

Class Update: Oral Antipsychotics

Date of Review: January 2018

Date of Last Review: May 2016

End Date of Literature Search: 10/27/2017

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

Evidence for the comparative effectiveness of first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in May 2016. Comparative effectiveness of parenteral antipsychotic products were reviewed in September 2017. This review examines recently published comparative evidence of oral first and second generation antipsychotics. In addition, new expanded indications are summarized for several products.

Research Questions:

1. Is there new comparative evidence of meaningful difference in efficacy or effectiveness outcomes (including symptom improvement, quality of life, response to treatment, social or functional status) for schizophrenia, bipolar mania or major depressive disorders (MDD) between oral antipsychotic agents (first- or second-generation) or compared to 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 compared to parenteral antipsychotic agents?
3. Is there new comparative evidence of meaningful difference in effectiveness or harms in certain subpopulations based on demographic characteristics (age, gender, or comorbidities), treatment history (treatment naive or treatment resistant), or concomitant medications?

Conclusions:

Schizophrenia

- No single SGA was superior to other SGAs for multiple clinically relevant outcomes. In general, clozapine, olanzapine, and risperidone oral did achieve superiority for more efficacy outcomes than other SGAs. Quetiapine and ziprasidone were not superior to any other SGAs for any outcomes.¹
 - There was low quality evidence of no difference in social or functional status between risperidone, olanzapine, quetiapine, perphenazine, and ziprasidone at 18 months.¹
 - There was no difference in quality of life at 12 months between olanzapine and risperidone (moderate strength of evidence), ziprasidone (moderate strength of evidence), or quetiapine (low strength of evidence).¹

- There was low quality evidence that response to treatment was statistically more common with olanzapine (odds ratio [OR] 1.71, 95% confidence interval [CI] 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) compared to quetiapine.¹ The absolute response rate for individual treatment groups varied depending on the study from 20 to 80%.¹ Other comparisons failed to achieve statistically significant differences.¹
- There was low quality evidence of statistically greater symptom improvement with clozapine versus other SGAs, with olanzapine and risperidone versus other SGAs and with paliperidone compared to lurasidone and iloperidone. Patients with treatment-resistant schizophrenia had greater improvement when treated with olanzapine compared to quetiapine (standardized mean difference [SMD] -0.29, 95% CI -0.56 to -0.13; small effect size corresponding to an average of -6.08 points on the Positive and Negative Syndrome Scale [PANSS]).¹ Overall differences between treatments were small and may not represent a clinically meaningful change in symptoms between treatment groups. The average improvement in symptoms was generally less than the estimated minimally important difference (11.5 points on the PANSS scale). There was no statistical difference in symptom improvement for other comparisons (low quality of evidence).¹
- There was low quality evidence of no difference in all-cause mortality between SGAs.¹
- There was low quality evidence that treatment with clozapine significantly reduced suicide attempts or hospitalizations to prevent suicide (hazard ratio [HR] 0.76, 95% CI 0.58 to 0.97) and symptoms of suicidality (HR 0.78, 95% CI 0.61 to 0.99) compared to olanzapine in patients at high risk for suicide.¹ It is unclear whether these differences are due to treatment itself or a result of the frequent monitoring required with clozapine.
- No difference was observed in the proportion of patients reporting overall adverse effects between SGAs.¹ For most studies the proportion of patients with adverse effects was greater than 60%.¹ A network meta-analysis of 90 head-to-head RCTs provides low quality evidence that treatment with risperidone LAI, olanzapine, aripiprazole, cariprazine and iloperidone had fewer withdrawals due to adverse effects compared to other SGAs.¹
- Evidence regarding other outcomes (including relapse rate, overall treatment discontinuation, cardiovascular outcomes, diabetes and ketoacidosis and sexual function) was inconsistent between studies and insufficient to draw definitive conclusions between treatment groups.¹
- Overall, olanzapine, risperidone, ziprasidone, and aripiprazole were comparable to haloperidol or perphenazine regarding improvements in quality of life (low quality evidence) or symptom improvement (low to moderate strength of evidence), but had fewer overall adverse effects and withdrawals due to adverse events.¹
- There was no difference in withdrawals due to adverse effects upon comparison of haloperidol and clozapine or quetiapine (low quality evidence) and there was insufficient evidence for other comparisons.¹
- There was insufficient evidence for comparisons of newer SGAs including brexpiprazole, cariprazine, iloperidone or lurasidone for the treatment of schizophrenia.

Bipolar Disorder

- There was no difference in efficacy outcomes (including remission rates, mania symptoms or treatment discontinuation) between olanzapine monotherapy and divalproex or valproate for acute mania in adults with bipolar I (low quality evidence from 4 RCTs [n=867]).² There was low quality evidence from a single study (n=488) which reported greater response rate with asenapine compared to olanzapine but no difference in remission rate between therapies.² There was insufficient evidence for all other antipsychotic drug comparisons (as monotherapy or in combination with mood stabilizers) for treatment of acute mania.
- One study noted that clinically important weight gain of at least 7% was more common in patients treated with olanzapine, though statistical significance of weight gain was not documented in all studies.² Overall, evidence was limited by a lack of direct comparative evidence and there was insufficient comparative evidence to determine differences in safety outcomes or adverse events for patients with bipolar disorder.

Children and Young Adults

- Overall there is insufficient comparative evidence for use of FGAs or SGAs for children or adolescents with bipolar disorder, autism spectrum disorder, ADHD or other conduct disorders, depression, eating disorders, or tic disorders.

- Indirect comparisons between agents indicate that pediatric patients treated with clozapine, lurasidone, and olanzapine had on average more weight gain (2-5 kg over 6 to 12 weeks) than other antipsychotics (low quality evidence).³ Upon comparison between classes, there was moderate strength of evidence that SGAs are likely associated with more weight gain (mean difference [MD] -2.62 kg; 95% CI -4.35 to -0.86) and increase in BMI (MD -1.57 kg/m²; 95% CI -2.49 to -0.53) compared to FGAs.³ There was low quality evidence that use of SGAs was associated with fewer extrapyramidal symptoms compared to FGAs (relative risk [RR] 2.59; 95% CI 1.00 to 7.00) and low quality evidence of no difference in sedation between groups.³
- Subgroup analyses demonstrated no difference in efficacy or harms based on age, sex, or prior treatment history. Duration of treatment did have a slight effect on weight gain, with longer treatment durations associated with larger increases in weight over time (0.04 kg/week; 95% CI 0.014 to 0.071).³

Recommendations:

- No changes to the PDL are recommended for oral antipsychotics based on efficacy or safety data.
- There is a lack of evidence to recommend any new safety edits for the antipsychotic medications.
- Evaluate comparative costs in executive session.

Previous Conclusions (May 2016):

- 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.
- 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.

Previous 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).

Background:

Antipsychotic medications are typically categorized as FGAs and SGAs. **Appendix 1** lists the oral FGAs and SGAs which are currently available. Antipsychotic medications are indicated for a variety of conditions including schizophrenia and schizoaffective disorder, bipolar disorder (acute and maintenance treatment), adjunct treatment for depression, autism, and Tourette's syndrome.⁴ They are often used off-label for other mental health conditions including borderline personality disorder, agitation, aggression and nausea or vomiting.⁴

Schizophrenia is characterized by presence of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms. Diagnosis based on the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) criteria requires presence of at least 2 of these symptoms (one must be either delusions, hallucinations or disorganized speech) for longer than 6 months. Symptoms are commonly categorized as positive symptoms

(delusions and hallucinations) or negative symptoms (blunted affect, avolition, asociality, anhedonia, and avolition).⁵ Onset of schizophrenia occurs most commonly in early adulthood and can have a significant impact on quality of life. Approximately 20% of patients remain relapse-free after a first psychotic episode.¹ However, the majority of patients experience relapse or continued symptoms which can decrease quality of life and create social or occupational difficulties. Factors associated with worse prognosis and disease course include presence of negative symptoms, longer duration of untreated psychosis, and slow or early disease onset at less than 18 years of age.⁶ Schizophrenia has been associated with increased risk of mortality, and is often also associated with increased cannabis use, substance abuse, and higher rates of depression.⁶ Treatment indicated for schizophrenia includes both FGAs and SGAs. First-generation antipsychotics are generally associated with higher incidence of extrapyramidal side effects whereas second-generation antipsychotics may have increased risk for long-term cardiovascular adverse effects.¹ Non-pharmacological therapy including psychological counseling, skills training, psychoeducation, or cognitive therapy is also often combined with pharmacological therapy.⁶ Initial medication selection is often dependent on effectiveness and risks for adverse effects.

Bipolar disorder is characterized by episodes of mania and episodes of depression or hypomania and is estimated to occur in approximately 2% of the world population.^{7,8} Initial diagnosis is most common in patients less than 25 years of age.⁷ It is classified as bipolar I disorder (characterized by at least one manic episode) or bipolar II disorder (primarily characterized by history of depressive and hypomanic episodes).⁷ It can be further classified as rapid cycling with at least 4 episodes of mania, hypomania or depression per year, mania with mixed features, or mania with psychotic features (including hallucinations or delusions).⁷ Frequently bipolar disorder is associated with other mental health conditions including anxiety disorder, ADHD and substance use disorders.⁷ First-line treatment for bipolar disorder is medication therapy including antipsychotics or mood stabilizers such as lithium, divalproex, or lamotrigine.⁷ Goals of treatment include resolution of acute symptoms and long-term prevention of recurrent mania or depressive episodes.⁸ Typically, if acute symptoms do not resolve with treatment, the patient is switched to an alternative medication or an additional medication is added.⁷ Other treatments include electroconvulsive therapy (ECT), psychoeducational therapy, cognitive behavioral therapy and social therapy. The American Psychiatric Association and the National Institute for Health and Clinical Excellence (NICE) recommends ECT as an option for patients with life-threatening suicidality, psychosis or refusal to eat.⁷ ECT may also be considered with severe or treatment-resistant bipolar depression and as a first-line option for pregnant women with severe depression.⁷

Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales. The Clinical Global Impression Scale (CGI) evaluates disease severity and improvement using a 7 point analogue scale with lower scores indicating less severe symptoms and a change of 1 point corresponding to a minimum clinically important difference.^{2,5} The Positive and Negative Syndrome Scale (PANSS) evaluates 30 items in schizophrenic patients each scored on a 7 point scale with lower scores indicating less severe symptoms. This scale can also be sub-divided to assess general psychopathology, positive symptoms, or negative symptoms. Typically response to treatment is defined as greater than 20% improvement in the PANSS score though this definition can vary among trials.^{1,9} Negative symptoms of schizophrenia may also be assessed using the Scale for Assessment of Negative Symptoms (SANS) score which assesses negative symptoms including avolition, affective blunting, avolition-apathy, anhedonia-asociality, and attention impairment. Each item is assessed on a 0-5 point scale with higher scores indicating more severe symptoms. The Brief Psychiatric Rating Scale (BPRS) assesses schizophrenia symptom severity via assessment of 16-18 items (each assessed on a 7-point scale with a total score of 0 to 126). Similarly, quality of life and functional improvement may be assessed using a variety of metrics. The Global Assessment Scale of Functioning (GAF) scale is commonly used for patients with schizophrenia and assesses functional improvement on a 0 to 100 scale. Clinically important improvements in function have been correlated to changes of at least 10 points.¹

For patients with bipolar disorder, symptom improvement is commonly evaluated using the 11-item Young Mania Rating Scale (YMRS). Using this scale, changes of at least 6 points have been correlated with clinically significant improvements.^{8,10} Symptom improvement and severity for patients with bipolar disorder may also be evaluated using the CGI scale (range 1-7 with a minimum clinically important difference of 1 point).^{2,5}

In the Oregon Health Plan, antipsychotic medications are exempt from traditional preferred drug list (PDL) and PA requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use and for pimavanserin to promote safe use in patients with Parkinson's disease psychosis. The majority of antipsychotic use is for SGAs. Each quarter, approximately 25,000 patients receive a prescription for a SGA and 1700 patients have claims for a FGA. This review will assess new evidence for the use of oral antipsychotics.

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), the Cochrane Collaboration, 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 evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Schizophrenia

An AHRQ report examining the effectiveness of first or second generation antipsychotic medications for the treatment of adults with schizophrenia was published in 2017.¹ First generation antipsychotics included in the review were fluphenazine, haloperidol, and perphenazine. Second-generation antipsychotics included aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Comparisons were made between first and second generation antipsychotics and for the following clinical outcomes: functional outcomes (i.e. social or occupational), quality of life, remission rate, mortality, self-harm, symptom improvement, overall adverse effects, and withdrawals due to adverse effects. Re-hospitalization was not assessed as a clinical outcome due to important differences in rationale or indication for re-hospitalization and definition of re-hospitalization between studies. Trials and systematic reviews were included if they had a minimum duration of 12 weeks, were conducted in an outpatient setting, and had fair to good methodological quality.¹ Trials not applicable to a US population, trials reporting only placebo comparisons, trials including only comparisons to older antipsychotic drugs and trials reporting only intermediate outcomes were excluded. Overall, one systematic review (n=47,189) and 24 RCTs (n=6,672) were included which compared differences between second generation antipsychotics.¹ One systematic review (n=118,503) and 5 RCTs (n=1,055) were included which compared first generation to second generation antipsychotics.¹ The majority of patients included in these trials were 25 to 50 years of age with moderate to severe disease and most included studies were 6 to 12 weeks in duration.¹ In trials assessing first-episode schizophrenia, the mean age was 26 years. Few studies assessed long-term outcomes up to 1 to 2 years.¹ There was little evidence which assessed newer second-generation antipsychotics including brexpiprazole, cariprazine, iloperidone or lurasidone.

- SGA comparisons: No single SGA was superior to other SGAs for multiple clinically relevant outcomes. In general, clozapine, olanzapine, risperidone oral and LAI did achieve superiority for more efficacy outcomes than other SGAs. Quetiapine and ziprasidone were not superior to any other SGAs for any outcomes.¹

- There was low quality evidence of no difference in social or functional status (as assessed by the Global Assessment of Functioning [GAF] scale) between risperidone, olanzapine, quetiapine, perphenazine, and ziprasidone at 18 months based on a single large RCT.¹ The GAF scale assesses functional improvement on a 0 to 100 scale and clinically important improvements in functions have been correlated to changes of at least 10 points.¹ There was insufficient evidence to assess differences in employment or residential status between SGAs due to few trials which report these outcomes and limitations in the quality of evidence.¹
- Similarly, there was no difference in quality of life at 12 months between olanzapine and risperidone (moderate strength of evidence), ziprasidone (moderate strength of evidence), or quetiapine (low strength of evidence).¹ There was no difference in quality of life between oral risperidone (oral or LAI) and quetiapine or ziprasidone at 12 months (low strength of evidence).¹ For other comparisons of SGAs, there was insufficient data or quality of evidence to draw any meaningful conclusions regarding quality of life.
- There was low quality evidence that response to treatment was statistically more common with olanzapine (odds ratio [OR] 1.71, 95% CI 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) than quetiapine based on a network meta-analysis of 46 head-to-head RCTs.¹ The absolute response rate for individual treatment groups varied depending on the study from 20 to 80%.¹ Other comparisons demonstrated no difference in treatment response.¹ The definition of response varied among trials, but was most commonly defined as greater than 20% improvement in the PANSS.¹ Other definitions included improvement of more than 20% on BPRS with either CGI-S score of less than or equal to 3 or BPRS less than 35; 30%, 40%, and 50% improvements in PANSS or BPRS; or a score of less than or equal to 3 on all PANSS items and less than 3 on the CGI-S.¹ Results were based on a network meta-analysis of trials and should be interpreted with caution as results represent indirect comparisons between treatments.¹ In addition, the analysis included limited evidence for the newer SGAs including injectable paliperidone, lurasidone, iloperidone, brexpiprazole, and cariprazine).¹ Remission, defined as complete resolution of symptoms, was rarely reported and there was insufficient evidence to assess treatment differences.
- There was low quality evidence of no difference in all-cause mortality between SGAs.¹ Mortality rates ranged from 0 to 1.17% at 4 to 24 months. Evidence included large retrospective cohort studies assessing all-cause mortality (n=48,595) or cardiovascular mortality (n=55,582) and 6 RCTs comparing asenapine with olanzapine, quetiapine with risperidone, and paliperidone LAI with risperidone LAI.¹ There was limited evidence in specific populations including elderly patients with dementia-related psychosis or patients with specific diagnosis of schizophrenia due to lack of reported data in these populations and poor quality evidence.
- There was low quality evidence that treatment with clozapine significantly reduced suicide attempts or hospitalization to prevent suicide (HR 0.76, 95% CI 0.58 to 0.97) and symptoms of suicidality (based on the Clinical Global Impression of Severity-Suicidality scale; HR 0.78, 95% CI 0.61 to 0.99) compared to olanzapine in patients at high risk for suicide.¹ Evidence was based on a single good-quality RCT of 980 patients at high risk of suicide which reported a significantly reduced 2-year event rate with clozapine treatment (NNT 12).¹ Similar trends were observed in observational studies with lower risk of suicidal symptoms associated with clozapine treatment compared to other SGAs.¹ However, it is unclear whether symptom improvement is a result of the treatment itself or if it may be due in part to more frequent check-ins and follow-up required with clozapine treatment. There is insufficient evidence to assess risk between other SGAs.
- Evidence for symptom improvement relied on 3 large network meta-analyses.¹ These analyses assessed symptom improvement using a standardized mean difference based on pooled analyses of various symptom rating scales including the PANSS and BPRS. The PANSS scale ranges from 30 to 180 possible points with changes of 11.5 points suggested as a minimally clinically important differences for patients with severe disease.¹ Treatment with clozapine resulted in a statistically greater improvement in core illness symptoms compared to other SGAs (SMD of -0.32 to -0.55 associated with a small to medium effect size; low quality evidence).¹ Olanzapine and risperidone had greater improvement in core illness symptoms compared to other SGAs (SMD -0.13 to -0.26; small effect size) and paliperidone had greater improvement compared to lurasidone and iloperidone (SMD -0.17; small effect size; low quality evidence).¹ Patients with treatment-resistant schizophrenia had greater

improvement when treated with olanzapine compared to quetiapine (SMD -0.29, 95% CI -0.56 to -0.13; low quality evidence; small effect size corresponding to an average of -6.08 points on the PANSS).¹ Overall differences between treatments were small and may not represent clinically meaningful changes in symptoms between treatment groups. There was no statistical difference in symptom improvement with other agents including clozapine, risperidone, olanzapine, quetiapine, and ziprasidone (low quality of evidence).¹

- No difference was observed in the proportion of patients reporting overall adverse effects between SGAs.¹ For most studies, the proportion of patients with adverse effects was greater than 60%.¹ A network meta-analysis of 90 head-to-head RCTs provides low quality evidence that treatment with risperidone LAI, olanzapine, aripiprazole, cariprazine and iloperidone had fewer withdrawals due to adverse effects compared to other SGAs.¹ Specifically, risperidone LAI had fewer withdrawals compared clozapine (OR 0.27, 95% CI 0.10 to 0.71); lurasidone (OR 0.39, 95% CI 0.18 to 0.84); quetiapine extended release (ER) (OR 0.43, 95% CI 0.22 to 0.81); risperidone (OR 0.50, 95% CI 0.25 to 0.99); and ziprasidone (OR 0.40, 95% CI 0.20 to 0.82).¹ Olanzapine had a fewer withdrawals compared to clozapine (OR 0.39, 95% CI 0.19 to 0.79); lurasidone (OR 0.57, 95% CI 0.34 to 0.94); quetiapine (OR 0.62, 95% CI 0.44 to 0.87); risperidone (OR 0.72, 95% CI 0.55 to 0.96); and ziprasidone (OR 0.58, 95% CI 0.41 to 0.82).¹ Aripiprazole had lower risk of withdrawals than ziprasidone (OR 0.64, 95% CI 0.44 to 0.94) and clozapine (OR 0.43, 95% CI 0.21 to 0.88).¹ Cariprazine (OR 0.40, 95% CI 0.17 to 0.95) and iloperidone (OR 0.34, 95% CI 0.13 to 0.91) had fewer withdrawals due to adverse effects than clozapine.¹ There was no difference in withdrawals due to adverse effects when comparing other SGAs, though results for the newer SGAs should be interpreted with caution as less data for these agents is available.¹
- Evidence regarding other outcomes (including relapse rate, overall treatment discontinuation, cardiovascular outcomes, diabetes, ketoacidosis and sexual function) was inconsistent between studies and insufficient to draw definitive conclusions between treatment groups.¹ Similarly, there was limited evidence regarding incidence of tardive dyskinesia. A single observational study suggests an increased risk with risperidone compared with olanzapine (OR 1.70, 95% CI 1.35 to 2.14), but absolute difference in risk was small (3% vs. 1-2%).¹ In addition, severity and incidence of extrapyramidal adverse effects were similar between treatments, though evidence for comparisons between medications was often limited to single studies and use of anticholinergic medications did differ for some comparisons.¹
- One systematic review evaluated the proportion of patients with a clinically significant weight gain of at least 7%.¹ Greater differences in risk were observed with olanzapine compared to ziprasidone (RR 5.76), asenapine (RR 2.59), aripiprazole (RR 2.31), quetiapine (RR 1.82) and risperidone (RR 1.81) over 3.7 to 24 months.¹ Similarly, olanzapine had a higher risk of metabolic syndrome compared to risperidone (OR 1.60, 95% CI 1.10 to 2.21, I²=0% at 6 weeks to 3 months) and aripiprazole (OR 2.50, 95% CI 1.32 to 4.76; I²=0% at 3.5 to 12 months).¹
- FGA versus SGA: Overall, olanzapine, risperidone, ziprasidone, and aripiprazole were comparable to haloperidol regarding improvements in quality of life or symptom improvement, but had fewer overall adverse effects and withdrawals due to adverse events.¹
 - Few trials reported improvements in functional status, and evidence was insufficient to evaluate differences between treatment groups. Similarly, there was insufficient evidence to assess difference in mortality or rates of suicide/self-harm between FGAs and SGAs due to lack of reported outcome data.
 - Evidence evaluating differences in quality of life between treatment groups was limited. There was low quality evidence of no difference in quality of life between ziprasidone and haloperidol.¹ Evidence was limited by inconsistencies in treatment effects between trials. Similarly, there was no difference between haloperidol and olanzapine (moderate quality evidence) or between perphenazine and olanzapine, quetiapine, risperidone, or ziprasidone (low strength of evidence).¹ There was insufficient evidence to determine differences in quality of life for other comparisons.¹
 - Olanzapine had a statistically greater response rate compared to haloperidol (RR 0.86, 95% CI 0.78 to 0.96) based on low strength evidence from a systematic review of 14 RCTs (n=4,099).¹ Similarly, remission rates were greater with olanzapine than haloperidol (RR 0.64, 95% CI 0.45 to 0.94) based on low quality evidence from 3 RCTs.¹ There was no difference in response rates when comparing haloperidol versus aripiprazole,

quetiapine, risperidone, and ziprasidone (moderate strength of evidence for haloperidol vs risperidone; low strength of evidence for all other comparisons).¹ There was no difference in remission rates between haloperidol and risperidone (low strength of evidence) and insufficient evidence for other comparisons.¹ Analyses were limited by moderate to high heterogeneity between studies (I²=29% to 83%).¹

- Overall, there was no clinically meaningful differences in symptom improvement for core symptoms of schizophrenia upon comparison of FGAs to SGAs.¹ There was a statistically significant differences in symptom improvement with olanzapine compared to haloperidol (MD 2.31 points on the PANSS, 95% CI 0.44 to 4.18) and risperidone versus haloperidol (MD 3.24 points, 95% CI 1.62 to 4.86) based on moderate strength of evidence from an analysis 15 and 21 RCTs, respectively.¹ The clinical significance of these differences is unclear as the minimum clinically important difference for the PANSS scale is suggested to be 11.5 points.¹ Comparisons of other FGAs to other SGAs failed to demonstrate any statistically significant differences (low strength of evidence).¹
- Negative symptoms (as assessed by the SANS score) were more improved with olanzapine than haloperidol (MD 2.56, 95% CI 0.94 to 4.18; moderate strength of evidence).¹ Similarly, improvement in negative symptoms was better with aripiprazole (MD 0.80, 95% CI 0.14 to 1.46), olanzapine (MD 1.06, 95% CI 0.46 to 1.67), and risperidone (MD 0.80, 95% CI 0.14 to 1.46) compared to haloperidol (as assessed using the negative symptoms subscale of the PANSS scale; low strength of evidence).¹ There were no differences for improvement of negative symptoms upon comparison of other FGAs and SGAs (low quality of evidence).¹
- There was moderate strength of evidence that overall rates of adverse effects were lower with aripiprazole (RR 1.11; 95 % CI 1.06 to 1.17), risperidone (RR 1.20, 95% CI 1.01 to 1.42), and ziprasidone (RR 1.13, 95% CI 1.03 to 1.23) compared to haloperidol.¹ Similarly, withdrawals due to adverse events were higher with haloperidol compared to aripiprazole (RR 1.25, 95% CI 1.07 to 1.47), olanzapine (RR 1.89; 95% CI 1.57 to 2.27), risperidone (RR 1.32; 95% CI 1.09 to 1.60), and ziprasidone (RR 1.68, 95% CI 1.26 to 2.23; moderate quality evidence).¹ There was no difference in withdrawals due to adverse effect upon comparison of haloperidol and clozapine or quetiapine (low quality evidence) and evidence for other comparisons was insufficient to draw meaningful conclusions.¹
- Subgroup analyses: Overall results for treatment response and withdrawals due to adverse effects were similar to the general population when analyzed based on study duration, dose, treatment-resistant population, or patients with first-episode psychosis.¹ Slight differences were reported for the following outcomes and subgroups though the quality of evidence is of low quality.¹
 - In patients with first episode psychosis, there was no difference in response rates, remission, or core illness symptom measures when stratified by age, sex, study duration, or blinding of studies.¹ Evidence was based on a systematic review of 17 RCTs.¹ Evidence for treatment discontinuation was limited with conflicting results from five studies.
 - In analysis of patients with treatment resistance, patients treated with olanzapine had a slight benefit in core illness and negative symptom improvement compared to other SGAs though response rate and treatment discontinuations were not significantly different between groups.¹ Clozapine also had fewer treatment discontinuations due to lack of efficacy in treatment-resistant patients.¹
 - There was no difference between olanzapine and risperidone in treatment discontinuation, quality of life, symptom improvement when stratified by age or sex. Upon comparison of clozapine to olanzapine, more women had symptom improvement compared to men (using the CGI or EQ-5D visual analog scale).¹ In addition, women and younger patients (<40 years of age) had a higher risk of new onset diabetes than older or male patients when treated with olanzapine or risperidone compared to FGAs.¹ The exact rate of new onset diabetes remains unclear.¹

A 2017 Cochrane review examined the safety and efficacy of antipsychotic combination treatments to antipsychotic monotherapy for patients with schizophrenia and schizoaffective disorders.⁵ Of the 62 studies included in the review (n=4833), 31 studies compared combination treatment with clozapine to clozapine monotherapy.⁵ Most trials had moderate to high risk of bias due to unclear allocation concealment, randomization and blinding methods. In addition, the majority of trials examined treatment durations of less than 12 weeks and only 7 studies examined long-term treatment for greater than 26 weeks.⁵ Most

trials included populations who had previously failed monotherapy antipsychotics and approximately half of the studies included patients admitted to a facility.⁵ Outcomes assessed included clinical response to treatment, relapse, early study discontinuation, hospital admission, change in hospital status, serious adverse events or adverse events requiring treatment discontinuation, and quality of life. For all outcomes, with the exception for early study discontinuation, evidence was assessed as either insufficient or very low quality limiting the ability to draw meaningful conclusions.⁵ There was low quality evidence that the number of patients who discontinued treatment was similar with combination antipsychotic treatment and monotherapy antipsychotic use (RR 0.90, 95% CI 0.76 to 1.07, n=3137).⁵ Data were limited by high risk or bias in included studies, high heterogeneity, lack of reported outcomes of interest, and short trial duration.

A rapid response report was published in 2016 from CADTH examining a similar topic, the use of combination second-generation antipsychotics for adolescents and adults with schizophrenia.¹¹ The report included 4 systematic reviews, 8 RCTs, and 2 evidence-based guidelines.¹¹ Symptom improvement with use of aripiprazole in addition to clozapine compared to clozapine monotherapy was mixed and was overall of insufficient quality to draw meaningful conclusions regarding efficacy. A systematic review of 4 RCTs (n=327) demonstrated no statistical difference in psychotic symptoms between groups, though qualitative synthesis from 6 RCTs (n=130) demonstrates addition of aripiprazole to clozapine may improve psychotic symptoms (especially negative symptoms).¹¹ In a systematic review of 5 RCTs (n=225), symptom improvement was not significantly different upon clozapine augmentation with risperidone compared to clozapine monotherapy.¹¹ Similarly, in a single RCT (n=106) comparing clozapine augmentation with either haloperidol or aripiprazole, there was no difference in symptom improvement.¹¹ However, trials overall were not powered to detect differences in efficacy between groups. There was limited evidence for other comparisons or outcomes due to small populations included in trials, limited duration of studies (<3 months), and lack of reported randomization or blinding methods.¹¹ Also there was a wide range of inclusion criteria for studies and most comparisons (with the exception of clozapine regimens) had results from only one study, increasing heterogeneity and limiting ability to pool results across trials. Guidelines included in the review recommend a 10-week trial of combination antipsychotic regimens only for patients who previously failed a dose-optimized clozapine regimen.¹¹

A 2017 Cochrane review examined efficacy and safety of combination antipsychotic treatment with clozapine for patients with treatment-resistant schizophrenia.¹² Three trials were identified which evaluated antipsychotics including aripiprazole versus haloperidol (n=105), risperidone versus ziprasidone (n=24), and ziprasidone versus quetiapine (n=63) when used in combination with clozapine.¹² Due to high heterogeneity between studies, results could not be combined in a meta-analysis.¹² For most outcomes, evidence was graded as very low quality, limiting confidence in the treatment effect.¹² There was no difference in mental state, clinically significant response, clinically significant symptom improvement, or treatment discontinuation upon comparison of aripiprazole to haloperidol or risperidone to ziprasidone (very low to low quality evidence).¹² There was low quality evidence from a single RCT that more patients treated with the combination of ziprasidone plus clozapine had a 50% reduction in PANSS score (RR 0.54, 95% CI 0.35 to 0.81) and global severity as assessed by CGI-Score (MD -0.70, 95% CI -1.18 to -0.22) compared to combination treatment with clozapine and quetiapine.¹² A similar systematic review was published in 2016 examining antipsychotic efficacy, acceptability and tolerability in for patients with treatment-resistant schizophrenia.⁹ Authors conducted a network meta-analysis of 40 RCTs (n=5172) which examined improvement in symptoms, response to treatment, and treatment discontinuation with various antipsychotic medications.⁹ Outcomes examined included overall change in symptoms, improvement in positive or negative symptoms, treatment response, and treatment discontinuation. Though some comparisons demonstrated statistically significant differences between groups, differences were small and not consistent across outcomes.⁹ The analysis also had several important limitations with approximately 30% of participants discontinued study treatment and 45% of RCTs with evidence of selective reporting.⁹ In addition, few studies reported methods of randomization or allocation concealment.⁹ Due to these significant limitations in the evidence, authors concluded that evidence was insufficient to determine differences between agents.⁹

A 2016 Cochrane review evaluated efficacy of chlorpromazine versus second generation antipsychotics for schizophrenia.¹³ The review included 71 studies which compared chlorpromazine to olanzapine (n=12), risperidone (n=14), or quetiapine (n=45).¹³ Thirty-three additional publications were identified which compared

chlorpromazine to other second-generation antipsychotics, the data from which have yet to be published.¹³ The majority of included studies were conducted in non-US populations (primarily China) limiting applicability to OHP patients, and participants included both inpatient and outpatient settings.¹³ Overall, the majority of included studies were of short duration (<8 weeks) and few included studies examined long-term outcomes beyond 6 months.¹³ In addition, few studies adequately described randomization, allocation concealment, or blinding methodology increasing risk of bias. Outcomes examined included changes in global or specific symptoms, adverse events, quality of life, and treatment discontinuation. For the majority of outcomes and comparisons, there was insufficient evidence to determine differences between treatment groups.¹³ There was low quality evidence based on results from 3 studies (n=204) that a greater proportion of patients treated with olanzapine had in clinical response to treatment at 6 to 12 weeks compared to treatment with chlorpromazine (RR 2.34, 95% CI 1.37 to 3.99).¹³ There was no difference in clinical response between chlorpromazine and quetiapine based on results from 28 RCTs (n=3241, RR 0.93, 95% CI 0.81 to 1.06; moderate quality evidence).¹³ There was insufficient quality evidence to evaluate outcomes for chlorpromazine compared to risperidone. Upon comparison of chlorpromazine and quetiapine (n=644), more patients treated with chlorpromazine reported extrapyramidal adverse effects (RR 8.03, 95% CI 4.78 to 13.51; low quality evidence).¹³ However, there was no difference between chlorpromazine and quetiapine in patients who discontinued the study treatment (n=1223; RR 1.04, 95% CI 0.77 to 1.41; moderate quality evidence).¹³

A 2016 Cochrane review examined efficacy of oral fluphenazine compared to second generation antipsychotics for patients with schizophrenia.¹⁴ Three relevant RCTs were included in the review comparing fluphenazine with risperidone, quetiapine and olanzapine.¹⁴ The included RCTs had limited population including 25 to 60 patients in each study and was of poor methodological quality.¹⁴ Overall, evidence was insufficient to determine differences in clinical efficacy or safety between the agents.¹⁴

A systematic review conducted in 2017 examined the impact of clozapine on hospital utilization and readmission for patients with psychosis.¹⁵ The review included data from 3 RCTs and 34 observational studies.¹⁵ Primary outcomes for the review were hospital use for any reason and the number of bed days after initiation of clozapine compared to hospital utilization before initiation of the medication. Comparator medications included both first and second-generation antipsychotics. Outcomes were reported using multiple time points ranging from 28 to 364 weeks.¹⁵ There were fewer patients hospitalized over the duration of the study upon comparison of clozapine to other antipsychotics (RR 0.75, 95% CI 0.67 to 0.83, P<0.001, 13 studies, n=29,559).¹⁵ Similar trends were noted upon comparison to individual agents including risperidone (RR 0.74, 95% CI 0.60 to 0.93, P=0.009, 12 studies, n=8634), quetiapine (RR 0.60, 95% CI 0.45 to 0.79, P=0.0003, 4 studies, n=2686), and olanzapine (RR 0.82, 95% CI 0.69 to 0.97, P=0.02, 8 studies, n=14,617).¹⁵ Similar results were observed in upon subgroup analysis when stratified by duration of treatment (greater than or less than 1 year), diagnosis (patients with treatment-resistant schizophrenia), and reason for hospitalization (psychiatric illness vs. no reason stated).¹⁵ Comparison of clozapine to haloperidol or to depot treatment with any antipsychotic failed to achieve statistically different results in the proportion of patients hospitalized.¹⁵ Analysis comparing depot injections is limited as evidence regarding use of SGA depot formulations was lacking. Two controlled observational studies compared hospitalization bed days to other antipsychotics (n=162).¹⁵ Clozapine treatment resulted in fewer bed days after treatment compared to control medications (MD -34.41 days, 95% CI -68.22 to -0.60 days, P=0.046).¹⁵ Similar results were observed in uncontrolled studies with an average of 52.86 fewer days after treatment initiation (95% CI -79.86 days to -25.86 days, P<0.001, n = 2917).¹⁵ Subgroup analyses demonstrated that duration of treatment had a significant impact upon hospitalization days. Patients given clozapine for less than 1 year had an average of 24.0 fewer days (95% CI -32.4 days to -15.7 days, P<0.001) compared to patients with treatment durations longer than 1 year (MD -84.23 days, 95% CI -133.08 days to -35.37 days, P=0.001).¹⁵ There was no difference observed in time to hospitalization (n=5 studies).¹⁵ Though results assessing efficacy of clozapine are significant, this analysis has several important limitations. First, the majority of trials had moderate risk of bias and data from this analysis is limited by the lack of good quality RCTs available.¹⁵ Patients prescribed clozapine were also significantly younger by an average 1.33 years and had earlier disease onset (1.92 years) compared to patients prescribed other antipsychotics.¹⁵ In addition, reasons for hospitalization varied between studies with substantial inter-study

heterogeneity. Finally, the majority of studies included in the analysis were published before 2005 which limits applicability in today's healthcare setting and limits comparative evidence for newer antipsychotics.

Bipolar Disorder

At the time of this review, a 2017 draft AHRQ report was available which examines the effectiveness of drugs for the treatment of adults with bipolar disorder.² Drugs included in the review included second-generation antipsychotics (aripiprazole, asenapine, cariprazine, lurasidone, olanzapine, olanzapine/fluoxetine, quetiapine, risperidone, and ziprasidone), anticonvulsants (carbamazepine, divalproex, and lamotrigine), chlorpromazine, and lithium.² RCTs and prospective cohort studies were included if they had a minimum duration of 3 weeks for acute mania, 3 months for depression, and 6 months for maintenance treatments.² Trials included both inpatient and outpatient populations for mania and mixed episodes and outpatient populations for depression or maintenance treatment. Studies were excluded if more than 50% of participants were lost to follow-up.² Overall, 111 publications including 67 drug studies for acute mania, 6 studies for depression, and 30 studies for maintenance drug treatment were included in the review.² The majority of studies for acute mania were focused on adults with bipolar I.² Studies assessing improvement in depression included only adults with bipolar II, and approximately 60% of studies assessing maintenance treatment enrolled adults with bipolar I.² The majority of included studies were placebo-controlled comparisons and will only be discussed briefly here. Only a few studies included direct comparisons between different drug treatments. Most treatment comparisons (including antipsychotics as monotherapy and in combination with mood stabilizers) had evidence from a single study, and only 3 comparisons involving antipsychotic medications had 4 or more studies which contributed evidence.² The following clinical outcomes were evaluated: functional outcomes (i.e. social or occupational, change in disability status), quality of life, reduction of episodes, remission rate, reduced hospitalization, remission of concomitant substance use disorder, self-harm, symptom severity, treatment response, adverse effects (including metabolic syndrome, glucose dysregulation, weight gain), and withdrawals due to adverse effects and treatment adherence.²

- There is low quality evidence that FDA-approved antipsychotics (except aripiprazole) improve acute mania symptoms in the short term (at 3 weeks) compared to placebo.² Evidence for aripiprazole compared to placebo was of insufficient quality primarily due to high risk of bias and lack of precision.² The average improvement of manic symptoms was generally less than the estimated minimally important difference (6 points on the YMRS scale or 1 point on the CGI scale). However, differences were large enough that it is reasonably likely some patients had benefit from treatment.²
 - Asenapine versus placebo (3 studies): YMRS mean difference 4.37 (95% CI 1.27 to 7.47) and CGI mean difference 0.5 (95% CI 0.29 to 0.71)²
 - Cariprazine versus placebo (3 studies): response rate OR 2.14 (95% CI 1.08 to 4.23) and remission rate OR 1.95 (95% CI 1.45 to 2.63), YMRS mean difference 5.38 (95% CI 1.84 to 8.92) and CGI-BP-S mean difference 0.54 (95% CI 0.35 to 0.73)²
 - Olanzapine versus placebo (5 studies): response rate OR 1.99 (95% CI 1.29 to 3.08), remission rate OR 1.75 (95% CI 1.19 to 2.58), YMRS mean difference 4.9 (95% CI 2.34 to 7.45), CGI was not significantly different between groups²
 - Quetiapine versus placebo (4 studies): response rates OR 2.07 (95% CI 1.39 to 3.09), YMRS mean difference 4.92 (95% CI 0.31 to 9.53), CGI mean difference 0.54 (95% CI 0.35 to 0.74)²
 - Risperidone versus placebo (2 studies): data not pooled but findings favor risperidone and were consistent across studies with greater improvement with risperidone compared to placebo for response rate, manic symptom improvement (YMRS), and CGI.²
 - Ziprasidone versus placebo (2 studies): data not pooled but findings favor ziprasidone and were consistent across studies with greater improvement with ziprasidone compared to placebo for response rate, manic symptom improvement (YMRS), and CGI.²
 - There was insufficient evidence comparing haloperidol and aripiprazole for improvement of mania symptoms.²
 - Though not FDA-approved for bipolar disorder, there was low strength of evidence from 2 RCTs that paliperidone improved manic symptoms compared to placebo with a YMRS mean difference of 3.4 (p=0.025).²
- Direct comparisons for treatment of acute mania were limited. There was no difference in efficacy outcomes (including remission rates, mania symptoms or treatment discontinuation) between olanzapine monotherapy and divalproex or valproate for acute mania in adults with bipolar I (low

quality evidence from 4 RCTs [n=867]).² One study noted that clinically important weight gain of at least 7% was more common in patients treated with olanzapine, though statistical significance weight gain was not documented in all studies.² There was low quality evidence from a single study (n=488) which reported greater response rate with asenapine compared to olanzapine but no difference in remission rate between therapies.²

- There was insufficient evidence for all other antipsychotic drug comparisons (as monotherapy or in combination with mood stabilizers) for treatment of acute mania.² Similarly, there was insufficient evidence for any treatment and all outcomes for bipolar depression or maintenance treatment.² Data was limited by reliance on single studies for specific comparisons, low study quality, high attrition rates, short treatment duration, and small population sizes.²

A 2016 CADTH rapid response report examined aripiprazole use as monotherapy or adjunct therapy in combination with lithium or divalproex.¹⁶ A single systematic review (n=2505) and 3 evidence-based guidelines provided clinical evidence for the report. Relevant comparators included haloperidol, lithium and valproic acid.¹⁶ Outcomes included response rate, treatment discontinuation and adverse effects. Overall, response rate with greater than 50% improvement in symptom score, symptom improvement, and treatment discontinuation were similar between aripiprazole and other traditional treatments for bipolar disorder including lithium, divalproex, and haloperidol.¹⁶ Comparisons to individual agents were not evaluated and there was high heterogeneity among analyses.¹⁶ Guidelines included in this review list aripiprazole as one of many possible first line pharmacological treatments for acute mania or maintenance treatment in patients with bipolar disorder and recent mania or mixed episodes, but it is not recommended for acute bipolar depression.¹⁶

Another rapid response report published by CADTH in 2016 found no published literature regarding the use of combination second-generation antipsychotics for adults or adolescents with bipolar disorder.¹⁷

Antipsychotic Treatment for Pediatric and Young Adult Patients

An AHRQ report published in 2016 examined efficacy and safety of FGA and SGA use in children and young adults (less than 25 years of age).³ The report included 135 studies which primarily compared antipsychotic use to placebo.³ Direct comparative evidence (which will be the focus of this summary) was generally of insufficient or low quality particularly for clinical outcomes. Results were analyzed by class and for individual agents. When grouped by class, there was low quality evidence of no difference between FGAs and SGAs for improvement of negative symptoms, positive symptoms, response rate, and global impression of illness severity for patients with schizophrenia or related psychosis.³ For the comparison of olanzapine and risperidone, there was no difference in symptom improvement, response rate, or global impressions of severity (low quality evidence based on 6 studies).³ There was insufficient evidence for comparisons of other agents for the treatment of schizophrenia.³ There were no studies identified which examined direct comparative efficacy or safety of either FGAs or SGAs in patients with bipolar disorder, autism spectrum disorder, ADHD or other conduct disorders, depression, eating disorders, or tic disorders.³ Similarly, there was insufficient evidence regarding efficacy or safety of SGAs in patients with obsessive-compulsive disorder.³ Due to the lack of head to head data, a network meta-analysis was conducted to compare differences in body mass index and weight gain between agents. Results of this analysis should be interpreted with caution due to the indirect nature of the results. Overall, ziprasidone may have less weight gain compared to other FGAs or SGAs.³ Patients treated with clozapine, lurasidone, and olanzapine had on average more weight gain (2-5 kg over 6-12 weeks) than other antipsychotics (low quality evidence).³ Evidence was strongest for comparisons of olanzapine versus risperidone or quetiapine (greater weight gain and change in BMI with olanzapine) and for quetiapine versus risperidone (no difference in BMI or clinically significant weight gain).³ Upon comparison between classes, there was moderate strength of evidence that SGAs are likely associated with more weight gain (MD -2.62 kg; 95% CI -4.35 to -0.86) and increase in BMI (MD -1.57 kg/m²; 95% CI -2.49 to -0.53) compared to FGAs.³ There was low quality evidence that use of SGAs was associated with fewer extrapyramidal symptoms compared to FGAs (RR 2.59; 95% CI 1.00 to 7.00) and low quality evidence of no difference in sedation between groups.³ Regarding long-term serious adverse events, there was moderate quality evidence of no difference in mortality upon comparison of SGAs and placebo.³ There was low quality evidence based on a large retrospective cohort study that

use of SGAs for over 1 year increases risk of diabetes compared to patients not treated with antipsychotics (HR 2.89, 95% CI 1.64 to 5.10; 25.3 vs. 7.8 cases per 10,000 person-years follow-up).³ Subgroup analyses demonstrated no difference in efficacy or harms based on age, sex, or prior treatment history. Duration of treatment did have a slight effect on weight gain, with longer treatment durations associated with larger increases in weight over time (0.04 kg/week; 95% CI 0.014 to 0.071).³ Overall, these analyses were limited by the populations enrolled in the included studies. Few trials enrolled young adults or children less than 8 years of age and many excluded patients with mild symptom severity or patients with comorbidities. In addition, the majority of studies were of short duration (<6 months) which limits estimates of long-term efficacy and adverse effects.

In May 2017, an AHRQ report was published which examined medical treatment for children with autism spectrum disorder.¹⁸ The report included 11 RCTs and one retrospective cohort which examined use of aripiprazole, risperidone, and haloperidol in children 2 to 12 years of age with autism spectrum disorder.¹⁸ Studies were excluded if the population had less than 10 participants for an RCT or 20 participants for observational studies.¹⁸ Of the studies included, 7 had low risk of bias and 5 had moderate risk of bias.¹⁸ Only 4 of these studies included direct comparative evidence between agents. Data from these studies had significant limitations in that there was limited evidence for long-term outcomes (>6 months) and few studies address similar interventions or outcomes.¹⁸ Upon comparison of aripiprazole to risperidone in 3 small studies, there was no difference in challenging behavior or general improvement between groups at 8 weeks, 24 weeks, or up to 1-2 years (low quality evidence).¹⁸ A single small RCT demonstrated significant symptom improvement with risperidone compared to haloperidol.¹⁸ However, due to the limited population and moderate risk of bias evidence was insufficient to form meaningful conclusions.¹⁸ The most common adverse effects associated with treatment included weight gain, increased appetite and drowsiness. All antipsychotic treatments were associated with increased weight gain over time, but differences were not statistically different between groups.¹⁸

CADTH published a rapid response report in 2016 examining antipsychotic use in pediatric patients (<18 years of age).¹⁹ Evidence was limited to systematic reviews (n=9) and evidence based guidelines (n=3) which provide evidence regarding the efficacy and safety of antipsychotics.¹⁹ Overall, direct comparative evidence was limited. Two systematic reviews including patients with Tourette's syndrome or tic disorders provided evidence of no difference in symptom severity upon comparison of aripiprazole and haloperidol or risperidone.¹⁹ For children with psychosis or schizophrenia, available evidence from 2 systematic reviews demonstrated no difference in efficacy between individual antipsychotic agents or between FGAs and SGAs.¹⁹ There was no comparative evidence for efficacy and safety of antipsychotics in children with other conditions including disruptive behavior disorders or autism spectrum disorders.¹⁹ Evidence regarding adverse events was mixed. The most common adverse events associated with treatment were weight gain, drowsiness, increased appetite, and extrapyramidal adverse effects.¹⁹ In patients with schizophrenia, increased weight gain was observed with olanzapine compared to risperidone (MD 6.1 ± 3.6 kg vs. 3.6 ± 4 kg, p-value not reported), but there was no difference upon comparison of clozapine and olanzapine.¹⁹ Other trials report no difference in adverse effects between agents, though the ability to detect differences between groups was limited by small population sizes, large heterogeneity, and poor quality of trials included in these systematic reviews.¹⁹

Other Conditions

In 2017, CADTH published a rapid response report assessing available evidence of aripiprazole treatment for borderline personality disorder.²⁰ First-line treatment for borderline personality disorder is psychotherapy though pharmacotherapy (including off-label use of antipsychotics, antidepressants and mood stabilizers) may be used as adjunct treatment.²⁰ Only 2 RCTs (one with direct comparative evidence to olanzapine and one with only placebo comparisons) were included in the review, and evidence was insufficient to assess efficacy, safety, or generalizability to a broader population. Data were limited by small population size (n=76), lack of reported randomization or blinding methods, and inadequate reporting of baseline population characteristics or concomitant medications use.²⁰

A Cochrane review published in 2016 attempted to evaluate evidence for haloperidol as a treatment for long-term or persistent aggression in patients with psychosis.²¹ Only one low-quality RCT (n=110) with high risk of bias was identified which compared haloperidol to olanzapine or clozapine.²¹ There was low quality evidence of no difference in discontinuation rate between treatment groups.²¹ Data for other outcomes including treatment efficacy was limited by unclear randomization, allocation concealment or blinding methodology, high attrition rate, and high risk of reporting bias.²¹

New Guidelines:

Guidelines from the Department of Veterans Affairs and Department of Defense were updated in 2016 for the management of major depressive disorder.²² Recommended first-line pharmacological treatments for mild to moderate major depressive disorder include SSRIs (except fluvoxamine), SNRIs, mirtazapine, or bupropion (strong recommendation).²² Treatment selection is recommended based on patient preference, safety and adverse effect profile, history of prior treatment response, family history of response to a medication, concurrent comorbidities or medications, cost and provider training.²² In patients with only partial response or no response to initial treatment, treatment should be switched to another treatment or augmented with another medication or psychotherapy. Similarly, for patients with severe depression, combination psychotherapy and pharmacotherapy is recommended (strong recommendation).²² Medication augmentation strategies include addition of bupropion, buspirone, lithium, liothyronine, or SGAs to first-line pharmacotherapy.²² Due to the significant potential of adverse effects with SGAs, they are recommended only when other strategies have failed.²² Recommendation was based on 2 systematic reviews demonstrating aripiprazole, olanzapine, quetiapine, and risperidone improved remission rates compared to placebo.²² However, there was fair quality evidence that adverse effects including akathisia were statistically more common with aripiprazole, and sedation were more common with olanzapine and quetiapine.²² Aripiprazole, olanzapine, quetiapine and risperidone were also more commonly associated with weight gain compared to placebo (fair quality evidence).²²

The Department of Veterans Affairs and Department of Defense also updated guidelines for the management of post-traumatic stress disorder (PTSD) in 2017.¹¹ Briefly, second-generation antipsychotics are not recommended as monotherapy or as augmentation therapy for the treatment of PTSD due to a lack of evidence regarding efficacy in this population and known adverse effects associated with treatment (weak recommendation).¹¹

In 2016, the American Psychiatric Association updated guideline recommendations for the use of antipsychotics in patients with dementia.²³ Most recommendations focus on use of antipsychotics in the nonemergency setting. Overall, evidence was based on low to moderate quality evidence and few recommendations were made for specific antipsychotic regimens. In general, frequent assessment (at least monthly) and evaluation of risks and benefits of treatment is recommended.²³ In addition, nonemergency antipsychotics should be used for treatment of agitation or psychosis only when symptoms are severe, dangerous, or cause significant distress for the patient (strong recommendation; moderate quality evidence).²³ The minimum effective dose should be used, and discontinuation of the medication is recommended if no significant response is observed after a trial of 4 weeks (strong recommendation; moderate quality evidence).²³ In patients with an adequate treatment response, an attempt to taper the medication should be made within 4 months unless symptoms reoccur upon treatment discontinuation (strong recommendation based on low quality evidence).²³ Haloperidol is not recommended as a first-line nonemergency medication in patients with dementia and without delirium (strong recommendation; moderate quality evidence).²³ In addition, long-acting injectable antipsychotic medications are not recommended unless used for patients with concomitant chronic psychotic disorders (strong recommendation; moderate quality evidence).²³

Guidelines from the American Society of Clinical Oncology were updated in 2017 to include olanzapine as a recommended option for prevention of chemotherapy-induced nausea and vomiting in patients with high-emetic-risk chemotherapy regimens (strong recommendation based on high quality evidence).²⁴ Olanzapine is recommended as prophylaxis in combination with a neurokinin 1 receptor antagonist (eg, aprepitant, fosaprepitant, or rolapitant), a

serotonin receptor antagonist (eg, ondansetron, palonosetron, or granisetron) and dexamethasone.²⁴ The recommendation is primarily based on one phase 3 RCT in which olanzapine was added to standard antiemetic prophylaxis. The proportion of patients without symptoms of nausea at 24 hours and 120 hours was significantly greater in those prescribed olanzapine compared to the standard of care (74% vs. 45% of patients at 24 hours and 37% vs. 22% at 120 hours following chemotherapy).²⁴ Similarly, for patients who were not prescribed prophylactic olanzapine, it is recommended as an option for breakthrough nausea and vomiting in addition to the standard antiemetic regimen (moderate strength recommendation based on intermediate quality evidence).²⁴

New Formulations or Indications:

In May 2016, Fanapt® (iloperidone) received an expanded indication for maintenance treatment of schizophrenia. It had previously been indicated only for short-term treatment. In addition, Saphris® (asenapine) was approved for pediatric patients 10 to 17 years with bipolar I disorder and Latuda® (lurasidone) received approval from the FDA for treatment of schizophrenia in adolescents aged 13 to 17 years.

New FDA Safety Alerts:

In 2017, the FDA updated warnings for all SGAs and haloperidol to include risk for falls. Labeling specifies that antipsychotics have been associated with somnolence, postural hypotension, and motor or sensory instability which may lead to falls. A complete fall risk assessment is advised upon initiation of these medications and intermittently for patients on long-term therapy.²⁵

In February 2017, the FDA updated clozapine labeling to include warnings for severe and life-threatening hepatotoxicity. Reports of hepatotoxicity occurred in post-marketing studies of clozapine and the exact incidence or frequency of hepatotoxicity is unclear. Monitoring is recommended for signs and symptoms of hepatotoxicity including fatigue, nausea, jaundice, and hepatic encephalopathy.²⁵

In October 2016, olanzapine labeling was updated to include a warning for drug reaction with eosinophilia and systemic symptoms. Discontinuation of treatment is recommended if symptoms are observed.²⁵

Labeling for aripiprazole was updated in 2016 to include warnings for pathological gambling and other compulsive behaviors. Compulsive urges, particularly for gambling, have been reported in post-marketing experience. Dose reduction or treatment discontinuation should be considered if symptoms are present.²⁵

Randomized Controlled Trials:

A total of 344 citations were manually reviewed from the initial literature search. After further review, 340 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical or exploratory). Only trials reporting new comparative evidence were considered for inclusion, and trials which offered no new additional information from sources already in the review were excluded. The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Mohamed S, et al. ²⁶	1. Switch to bupropion 150-400 mg daily	Veterans with MDD unresponsive to	Remission at 12 weeks defined as a score of ≤5 on the 16-item Quick Inventory of Depressive	1. 114/511 (22.3%) 2. 136/506 (26.9%) 3. 146/505 (28.9%)

AC, single-blind, MC, PG, RCT N=1522 Duration: 36 weeks	2. Add bupropion 150-400 mg daily 3. Add aripiprazole 5-15 mg daily Doses titrated based on tolerability and treatment effect	at least one antidepressant	Symptomatology-Clinician Rated (QIDS-C16) score	1 vs. 3: ARR: 6.6%; RR 1.30 (95% CI 1.05-1.60); $p=0.02$ 1 vs. 2 and 2 vs. 3 were not significant
Cheon E, et al. ²⁷ AC, MC, OL, PG, RCT N=103 Duration: 6 weeks	1. Addition of aripiprazole 2.5 to 20 mg daily (mean 2.99 mg/day) 2. Addition of bupropion 150 to 300 mg daily (mean 199 mg/day)	MDD unresponsive to SSRI treatment of at least 4 weeks	Mean change in the Montgomery Asberg Depression Rating Scale total score from baseline to 6 weeks	1. -13.77 (SD 8.59) 2. -9.45 (SD 9.45) Difference between groups was not significant
Nierenberg A, et al. ²⁸ MC, PG, Single-blind RCT N=482 Duration: 6 months	1. Lithium (mean dose 1007 mg) 2. Quetiapine (mean dose 345 mg) Medication titrated to maximum tolerated dose. Treatment given in combination with adjunctive personalized treatment which could include any medication except SGAs or lithium.	Bipolar I or II disorder	Clinical Global Impressions-Efficacy Index (range -3 [no benefit, significant harms] to +3 [significant benefit, no harm]) Necessary clinical adjustments (defined as the number of changes necessary in adjunctive treatment due to new, persistent or worsened symptoms or adverse effects)	Clinical Global Impressions-Efficacy Index 1. 1.58 (95% CI 1.32 to 1.84) 2. 1.52 (95% CI 1.26 to 1.78) MD 0.06 (95% CI -0.16 to 0.29); $p=0.59$ Average number of necessary clinical adjustments per month 1. 0.8 (SD 0.8) per month 2. 0.9 (SD 1.0) per month P=0.15
Lamberti M, et al. ²⁹ OL, RCT	1. Risperidone 0.25 to 3 mg daily 2. Aripiprazole 1.25 to 15 mg daily	Italian patients with autism spectrum disorder and ADHD	Change in ADHD-rating scale (18 questions evaluating symptom improvement) or CGI-I (range 1-7) rating scales from baseline	ADHD-RS at 24 weeks 1. 19.1 (SD 3) 2. 26.7 (SD 7.8) P=0.842

N=44	Dose titrated based on clinical response			CGI-I at 24 weeks 1. 2.7 (SD 0.7) 2. 3.0 (SD 1.2) P=0.356
Duration: 24 weeks				

Abbreviations: AC = active comparator; ADHD = attention-deficit/hyperactivity disorder; FGA = first generation antipsychotic; MC = multicenter; MD = mean difference; MDD = major depressive disorder; OL = open label; PG = parallel-group; RCT = randomized clinical trial; RR = relative risk; SD = standard deviation; SGA = second generation antipsychotic

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Appendix 1: Current Preferred Drug List

ROUTE	FORM	BRAND	GENERIC	PDL	CARVEOUT
<u>FIRST GENERATION ORAL ANTIPSYCHOTICS</u>					
ORAL	ELIXIR	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	ORAL CONC	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	TABLET	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	TABLET	HALOPERIDOL	HALOPERIDOL	Y	Y
ORAL	ORAL CONC	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
ORAL	CAPSULE	LOXAPINE	LOXAPINE SUCCINATE	Y	Y
ORAL	TABLET	PERPHENAZINE	PERPHENAZINE	Y	Y
ORAL	TABLET	THIORIDAZINE HCL	THIORIDAZINE HCL	Y	Y
ORAL	CAPSULE	THIOTHIXENE	THIOTHIXENE	Y	Y
ORAL	TABLET	TRIFLUOPERAZINE HCL	TRIFLUOPERAZINE HCL	Y	Y
ORAL	TABLET	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	V	Y
ORAL	TABLET	ORAP	PIMOZIDE	V	Y
ORAL	TABLET	PIMOZIDE	PIMOZIDE	V	Y
<u>SECOND GENERATION ORAL ANTIPSYCHOTICS</u>					
SUBLINGUAL	TAB SUBL	SAPHRIS	ASENAPINE MALEATE	Y	Y
ORAL	TABLET	CLOZAPINE	CLOZAPINE	Y	Y
ORAL	TABLET	LATUDA	LURASIDONE HCL	Y	Y
ORAL	TABLET	OLANZAPINE	OLANZAPINE	Y	Y
ORAL	TABLET	ZYPREXA	OLANZAPINE	Y	Y
ORAL	TABLET	QUETIAPINE FUMARATE	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	SEROQUEL	QUETIAPINE FUMARATE	Y	Y
ORAL	SOLUTION	RISPERDAL	RISPERIDONE	Y	Y
ORAL	SOLUTION	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERDAL	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	SOLUTION	ARIPIRAZOLE	ARIPIRAZOLE	V	Y
ORAL	TAB RAPDIS	ARIPIRAZOLE ODT	ARIPIRAZOLE	V	Y
ORAL	TABLET	ABILIFY	ARIPIRAZOLE	V	Y
ORAL	TABLET	ARIPIRAZOLE	ARIPIRAZOLE	V	Y
ORAL	TABLET	REXULTI	BREXPIRAZOLE	V	Y
ORAL	CAP DS PK	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	CAPSULE	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	ORAL SUSP	VERSACLOZ	CLOZAPINE	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	ZYPREXA ZYDIS	OLANZAPINE	V	Y
ORAL	TAB ER 24	INVEGA	PALIPERIDONE	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	PALIPERIDONE	V	Y
ORAL	TABLET	NUPLAZID	PIMAVANSERIN TARTRATE	V	Y
ORAL	TAB ER 24H	QUETIAPINE FUMARATE ER	QUETIAPINE FUMARATE	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	QUETIAPINE FUMARATE	V	Y
ORAL	TAB RAPDIS	RISPERDAL M-TAB	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	RISPERIDONE	V	Y
ORAL	CAPSULE	GEODON	ZIPRASIDONE HCL	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ZIPRASIDONE HCL	V	Y

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Appendix 2: Abstracts of Comparative Clinical Trials

1. Cheon E-J, Lee K-H, Park Y-W, et al. Comparison of the Efficacy and Safety of Aripiprazole Versus Bupropion Augmentation in Patients With Major Depressive Disorder Unresponsive to Selective Serotonin Reuptake Inhibitors: A Randomized, Prospective, Open-Label Study. *Journal of clinical psychopharmacology*. 2017;37(2):193-199.

PURPOSE: The purpose of this study was to compare the efficacy and safety of aripiprazole versus bupropion augmentation in patients with major depressive disorder (MDD) unresponsive to selective serotonin reuptake inhibitors (SSRIs)., **METHODS:** This is the first randomized, prospective, open-label, direct comparison study between aripiprazole and bupropion augmentation. Participants had at least moderately severe depressive symptoms after 4 weeks or more of SSRI treatment. A total of 103 patients were randomized to either aripiprazole (n = 56) or bupropion (n = 47) augmentation for 6 weeks. Concomitant use of psychotropic agents was prohibited. Montgomery Asberg Depression Rating Scale, 17-item Hamilton Depression Rating scale, Iowa Fatigue Scale, Drug-Induced Extrapyramidal Symptoms Scale, Psychotropic-Related Sexual Dysfunction Questionnaire scores were obtained at baseline and after 1, 2, 4, and 6 weeks of treatment., **RESULTS:** Overall, both treatments significantly improved depressive symptoms without causing serious adverse events. There were no significant differences in the Montgomery Asberg Depression Rating Scale, 17-item Hamilton Depression Rating scale, and Iowa Fatigue Scale scores, and response rates. However, significant differences in remission rates between the 2 groups were evident at week 6 (55.4% vs 34.0%, respectively; P = 0.031), favoring aripiprazole over bupropion. There were no significant differences in adverse sexual events, extrapyramidal symptoms, or akathisia between the 2 groups. **CONCLUSIONS:** The present study suggests that aripiprazole augmentation is at least comparable to bupropion augmentation in combination with SSRI in terms of efficacy and tolerability in patients with MDD. Both aripiprazole and bupropion could help reduce sexual dysfunction and fatigue in patients with MDD. Aripiprazole and bupropion may offer effective and safe augmentation strategies in patients with MDD who are unresponsive to SSRIs. Double-blinded trials are warranted to confirm the present findings.

2. Lamberti M, Siracusano R, Italiano D, et al. Head-to-Head Comparison of Aripiprazole and Risperidone in the Treatment of ADHD Symptoms in Children with Autistic Spectrum Disorder and ADHD: A Pilot, Open-Label, Randomized Controlled Study. *Paediatric drugs*. 2016;18(4):319-329.

BACKGROUND: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are frequently overlapping neurodevelopmental disorders. Individuals in whom the disorders are comorbid show more severe impairment because of deficits in the processing of social situations, adaptive functioning, and executive control than individuals with either disorder alone., **OBJECTIVE:** This open-label pilot study aimed to evaluate and compare the efficacy and tolerability of risperidone and aripiprazole for treating ADHD symptoms in patients with both ASD and ADHD over the course of 24 weeks of treatment., **METHODS:** Patients (n = 44) were randomly assigned to start treatment with risperidone (22 patients) or aripiprazole (22 patients). Children were evaluated before starting treatment (T0), and after 12 weeks (T1) and 24 weeks (T2) of treatment. At each visit, specific psychiatric clinical scales were administered to assess the efficacy of the two drugs. **RESULTS:** The mean age was 8.4 +/- 2.9 years in the aripiprazole group and 7.8 +/- 2.3 years in the risperidone group. A total of 37 children (29 boys and 8 girls) completed the study (18 in the aripiprazole group and 19 in the risperidone group). Aripiprazole and risperidone appeared to have similar benefits in terms of efficacy and tolerability, although there were slight differences between the two drugs. Both groups showed a significant improvement in ADHD symptoms after 24 weeks of treatment (ADHD Rating Scale, Conners Parent Rating Scale-Hyperactivity, and Clinical Global Improvement-Severity Scale). No significant difference between the two drugs on any parameters at 24 weeks were found. Prolactin levels were decreased in the aripiprazole group. Both drugs were well tolerated, with no serious adverse events detected. **CONCLUSIONS:** Our study confirms the efficacy of both aripiprazole and risperidone in ameliorating ADHD symptoms of children also presenting with ASD.

3. Mohamed S, Johnson GR, Chen P, et al. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. *Jama*. 2017;318(2):132-145.

Importance: Less than one-third of patients with major depressive disorder (MDD) achieve remission with their first antidepressant., **Objective:** To determine the relative effectiveness and safety of 3 common alternate treatments for MDD., **Design, Setting, and Participants:** From December 2012 to May 2015, 1522 patients at 35 US Veterans Health Administration medical centers who were diagnosed with nonpsychotic MDD, unresponsive to at least 1 antidepressant course meeting minimal

standards for treatment dose and duration, participated in the study. Patients were randomly assigned (1:1:1) to 1 of 3 treatments and evaluated for up to 36 weeks., Interventions: Switch to a different antidepressant, bupropion (switch group, n=511); augment current treatment with bupropion (augment-bupropion group, n=506); or augment with an atypical antipsychotic, aripiprazole (augment-aripiprazole group, n=505) for 12 weeks (acute treatment phase) and up to 36 weeks for longer-term follow-up (continuation phase)., Main Outcomes and Measures: The primary outcome was remission during the acute treatment phase (16-item Quick Inventory of Depressive Symptomatology-Clinician Rated [QIDS-C16] score ≤ 5 at 2 consecutive visits). Secondary outcomes included response ($\geq 50\%$ reduction in QIDS-C16 score or improvement on the Clinical Global Impression Improvement scale), relapse, and adverse effects. Results: Among 1522 randomized patients (mean age, 54.4 years; men, 1296 [85.2%]), 1137 (74.7%) completed the acute treatment phase. Remission rates at 12 weeks were 22.3% (n=114) for the switch group, 26.9% (n=136) for the augment-bupropion group, and 28.9% (n=146) for the augment-aripiprazole group. The augment-aripiprazole group exceeded the switch group in remission (relative risk [RR], 1.30 [95% CI, 1.05-1.60]; $P=.02$), but other remission comparisons were not significant. Response was greater for the augment-aripiprazole group (74.3%) than for either the switch group (62.4%; RR, 1.19 [95% CI, 1.09-1.29]) or the augment-bupropion group (65.6%; RR, 1.13 [95% CI, 1.04-1.23]). No significant treatment differences were observed for relapse. Anxiety was more frequent in the 2 bupropion groups (24.3% in the switch group [n=124] vs 16.6% in the augment-aripiprazole group [n=84]; and 22.5% in augment-bupropion group [n=114]). Adverse effects more frequent in the augment-aripiprazole group included somnolence, akathisia, and weight gain. Conclusions and Relevance: Among a predominantly male population with major depressive disorder unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy. Given the small effect size and adverse effects associated with aripiprazole, further analysis including cost-effectiveness is needed to understand the net utility of this approach.

4. Nierenberg AA, McElroy SL, Friedman ES, et al. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. *The Journal of clinical psychiatry*. 2016;77(1):90-99.

BACKGROUND: Bipolar disorder is among the 10 most disabling medical conditions worldwide. While lithium has been used extensively for bipolar disorder since the 1970s, second-generation antipsychotics (SGAs) have supplanted lithium since 1998. To date, no randomized comparative-effectiveness study has compared lithium and any SGA. METHOD: Within the duration of the study (September 2010-September 2013), participants with bipolar I or II disorder (DSM-IV-TR) were randomized for 6 months to receive lithium (n = 240) or quetiapine (n = 242). Lithium and quetiapine were combined with other medications for bipolar disorder consistent with typical clinical practice (adjunctive personalized treatment [APT], excluding any SGA for the lithium + APT group and excluding lithium or any other SGA for the quetiapine + APT group). Coprimary outcome measures included Clinical Global Impressions-Efficacy Index (CGI-EI) and necessary clinical adjustments, which measured number of changes in adjunctive personalized treatment. Secondary measures included a full range of symptoms, cardiovascular risk, functioning, quality of life, suicidal ideation and behavior, and adverse events. RESULTS: Participants improved across all measures, and over 20% had a sustained response. Primary (CGI-EI, $P = .59$; necessary clinical adjustments, $P = .15$) and secondary outcome changes were not statistically significantly different between the 2 groups. For participants with greater manic/hypomanic symptoms, CGI-EI changes were significantly more favorable with quetiapine + APT ($P = .02$). Among those with anxiety, the lithium + APT group had fewer necessary clinical adjustments per month ($P = .02$). Lithium was better tolerated than quetiapine in terms of the burden of side effects frequency ($P = .05$), intensity ($P = .01$), and impairment ($P = .01$). CONCLUSIONS: Despite adequate power to detect clinically meaningful differences, we found outcomes with lithium + APT and quetiapine + APT were not significantly different across 6 months of treatment for bipolar disorder.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 3 2017, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2013 to Daily Update

1	exp Fluphenazine/	463
2	exp Haloperidol/	7642
3	exp Loxapine/	276
4	exp Perphenazine/	373
5	exp Thioridazine/	620
6	exp Thiothixene/	37
7	exp Trifluoperazine/	889
8	exp Chlorpromazine/	2727
9	exp Pimozide/	443
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9/	12619
11	limit 10 to english language/	11856
12	limit 11 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	3121
13	limit 12 to yr="2016 -Current"	158
14	remove duplicates from 13	71
1	exp aripiprazole/ or exp clozapine/ or exp paliperidone palmitate/ or exp quetiapine fumarate/ or exp risperidone/	18070
2	paliperidone.mp.	1521
3	ziprasidone.mp.	2279
4	pimavanserin.mp.	153
5	olanzapine.mp.	10231
6	cariprazine.mp.	171
7	brexpiprazole.mp.	151
8	exp Lurasidone Hydrochloride/	292
9	asenapine.mp.	488
10	iloperidone.mp.	246
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	27310
12	limit 11 to english language	25863
13	limit 12 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	8300
14	limit 13 to yr="2016 -Current"	722
15	limit 14 to humans	633

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Low Dose Quetiapine

Goal(s):

- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:

- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:

- Up to 12 months (criteria-specific)

Requires PA:

- Quetiapine (HSN = 14015) doses <50 mg/day
- Auto PA approvals for :
 - Patients with a claim for a second generation antipsychotic in the last 6 months
 - Patients with prior claims evidence of schizophrenia or bipolar disorder
 - Prescriptions identified as being written by a mental health provider

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	F3010; F302; F3160-F3164; F3177-3178; F319	
Major Depressive Disorder	F314-315; F322-323; F329; F332-333; F339; F3130	For Seroquel XR® only, Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	F205; F209; F2081; F2089	
Bipolar Mania	F3010; F339; F3110-F3113; F312	
Bipolar Depression	F3130	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than 50 mg/day? (verify days' supply is accurate)	Yes: Go to #3	No: Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	Yes: Go to #4	No: Approve for titration up to maintenance dose (60 days).
4. Is reason for dose <50 mg/day due to any of the following: <ul style="list-style-type: none"> low dose needed due to debilitation from a medical condition or age; unable to tolerate higher doses; stable on current dose; or impaired drug clearance? any diagnosis in table 1 or 2 above? 	Yes: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: 11/17 (SS) 9/15; 9/10; 5/10
Implementation: 1/1/18; 10/15; 1/1/11

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
5. What diagnosis is being treated?	Record ICD10 code	
6. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
7. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	Yes: Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	No: Go to #5
8. Has withdrawal or reduction of the triggering medication resolved symptoms?	Yes: Pass to RPh; Deny; medical appropriateness	No: Go to #5
9. Is the patient on a concomitant first- or second-generation antipsychotic drug?	Yes: Pass to RPh; Deny; medical appropriateness	No: Go to #6
10. Has the patient been recently evaluated for a prolonged QTc interval?	Yes: Approve for up to 6 months	No: Pass to RPh; Deny; medical appropriateness

P&T Review: 01/2017 (SS)
Implementation: 4/1/17