant psychotropic medications. The comparative benefit of other antipsychotics is unknown. One observational study found evidence to support the use of SGAs over first-generation antipsychotics for overt aggression; however, the overall evidence was deemed insufficient to determine clinical significance. For reduction in hostility, only paliperidone extended-release (moderate-quality) and quetiapine (low-quality) have placebo-controlled evidence for efficacy among inpatients with SSDs on concomitant psychotropics. There is low-quality evidence clozapine may be more effective than chlorpromazine, chlorpromazine, or haloperidol at reducing hostility among patients with SSDs. There is also low-quality evidence that risperidone may be associated with significantly greater reduction in hostility versus haloperidol. The investigators concluded clozapine is possibly more effective than chlorpromazine, and risperidone is possibly more effective than

haloperidol for the management of hostility among inpatients with SSDs who are receiving other psychotropics. Specific study methods were detailed for each of the 92 studies; however, specific effect estimates were not disclosed.<sup>12</sup>

The comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia were recently assessed by multiple-treatments meta-analysis.<sup>2</sup> The investigators aimed to compare two prototypical first-generation antipsychotics (haloperidol and chlorpromazine) and 13 SGAs used in patients with schizophrenia in order to provide evidence-based hierarchies of comparative efficacy, risk of all-cause discontinuation, and major adverse effects of these agents. Multiple-treatments meta-analysis allows the integration of direct and indirect comparisons of antipsychotic drugs (ie, how 2 or more drugs compare with a common comparator) and provides evidence-based hierarchies when head-to-head comparisons are limited. Eligible studies included published and unpublished single-blinded or double-blinded RCTs of oral antipsychotic monotherapy in patients with schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorder). Unblinded studies were excluded because they systematically favor SGAs. Studies in which sequence generation had a high risk of bias or in which allocation was not concealed were also excluded. To maintain homogeneity in the analysis, trials performed in patients with predominant negative symptoms, significant comorbidities, treatment resistance, and trials in patients with stable illness (ie, relapse prevention studies) were excluded. Doses of the antipsychotic could be flexible-dosed to allow titration to an adequate dose, or fixed-dose if doses were at target doses. The primary outcome was the mean overall change in symptoms, which was assessed by change in PANSS (total score from baseline to endpoint); if data from this scale were not available, change in Brief Psychiatric Rates scale from baseline to endpoint was used. Secondary outcomes were all-cause discontinuation, weight gain, use of antiparkinson drugs as a measure of extrapyramidal adverse effects, prolactin increase, QTc prolongation and sedation. A total of 212 studies reported between 1955 and September 2012 (n=43,049) were included in the analysis. The mean duration of illness was 12.4 years and the mean age was 38.4 years. Most studies (n=199, 94%) were double-blinded and the remaining 13 studies were single-blinded, but few details were reported about the methods of allocation concealment or how successful they were. Overall, premature discontinuation rates in the studies were around 35%, which is consistent with expectations of investigators of these studies. Standardized mean differences (SMD) between drugs were assessed. As a general rule, a SMD of -0.2 is small, -0.5 is medium, and -0.8 is larger. All drugs were superior to placebo (range of mean effect sizes -0.33 to -0.88). Clozapine was significantly more effective than all the other drugs (SMD 0.88; 95% CI, 0.73-1.03). After clozapine, olanzapine (SMD 0.59; 95% CI, 0.53-0.65) and risperidone (SMD 0.56; 95% CI, 0.50-0.63) were significantly more effective than the other drugs apart from paliperidone (SMD 0.50; 95% CI, 0.39-0.60) but these effect sizes were small. All-cause discontinuation was used as a measure of acceptability of treatments because it encompasses efficacy and tolerability. All of the U.S. approved drugs were significantly better than placebo. Olanzapine (range of significant mean odds ratios (OR) 0.58-0.76; numbers-needed-to-treat (NNT) 9-17), clozapine (OR 0.57-0.67; NNT 9-12), paliperidone (OR 0.60-0.71; NNT 9-14) and risperidone (OR 0.66-0.78; NNT 11-18) had significantly lower all-cause discontinuation than several other drugs. Haloperidol (OR 0.80; NNT 20) was worse than quetiapine (OR 1.32; NNT 15) and aripiprazole (OR 1.33; NNT 15). Apart from haloperidol, ziprasidone, and lurasidone, all drugs produced more weight gain than placebo, with olanzapine associated with the most weight gain (SMD -0.74). Olanzapine also produced significantly more weight gain than most other drugs. Clozapine, iloperidone, chlorpromazine, quetiapine, risperidone and paliperidone produced significantly more weight gain than haloperidol, ziprasidone, lurasidone, aripiprazole and asenapine. Standardized mean differences for these comparisons ranged from -0.18 to -0.57. Clozapine, olanzapine, quetiapine, aripiprazole, iloperidone and asenapine did not cause significantly more extrapyramidal side-effects than placebo. The range of OR and numbers-needed-to-harm (NNH) for the other drugs were 1.61-4.76 and 3-11, respectively. Clozapine produced fewer extrapyramidal side-effects than all other drugs and placebo (range of mean OR 0.06-0.40; NNT 5-9), and was followed by olanzapine and quetiapine. Haloperidol caused significantly more extrapyramidal side-effects than the other drugs except for chlorpromazine, for which the difference was not significant. Lurasidone, aripiprazole, paliperidone and asenapine were not associated with significant QTc prolongation compared to placebo. Paliperidone and iloperidone were not significantly more sedating than placebo, but mean ORs and NNHs for other drugs ranged from 1.84 and 10 for aripiprazole) to 8.82 and 2 for clozapine, respectively. The authors emphasized that the differences in efficacy between drugs were small (standardized mean differences 0.11-0.55, median 0.24), and smaller overall than for harms outcomes for which there was more robust differences between antipsychotics. The efficacy differences compared to

placebo were of medium size (0.33-0.88, median 0.44), so the differences in efficacy found between the drugs are possibly substantial enough to be clinically important.

The effects of quetiapine were compared with other SGA drugs in a systematic review with meta-analysis published by the Cochrane Collaboration.<sup>7</sup> All RCTs that evaluated oral quetiapine with other oral SGA drugs in patients with schizophrenia or with schizophrenia-like psychosis were included.<sup>7</sup> Extensive literature searches were used without restriction to language or publication status.<sup>7</sup> Authors of manuscripts and drug sponsors were contacted for missing information.<sup>7</sup> Risk ratios (RR) were calculated for dichotomous outcomes based on an intention-to-treat (ITT) analysis and random effects model.<sup>7</sup> Mean differences (MD) were calculated for continuous outcomes and were also analyzed based on a random-effects model.<sup>7</sup> Risk of bias for each included study and used GRADE approach to rate quality of evidence.<sup>7</sup> Overall, efficacy tended to favor other SGA drugs compared to quetiapine but the clinical relevance of these differences remains unclear.<sup>7</sup> There is low quality evidence from 11 RCTs (n=1486) that the total PANSS score was superior with olanzapine compared to quetiapine by a mean score of 3.67 (95% CI, 1.95 to 5.39).<sup>7</sup> There is moderate quality evidence from 13 RCT (n=2155) that the total PANSS score was superior with risperidone compared to quetiapine by a mean score of 1.74 (95% CI, 0.19 to 3.29).<sup>7</sup> There is moderate quality evidence from 1 RCT (n=319) that the total PANSS score was superior with risperidone compared to quetiapine by a mean score of 1.74 (95% CI, 0.19 to 3.29).<sup>7</sup> There is moderate quality evidence from 1 RCT (n=319) that the total PANSS score was superior with paliperidone compared to quetiapine by a mean score of 6.30 (95% CI, 2.77 to 9.83).<sup>7</sup> There were no clear differences in efficacy between quetiapine and clozapine, aripiprazole or ziprasidone.<sup>7</sup> In terms of harms outcomes, moderate quality evidence tended to favor quetiapine over olanzapine.<sup>7</sup> Quetiapine produced fewer movement disorders in the clinical trials (RR for use of antiparkinson drug = 0.51; 95% CI, 0.32 to 0.81; 7 RCTs [n=1127]), led to less weight gain (RR 0.68; 95% CI, 0.51 to 0.92; 8 RCTs [n=1667]), and did not result in as much glucose elevation; however, incidence of QTc prolongation was higher with quetiapine compared to olanzapine (MD 4.81%; 95% CI 0.34 to 0.98; 3 RCTs [n=643]).<sup>7</sup> There is moderate quality evidence that quetiapine induced fewer movement disorders (RR for use of antiparkinson drug = 0.50; 95% CI, 0.36 to 0.69; 8 RCTs [n=2163]) but increased total cholesterol levels compared to risperidone (MD 8.57 mg/dL; 95% CI, 4.85 to 12.29; 6 RCTs [n=1473]).<sup>7</sup> There is also moderate quality evidence, though based on more limited data, that paliperidone induced more movement disorders (RR for use of antiparkinson drug = 0.64; 95% CI, 0.45 to 0.91; 1 RCT [n=319]) and more weight gain compared to quetiapine (RR for total body weight gain  $\geq 7\%$  = 2.52; 95% CI, 0.50 to 12.78; 1 RCT [n=319]).<sup>7</sup> Compared to ziprasidone, there is moderate quality evidence quetiapine produced slightly fewer movement disorders (RR for use of antiparkinson drug = 0.43; 95% CI, 0.20 to 0.93; 1 RCT [n=522]).<sup>7</sup> Compared to ziprasidone, however, there is moderate quality evidence that quetiapine resulted in more sedation, increased cholesterol and led more weight gain (RR 2.22; 95% CI, 1.35 to 3.63; 2 RCTs [n=754]).<sup>7</sup> About 60% of subjects who started quetiapine in the RCTs quit taking it within a few weeks.<sup>7</sup> Differences found in the meta-analysis were small and it is unclear whether the differences are clinically meaningful. The authors found that most of the direct head-to-head comparisons were of limited value because of the assumptions and biases identified in the studies.<sup>7</sup>

The efficacy and tolerability of aripiprazole was compared to other SGA drugs in an updated systematic review with meta-analysis published by the Cochrane Collaboration.<sup>13</sup> All RCTs (both open and double-blinded) that evaluated oral aripiprazole with other SGA drugs in patients with schizophrenia or with schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders) were included.<sup>13</sup> Open-label studies were only included because the investigators felt that important data could be provided that might otherwise be overlooked.<sup>13</sup> Comparator SGAs included oral or parenteral formulations of clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Extensive literature searches were used without restriction to language or publication status.<sup>13</sup> Authors of manuscripts and drug sponsors were contacted for missing information.<sup>13</sup> Risk ratios were calculated for dichotomous outcomes based on an ITT analysis and random effects model.<sup>13</sup> Mean differences were calculated for continuous outcomes and were also analyzed based on a random-effects model.<sup>13</sup> Risk of bias for each included study and used GRADE approach to rate quality of evidence.<sup>13</sup> Data from 174 RCTs (n=17,244) were included in the updated systematic review. Overall, 30-40% of study participants in these trials discontinued the study prematurely but there were no differences between groups.<sup>13</sup> The primary outcomes used by the Cochrane investigators were: 1) global state, defined as 'no clinically important response' as defined by the individual studies

(e.g., global impression less than much improved or less than 50% reduction on a rating scale); 2) general functioning, defined as 'no clinically important change in general functioning'; and 3) adverse effects, defined as 'clinically important specific adverse effects'.<sup>13</sup> When compared to clozapine, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (29 RCTs; n=2132); mental state (Brief Psychiatric Rating Scale [BPRS]) (5 RCTs; n=426) or premature study discontinuation (3 RCTs; n=240).<sup>13</sup> Quality of life (as assessed by the WHO-QOL-100 scale) was statistically superior with aripiprazole compared to clozapine (RR 2.59; 95% CI, 1.43 to 3.74; 2 RCTs; n=132) based on low quality evidence but no difference was seen between aripiprazole and clozapine with regard to extrapyramidal symptoms (EPS).<sup>13</sup> When compared to quetiapine, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (12 RCTs; n=426); mental state (PANSS positive symptoms) (7 RCTs; n=583); premature study discontinuation (2 RCTs; n=168); or EPS (4 RCTs; n=348).<sup>13</sup> Quality of life (as assessed by the WHO-QOL-100 scale) was statistically superior with aripiprazole compared to quetiapine (MD 2.60; 95% CI, 1.31 to 3.89; 1 RCT; n=100) based on low quality evidence.<sup>13</sup> When compared to risperidone, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (80 RCTs; n=6381) or premature study discontinuation (12 RCTs; n=1239).<sup>13</sup> Mental state status (BPRS) (5 RCTs; n=570) was statistically superior with aripiprazole compared to risperidone (MD 1.33; 95% CI, 2.24 to 0.42) based on low quality evidence.<sup>13</sup> Risperidone use was associated with more EPS compared to aripiprazole (RR 0.39; 95% CI, 0.31 to 0.50; 31 RCTs; n=2605).<sup>13</sup> When compared to ziprasidone, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (6 RCTs; n=442); mental state (BPRS) (1 RCT; n=247) or premature study discontinuation (2 RCTs; n=316).<sup>13</sup> Weight gain was significantly greater in people who received aripiprazole compared to ziprasidone (RR 4.01; 95% CI, 1.10 to 14.60; 3 RCTs; n=232) based on low quality evidence.<sup>13</sup> When compared to olanzapine, there is low quality evidence of no statistically significant difference with aripiprazole in regard to global state (no clinically significant response) (11 RCTs; n=1739); mental state (PANSS) (11 RCTs; n=1500) or quality of life using the GQOLI-74 scale (1 RCT; n=68).<sup>13</sup> Significantly more patients on aripiprazole discontinued the study prematurely compared to patients on olanzapine (RR 1.15; 95% CI, 1.05 to 1.25; 9 RCTs; n=2331) based on low quality evidence.<sup>13</sup> However, less patients gained weight on aripiprazole versus olanzapine (RR 0.25; 95% CI, 0.15 to 0.43; 9 RCTs; n=1538) based on low quality evidence.<sup>13</sup> The investigators found large gaps in important outcomes and found all comparisons of limited quality and problematic for clinical application.<sup>13</sup> Long-term data are sparse.<sup>13</sup>

Perphenazine is a first-generation antipsychotic drug with similar potency to haloperidol.<sup>14</sup> The efficacy and tolerability of perphenazine was compared to other antipsychotic drugs and placebo in a systematic review with meta-analysis published by the Cochrane Collaboration.<sup>14</sup> All double-blind RCTs that evaluated perphenazine (depot formulations were excluded) with other antipsychotic drugs or placebo in patients with schizophrenia or with schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders) were included.<sup>14</sup> Extensive literature searches were used without restriction to publication status.<sup>14</sup> Authors of manuscripts and drug sponsors were contacted for missing information.<sup>14</sup> Risk ratios were calculated for dichotomous outcomes based on an ITT analysis and random effects model.<sup>14</sup> Mean differences were calculated for continuous outcomes and were also analyzed based on a random-effects model.<sup>14</sup> Risk of bias for each included study and used GRADE approach to rate quality of evidence.<sup>14</sup> Thirty-one parallel group studies, most commonly 12 weeks in duration (range 10 days to 18 months), met inclusion criteria (n=4662).<sup>14</sup> The trial centers were located in Europe, Japan and North America.<sup>14</sup> The primary outcomes were clinical response in global state or mental state, as defined by the individual studies.<sup>14</sup> When perphenazine was compared to placebo, there is low quality evidence that more patients who received placebo either had no improvement in symptoms or deterioration of symptoms when global state was assessed than patients who received perphenazine (RR 0.32; 95% CI, 0.13 to 0.78; 1 RCT; n=61).<sup>14</sup> There was also a non-statistically significant and very imprecise increase in the number of patients who took placebo and relapsed compared to placebo (RR 0.14; 95% CI, 0.02 to 1.07; 1 RCT; n=48) based on low quality evidence.<sup>14</sup> There were no differences between perphenazine and placebo in rates of dystonia (RR 1.00; 95% CI, 0.07 to 15.08; 1 RCT; n=48) based on low quality and imprecise data.<sup>14</sup> There is low quality evidence that there are no differences between perphenazine and other antipsychotic drugs in terms of lack of clinical response (RR 1.04; 95% CI, 0.91 to 1.17; 17 RCTs; n=1879).<sup>14</sup> For the mental state outcome of 'no effect', as defined by individual trials, there was also no significant difference between perphenazine and other antipsychotic drugs (RR 1.24; 95% CI, 0.61 to 2.52; 4 RCTs; n=383) based on low quality evidence.<sup>14</sup> There



was no difference seen in rates of dystonia with perphenazine and other antipsychotic drugs (RR 1.36; 95% CI, 0.23 to 8.16; 4 RCTs; n=416) or serious adverse events (RR 0.98; 95% CI, 0.68 to 1.41; 2 RCTs; n=1760) based on low quality evidence.<sup>14</sup> No deaths were reported in the included studies.<sup>14</sup> The investigators concluded that the reporting of outcomes varied greatly over the span of 50 years of clinical trials of perphenazine, which make it impossible to draw clear conclusions.<sup>14</sup> Evidence for perphenazine is of low quality and the assumptions so far indicate that perphenazine may be equally effective and safe as other antipsychotic drugs in the management of schizophrenia.<sup>14</sup>

Treatment guidelines state that there is no difference in efficacy between first-generation antipsychotic agents.<sup>15</sup> A series of systematic reviews with meta-analyses were conducted by the Cochrane Collaboration to determine whether oral first-generation antipsychotics considered to be highly potent differed in efficacy or safety to oral first-generation antipsychotic agents considered to have low potency in patients with schizophrenia or schizophrenia-like psychosis.<sup>15</sup> Typical examples of low-potency oral antipsychotic drugs are chlorpromazine, chlorprothixene, thioridazine or levomepromazine.<sup>15</sup> In each review, the Cochrane Schizophrenia Group Trials Register was searched to find RCTs that compared high-potency first-generation antipsychotic drugs with first-generation, low-potency antipsychotic drugs for people with schizophrenia or schizophrenia-like psychosis.<sup>15</sup> Risk ratios and 95% CIs were calculated for dichotomous data and MDs were calculated for continuous data on an ITT basis and using a random-effects model.<sup>15</sup> The GRADE approach was used to interpret findings in each review.

The first systematic review compared perphenazine to low-potency first-generation antipsychotic drugs for schizophrenia or schizophrenia-like psychosis.<sup>15</sup> Four RCTs (n=365) met inclusion criteria.<sup>15</sup> Methods of sequence generation and concealment of allocation were inadequately reported but most studies were rated as low risk of bias in terms of blinding.<sup>15</sup> Attrition bias in the studies was high.<sup>15</sup> There is moderate quality evidence that perphenazine and low-potency antipsychotic drugs have similar 'response to treatment', as defined by the individual trials (58% for perphenazine vs. 59% for low-potency antipsychotic agents; RR 0.97; 95% CI, 0.74 to 1.26; 2 RCTs; n=138).<sup>15</sup> Early discontinuation in the trials was also similar between the groups (30% for perphenazine vs. 28% for low-potency antipsychotic agents; RR 0.78; 95% CI, 0.35 to 1.76; 3 RCTs; n=323) based on low quality evidence.<sup>15</sup> There were also no significant differences in the incidence of at least one adverse effect and experiencing at least one movement disorder but the overall numbers were low and the data imprecise.<sup>15</sup> Akathisia was more frequent in the perphenazine group (25%) compared to low-potency antipsychotic agents (22%).<sup>15</sup> No data were available for quality of life or sedation.<sup>15</sup> Thus, there is low-quality evidence that suggests perphenazine, considered a high-potency first-generation antipsychotic, may not be superior to less potent first-generation antipsychotic agents in terms of safety and efficacy.<sup>15</sup>

The second systematic review compared haloperidol to oral low-potency first-generation antipsychotic drugs for schizophrenia or schizophrenia-like psychosis.<sup>16</sup> Seventeen RCTs (n=877) of 2 to 12 weeks' duration met inclusion criteria.<sup>16</sup> All studies had poorly described sequence generation, allocation procedures and blinding.<sup>16</sup> There is low quality evidence that haloperidol and low-potency antipsychotic drugs have similar 'response to treatment', as defined by the individual trials (40% for haloperidol vs. 36% for low-potency antipsychotic agents; RR 1.11; 95% CI, 0.86 to 1.44; 14 RCTs; n=574).<sup>16</sup> Early discontinuation in the trials was also similar between the groups (13% for haloperidol vs. 17% for low-potency antipsychotic agents; RR 0.82; 95% CI, 0.38 to 1.77; 11 RCTs; n=408) based on low quality evidence.<sup>16</sup> There were also no significant differences in the incidence of at least one adverse effect but the overall numbers were low and the data imprecise and of low quality.<sup>16</sup> There is moderate evidence that more patients on low-potency antipsychotic drugs experienced sedation (haloperidol 14% vs. low-potency antipsychotics 41%; RR 0.30; 95% CI, 0.11 to 0.82; 2 RCTs; n=44), orthostatic symptoms (haloperidol 25% vs. low-potency antipsychotics 71%; RR 0.35; 95% CI, CI 0.16 to 0.78; 1 RCT; n=41), and weight gain (haloperidol 5% vs. low-potency antipsychotics 29%; RR 0.22, 95% CI, 0.06 to 0.81; 3 RCTs, n=88).<sup>16</sup> However, movement disorders were more frequent reported in the haloperidol group (haloperidol 72% vs. low-potency antipsychotics 41%; RR 1.64; 95% CI, 1.22 to 2.21; 5 RCTs; n=170) based on low quality evidence.<sup>16</sup> No data were available for death or quality of life.<sup>16</sup> Thus, there is low-quality evidence that

suggests haloperidol, considered a high-potency first-generation antipsychotic, may not be superior to less potent first-generation antipsychotic agents in terms of efficacy but there may be differing harms.<sup>16</sup>

The third systematic review compared trifluoperazine to oral low-potency first-generation antipsychotic drugs for schizophrenia or schizophrenia-like psychosis.<sup>17</sup> Seven RCTs (n=422) of 4 to 52 weeks' duration met inclusion criteria.<sup>17</sup> All studies had poorly described sequence generation, allocation procedures and blinding.<sup>17</sup> There is moderate quality evidence that trifluoperazine and low-potency antipsychotic drugs have similar 'response to treatment', as defined by the individual trials (26% for trifluoperazine vs. 27% for low-potency antipsychotic agents; RR 0.96; 95% CI, 0.59 to 1.56; 3 RCTs; n=120).<sup>17</sup> Early discontinuation in the trials was also similar between the groups (20% for trifluoperazine vs. 16% for low-potency antipsychotic agents; RR 1.26; 95% CI, 0.72 to 2.17; 3 RCTs; n=239) based on low quality evidence.<sup>17</sup> There were also no significant differences in the incidence of at least one adverse effect but the overall numbers were low and the data imprecise and of low quality.<sup>17</sup> However, movement disorders were more frequently reported with trifluoperazine (23%) than with low-potency antipsychotic agents (13%) (RR 2.08; 95% CI, 0.78 to 5.55; 2 RCTs; n=123) based on low quality an imprecise data.<sup>17</sup> No data were available for death, sedation and quality of life.<sup>17</sup> Thus, there is low-quality evidence that suggests trifluoperazine, considered a high-potency first-generation antipsychotic, may not be superior to less potent first-generation antipsychotic agents in terms of safety and efficacy.<sup>17</sup>

Tic disorders (TD) are classified as transient tic disorder (TTD), chronic tic disorder (CTD) and Tourette syndrome (TS), and are common neuropsychiatric disorders in children who commonly have other concurrent comorbidities such as attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, oppositional defiant disorder and other mood disorders.<sup>18</sup> Symptoms include sudden, fast, repetitive, non-rhythmic motor movements and/or phonic production.<sup>18</sup> Management of these symptoms have been controlled by antipsychotic medications like haloperidol, but dystonia typically draw prescribers to use SGA drugs like aripiprazole or risperidone. Oral formulations of aripiprazole recently received an expanded FDA-approved indication for Tourette disorder in December 2014.<sup>19</sup> A recent systematic review assessed to efficacy and safety of aripiprazole for children with TDs.<sup>18</sup> All RCTs and open-label control studies that compared aripiprazole to placebo or other drugs used in the management of TDs (e.g., haloperidol) in children were included.<sup>18</sup> Trials were excluded if the data for the children could not be obtained by the study authors or drug sponsors and if the doses studied were unfair comparisons (e.g., high vs. low doses).<sup>18</sup> Scales used to assess TD symptoms included the Yale Global Tic Severity Scale (YGTSS); the Clinical Global Impression (CGI) Scale; the Tourette Syndrome Global Scale; the Tourette Syndrome Global List; the Clinical Global Impression Tic Severity Scale; and the Tourette Syndrome Severity Scale.<sup>18</sup> Results for dichotomous outcomes are expressed as RR with 95 % CIs.<sup>18</sup> Results for continuous outcomes are expressed as the MD.<sup>18</sup> We evaluated heterogeneity among the included studies using the I<sup>2</sup> test.<sup>18</sup> Twelve poor quality studies (n=935; 76% male; age range between 4 and 18 years) were included.<sup>18</sup> Nine studies were conducted in China, 2 studies in Korea and one in Iran.<sup>18</sup> Studies were short-term and ranged from 8 to 12 weeks in duration.<sup>18</sup> All of the studies used an active control (haloperidol (n=7); tiapride (n=3); risperidone (n=1) and one study used a placebo control.<sup>18</sup> Seven studies (n=600) used the YGTSS scale as the outcome measurement.<sup>18</sup> There was no significant difference in reduction of the total YGTSS score between the aripiprazole and active control groups (MD -0.48; 95% CI, -6.22 to 5.26; p=0.87; I<sup>2</sup>=87%).<sup>18</sup> Meta-analysis of 4 studies (n=285) that compared aripiprazole with haloperidol showed that there was no significant difference in reduction of the total YGTSS score (MD 2.50; 95% CI, -6.93 to 11.92; p=0.60; I<sup>2</sup>=88%).<sup>18</sup> Meta-analysis of 2 studies (n=255) that compared aripiprazole with tiapride showed that there was no significant difference in reduction of the total YGTSS score (MD -3.15; 95% CI, -11.38 to 5.09; p=0.45; I<sup>2</sup>=86%).<sup>18</sup> One double-blind, placebo-controlled RCT also used the total YGTSS score as a primary endpoint and showed a statistically significant reduction of the total YGTSS score (13.6 ±9.1 vs. 19.9 ±9.5; p<0.05) and vocal tic score (5.0 ±4.6 vs. 8.0 ±5.5; p<0.05) with aripiprazole compared to placebo.<sup>18</sup> However, there was no statistically significant difference in reduction of the motor tic score (8.6 ±6.1 vs. 11.9 ±5.5; p>0.05).<sup>18</sup> Overall, aripiprazole has demonstrated efficacy in management of TDs, with comparable effectiveness to haloperidol.

Robust epidemiologic evidence was recently systematically reviewed to compare mortality and risk for significant medical events, such as stroke, ventricular arrhythmia, venous thromboembolism, myocardial infarction, pneumonia and hip fracture between first-generation antipsychotic agents and SGAs.<sup>20</sup> An additional objective was to quantify how much these medical events explain the observed mortality difference between first- and second-generation antipsychotic agents.<sup>20</sup> Studies that evaluated these outcomes in patients with a mean age of 65 years and older were included.<sup>20</sup> Twenty observational cohort studies that reported on 28 associations met inclusion criteria.<sup>20</sup> Among these studies, a higher mortality rate occurred in patients on first-generation antipsychotic drugs compared to SGAs in the first 6 months after initiation of antipsychotic therapy (avg. relative risk = 1.4; risk difference = 4.3% [range 2.5% to 7.3%] in community dwelling and long-term care residents.<sup>20</sup> Based on the model used by the investigators, up to 6.7% of the higher mortality for first-generation antipsychotic drugs was due to stroke, 6.6% to hip fracture, 3.5% to myocardial infarction, and 0.9% to ventricular arrhythmia (17.4% combined).<sup>20</sup> The lower and upper bounds that adjust for poor diagnostic sensitivity and other potential biases were 7.4% and 18.9% for stroke, 1.3% and 9.2% for hip fracture, 4.2% and 9.5% for myocardial infarction, and 3.9% to 4.8% for ventricular arrhythmia (16.8% and 42.4% combined); the lower bounds are higher than the point estimate because poor sensitivity of diagnostic algorithms leads to downward bias.<sup>20</sup> The authors concluded that the current evidence suggests that hip fracture, stroke, myocardial infarction, and ventricular arrhythmias partially explain the mortality difference between first-generation antipsychotic drugs and SGAs.<sup>20</sup>

A systematic review was conducted to assess absolute changes in body weight and body mass index (BMI) as well as the proportion of patients with greater than a 7% increase or decrease in body weight after initiation of a first- or second-generation antipsychotic drug.<sup>21</sup> A 7% weight gain or loss was deemed clinically relevant.<sup>21</sup> Any RCT or controlled clinical trial where patients were randomized into various antipsychotic intervention groups was eligible to be included.<sup>21</sup> No restrictions with regard to diagnosis, age, drug dose or duration of drug exposure were applied.<sup>21</sup> Data from 307 RCTs with ITT analysis were included.<sup>21</sup> Four drug exposure categories were defined based on duration of antipsychotic use: short-term ( $\leq 6$  weeks), medium short-term (6-16 weeks), medium term (16-38 weeks) and long term ( $>38$  weeks).<sup>21</sup> Most drugs showed a statistically significant change in weight post-baseline, with the exception of amisulpride, aripiprazole, asenapine, sertindole, ziprasidone and placebo, which showed no statistically significant weight change.<sup>21</sup> Although a comparison between antipsychotic agents was not tested, crude data suggested that clozapine and olanzapine were associated with the most severe weight gain post-baseline, while first-generation antipsychotic drugs (e.g., haloperidol) are also associated with significant weight gain.<sup>21</sup> Even over the shortest exposure period of 6 weeks, an increase in body weight post-baseline was evident for most antipsychotic agents.<sup>21</sup> The number of studies reporting data on BMI change in treatment-naïve patients was limited to 18 studies.<sup>21</sup> All antipsychotic agents studied showed a statistically significant increase in BMI.<sup>21</sup> Only 11 studies presented data of 7% weight gain in treatment-naïve patients.<sup>21</sup> Almost all antipsychotic agents reported a statistically significant increase in the proportion of subjects with clinically relevant weight gain.<sup>21</sup> Apart from the short-term exposure (6 weeks), treatment with aripiprazole resulted in an elevated number of subjects with clinically relevant weight gain at each duration of exposure category.<sup>21</sup> Twenty-four studies reported on proportional weight loss.<sup>21</sup> Only data for amisulpride, aripiprazole, asenapine, olanzapine, paliperidone, ziprasidone and placebo were available.<sup>21</sup> Results showed that a statistically significant proportion of the patients had clinically relevant weight loss after initiation of any of these drugs, a duration-response pattern was not observed.<sup>21</sup> The investigators concluded that given prolonged exposure to these drugs, virtually all antipsychotic drugs are associated with weight gain and the rationale of switching antipsychotic agents to achieve weight reduction may be overrated.<sup>21</sup>

A systematic review was conducted to identify and analyze data on first-trimester exposure to olanzapine, quetiapine, risperidone and aripiprazole and risk of congenital malformations.<sup>22</sup> Any studies that contained original data on first-trimester exposure and pregnancy outcome with respect to congenital malformations were included.<sup>22</sup> Cumulated data for olanzapine were 1090 first-trimester-exposed pregnancies with 38 malformations resulting in a malformation rate of 3.5%.<sup>22</sup> The corresponding numbers for quetiapine, risperidone and aripiprazole were 443/16 (3.6%), 432/22 (5.1%) and 100/5 (5.0%), respectively.<sup>22</sup> Relative risk estimates were 1.0 (95% CI, 0.7 to 1.4) for olanzapine, 1.0 (95% CI, 0.6 to 1.7) for quetiapine, 1.5 (95% CI, 0.9 to 2.2) for risperidone,

and 1.4 (95% CI, 0.5 to 3.1) for aripiprazole.<sup>22</sup> The authors concluded that first-trimester exposure to olanzapine is not associated with an increased risk of congenital malformation.<sup>22</sup> Data for quetiapine and risperidone also do not suggest a substantially increased risk, while the risk estimate for aripiprazole remains imprecise owing to limited data.<sup>22</sup>

The aim of a recent systematic review was to compare the long-term effects of various antipsychotic drugs on overall cognition and on specific cognitive domains in patients with schizophrenia.<sup>23</sup> To identify relevant publications, multiple databases were searched without language restrictions for RCTs in which an oral formulation of SGA drug (amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, and zotepine) was compared to placebo or haloperidol or other SGA drugs, for the treatment of schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorders).<sup>23</sup> Nine RCTs of at least 6 months duration (median 52 weeks) were included.<sup>23</sup> A network meta-analysis was used to combine direct and indirect comparisons of the cognitive effects between antipsychotics.<sup>23</sup> The comparison between each treatment on the overall cognitive score showed that quetiapine and olanzapine led to more improvement than amisulpride ( $p < 0.05$ ) and haloperidol ( $p < 0.05$ ).<sup>23</sup> The significant effect sizes were 0.27 [0.13-0.41] for quetiapine; 0.21 [0.10-0.32] for olanzapine; and 0.16 [0.02-0.30] for risperidone.<sup>23</sup> Quetiapine and olanzapine also provided better improvement in overall cognitive score than amisulpride in cognitive tasks (effect sizes: 0.27 [0.10-0.44], and 0.20 [0.04-0.37], respectively).<sup>23</sup> No statistically significant difference between quetiapine, olanzapine and risperidone in overall cognitive scores was found.<sup>23</sup> When memory tasks were considered, ziprasidone fared better than amisulpride (0.28 [0.02-0.54]) and haloperidol (0.32 [0.09-0.55]).<sup>23</sup> Quetiapine was better than other drugs ( $p < 0.001$ ) on attention and processing speed tasks, followed by ziprasidone ( $p < 0.05$ ) and olanzapine ( $p < 0.05$ ).<sup>23</sup> The effects of quetiapine, risperidone and olanzapine were better than those of amisulpride ( $p < 0.05$ ) on executive functions.<sup>23</sup> The authors concluded that differences between antipsychotics in their effect on the overall cognitive score in schizophrenia may exist.<sup>23</sup> Quetiapine and olanzapine were associated with the most positive effects on cognitive function, followed by risperidone, ziprasidone, amisulpride and haloperidol.<sup>23</sup>

#### **New Guidelines:**

U.S. Department of Health & Human Services Officer of Inspector General (OIG) analysis of Medicaid claims in five states, 2014.

Second-generation antipsychotics are widely used to treat children enrolled in Medicaid who have mental health conditions.<sup>24</sup> However, SGAs can have serious side effects and little clinical research has been conducted on the safety of treating children with these drugs.<sup>24</sup> Consequently, children's treatment with SGAs needs careful management and monitoring.<sup>24</sup> This OIG report examined the quality of care provided to children receiving SGAs that were paid for by Medicaid based a sample of 687 claims for SGAs prescribed to children in California, Florida, Illinois, New York, and Texas, which represented 39% of total Medicaid payments for SGAs in 2011.<sup>24</sup> Board-certified child and adolescent psychiatrists reviewed medical records related to the sampled claims using 7 criteria related to quality-of-care concerns, which were established on the basis of information and guidelines issued by various Federal and State agencies and professional associations regarding the prescribing of psychotropic drugs to children.<sup>24</sup> Of the claims reviewed, 67% showed quality-of-care concerns, which were further categorized by the 7 identified criteria<sup>24</sup>:

- 41% wrong treatment
- 17% too young
- 7% side effects
- 53% poor monitoring
- 34% taken too long
- 23% wrong dose
- 37% too many drugs

In the 5 states, 8% of SGAs were prescribed for the limited number of medically accepted pediatric indications.<sup>24</sup> There are only 5 SGAs with medically accepted pediatric indications.<sup>24</sup> Medically accepted indications include both uses of drugs approved by the Food and Drug Administration (FDA) and uses supported by one or more of 3 drug compendia.<sup>24</sup> Three of the 11 SGAs carry an FDA boxed warning regarding increased chances of suicidal thinking and behavior in pediatric patients.<sup>24</sup> The investigators found that over a third of SGAs were prescribed in the presence of conditions described in the FDA boxed warning.<sup>24</sup>

To ensure the quality of the care provided to children receiving SGAs, The OIG report made 3 recommendations to the Centers for Medicare & Medicaid Services (CMS). First, the OIG recommended that CMS work with State Medicaid programs to perform utilization reviews of SGAs prescribed to children.<sup>24</sup> Second, the OIG recommended that CMS work with State Medicaid programs to conduct periodic reviews of medical records associated with claims for SGAs prescribed to children.<sup>24</sup> Third, the OIG recommended that CMS work with States to consider other methods of enhanced oversight of SGAs prescribed to children, such as implementing peer review programs.<sup>24</sup> CMS concurred with all three recommendations.<sup>24</sup>

#### **New Safety Alerts:**

##### GEODON (ziprasidone)<sup>25</sup>

FDA labeling addition to Warnings and Precautions [December 2014]: Severe Cutaneous Adverse Reactions, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome have been reported with ziprasidone exposure. DRESS and other Severe Cutaneous Adverse Reactions (SCAR) are sometimes fatal.<sup>25</sup> Discontinue Geodon if DRESS or other types of SCAR are suspected.<sup>25</sup> The FDA urges health care professionals, patients and caregivers to report adverse effects involving ziprasidone.

##### ZYPREXA (olanzapine)<sup>26</sup>

FDA has warned that olanzapine can cause rare but serious skin reactions, including DRESS. A new warning to product labeling of all olanzapine products will describe DRESS.<sup>26</sup> The FDA urges health care professionals, patients and caregivers to report adverse effects involving olanzapine.

##### ABILIFY (aripiprazole)<sup>27</sup>

The use of aripiprazole has been associated with new impulse-control problems.<sup>27</sup> The FDA has warned of new compulsive or uncontrollable urges to gamble, binge eat, shop, and have sex have been reported with the use of any aripiprazole product.<sup>27</sup> These uncontrollable urges were reported to have stopped when aripiprazole was discontinued or the dose was reduced.<sup>27</sup> The FDA urges health care professionals, patients and caregivers to report adverse effects involving aripiprazole.

#### **New Formulations or Indications:**

Oral formulations of aripiprazole received an expanded FDA-approved indication for Tourette disorder in December 2014.<sup>19</sup> The recommended dosage range for Tourette's disorder is 5-10 mg daily.<sup>19</sup> Doses should be initiated at 2 mg daily and adjusted gradually in increments of 5 mg daily at intervals of no less than 1 week to achieve adequate control of tics.<sup>19</sup> FDA approval was based on 2 short-term placebo-controlled trials (8-10 weeks) in pediatric patients (ages 6-18 years) who met DSM-IV criteria for Tourette's disorder and had a Total Tic score (TTS) of  $\geq 20$ -22 on the YGTSS.<sup>19</sup> The primary endpoint in both trials was the change from baseline in the TTS of the YGTSS.<sup>19</sup> Ratings for the TTS are made from 5 domains on a 0-5 scale for motor and vocal tics each (summation of these 10 scores provides a TTS, 0-50).<sup>19</sup> In these trials, aripiprazole statistically significantly reduced YGTSS TTS by -5.3 to -9.3 relative to placebo.<sup>19</sup>

ARISTADA (aripiprazole lauroxil) is an extended-release suspension for intramuscular (IM) injection approved by the FDA in October 2015 for schizophrenia in patients who have established tolerability with oral aripiprazole.<sup>28</sup> Aripiprazole lauroxil (N-lauroyloxymethyl aripiprazole) is a prodrug of N-hydroxymethyl

aripiprazole, which in turn is a prodrug of aripiprazole.<sup>29</sup> Because aripiprazole lauroxil contains an active moiety (N-hydroxymethyl aripiprazole) that has not been approved in any new drug application by the FDA, it was considered a new drug entity.<sup>29</sup> The efficacy of aripiprazole lauroxil extended-release IM injection was evaluated in a Phase 3 safety and efficacy trial that demonstrated efficacy of 2 doses (441 mg and 882 mg, both given monthly) in patients with schizophrenia.<sup>30</sup> In addition, the FDA considered previous evidence of the safety and efficacy of oral aripiprazole when data were reviewed for aripiprazole lauroxil, as well as pharmacokinetic evidence from the sponsor that demonstrated similar serum concentrations for oral aripiprazole given daily at approved doses with aripiprazole lauroxil given monthly at the studied doses.<sup>29</sup> The Phase 3 trial enrolled adult patients with an acute exacerbation of schizophrenia that required hospital admission.<sup>30</sup> All other antipsychotic medications were discontinued.<sup>30</sup> The primary endpoint was change in the PANSS total score from baseline to day 85 using LOCF at the imputation method.<sup>30</sup> The PANSS total score was statistically significantly reduced for the 441 mg dose (LSMD -10.65; 95% CI, -14.30, -6.99) and the 882 mg dose (LSMD -11.94; 95% CI, -15.56, -8.32) compared to placebo.<sup>30</sup> During the first 21 days of the trial, the active treatment arms also received oral aripiprazole while patients who received IM placebo did not.<sup>29</sup> The FDA was concerned that this may confound the study results, and so the primary analysis was repeated using PANSS data from Day 22 and Day 29 as the baseline.<sup>29</sup> The mean difference from placebo was less using data from day 22 for the 441 mg dose (LSMD -5.3; 95% CI, -8.3, -2.3) and 882 mg dose (LSMD -4.6; 95% CI, -7.6, -1.7) but these data were still statistically significant.<sup>29</sup> From Day 29, the mean difference from placebo was also less for the 441 mg dose (LSMD -4.5; 95% CI, -7.4, -1.6) and 882 mg dose (LSMD -4.0; 95% CI, -6.9, -1.1) but these data were also still statistically significant.<sup>29</sup> There were no new safety findings for aripiprazole lauroxil compared to what is known about oral aripiprazole, except for injection site reactions.<sup>29</sup>

INVEGA TRINZA (paliperidone palmitate; PP3M) is an extended-release suspension for IM injection (administered every 3 months) approved by the FDA in May 2015 for schizophrenia in patients who already adequately treated with INVEGA SUSTENNA (paliperidone palmitate; PP1M) administered once monthly for at least 4 months.<sup>31</sup> Paliperidone is the metabolite of risperidone, which is an atypical antipsychotic approved since 1993.<sup>32</sup> The efficacy of PP3M was based on one randomized, double-blind, placebo-controlled relapse-prevention study wherein patients were stabilized for 12 weeks on PP3M after a 17-week transition phase from PP1M.<sup>33</sup> The primary efficacy endpoint was time to relapse after randomization of patients to continue PP3M after the 12-week maintenance phase or switch to placebo.<sup>33</sup> The study was stopped in accordance with the protocol when statistical significance in favor of PP3M was demonstrated at the pre-planned interim analysis of time to relapse data.<sup>33</sup> Approximately 3-time as many patients in the placebo group (29%) as in the PP3M group (9%) experienced a relapse event (hazard ratio 3.45; 95% CI, 1.73 to 6.88), with the most common relapse events being worsening of psychotic symptoms or psychiatric hospitalization.<sup>33</sup> No unique safety findings were noted for PP4M other than a small increase in subjectively rated injection site pain, which may be related to the increased injection volume with PP3M versus PP1M.<sup>31</sup>

SAPHRIS (asenapine) received an expanded FDA-approved indication as monotherapy for pediatric patients ages 10 to 17 years with Bipolar mania in March 2015.<sup>34</sup> The efficacy of asenapine for the management of acute mania associated with Bipolar I disorder was established in one 3-week, placebo-controlled, double-blind trial of 403 pediatric patients 10 to 17 years of age.<sup>35</sup> A total of 302 patients received fixed doses of 2.5 mg, 5 mg and 10 mg twice daily (all initiated at 2.5 mg twice daily).<sup>35</sup> All doses of asenapine were statistically superior to placebo in improving YMRS total score compared to placebo (2.5 mg: LSMD -3.2; 95% CI, -5.6, -0.8; 5 mg: LSMD -5.3; 95% CI, -7.7, -2.9; 10 mg: LSMD -6.2; 95% CI, -8.6, -3.8).<sup>35</sup>

## **NEW DRUG EVALUATIONS:**

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

### **Clinical Efficacy:**

#### **Brexipiprazole**

Brexipiprazole is an oral SGA approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia and for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD).<sup>36</sup>

The efficacy of brexipiprazole for schizophrenia was established in two 6-week randomized, placebo-controlled studies with unclear levels of bias at doses from 0.25 to 4 mg daily (see Table 3).<sup>37,38</sup> Overall, 1,310 patients with schizophrenia requiring hospitalization for active psychosis (total Brief Psychiatric Rating Scale (BPRS) score  $\geq 40$ ) were enrolled from multiple countries, with 36% of sites reporting from the U.S.<sup>37,38</sup> Both studies enrolled similar patients based on extensive and identical inclusion and exclusion criteria that used the same primary endpoint (change from baseline in total PANSS score at week 6) and the same key secondary endpoint (change from baseline in CGI-S score at week 6).<sup>37,38</sup> Demographic and baseline characteristics were generally similar across treatment groups. Mixed-effects model for repeated measures (MMRM) approach to data analyses was utilized in both trials.<sup>37,38</sup> In the first trial, an improvement in PANSS total score at week 6 was statistically superior for brexipiprazole 4 mg daily arm compared to placebo (least squares mean difference (LSMD) -6.47; 95% CI -10.60, -2.35) but doses of 1 or 2 mg daily did not provide any statistically difference than placebo.<sup>37</sup> Relative to placebo, the CGI-S scores were also improved with brexipiprazole 4 mg daily arm (LSMD -0.38; 95% CI -0.62, -0.15) but not with the 1 or 2 mg daily doses.<sup>37</sup> In the second trial, an improvement in the PANSS total score at week 6 was statistically superior for brexipiprazole 4 mg daily (LSMD -7.64; 95% CI -12.0, -3.30) and 2 mg daily (LSMD -8.72; 95% CI -13.1, -4.37) compared to placebo, but lower doses did not demonstrate efficacy.<sup>38</sup> Relative to placebo, the CGI-S scores were also improved with brexipiprazole for the 2 and 4 mg daily doses (LSMD -0.33; 95% CI -0.56, -0.10, and LSMD -0.38; 95% CI -0.61, -0.15, respectively).<sup>38</sup> There was no clear dose-response observed in the clinical trials for schizophrenia, but daily doses of 2-4 mg appear to be effective and statistically superior to placebo in total PANSS scores by Week 2.<sup>39</sup>

The efficacy of brexipiprazole for use as an adjunctive therapy to antidepressants for the treatment of MDD was established in two 6-week randomized, placebo-controlled studies with unclear levels of bias at doses from 1 to 3 mg daily (see Table 3).<sup>40,41</sup> Overall, 2,887 patients with MDD and inadequate response to antidepressant therapy were enrolled from multiple countries, but most centers were located in the U.S.<sup>40,41</sup> In both studies, enrolled patients entered an 8-week, single-blind placebo phase when patients received open-label antidepressant therapy. Patients with an inadequate response at week 8 (<50% reduction in HAM-D17, with HAM-D17 scores that remain  $\geq 14$  and CGI-I scores that remain  $\geq 3$ ) entered a double-blind phase, where they were randomized to brexipiprazole (with continued open-label antidepressant therapy) or placebo (with continued open-label antidepressant therapy) for 6 weeks. Demographic and baseline characteristics were generally similar across treatment groups. In the first trial, a 1 and 3 mg daily doses were studied;<sup>40</sup> in the second trial, a 2 mg daily dose was studied.<sup>41</sup> Both studies enrolled similar patients based on identical inclusion and exclusion criteria and antidepressant therapy was limited to a selection of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).<sup>40,41</sup> The primary endpoint for both trials was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at week 14 (end of 6-week double-blind treatment phase).<sup>40,41</sup> The key secondary endpoint for both trials was change from baseline in the Sheehan Disability Score (SDS) at week 14 (end of 6-week double-blind treatment phase).<sup>40,41</sup> The study that evaluated the 1 and 3 mg daily doses found a statistical significant improvement in MADRS for the 3 mg dose (LSMD -1.52; 95% CI -2.92, -0.13);<sup>40</sup> likewise, the statistical superiority for the 2 mg daily dose in the second trial was seen (LSMD -3.12; 95% CI -4.70, -1.54).<sup>41</sup> Statistical superiority to placebo of the 2 mg

and 3 mg doses were seen from week 1 and continued through the end of the study periods.<sup>39</sup> A similar statistical trend was also seen with the key secondary endpoint SDS.<sup>40,41</sup> A dose response was not observed between the 2 and 3 mg daily doses, but both were effective as adjunctive therapy with antidepressant drugs.

### Cariprazine

Cariprazine is an oral atypical antipsychotic approved by the FDA for the treatment of schizophrenia and bipolar mania/mixed episodes.<sup>42</sup>

The efficacy of cariprazine for schizophrenia was established in three 6-week randomized, placebo-controlled studies with unclear levels of bias at doses from 1.5 to 9 mg daily (see Table 4).<sup>43-45</sup> Overall, 1,049 patients with schizophrenia requiring hospitalization for active psychosis were enrolled (mostly from the U.S., Russia, India, Ukraine and Romania). Two studies were a fixed-dose design with atypical antipsychotics risperidone and aripiprazole as active comparators<sup>43,44</sup> and one study was a flexible dose-range study design.<sup>45</sup> All 3 studies enrolled similar patients based on extensive and identical inclusion and exclusion criteria and used the same primary endpoint (change from baseline in total PANSS score at week 6) and the same key secondary endpoint (change from baseline in CGI-S score at week 6). Demographic and baseline characteristics were generally similar across treatment groups. A statistically significant difference in change in PANSS scores at week 6 were evident at all doses compared to placebo by both MMRM and last observation carried forward (LOCF) approaches to data analyses.<sup>43-45</sup> The change from baseline in PANSS was similar between cariprazine 3-6 mg daily and aripiprazole in one trial.<sup>44</sup> In a separate trial, risperidone 4 mg daily improved PANSS by an additional 5 points compared to cariprazine.<sup>44</sup> Though these studies were not powered to detect superiority between the active arms, the limited data available show that cariprazine up to 6 mg daily has efficacy within the range of approved atypical antipsychotics, with a safety profile similar to these approved drugs at doses of 6 mg daily or less. Overall, results show a modest dose-response with cariprazine. In addition, statistically significant improvement in PANSS scores were observed after one week 1 with higher doses compared to 2-3 weeks with lower doses.<sup>46</sup> Though higher doses of cariprazine appear to be more effective and work more quickly than lower doses, long-term studies are needed to determine how the accumulation of DDCAR affects the safety profile of cariprazine and how this might affect long-term maintenance dosing of the drug (see Clinical Safety below).

The efficacy of cariprazine for bipolar mania/mixed episodes was established in three 3-week randomized, placebo-controlled studies with unclear levels of bias at doses from 3 to 12 mg daily (see Table 4).<sup>47-49</sup> Overall, 962 patients were enrolled (mostly from the U.S., India and Russia). Two of the studies used flexible doses of 3-12 mg daily<sup>47,48</sup> and the third study used flexible doses of 3-6 mg daily or 6-12 mg daily.<sup>49</sup> All 3 trials enrolled similar patients based on extensive and identical inclusion and exclusion criteria (primary inclusion criteria was YMRS total score  $\geq 20$ ). Change from baseline in the YMRS total score at week 3 was the primary endpoint in all 3 studies; the same key secondary endpoint, change from baseline in the CGI-S at week 3, was also assessed in each trial. Demographic and baseline characteristics were generally similar across treatment groups. Statistically significant differences from placebo in the YMRS total score were evident between 4 and 7 days, and the effect persisted to Week 3.<sup>46</sup> There was no evidence of dose response in the flexible dose-range study that compared 3-6 mg daily to 6-12 mg daily.<sup>49</sup> The trials demonstrated efficacy at daily dose up to 6 mg in patients with bipolar mania/mixed episodes with no evidence to suggest higher daily doses are more efficacious.

### **Clinical Safety:**

In all of the clinical trials, there was a high attrition rate across all arms. However, attrition rates were consistent with attrition rates commonly seen in other clinical trials that study these populations.

The safety profile of brexpiprazole was similar for both the schizophrenia and MDD cohorts and with atypical antipsychotics generally. The FDA did not identify any unique safety concerns with brexpiprazole.<sup>39</sup> Thirteen deaths were reported during the clinical development of brexpiprazole, 9 in patients who were taking



brexpiprazole. However, causes of death varied and no patterns were identified.<sup>39</sup> Deaths were unlikely to be due to the drug but rather the disease itself (e.g., suicide).<sup>39</sup> Serious adverse events were identified in 5.2% of brexpiprazole-treated patients, with most attributed to exacerbation of the psychotic disorder. The most common treatment-emergent adverse events (TEAE) were increased weight, headache, akathisia, somnolence, fatigue, anxiety and increased appetite.<sup>37,38,40,41</sup> Adverse metabolic effects were not any different than what is expected from drugs in this class.

The most frequently reported treatment-emergent adverse events with cariprazine were akathisia, extrapyramidal symptoms, constipation and nausea or vomiting.<sup>43,44,47-50</sup> The primary concern with cariprazine was the dose-relation of adverse events observed during the 6-week schizophrenia trials.<sup>46</sup> Significant dose-related toxicities related to cariprazine were identified with increasing frequency over time during the 6-week clinical trials.<sup>46</sup> Because of the long half-life of the major accumulating active metabolite didesmethylcariprazine (DDCAR), troubling and serious adverse effects like akathisia and other extrapyramidal symptoms were seen as DDCAR approached steady-state (4-6 weeks) in the clinical trials.<sup>46</sup> Overall, the incidence of akathisia, an adverse effect that has been linked to suicide and other dangerous behaviors (i.e., violence) if left untreated, was the most prominent dose-related adverse event associated with cariprazine. Akathisia was evident even at the low doses and was higher than the percentage seen with aripiprazole, the drug with the most obvious association with akathisia to date.<sup>46</sup> The incidence of akathisia was commonly around 15% in short-term clinical trials that assessed daily doses of 6 mg.<sup>46</sup> The drug sponsor responded to such concerns by the FDA by resubmitting a new drug application (NDA) that sought approval of doses that were limited to up to 6 mg daily.<sup>46</sup> The FDA accepted the NDA because the 6-week safety follow-up in the clinical trials would have been sufficient enough to see some of the adverse events associated with accumulation of the DDCAR at steady-state.<sup>46</sup> Besides akathisia, harm outcomes of interest include pulmonary and ocular toxicity, based on reports of pulmonary fibrosis and cataracts found in a 1-year dog study, though the risk for pulmonary and ocular toxicity is yet unclear in humans due to the short duration of the clinical trials.<sup>46</sup> Increased systolic and diastolic blood pressure was also noted with cariprazine and routine monitoring for hypertension is advised.<sup>42</sup> Other adverse events observed with cariprazine, such as extrapyramidal disorders and adverse metabolic effects are well known and predicted with all atypical antipsychotics. Prolongation of the QTc interval does not appear to be a clinically relevant safety concern with cariprazine.<sup>42</sup> Other available treatments for schizophrenia and bipolar disorder have much shorter half-lives than DDCAR. Treatment recommendations after acute response are to continue treatment at the dose that worked acutely.<sup>46</sup> However, this practice may not be prudent with cariprazine because of DDCAR though the safety profile of the drug appears to be similar to other atypical antipsychotics over a 6-week period. Long-term follow-up studies are needed to clarify appropriate long-term maintenance dosing of cariprazine.

#### **Pharmacology and Pharmacokinetic Properties:**

Brexpiprazole is a new molecular entity. Brexpiprazole acts as a partial agonist with similar potency at serotonin 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and acts as a potent antagonist at serotonin 5-HT<sub>2A</sub> receptors. Brexpiprazole has a similar pharmacological profile as aripiprazole except for a lower affinity to the dopamine D<sub>2</sub> receptor, but it is unknown if this translates clinically to less dopamine-related adverse effects, such as EPS, hyperprolactinemia and tardive dyskinesia.

Specific pharmacology and pharmacokinetic properties of brexpiprazole are listed in table 1.

Table 1. Pharmacology and Pharmacokinetic Properties of Brexpiprazole.<sup>36</sup>

Parameter	
Mechanism of Action	Partial agonist at serotonin 5-HT <sub>1A</sub> and dopamine D <sub>2</sub> receptors, and an antagonist at serotonin 5-HT <sub>2A</sub> receptors
Absorption	C <sub>max</sub> = 4 hours; F = 95%; steady-state = 10-12 days
Distribution and Protein Binding	V <sub>d</sub> = 1.56 L/kg, indicating extravascular distribution 99% protein-bound in plasma (albumin and α1-acid glycoprotein)
Metabolism	CYP3A4 and CYP2D6 without active metabolites
Half-Life	T <sub>1/2</sub> = 91 hours
Elimination	25% in urine (1% unchanged); 46% in feces (14% unchanged)

Abbreviations: C<sub>max</sub> = maximum plasma concentration of drug; F = oral bioavailability; kg = kilograms; L = Liters; T<sub>1/2</sub> = terminal elimination half-life; V<sub>d</sub> = volume of distribution.

Cariprazine is a new molecular entity. Cariprazine is similar to other atypical antipsychotics with activity at dopamine (D<sub>2</sub> and D<sub>3</sub>) and serotonin (5-HT<sub>1A</sub>) receptors. Similar to aripiprazole, it acts as a partial agonist at dopamine D<sub>2</sub> receptors rather than as an antagonist like other atypical antipsychotics. The drug preferentially binds D<sub>3</sub> receptors by 3-10-fold, but the contribution of activity to D<sub>3</sub> to clinical efficacy is unknown.<sup>46</sup> In terms of pharmacokinetics, cariprazine is unique because of the long half-life (3-9 days) of the parent compound and its equipotent metabolite DDCAR (half-life 2-3 weeks).<sup>46</sup> The metabolite DDCAR accumulates, and so over time the total active drug exposure increases with the same daily dose of cariprazine.<sup>46</sup>

Specific pharmacology and pharmacokinetic properties of cariprazine are listed in table 2.

Table 2. Pharmacology and Pharmacokinetic Properties of Cariprazine.<sup>42</sup>

Parameter	
Mechanism of Action	Partial agonist at dopamine D <sub>3</sub> (very high affinity) and D <sub>2</sub> receptors (high affinity) and at serotonin 5-HT <sub>1A</sub> receptors. Antagonist at serotonin 5-HT <sub>2B</sub> (high affinity) and 5-HT <sub>2A</sub> receptors (moderate affinity) and histamine H <sub>1</sub> receptors. Low affinity for serotonin 5-HT <sub>2C</sub> and α <sub>1A</sub> -adrenergic receptors; no affinity for cholinergic muscarinic receptors.
Absorption	C <sub>max</sub> = 3-6 hours
Distribution and Protein Binding	91-97% protein-bound in plasma
Metabolism	CYP3A4 (extensive) and CYP2D6 to DCAR and to DDCAR. DDCAR is equipotent to cariprazine and is metabolized by CYP3A4 to a hydroxylated metabolite
Half-Life	Cariprazine (3-9 days); DDCAR (2-3 weeks)
Elimination	21% excreted through urine (1% unchanged)

Abbreviations: C<sub>max</sub> = maximum plasma concentration of drug; DCAR = desmethylcariprazine; DDCAR = didesmethylcariprazine.

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**Comparative Clinical Efficacy:**

## Clinically Relevant Endpoints:

- 1) Reduction in total PANSS score (schizophrenia)
- 2) Improvement in total YMRS score (bipolar mania)
- 3) Improvement in total MADRS score (MDD)

## Primary Study Endpoints (brexpiprazole):

- 1) Change from baseline in PANSS score over 6 weeks (schizophrenia)
- 2) Change from baseline in MADRS score over 6 weeks (MDD)

## Primary Study Endpoints (cariprazine):

- 1) Change from baseline in PANSS score over 6 weeks (schizophrenia)
- 2) Change from baseline in YMRS score over 3 weeks (bipolar mania)

**Table 3. Comparative Evidence for Brexpiprazole.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Kane, et al. <sup>37</sup>  MC, DB, PC, PG, RCT  Phase 3	1. BRX 1 mg PO QD  2. BRX 2 mg PO QD  3. BRX 4 mg PO QD  4. PBO PO QD  2:3:3:3  6 weeks	<u>Demographics:</u> Mean age: 39 y Male: 63% White: 60% Mean PANSS: -total score: 95 -CGI-S score: 4.9 -Duration current psychosis: 2.5 wk  <u>Inclusion Criteria:</u> -Age 18-65 y -Schizophrenia (DSM-IV) -Acute psychosis (total BPRS score ≥40; BPRS score ≥4 on ≥2 items (hallucinatory behavior, unusual or disorganized thought content) and CGI-S score ≥4) -h/o relapse and/or untreated symptom exacerbation  <u>Exclusion Criteria:</u> -First episode of schizophrenia -Tardive dyskinesia -Severe akathisia -h/o substance abuse ≤6 months -Any psychotropic drug, sleep aid, antihistamine, vitamin or herbal supplement, CYP2D6 inhibitor; CYP3A4 inhibitor or inducer, or varenicline	<u>n:</u> 1. 120 2. 186 3. 184 4. 184  <u>mITT:</u> 1. 117 2. 179 3. 181 4. 180  <u>Attrition:</u> 1. 33% 2. 31% 3. 29% 4. 36%	<u>Primary Endpoint:</u> LS mean Δ PANSS total score from baseline to week 6: 1. -16.90 (SE 1.86) 2. -16.1 (SE 1.49) 3. -20.00 (SE 1.48) 4. -13.53 (SE 1.52)  1 vs. 4: -3.37 (95% CI -8.06, 1.32) 2 vs. 4: -3.08 (95% CI -7.23, 1.07) 3 vs. 4: -6.47 (95% CI -10.6, -2.35)  <u>Key Secondary Endpoint:</u> LS mean Δ CGI-S score from baseline to week 6: 1. -0.91 (SE 0.11) 2. -0.99 (SE 0.09) 3. -1.19 (SE 0.08) 4. -0.81 (SE 0.09)  1 vs. 4: -0.10 (95% CI -0.37, 0.16) 2 vs. 4: -0.19 (95% CI -0.42, 0.05) 3 vs. 4: -0.38 (95% CI -0.62, -0.15)	NS  NS  NA  NS  NS  NS	<u>SAE:</u> * 1. 2.5% 2. 2.2% 3. 2.2% 4. 5.4%  *most indicative of underlying disorder: acute psychosis; psychotic disorder; aggression; schizophrenia  <u>D/C due to TEAE:</u> 1. 9.2% 2. 5.9% 3. 7.1% 4. 12.0%  <u>Insomnia:</u> 1. 12.5% 2. 13.4% 3. 15.2% 4. 14.7%  <u>Headache:</u> 1. 7.5% 2. 10.8% 3. 10.3% 4. 14.7%  <u>Akathisia:</u> 1. 4.2% 2. 4.8% 3. 6.5% 4. 7.1%  Weight gain: 1. 1.23 kg 2. 1.89 kg 3. 1.52 kg 4. 0.35 kg	NA for all	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> LOW. Central permuted-block randomization by IVRS/IWRS. Baseline characteristics relatively equal. <u>Performance Bias:</u> LOW. Double-blinding maintained by using identical tablets and packaging for all treatment arms. <u>Detection Bias:</u> LOW. Sponsor personnel blinded to treatment allocation. Power assumptions appropriate. <u>Attrition Bias:</u> HIGH. mITT analysis of efficacy based on population w/ ≥1 baseline and post-baseline efficacy measurement who received ≥1 dose of study medication. High attrition rate across all groups. Missing values imputed by MMRM. <u>Reporting Bias:</u> UNCLEAR. All reported endpoints were pre-specified but the sponsors were responsible for study design and conduct and the collection, management, analysis, and interpretation of the data.  <b>Applicability:</b> <u>Patient:</u> Extensive exclusion criteria limit applicability to persons commonly encountered in practice. <u>Intervention:</u> It is unknown whether doses lower than 4 mg/d are more efficacious than placebo at reducing positive and negative symptoms of schizophrenia. <u>Comparator:</u> Placebo demonstrates efficacy but does not allow a comparison with other SGAs. <u>Outcomes:</u> 6 weeks is a limited duration to assess long-term efficacy. Follow-up for safety occurred at 30 days after the last dose of trial medication. <u>Setting:</u> Patients followed weekly at 64 centers from Columbia, Croatia, Mexico, Philippines, Russia, Slovakia, Taiwan, and USA (36%).

<p>2. Correll, et al.<sup>38</sup></p> <p>MC, DB, PC, PG, RCT</p> <p>Phase 3</p>	<p>1. BRX 0.25 mg PO QD</p> <p>2. BRX 2 mg PO QD</p> <p>3. BRX 4 mg PO QD</p> <p>4. PBO PO QD</p> <p>1:2:2:2</p> <p>6 weeks</p>	<p><b>Demographics:</b>  Mean age: 40 y  Male: 63%  White: 67%  Mean PANSS:  -total score: 95  -CGI-S score: 4.9  -Duration current psychosis: 2.6 wk</p> <p><b>Key Inclusion Criteria:</b>  See Kane, et al.<sup>37</sup></p> <p><b>Key Exclusion Criteria:</b>  See Kane, et al.<sup>37</sup></p>	<p><b>n:</b></p> <p>1. 90  2. 182  3. 180  4. 184</p> <p><b>mITT:</b></p> <p>1. 87  2. 180  3. 178  4. 178</p> <p><b>Attrition:</b></p> <p>1. 38%  2. 32%  3. 33%  4. 40%</p>	<p><b>Primary Endpoint:</b>  LS mean Δ PANSS total score from baseline to week 6:</p> <p>1. -14.90 (SE 2.23)  2. -20.73 (SE 1.55)  3. -19.65 (SE 1.54)  4. -12.01 (SE 1.60)</p> <p>1 vs. 4: -2.89 (95% CI -8.27, 2.49)  2 vs. 4: -8.72 (95% CI -13.1, -4.37)  3 vs. 4: -7.64 (95% CI -12.0, -3.30)</p> <p><b>Key Secondary Endpoint:</b>  LS mean Δ CGI-S score from baseline to week 6:</p> <p>1. -0.85 (SE 0.12)  2. -1.15 (SE 0.08)  3. -1.20 (SE 0.08)  4. -0.82 (SE 0.09)</p> <p>1 vs. 4: -0.03 (95% CI -0.31, 0.26)  2 vs. 4: -0.33 (95% CI -0.56, -0.10)  3 vs. 4: -0.38 (95% CI -0.61, -0.15)</p>	<p>NS</p> <p>NA</p> <p>NA</p> <p>NS</p> <p>NA</p> <p>NA</p>	<p><b>SAE:*</b></p> <p>1. 4.4%  2. 2.2%  3. 1.1%  4. 3.8%</p> <p>*most indicative of underlying disorder: acute psychosis; psychotic disorder; aggression; schizophrenia</p> <p><b>D/C due to TEAE:</b></p> <p>1. 13.3%  2. 8.2%  3. 9.4%  4. 17.4%</p> <p><b>Insomnia:</b></p> <p>1. 8.9%  2. 8.8%  3. 8.3%  4. 9.8%</p> <p><b>Headache:</b></p> <p>1. 10.0%  2. 9.3%  3. 12.2%  4. 8.2%</p> <p><b>Akathisia:</b></p> <p>1. 0.0%  2. 4.4%  3. 7.2%  4. 2.2%</p> <p><b>Weight gain:</b></p> <p>1. NR  2. 1.45 kg  3. 1.28 kg  4. 0.42 kg</p>	<p>NA for all</p>	<p><b>Risk of Bias (low/high/unclear):</b></p> <p><b>Selection Bias:</b> LOW. Central permuted-block randomization by IVRS/IWRS. Baseline characteristics relatively equal.</p> <p><b>Performance Bias:</b> UNCLEAR. Unknown what precautions were taken to ensure double-blinding maintained.</p> <p><b>Detection Bias:</b> UNCLEAR. Unknown what precautions were taken to ensure data assessors were blinded. Power assumptions appropriate.</p> <p><b>Attrition Bias:</b> HIGH. mITT analysis of efficacy based on population w/ ≥1 baseline and post-baseline efficacy measurement who received ≥1 dose of study medication. High attrition rate across all groups.</p> <p><b>Reporting Bias:</b> UNCLEAR. All reported endpoints were pre-specified but the sponsors were responsible for study design and conduct and the collection, management, analysis, and interpretation of the data.</p> <p><b>Applicability:</b></p> <p><b>Patient:</b> Extensive exclusion criteria limit applicability to persons commonly encountered in practice.</p> <p><b>Intervention:</b> Doses lower than 2 mg/d may not be any more efficacious than placebo at reducing positive and negative symptoms of schizophrenia.</p> <p><b>Comparator:</b> Placebo demonstrates efficacy but does not allow a comparison with other SGAs.</p> <p><b>Outcomes:</b> 6 weeks is a limited duration to assess long-term efficacy. Follow-up for safety occurred at 30 days after the last dose of trial medication.</p> <p><b>Setting:</b> Patients followed weekly at 65 centers from U.S. (36%), Ukraine, Romania, Serbia, Latvia, Malaysia, Japan, Poland, South Korea and Canada.</p>
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<p>3. Thase, et al.<sup>40</sup></p> <p>MC, DB, PC, PG, RCT</p> <p>Phase 3</p>	<p>1. BRX 1 mg PO QD</p> <p>2. BRX 3 mg PO QD</p> <p>3. PBO PO QD</p> <p>1:1:1</p> <p>7-28-day screening phase</p> <p>8-week OL titration phase of 1-3 antidepressant(s)</p> <p>6 weeks</p>	<p><b>Demographics:</b>  Mean age: 46 y  Male: 32%  White: 85%  Mean MADRS: 26.5  Mean SDS: 5.7</p> <p><b>Inclusion Criteria:</b>  -Age 18-65 y  -MDD (DSM-IV) ≥8 wk  -Inadequate response to 1-3 trials of OL antidepressants* (HDRS-17 ≥14; &lt;50% reduction from baseline and MADRS scores; CGI-I score ≥3 at each follow-up visit during 8-wk tx phase prior to randomization)</p> <p><b>Exclusion Criteria:</b>  -Antipsychotic drug &gt;3 wk  -Electroconvulsive therapy  -Psychotherapy  -hospitalization  -hallucinations or delusions  -Other psychiatric disorder  -Substance abuse, including alcoholism  -Abnormal ECG or laboratory result</p> <p>*Titrated to maximum tolerated dose</p>	<p><b>n:</b>  1. 226  2. 230  3. 221</p> <p><b>mITT:</b>  1. 211  2. 213  3. 203</p> <p><b>Attrition:</b>  1. 7%  2. 7%  3. 8%</p>	<p><b>Primary Endpoint:</b>  LS mean Δ MADRS total score from baseline to week 6:  1. NR for mITT population  2. NR for mITT population</p> <p>1 vs. 3: -1.19  (95% CI -2.58, 0.20)  2 vs. 3: -1.52  (95% CI -2.92, -0.13)</p> <p><b>Key Secondary Endpoints:</b>  LS mean Δ SDS score, measured at week 3 and 6:  1. -1.33 (SE 0.14)  2. -1.21 (SE 0.13)  3. -0.84 (SE 0.13)</p> <p>1 vs. 3: -0.49  (95% CI -0.87, -0.12)  2 vs. 3: -0.37  (95% CI -0.73, -0.00)</p> <p>LS mean Δ individual SDS scores for work/school, measured at week 3 and 6:  1. -1.16 (SE 0.17)  2. -0.91 (SE 0.18)  3. -0.73 (SE 0.17)</p> <p>1 vs. 3: -0.43  (95% CI -0.91, 0.04)  2 vs. 3: -0.18  (95% CI -0.66, 0.31)</p> <p>LS mean Δ individual SDS scores for social life, measured at week 3 and 6:  1. -1.39 (SE 0.15)  2. -1.31 (SE 0.15)  3. -0.91 (SE 0.15)</p> <p>1 vs. 3: -0.48  (95% CI -0.89, -0.07)  2 vs. 3: -0.40</p>	<p>NS</p> <p>NA</p> <p>NA</p> <p>NS</p> <p>NS</p> <p>NA</p>	<p><b>SAE:*</b>  1. 0.4%  2. 0.4%  3. 0%</p> <p><b>D/C due to TEAE:</b>  1. 1.3%  2. 3.5%  3. 1.4%</p> <p><b>Headache:</b>  1. 9.3%  2. 6.1%  3. 7.7%</p> <p><b>Akathisia:</b>  1. 4.4%  2. 13.5%  3. 2.3%</p> <p><b>Mean Weight gain:</b>  1. 1.4 kg  2. 1.6 kg  3. 0.2 kg</p> <p><b>Somnolence:</b>  1. 4.0%  2. 5.7%  3. 0.5%</p> <p><b>Tremor:</b>  1. 4.0%  2. 5.2%  3. 3.2%</p> <p><b>Nasopharyngitis:</b>  1. 6.6%  2. 3.1%  3. 1.8%</p>	<p>NA for all</p>	<p><b>Risk of Bias (low/high/unclear):</b>  <b>Selection Bias:</b> LOW. Central permuted-block randomization by IVRS/IWRS. Baseline characteristics relatively equal.  <b>Performance Bias:</b> UNCLEAR. Unknown what precautions were taken to ensure double-blinding maintained.  <b>Detection Bias:</b> UNCLEAR. Unknown what precautions were taken to ensure data assessors were blinded. Power assumptions appropriate.  <b>Attrition Bias:</b> HIGH. mITT analysis of efficacy based on population w/ ≥1 baseline and post-baseline efficacy measurement who received ≥1 dose of study medication.  <b>Reporting Bias:</b> HIGH. All reported endpoints emphasize per-protocol population, which is a less conservative measure. The sponsors were responsible for study design and conduct and the collection, management, analysis, and interpretation of the data.</p> <p><b>Applicability:</b>  <b>Patient:</b> MADRS scores largely reflects moderate depression.  <b>Intervention:</b> Used as adjunctive to 1 antidepressant (78%); 2 antidepressants (18%); 3 antidepressants (3%)  <b>Comparator:</b> Placebo is appropriate if efficacy needs to be established. Adjunctive antidepressant applicable to MDD.  <b>Outcomes:</b> 6 weeks is a limited duration to assess long-term efficacy. Difference of 1.91 points vs placebo may have met threshold of MCID. Follow-up for safety occurred at 30 days after the last dose of trial medication.  <b>Setting:</b> Patients followed weekly at 92 centers from U.S. (71.7%), Germany, Ukraine, Russia, Hungary, Canada and Romania.</p>
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				(95% CI -0.80, 0.01)  LS mean Δ individual SDS scores for family life, measured at week 3 and 6: 1. -1.35 (SE 0.15) 2. -1.28 (SE 0.16) 3. -0.80 (SE 0.15)  1 vs. 3: -0.55 (95% CI -0.97, -0.14) 2 vs. 3: -0.48 (95% CI -0.90, -0.06)	NS     NA  NA			
4. Thase, et al. <sup>41</sup>  MC, DB, PC, PG, RCT  Phase 3	1. BRX 2 mg PO QD  2. PBO PO QD  1:1  7-28-day screening phase  8-week OL titration phase of 1-3 antidepressant(s)  6 weeks	<u>Demographics:</u> Mean age: 45 y Male: 30% White: 90% Mean MADRS: 26.9 Mean SDS: 6.2  <u>Inclusion Criteria:</u> Thase, et al. <sup>40</sup>  <u>Exclusion Criteria:</u> Thase, et al. <sup>40</sup>	<u>n:</u> 1. 188 2. 191  <u>mITT:</u> 1. 187 2. 191  <u>Attrition:</u> 1. 7% 2. 7%	<u>Primary Endpoint:</u> LS mean Δ MADRS total score from baseline to week 6: 1. -8.27 (SE NR) 2. -5.15 (SE NR)  MD: -3.12 (95% CI -4.70, -1.54)  <u>Key Secondary Endpoints:</u> LS mean Δ SDS score, measured at week 3 and 6: 1. -1.35 (SE 0.17) 2. -0.91 (SE 0.17)  MD: -0.45 (95% CI -0.86, -0.03)  LS mean Δ individual SDS scores for work/school, measured at week 3 and 6: 1. -1.09 (SE 0.22) 2. -0.90 (SE 0.22)  MD: -0.19 (95% CI -0.73, 0.34)  LS mean Δ individual SDS scores for social life, measured at week 3 and 6: 1. -1.54 (SE 0.19) 2. -1.04 (SE 0.18)	NA     NA     NS	<u>SAE:</u> * 1. 1.1% 2. 1.0%  <u>D/C due to TEAE:</u> 1. 3.2% 2. 0%  <u>Akathisia:</u> 1. 7.4% 2. 1.0%  <u>Mean Weight gain:</u> 1. 1.64 kg 2. 0.36 kg  <u>Restlessness:</u> 1. 3.2% 2. 0%  <u>Somnolence:</u> 1. 4.3% 2. 0.5%  <u>Anxiety:</u> 1. 3.7% 2. 1.6%  <u>Sedation:</u> 1. 1.1% 2. 0%	NA for all	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> LOW. See Thase, et al. <sup>40</sup> <u>Performance Bias:</u> UNCLEAR. See Thase, et al. <sup>40</sup> <u>Detection Bias:</u> UNCLEAR. See Thase, et al. <sup>40</sup> <u>Attrition Bias:</u> HIGH. See Thase, et al. <sup>40</sup> <u>Reporting Bias:</u> HIGH. See Thase, et al. <sup>40</sup>  <b>Applicability:</b> <u>Patient:</u> MADRS scores largely reflects moderate depression. <u>Intervention:</u> Used as adjunctive to 1-3 antidepressants (most common were escitalopram, duloxetine, and venlafaxine XR) <u>Comparator:</u> Placebo is appropriate if efficacy needs to be established. Adjunctive antidepressant applicable to MDD. <u>Outcomes:</u> 6 weeks is a limited duration to assess long-term efficacy. Difference of 1.91 points vs placebo may have met threshold of MCID. Follow-up for safety occurred at 30 days after the last dose of trial medication. <u>Setting:</u> Patients followed weekly at 59 centers from U.S. (74.9%), Poland, France, Canada and Slovakia.

				MD: -0.50 (95% CI -0.96, -0.04)  LS mean $\Delta$ individual SDS scores for family life, measured at week 3 and 6: 1. -1.33 (SE 0.19) 2. -0.73 (SE 0.19)  MD: -0.60 (95% CI -1.07, -0.13)	NA          NA			
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**Abbreviations** ARR = absolute risk reduction; ATRQ = Antidepressant Treatment Response Questionnaire, Massachusetts General Hospital; BPRS = Brief Psychiatric Rating Scale; BRX = brexpiprazole; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity; CI = confidence interval; DB = double blinded; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; HDRS-17 = Hamilton Depression Rating Scale, 17-item; IM = intramuscular; ITT = intention to treat; IVRS = interactive voice response system; IWRS = interactive web response system; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; MC = multi-centered; MCID = minimum clinically important difference; MD = mean difference; MDD = major depressive disorder; mITT = modified intention to treat; MMRM = mixed-effects model for repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PC = placebo controlled; PBO = placebo; PG = parallel group; PO = oral; PSP = Personal and Social Performance Scale; QD = once daily; RCT = randomized controlled trial; SAE = serious adverse effect; SDS = Sheehan Disability Score; SE = standard error; SEM = standard error of the mean; SGA = second-generation antipsychotics; TEAE = treatment emergent adverse events; y = years.



**Table 4. Comparative Evidence for Cariprazine.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
<b>SCHIZOPHRENIA</b>								
1. Durgam, et al. <sup>43</sup>  MC, DB, AC, PC, PG, RCT	1. CAR 1.5 mg PO QD  2. CAR 3 mg PO QD  3. CAR 4.5 mg PO QD  4. risperidone 4 mg/d  5. PBO  1:1:1:1:1  6 weeks	<u>Demographics:</u> Mean age: 36 y Males: 69% White: 51% PANSS total score: 1. 97.1 (SEM 0.8) 2. 97.2 (SEM 0.7) 3. 96.7 (SEM 0.8) 4. 98.1 (SEM 0.8) 5. 97.3 (SEM 0.8) <u>CGI-S score:</u> 1. 4.7 (SEM 0.1) 2. 4.9 (SEM 0.1) 3. 4.8 (SEM 0.1) 4. 4.8 (SEM 0.1) 5. 4.9 (SEM 0.1)  <u>Inclusion Criteria:</u> -Age 18-60 y -Schizophrenia dx per DSM-IV ≥1 y -Current exacerbation <2 wk -≥1 hospitalization in past year for psychotic episode -total PANSS score 80-120 -score ≥4 (moderate) on ≥2 of 4 PANSS positive sx (delusions, hallucinations, conceptual disorganization, suspiciousness) -CGI-S ≥4 -BMI 18-35 mg/m <sup>2</sup>  <u>Exclusion Criteria:</u> -First psychotic episode	<u>n:</u> 1. NR 2. NR 3. NR 4. NR 5. NR (total n=732)  <u>mITT:</u> 1. 145 2. 146 3. 147 4. 140 5. 151  <u>Attrition:</u> 1. 38% 2. 34% 3. 33% 4. 28% 5. 48%	<u>Primary Endpoint:</u> Mean Δ PANSS total score from baseline to week 6: 1. -19.4 (SEM 1.6) 2. -20.7 (SEM 1.6) 3. -22.3 (SEM 1.6) 4. -26.9 (SEM 1.6) 5. -11.8 (SEM 1.5)  <u>Key Secondary Endpoint:</u> LS mean Δ CGI-S score from baseline to week 6: 1. -1.0 (SEM 0.1) 2. -1.1 (SEM 0.1) 3. -1.3 (SEM 0.1) 4. -0.5 (SEM 0.1) 5. -0.7 (SEM 0.1)  1 vs. 5: -7.6 (95% CI -11.8, -3.3) 2 vs. 5: -8.8 (95% CI -13.1, -4.6) 3 vs. 5: -10.4 (95% CI -14.6, -6.2) 4 vs. 5: -15.1 (95% CI -19.4, -10.8)  1 vs. 5: -0.4 (95% CI -0.6, -0.1) 2 vs. 5: -0.5 (95% CI -0.7, -0.2) 3 vs. 5: -0.6 (95% CI -0.9, -0.4) 4 vs. 5: -0.8 (95% CI -1.1, -0.6)	NA  NA  NA  NA  NA  NA  NA	<u>Early D/C from AE:</u> 1. 9.7% 2. 5.5% 3. 8.2% 4. 9.3% 5. 14.6%  <u>SAE*:</u> 1. 3.4% 2. 0% 3. 2.7% 4. 2.1% 5. 4.6%  <u>Akathisia:</u> 1. 9.0% 2. 9.6% 3. 7.5% 4. 8.6% 5. 4.6%  <u>EPS:</u> 1. 9.0% 2. 8.9% 3. 11.6% 4. 12.9% 5. 4.6%  <u>Insomnia:</u> 1. 10.3% 2. 16.4% 3. 16.3% 4. 15.0% 5. 7.3%  <u>Mean Δ FBG:</u> 1. -0.1 mg/dL 2. +0.8 mg/dL 3. +5.1 mg/dL 4. -0.9 mg/dL 5. +3.3 mg/dL	NA for all	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> UNCLEAR. Method of randomization not disclosed. Allocation concealment unknown. <u>Performance Bias:</u> UNCLEAR. Methods of blinding and to maintain blinding unknown. Washout period 7 days and may be insufficient. <u>Detection Bias:</u> UNCLEAR. Methods to blind data assessors unknown. Appropriate statistical tests used. Power assumptions unclear. Short study duration. Safety outcomes only followed for 2 weeks after study ended. <u>Attrition Bias:</u> HIGH. mITT population assessed for efficacy, which had to take study drug and have ≥1 post-baseline assessment of PANSS. Missing values imputed by LOCF and MMRM. <u>Reporting Bias:</u> UNCLEAR. All study outcomes were pre-specified but the sponsor was responsible for the study design, implementation, analysis and interpretation of data, decision to publish, and funding for editorial support.  <b>Applicability:</b> <u>Patient:</u> extensive inclusion and exclusion criteria limit population studied that may not reflect who is commonly seen in clinical practice. <u>Intervention:</u> studied as monotherapy; initiated at 1.5 mg, and dose titrated rapidly. No other psychotropic drugs were allowed. <u>Comparator:</u> placebo appropriate to establish efficacy; risperidone and placebo compared to 'assess assay sensitivity'; no testing was done to compare to CAR. <u>Outcomes:</u> PANSS assessed weekly; it is a frequently utilized scale in clinical trials to assess symptoms of schizophrenia; however, duration of study may be too short to know if

		-psychotropic drugs -‘various DSM-IV disorders’ (e.g., schizoaffective, schizophreniform, bipolar I and II) -alcohol/substance abuse/dependence -tx-resistant schizophrenia (poor response to ≥2 antipsychotics) -suicidal or attempt				*most commonly schizophrenia exacerbation or psychotic disorder		study results will reflect what will be seen in clinical practice. <u>Setting:</u> All patients hospitalized for screening and for ≥4 weeks of double-blind treatment. Patients rehospitalized after discharge if condition worsened. 65 centers in the U.S. (38%), India (22%), Russia (22%), Ukraine (16%) and Malaysia (3%).
2. Durgam, et al. <sup>44</sup>  MC, DB, AC, PC, PG, RCT	1. CAR 3 mg PO QD  2. CAR 6 mg PO QD  3. aripiprazole 10 mg/d  4. PBO  1:1:1:1  6 weeks	<u>Demographics:</u> Mean age: 38 y Males: 63% White: 64% PANSS total score: 1. 96.1 (SD 8.7) 2. 95.7 (SD 9.4) 3. 95.6 (SD 9.0) 4. 96.5 (SD 9.1) CGI-S score: 1. 4.9 (SD 0.6) 2. 4.8 (SD 0.6) 3. 4.8 (SD 0.6) 4. 4.8 (SD 0.6)  <u>Inclusion Criteria:</u> See Durgam, et al. <sup>43</sup>  <u>Exclusion Criteria:</u> See Durgam, et al. <sup>43</sup>	<u>n:</u> 1. 155 2. 157 3. 152 4. 153  <u>mITT:</u> 1. 151 2. 154 3. 150 4. 149  <u>Attrition:</u> 1. 33% 2. 38% 3. 25% 4. 38%	<u>Primary Endpoint:</u> Mean Δ PANSS total score from baseline to week 6: 1. -20.2 (SEM 1.5) 2. -23.0 (SEM 1.5) 3. -21.2 (SEM 1.4) 4. -14.3 (SEM 1.5)  1 vs. 4: -6.0 (95% CI -10.1, -1.9) 2 vs. 4: -8.8 (95% CI -12.9, -4.7) 3 vs. 4: -7.0 (95% CI -11.0, -2.9)  <u>Key Secondary Endpoint:</u> LS mean Δ CGI-S score from baseline to week 6: 1. -1.4 (SEM 0.1) 2. -1.5 (SEM 0.1) 3. -1.4 (SEM 0.1) 4. -1.0 (SEM 0.1)  1 vs. 4: -0.4 (95% CI -0.6, -0.2) 2 vs. 4: -0.5 (95% CI -0.7, -0.3) 3 vs. 4: -0.4 (95% CI -0.6, -0.2)		<u>Early D/C from AE:</u> 1. 9.7% 2. 12.7% 3. 9.2% 4. 11.1%  <u>SAE*:</u> 1. 2.6% 2. 4.5% 3. 2.6% 4. 1.3%  <u>Akathisia:</u> 1. 7.1% 2. 14.6% 3. 7.2% 4. 4.6% 2 vs. 4: <i>p</i> <0.05  <u>Insomnia:</u> 1. 13.5% 2. 14.0% 3. 10.5% 4. 16.3%  <u>Deaths:</u> 1. 0% 2. 1.3% 3. 0% 4. 0%  <u>Mean Δ FBG:</u> 1. +2.8 mg/dL	NA NA NA  NA NA NA  NA 10%/10 NA  NA NA NA  NA NA NA NA	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> UNCLEAR. See Durgam, et al. <sup>43</sup> <u>Performance Bias:</u> UNCLEAR. See Durgam, et al. <sup>43</sup> <u>Detection Bias:</u> UNCLEAR. See Durgam, et al. <sup>43</sup> <u>Attrition Bias:</u> HIGH. See Durgam, et al. <sup>43</sup> <u>Reporting Bias:</u> UNCLEAR. See Durgam, et al. <sup>43</sup>  <b>Applicability:</b> <u>Patient:</u> See Durgam, et al. <sup>43</sup> <u>Intervention:</u> See Durgam, et al. <sup>43</sup> <u>Comparator:</u> placebo appropriate to establish efficacy; aripiprazole and placebo compared to ‘assess assay sensitivity’; no testing was done to compare to CAR. <u>Outcomes:</u> See Durgam, et al. <sup>43</sup> <u>Setting:</u> All patients hospitalized for screening and for ≥4 weeks of double-blind treatment. Patients rehospitalized after discharge if condition worsened. 65 centers in the U.S., Romania, Russia and Ukraine.

						2. +5.6 mg/dL 3. +0.0 mg/dL 4. -5.8 mg/dL	NA NA	
						*most commonly schizophrenia exacerbation or psychotic disorder		
3. Kane, et al. <sup>45</sup>  MC, DB, PC, PG, RCT	1. CAR 3-6 mg PO QD  2. CAR 6-9 mg PO QD  3. PBO  1:1:1  6 weeks	<u>Demographics:</u> Mean age: 38 y Males: 77% Asian: 38% Black: 36% PANSS total score: 1. 96.3 (SD 9.3) 2. 96.3 (SD 9.0) 3. 96.6 (SD 9.3) CGI-S score: 1. 4.8 (SD 0.7) 2. 4.9 (SD 0.7) 3. 4.9 (SD 0.7)  <u>Inclusion Criteria:</u> See Durgam, et al. <sup>43</sup>  <u>Exclusion Criteria:</u> See Durgam, et al. <sup>43</sup>	<u>n:</u> 1. 151 2. 148 3. 147  <u>mITT:</u> 1. 147 2. 147 3. 145  <u>Attrition:</u> 1. 36% 2. 42% 3. 40%	<u>Primary Endpoint:</u> LSMD Δ PANSS total score from baseline to week 6: 1. -22.8 (SE 1.6) 2. -25.9 (SE 1.7) 3. -16.0 (SE 1.6)  1 vs. 3: -6.8 (95% CI -11.3, -2.4) 2 vs. 3 -9.9 (95% CI -14.5, -5.3)  <u>Key Secondary Endpoint:</u> LS mean Δ CGI-S score from baseline to week 6: 1. -1.4 (SE 0.1) 2. -1.6 (SE 0.1) 3. -1.0 (SE 0.1)  1 vs. 3: -0.3 (95% CI -0.6, -0.1) 2 vs. 3: -0.5 (95% CI -0.8, -0.3)		<u>Early D/C from AE:</u> 1. 9.3% 2. 8.8% 3. 8.8%  <u>SAE*:</u> 1. 6.0% 2. 2.0% 3. 8.2%  <u>Akathisia:</u> 1. 15.9% 2. 16.9% 3. 3.4%  <u>Insomnia:</u> 1. 6.6% 2. 10.8% 3. 10.9%  <u>Mean Δ FBG:</u> 1. +7.1 mg/dL 2. +3.2 mg/dL 3. +2.5 mg/dL  *most commonly worsening schizophrenia; also HTN and hepatitis were noted to be related to CAR	NA for all  NA  NA  NA  NA	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> UNCLEAR. See Durgam, et al. <sup>43</sup> <u>Performance Bias:</u> UNCLEAR. See Durgam, et al. <sup>43</sup> <u>Detection Bias:</u> UNCLEAR. See Durgam, et al. <sup>43</sup> <u>Attrition Bias:</u> HIGH. See Durgam, et al. <sup>43</sup> <u>Reporting Bias:</u> UNCLEAR. See Durgam, et al. <sup>43</sup>  <b>Applicability:</b> <u>Patient:</u> See Durgam, et al. <sup>43</sup> <u>Intervention:</u> CAR initiated at 1.5 mg/d day 1, 3 mg day 2 and 3, then titrated to specific treatment arm. <u>Comparator:</u> placebo appropriate to establish efficacy but comparison with another antipsychotic would be more beneficial. <u>Outcomes:</u> See Durgam, et al. <sup>43</sup> <u>Setting:</u> All patients hospitalized for screening and for ≥4 weeks of double-blind treatment. Patients rehospitalized after discharge if condition worsened. 41 centers in the U.S., India, Columbia and South Africa.

**BIPOLAR MANIA/MIXED EPISODES**

<p>4. Durgam, et al.<sup>47</sup></p> <p>MC, DB, PC, PG, RCT</p>	<p>1. CAR 3-12 mg PO QD</p> <p>2. PBO</p> <p>1:1</p> <p>3 weeks</p>	<p><b>Demographics:</b>  Mean age: 38 y  Males: 66%  White: 43%  YMRS total score:  1. 30.6 (SEM 0.5)  2. 30.2 (SEM 0.5)  CGI-S score:  1. 4.7 (SEM 0.1)  2. 4.6 (SEM 0.1)</p> <p><b>Inclusion Criteria:</b>  -Age 18-65 y  -Bipolar I disorder, manic or mixed type, w/ or w/o psychotic symptoms (DSM-IV)  -YMRS total score ≥20, w/ ≥4 score on ≥2 of the following: irritability, speech, content, and disruptive/aggressive behavior.</p> <p><b>Exclusion Criteria:</b>  -First manic episode  -Rapid cycling  -Axis I disorders other than bipolar I  -Severe Axis II disorders  -psyotropic drugs  -alcohol/substance abuse/dependence  -suicide risk  -MADRS score ≥18  -electroconvulsive therapy or depot neuroleptics  -h/o of malignancy, or hematologic, endocrine, CV, respiratory, renal,</p>	<p><b>n:</b>  1. 118  2. 120</p> <p><b>ITT:</b>  1. 118  2. 117</p> <p><b>Attrition:</b>  1. 36%  2. 38%</p>	<p><b>Primary Endpoint:</b>  Mean Δ YMRS total score at week 3:  1. -15.1 (SEM 0.5)  2. -8.9 (SEM 1.1)  LSMD -6.1 (95% CI, -8.9 to -3.3)</p> <p><b>Secondary Endpoints:</b>  Mean Δ CGI-S score at week 3:  1. -1.6 (SEM 0.1)  2. -0.9 (SEM 0.1)  LSMD -0.6 (95% CI, -1.0 to -0.3)</p>	<p>NA</p> <p>NA</p>	<p><b>Early D/C from AE:</b>  1. 14.4%  2. 10.2%</p> <p><b>SAE*:</b>  1. 3.4%  2. 4.2%</p> <p><b>Akathisia:</b>  1. 18.6%  2. 5.9%</p> <p><b>EPS:</b>  1. 24.6%  2. 9.3%</p> <p><b>Dyspepsia:</b>  1. 12.7%  2. 6.8%</p> <p><b>Nausea:</b>  1. 15.3%  2. 10.2%</p> <p><b>Constipation:</b>  1. 15.3%  2. 8.5%</p> <p><b>Mean Δ FBG:</b>  1. +7.7 mg/dL  2. -0.2 mg/dL</p> <p>*included worsening mania or bipolar disorder, EPS, convulsions, HTN</p>	<p>NA for all</p>	<p><b>Risk of Bias (low/high/unclear):</b>  <b>Selection Bias:</b> UNCLEAR. Method of randomization not disclosed. Allocation concealment unknown.  <b>Performance Bias:</b> UNCLEAR. Methods of blinding and to maintain blinding unknown. Washout period up to 4 days only and may be insufficient.  <b>Detection Bias:</b> UNCLEAR. Methods to blind data assessors unknown. Appropriate statistical tests used. Power assumptions unclear. Short study duration. Safety outcomes only followed for 2 weeks after study ended.  <b>Attrition Bias:</b> HIGH. mITT population assessed for efficacy, which had to take study drug and have ≥1 post-baseline assessment of PANSS. Missing values imputed by LOCF.  <b>Reporting Bias:</b> UNCLEAR. All study outcomes were pre-specified but the drug sponsor was responsible for the study design, implementation, analysis and interpretation of data, decision to publish, and funding for editorial support.</p> <p><b>Applicability:</b>  <b>Patient:</b> extensive exclusion criteria, including other DSM-IV Axis I diagnoses (e.g., dementia, schizophrenia, schizoaffective disorder, other psychotic disorders); population seen in real world may not reflect subjects in study. 37% patients had experienced current manic episode &gt;1 month.  <b>Intervention:</b> studied as monotherapy; initiated at 1.5 mg, and dose doubled up to 12 mg/d over 5 days, then titrated up to 12 mg/d, or as tolerated.  <b>Comparator:</b> placebo appropriate to establish efficacy but comparison with another antipsychotic would be more beneficial.  <b>Outcomes:</b> YMRS is a frequently utilized scale to assess manic symptoms; however, duration of study may be too short to know if study results will reflect what will be seen in clinical practice.</p>
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<p>6. Calabrese, et al.<sup>49</sup></p> <p>MC, DB, PC, PG, RCT</p> <p>Phase 3</p>	<p>1. CAR 3-6 mg PO QD</p> <p>2. CAR 6-12 mg PO QD</p> <p>3. PBO</p> <p>1:1:1</p> <p>3 weeks</p>	<p><b>Demographics:</b>  Mean age: 42 y  Males: 53%  White: 69%  YMRS total score:  1. 33.2 (SD 5.6)  2. 32.9 (SD 4.7)  3. 32.6 (SD 5.8)  CGI-S score:  1. 4.8 (SD 0.6)  2. 4.8 (SD 0.6)  3. 4.8 (SD 0.7)</p> <p><b>Inclusion Criteria:</b>  See Durgam, et al.<sup>47</sup></p> <p><b>Exclusion Criteria:</b>  See Durgam, et al.<sup>47</sup></p>	<p><b>n:</b>  1. 167  2. 169  3. 161</p> <p><b>mITT:</b>  1. 165  2. 167  3. 160</p> <p><b>Attrition:</b>  1. 23%  2. 30%  3. 24%</p>	<p><b>Primary Endpoint:</b>  Mean Δ YMRS total score at week 3:  1. -18.6 (SE 0.8)  2. -18.5 (SE 0.8)  3. -12.5 (SE 0.8)</p> <p>LSMD 1 vs. 3: -6.1 (95% CI, -8.4 to -3.8)  LSMD 2 vs. 3: -5.9 (05% CI, -8.2 to -3.6)</p> <p><b>Secondary Endpoints:</b>  Mean Δ CGI-S score at week 3:  1. -1.9 (SE 0.1)  2. -1.9 (SE 0.1)  3. -1.3 (SE 0.1)</p> <p>LSMD 1 vs. 3: -0.6 (95% CI, -0.9 to -0.4)  LSMD 2 vs. 3: -0.6 (95% CI, -0.9 to -0.3)</p>	<p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p>	<p><b>Early D/C from AE:</b>  1. 9.0%  2. 14.8%  3. 5.0%  2 vs. 3: p&lt;0.01</p> <p><b>SAE:</b>  1. 4.2%  2. 0%  3. 1.9%</p> <p><b>Akathisia:</b>  1. 17.4%  2. 21.9%  3. 3.7%</p> <p><b>Nausea:</b>  1. 9.6%  2. 11.2%  3. 5.6%</p> <p><b>Constipation:</b>  1. 4.8%  2. 10.7%  3. 2.5%</p> <p><b>Tremor:</b>  1. 2.4%  2. 5.3%  3. 1.9%</p> <p><b>Death:</b>  1. 0.6%  2. 0%  3. 0%</p>	<p>9.8%/10</p> <p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p>	<p><b>Risk of Bias (low/high/unclear):</b>  <b>Selection Bias:</b> UNCLEAR. See Durgam, et al.<sup>47</sup>  <b>Performance Bias:</b> UNCLEAR. Methods of blinding and to maintain blinding unknown. 1 week washout prior to study may be insufficient.  <b>Detection Bias:</b> UNCLEAR. See Durgam, et al.<sup>47</sup>  <b>Attrition Bias:</b> HIGH. See Durgam, et al.<sup>47</sup>  <b>Reporting Bias:</b> UNCLEAR. See Durgam, et al.<sup>47</sup></p> <p><b>Applicability:</b>  <b>Patient:</b> extensive exclusion criteria, population seen in real world may not reflect subjects in study. Most patients had experienced current manic episode &gt;7 days; 30% for &gt;21 days.  <b>Intervention:</b> studied as monotherapy, dose titrated by 1.5 mg to highest tolerable dose allowed within the respective treatment arm. Final mean daily doses were 4.8 mg and 9.1 mg for the 3-6 mg and 6-12 mg groups, respectively.  <b>Comparator:</b> See Durgam, et al.<sup>47</sup>  <b>Outcomes:</b> See Durgam, et al.<sup>47</sup>  <b>Setting:</b> 65 centers in the U.S. (56%), Romania, Russia, Ukraine, Croatia and Serbia. All patients hospitalized for screening and for ≥2 weeks of double-blind treatment. Efficacy evaluations occurred at baseline, day 3, 5, 7, 10, 14 and 21.</p>
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**Abbreviations:** AC = active controlled; AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CAR = cariprazine; CGI-S = Clinical Global Impressions-Severity of Illness; CI = confidence interval; CV = cardiovascular; D/C = discontinuation; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; EPS = extrapyramidal symptoms or disorder; GI = gastrointestinal; HTN = hypertension; ITT = intention to treat; LOCF = last observation carried forward; LSMD = least squares mean difference; MADRS = Montgomery-Asberg Depression Rating Scale; mITT = modified intention to treat; MMRM = mixed-effects model for repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PANSS = Positive and Negative Syndrome Scale; PBO = placebo; PO = orally; PP = per protocol; QD = once daily; SAE = serious adverse event; SD = standard deviation; SE = standard error; SEM = standard error of the mean; YMRS = Young Mania Rating Scale; y = years.

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**Appendix 1: Current Status on Preferred Drug List**

<b>ROUTE</b>	<b>FORMULATION</b>	<b>BRAND</b>	<b>GENERIC</b>	<b>PDL</b>	<b>CARVEOUT</b>
<b>ANTIPSYCHOTICS, FIRST GENERATION ORAL</b>					
ORAL	CAPSULE	LOXAPINE	LOXAPINE SUCCINATE	Y	Y
ORAL	CAPSULE	THIOTHIXENE	THIOTHIXENE	Y	Y
ORAL	ELIXIR	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	ORAL CONC	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	ORAL CONC	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
ORAL	TABLET	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	Y	Y
ORAL	TABLET	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	TABLET	HALOPERIDOL	HALOPERIDOL	Y	Y
ORAL	TABLET	PERPHENAZINE	PERPHENAZINE	Y	Y
ORAL	TABLET	THIORIDAZINE HCL	THIORIDAZINE HCL	Y	Y
ORAL	TABLET	TRIFLUOPERAZINE HCL	TRIFLUOPERAZINE HCL	Y	Y
INHALATION	AER POW BA	ADASUVE	LOXAPINE	V	Y
ORAL	TABLET	ORAP	PIMOZIDE	V	Y
ORAL	TABLET	PIMOZIDE	PIMOZIDE	V	Y
<b>ANTIPSYCHOTICS, SECOND GENERATION ORAL</b>					
ORAL	CAPSULE	GEODON	ZIPRASIDONE HCL	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ZIPRASIDONE HCL	V	Y
ORAL	ORAL SUSP	VERSACLOZ	CLOZAPINE	V	Y
ORAL	SOLUTION	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	SOLUTION	RISPERDAL	RISPERIDONE	Y	Y
ORAL	SOLUTION	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	TAB ER 24	INVEGA	PALIPERIDONE	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	PALIPERIDONE	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	QUETIAPINE FUMARATE	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	ARIPIPRAZOLE	V	Y
ORAL	TAB RAPDIS	CLOZAPINE ODT	CLOZAPINE	V	Y
ORAL	TAB RAPDIS	FAZACLO	CLOZAPINE	V	Y
ORAL	TAB RAPDIS	OLANZAPINE ODT	OLANZAPINE	V	Y
ORAL	TAB RAPDIS	RISPERDAL M-TAB	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	ZYPREXA ZYDIS	OLANZAPINE	V	Y
ORAL	TABLET	ABILIFY	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TABLET	CLOZAPINE	CLOZAPINE	Y	Y

ORAL	TABLET	CLOZARIL	CLOZAPINE	Y	Y
ORAL	TABLET	FANAPT	ILOPERIDONE	V	Y
ORAL	TABLET	LATUDA	LURASIDONE HCL	V	Y
ORAL	TABLET	OLANZAPINE	OLANZAPINE	Y	Y
ORAL	TABLET	QUETIAPINE FUMARATE	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	REXULTI	BREXPIPIRAZOLE	V	Y
ORAL	TABLET	RISPERDAL	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	TABLET	SEROQUEL	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	ZYPREXA	OLANZAPINE	Y	Y
SUBLINGUAL	TAB SUBL	SAPHRIS	ASENAPINE MALEATE	V	Y

#### ANTIPSYCHOTICS, PARENTERAL

INJECTION	AMPUL	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	Y	Y
INJECTION	AMPUL	HALDOL	HALOPERIDOL LACTATE	Y	Y
INJECTION	AMPUL	HALOPERIDOL	HALOPERIDOL LACTATE	Y	Y
INJECTION	VIAL	FLUPHENAZINE DECANOATE	FLUPHENAZINE DECANOATE	Y	Y
INJECTION	VIAL	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
INJECTION	VIAL	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 100	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 50	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE 100	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	SUSER SYR	ABILIFY MAINTENA	ARIPIPIRAZOLE	V	Y
INTRAMUSC	SUSER SYR	ARISTADA	ARIPIPIRAZOLE LAUROXIL	V	Y
INTRAMUSC	SUSER VIAL	ABILIFY MAINTENA	ARIPIPIRAZOLE	V	Y
INTRAMUSC	SYRINGE	INVEGA SUSTENNA	PALIPERIDONE PALMITATE	V	Y
INTRAMUSC	SYRINGE	INVEGA TRINZA	PALIPERIDONE PALMITATE	V	Y
INTRAMUSC	SYRINGE	RISPERDAL CONSTA	RISPERIDONE MICROSPHERES	Y	Y
INTRAMUSC	VIAL	GEODON	ZIPRASIDONE MESYLATE	V	Y
INTRAMUSC	VIAL	HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	VIAL	OLANZAPINE	OLANZAPINE	V	Y
INTRAMUSC	VIAL	ZYPREXA	OLANZAPINE	V	Y
INTRAMUSC	VIAL	ZYPREXA RELPREVV	OLANZAPINE PAMOATE	V	Y

## Appendix 2: Highlights of Prescribing Information

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VRAYLAR safely and effectively. See full prescribing information for VRAYLAR.

VRAYLAR™ (cariprazine) capsules, for oral use

Initial U.S. Approval: 2015

#### WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
- VRAYLAR is not approved for the treatment of patients with dementia-related psychosis. (5.1)

### INDICATIONS AND USAGE

VRAYLAR is an atypical antipsychotic indicated for the:

- Treatment of schizophrenia (1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder (1)

### DOSAGE AND ADMINISTRATION

- Administer VRAYLAR once daily with or without food (2)

	Starting Dose	Recommended Dose
Schizophrenia (2.2)	1.5 mg/day	1.5 mg to 6 mg/day
Bipolar Mania (2.3)	1.5 mg/day	3 mg to 6 mg/day

- Doses above 6 mg daily do not confer significant benefit but increased the risk of dose-related adverse reactions.

### DOSAGE FORMS AND STRENGTHS

Capsules: 1.5 mg, 3 mg, 4.5 mg, and 6 mg (3)

### CONTRAINDICATIONS

Known hypersensitivity to VRAYLAR (4)

### WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia:* Discontinue if appropriate (5.4)
- *Late-Occurring Adverse Reactions:* Because of VRAYLAR's long half-life, monitor for adverse reactions and patient response for several weeks after starting VRAYLAR and with each dosage change (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6)
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq$  5% and at least twice the rate of placebo) were (6.1):

- Schizophrenia: extrapyramidal symptoms and akathisia
- Bipolar mania: extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-272-5525 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Strong CYP3A4 inhibitors: reduce VRAYLAR dosage by half (2.4, 7.1)
- CYP3A4 inducers: do not recommend use with VRAYLAR (2.4, 7.1)

### USE IN SPECIFIC POPULATIONS

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2015

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REXULTI® safely and effectively. See full prescribing information for REXULTI.

REXULTI® (brexpiprazole) tablets, for oral use  
Initial U.S. Approval: 2015

### WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis (5.1).
- Antidepressants increase the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.2).
- Safety and effectiveness of REXULTI have not been established in pediatric patients (8.4).

### INDICATIONS AND USAGE

REXULTI is an atypical antipsychotic indicated for:

- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) (1,14.1)
- Treatment of schizophrenia (1,14.2)

### DOSAGE AND ADMINISTRATION

- Administer REXULTI once daily with or without food (2.1, 2.2, 12.3)

Indication	Starting Dose	Recommended Dose	Maximum Dose
MDD (2.1)	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia (2.2)	1 mg/day	2 to 4 mg/day	4 mg/day

- *Moderate to Severe Hepatic Impairment (Child-Pugh score  $\geq 7$ ):* Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia (2.3)
- *Moderate, Severe or End-Stage Renal Impairment (CLcr  $< 60$  mL/minute):* Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia (2.4)
- *Known CYP2D6 Poor Metabolizers:* Reduce the usual dosage by half (2.5)

### DOSAGE FORMS AND STRENGTHS

Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg (3)

### CONTRAINDICATIONS

Known hypersensitivity to REXULTI or any of its components (4)

### WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack) (5.3)

- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.4)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing REXULTI if a clinically significant decline in WBC occurs in absence of other causative factors (5.7)
- *Orthostatic Hypotension and Syncope:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.9)

### ADVERSE REACTIONS

Most common adverse reactions were (6.1):

MDD: Weight increased and akathisia ( $\geq 5\%$  and at least twice the rate for placebo)

Schizophrenia: Weight increased ( $\geq 4\%$  and at least twice the rate for placebo)

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 ([www.fda.gov/medwatch](http://www.fda.gov/medwatch)).

### DRUG INTERACTIONS

Factors:	Dosage Adjustments for REXULTI (2.5)
Strong CYP2D6* or CYP3A4 inhibitors	Administer half of usual dose
Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors	Administer a quarter of usual dose
Known CYP2D6 Poor Metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers	Double the usual dose and further adjust based on clinical response

\* REXULTI may be administered without dosage adjustment in patients with MDD when administered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine).

### USE IN SPECIFIC POPULATIONS

*Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2015

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### Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2016

- 1 exp Aripiprazole/ 1695
- 2 asenapine.mp. 196
- 3 brexpiprazole.mp. 17
- 4 cariprazine.mp. 35
- 5 exp Clozapine/ 5220
- 6 iloperidone.mp. 128
- 7 exp Lurasidone Hydrochloride/ 103
- 8 olanzapine.mp. 6736
- 9 exp Paliperidone Palmitate/ 491
- 10 exp Quetiapine Fumarate/ 2238
- 11 exp Risperidone/ 5072
- 12 ziprasidone.mp. 1528
- 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 17888
- 14 limit 13 to (english language and yr="2014 -Current" and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial or systematic reviews)) 368

Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2016

- 1 exp Chlorpromazine/ 1507
- 2 exp Fluphenazine/ 281
- 3 exp Haloperidol/ 5380
- 4 exp Loxapine/ 167
- 5 exp Perphenazine/ 240
- 6 exp Thioridazine/ 375
- 7 exp Thiothixene/ 16
- 8 exp Trifluoperazine/ 568
- 9 exp Pimozide/ 264
- 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 8317
- 11 limit 10 to (english language and yr="2014 -Current" and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial or systematic reviews)) 67