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Class Update: Oral Antipsychotics

Date of Review: March 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, data regarding new expanded indications and one new formulation are summarized.

Research Questions:
1. Is there new comparative evidence of meaningful difference in clinical efficacy or effectiveness between oral first- or second-generation antipsychotic agents, or between oral antipsychotic agents compared to parenteral antipsychotic agents (first- or second-generation) for schizophrenia, bipolar mania, or major depressive disorder?
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
- In adults, no single SGA was superior to other SGAs for multiple clinically relevant outcomes.[1] Similarly, there was no difference in efficacy between FGAs and SGAs.[1] Results for individual efficacy and safety outcomes are reported in **Table 1**.[1] There was insufficient evidence for other comparisons or other outcomes.
- Subgroup analyses demonstrated no difference in efficacy or harms based on age, sex, or prior treatment history.
- There is insufficient evidence assess efficacy of combination antipsychotic treatment with clozapine compared to clozapine monotherapy.

- In children and adolescents, there was low quality evidence of no difference in symptom improvement, response rate, or global impressions of severity between risperidone and olanzapine.[2] There was insufficient evidence for comparisons of other agents for the treatment of schizophrenia.[2]

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]).[3]
- There was insufficient evidence for all other antipsychotic drug comparisons (as monotherapy or in combination with mood stabilizers) for treatment of acute mania. 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.[3]
- In children and young adults, there was insufficient evidence of a difference in clinical outcomes for bipolar disease.

Other Diagnoses

- There is no new evidence for the treatment of other mental health conditions including major depressive disorder. New evidence for the treatment conditions including borderline personality disorder and aggression is insufficient to form meaningful conclusions on comparative efficacy or safety.
- In children and adolescents, there is insufficient direct comparative evidence for FGAs or SGAs for bipolar disorder, autism spectrum disorder, ADHD or other conduct disorders, major depressive disorder, eating disorders, or tic disorders.

Harms

- Since the last review, there have been 4 new Food and Drug Administration (FDA) safety labeling updates for FGAs and SGAs.[4] In 2017, the FDA updated warnings for all SGAs and haloperidol to include risk for falls. Clozapine labeling was updated to include warnings for severe and life-threatening hepatotoxicity, and olanzapine labeling was updated to include a warning for drug reaction with eosinophilia and systemic symptoms. Warnings for pathological gambling and other compulsive behaviors were added to labeling for aripiprazole.
- There was moderate quality evidence that haloperidol was associated with a greater number of withdrawals due to adverse events compared to aripiprazole, olanzapine, risperidone, or ziprasidone in adults with schizophrenia (number needed to harm [NNH] 14 to 52).[1] Comparative evidence for other outcomes was insufficient.
- There was insufficient comparative evidence to determine differences in safety or harms for adults with bipolar disorder.
- In children or young adults, there was low quality evidence that use of SGAs was associated with fewer extrapyramidal symptoms compared to FGAs (absolute risk reduction [ARR] 25%, NNH 4; RR 2.59; 95% CI 1.00 to 7.00) and low quality evidence of no difference in sedation between groups.[2] There was moderate quality evidence of no difference in mortality upon comparison of SGAs and placebo.[2]
- In children and adolescents, 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 corresponding to an approximate NNH of 572 over 1 year).[2]

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.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

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 Maintena (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.[5] They are often used off-label for other mental health conditions including borderline personality disorder, agitation, aggression and nausea or vomiting.[5]

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, alogia, asociality, anhedonia, and avolition).[6] 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.[1] 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.[1] 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.[1] 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] 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.[3] 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.[3,6] 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 (range 30-210). 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.[1,8] There is no established minimum clinically important difference for the PANSS, though improvements of 4-8 points have been correlated to increases in employment and improvements of 10 points have been correlated with reduced hospitalization. Negative symptoms of schizophrenia may also be assessed using the Scale for Assessment of Negative Symptoms (SANS) score which assesses negative symptoms including alogia, 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 (range 0-125). 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.[3,9] 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).[3]

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. 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]

Results are reported in **Table 1**. There was little evidence which assessed newer second-generation antipsychotics and direct comparative evidence regarding other outcomes (including relapse rate, symptom improvement, overall treatment discontinuation, cardiovascular outcomes, diabetes, ketoacidosis and sexual function) was inconsistent between studies and insufficient to draw definitive conclusions between treatment groups.[1] Overall results for subgroup analyses were similar to the general population when analyzed based on study duration, dose, treatment-resistant population, or patients with first-episode psychosis (low quality evidence).[1] Similarly, 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]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]

Table 1. Outcomes and results of AHRQ report[1]

Outcome	**Comparators**	**Quality of evidence**	**Result**
Social or functional status	Risperidone, olanzapine, quetiapine, perphenazine, or ziprasidone	Low	No difference at 18 months
Quality of life	Olanzapine vs. risperidone Olanzapine vs. ziprasidone Olanzapine vs. quetiapine	Moderate Moderate Low	No difference at up to 12 months

	Risperidone vs. quetiapine or ziprasidone Ziprasidone vs. haloperidol Olanzapine vs. haloperidol Perphenazine vs. olanzapine, quetiapine, risperidone or ziprasidone	Low Low Low Low	
Treatment response*	Olanzapine vs. haloperidol Haloperidol vs. risperidone Haloperidol vs. aripiprazole or quetiapine	Low Moderate Low	52.6% vs. 46.5%;[10] RR 0.86, 95% CI 0.78 to 0.96 No difference No difference
Core symptom improvement	FGAs vs. SGAs	Low	No difference
Negative symptom improvement	Olanzapine vs. haloperidol Aripiprazole or risperidone vs. haloperidol Other FGAs vs. SGAs	Moderate Low Low	No clinical difference; MD 2.56, 95% CI 0.94 to 4.18 (SANS score) No clinical difference; MD 0.80, 95% CI 0.14 to 1.46 (PANSS scale) No difference
Remission (complete symptom resolution)	Olanzapine vs. haloperidol Risperidone vs. haloperidol	Low Low	RR 0.64, 95% CI 0.45 to 0.94 (favors olanzapine; ARR not reported) No difference
All-cause mortality or cardiovascular mortality	SGA comparisons	Low	No difference; range 0% to 1.17% at 4 to 24 months
Suicide at 2 years 1. Hospitalization to prevent suicide or suicide attempt 2. Symptoms of suicidality	Clozapine vs. olanzapine	Low Low	1. ARR 8%;[11] HR 0.76, 95% CI 0.58 to 0.97; NNT 12 (favors clozapine) 2. ARR 8.4%;[11] HR 0.78, 95% CI 0.61 to 0.99; NNT 12 (CGI-S - Suicidality scale; favors clozapine)
Overall adverse effects	SGA comparisons		No difference in overall rate of adverse events upon comparison of SGAs; For most studies, the proportion of patients with adverse effects was greater than 60%.
Withdrawals due to adverse events	Haloperidol vs. aripiprazole Haloperidol vs. olanzapine Haloperidol vs. risperidone Haloperidol vs. ziprasidone Haloperidol vs. clozapine or quetiapine	Moderate Moderate Moderate Moderate Low	16.2% vs. 14.3%; NNH 52; RR 1.25, 95% CI 1.07 to 1.47 11.6% vs. 6.0%; NNH 17; RR 1.89; 95% CI 1.57 to 2.27 11.1% vs. 8.4%; NNH 37; RR 1.32; 95% CI 1.09 to 1.60 16.0% vs. 9.2%; NNH 14; RR 1.68, 95% CI 1.26 to 2.23 No difference
Clinically important weight gain of >7%	Olanzapine vs aripiprazole Olanzapine vs. clozapine Olanzapine vs. quetiapine Olanzapine vs. risperidone Olanzapine vs. ziprasidone	Moderate Moderate Moderate Moderate Moderate	RR 2.31; 95% CI 1.96 to 2.72 (olanzapine more weight gain) RR 1.71; 95% CI 1.47 to 1.99 (olanzapine more weight gain) RR 1.82; 95% CI 1.34 to 2.46 (olanzapine more weight gain) RR 1.81; 95% CI 1.34 to 2.46 (olanzapine more weight gain) RR 5.76; 95% CI 3.46 to 9.59 (olanzapine more weight gain) Absolute values were not reported though mean differences in weight gain ranged from 1-7 kg over 3.7 to 24 months with larger weight gain generally associated with longer use.

Abbreviations: ARR = absolute risk reduction; CGI-S = Clinical Global Impression of Severity; CI = confidence interval; FGA = first generation antipsychotic; HR = hazard ratio; MD = mean difference; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; PANSS = positive and negative syndrome scale; RR = relative risk; SANS = scale for assessment of negative symptoms; SGA = second generation antipsychotic

*Treatment response 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]

A 2017 Cochrane review examined the safety and efficacy of antipsychotic combination treatments to antipsychotic monotherapy for patients with schizophrenia and schizoaffective disorders.[6] Of the 62 studies included in the review (n=4833), 31 studies compared combination treatment with clozapine to clozapine monotherapy.[6] 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.[6] Most trials included populations who had previously failed monotherapy antipsychotics and approximately half of the studies included patients admitted to a facility.[6] 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.[6]
- Early study discontinuation was not statistically significant between patients on combination antipsychotic treatment versus monotherapy antipsychotic use (low quality evidence; RR 0.90, 95% CI 0.76 to 1.07, n=3137).[6] Data were limited by high risk or bias in included studies, high heterogeneity, lack of reported outcomes of interest, and short trial duration.

Combination treatment was also assessed in a 2016 report from CADTH which included 4 systematic reviews, 8 RCTs, and 2 evidence-based guidelines.[12] Upon comparison of combination treatment with aripiprazole and clozapine versus clozapine monotherapy, results of trials were mixed and there was insufficient evidence to determine differences in symptom improvement.[12] Additionally, symptom improvement was not significantly different upon clozapine augmentation with risperidone (n=255) or augmentation with haloperidol or aripiprazole (n=106) compared to clozapine monotherapy.[12] Data were limited by small populations, limited duration (<3 months), high heterogeneity between trials, and lack of reported randomization or blinding methods.[12] 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.[12]

In patients with treatment-resistant schizophrenia, a 2017 Cochrane review examined efficacy and safety of combination antipsychotic treatment with clozapine.[13] 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.[13] For most outcomes, evidence was graded as very low quality, limiting confidence in the treatment effect.[13] 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).[13] 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 (MD 39%; 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.[13]

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.[3] Drugs included in the review included second-generation antipsychotics, anticonvulsants (carbamazepine, divalproex, and lamotrigine), chlorpromazine, and lithium.[3] 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]).[3] 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.[3] 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.[3]
- There was insufficient evidence for all other antipsychotic drug comparisons (as monotherapy or in combination with mood stabilizers) for treatment of acute mania.[3] Similarly, there was insufficient evidence for any treatment and all outcomes for bipolar depression or maintenance treatment.[3]

A 2016 CADTH rapid response report examined aripiprazole use as monotherapy or adjunct therapy in combination with lithium or divalproex.[14] 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.[14] 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.[14] Comparisons to individual agents were not evaluated and there was high heterogeneity among analyses.[14]

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.[15]

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).[2] The report included 135 studies which primarily compared antipsychotic use to placebo.[2] Direct comparative evidence (which will be the focus of this summary) was generally of insufficient or low quality particularly for clinical outcomes.

- 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.[2] 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).[2]
- There was insufficient evidence for comparisons of other agents for the treatment of schizophrenia.[2]
- 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.[2] There was insufficient evidence regarding efficacy or safety of SGAs in patients with obsessive-compulsive disorder.[2]
- There was low quality evidence that use of SGAs was associated with fewer extrapyramidal symptoms compared to FGAs (MD 25 %, NNH 4; RR 2.59; 95% CI 1.00 to 7.00) and low quality evidence of no difference in sedation between groups.[2] Regarding long-term serious adverse events, there was moderate quality evidence of no difference in mortality upon comparison of SGAs and placebo.[2]
- 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 corresponding to an approximate NNH of

572 over 1 year).[2] 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).[2] 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.[16] Only 4 of these studies included direct comparative evidence between agents. 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).[16] There was insufficient evidence for other comparisons.[16] 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.[16]

CADTH published a rapid response report in 2016 including 9 systematic reviews which examined antipsychotic use in pediatric patients (<18 years of age).[17] 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.[17] 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.[17] There was no comparative evidence for efficacy and safety of antipsychotics in children with other conditions including disruptive behavior disorders or autism spectrum disorders.[17] Evidence regarding adverse events was mixed. The most common adverse events associated with treatment were weight gain, drowsiness, increased appetite, and extrapyramidal adverse effects.[17] 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.[17] 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.[17]

<u>Other Conditions</u>

In 2017, CADTH published a rapid response report assessing available evidence of aripiprazole treatment for borderline personality disorder.[18] 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.[18] 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.[18]

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.[19] Only one low-quality RCT (n=110) with high risk of bias was identified which compared haloperidol to olanzapine or clozapine.[19] There was low quality evidence of no difference in discontinuation rate between treatment groups.[19] 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.[19]

Several other systematic reviews and meta-analyses were not included due to poor methodological quality, because the evidence available for the analysis was of poor quality, or evidence was not applicable to the OHP population.[8,20-37]

New Guidelines:
Guidelines from the Department of Veterans Affairs and Department of Defense were updated in 2016 for the management of major depressive disorder.[38] Recommended first-line pharmacological treatments for mild to moderate major depressive disorder include SSRIs (except fluvoxamine), SNRIs, mirtazapine, or bupropion (strong recommendation).[38] 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.[38] 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).[38] Medication augmentation strategies include addition of bupropion, buspirone, lithium, liothyronine, or SGAs to first-line pharmacotherapy.[38] Due to the significant potential of adverse effects with SGAs, they are recommended only when other strategies have failed.[38] Recommendation was based on 2 systematic reviews demonstrating aripiprazole, olanzapine, quetiapine, and risperidone improved remission rates compared to placebo.[38] 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.[38] Aripiprazole, olanzapine, quetiapine and risperidone were also more commonly associated with weight gain compared to placebo (fair quality evidence).[38]

The Department of Veterans Affairs and Department of Defense also updated guidelines for the management of post-traumatic stress disorder (PTSD) in 2017.[39] 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).[39]

In 2016, the American Psychiatric Association updated guideline recommendations for the use of antipsychotics in patients with dementia.[40] The majority of guideline committee members reported no conflicts of interest. Only one member reported receiving funding from industry and government which could be perceived as a conflict of interest, and this member abstained from voting on medication-related recommendations.[40] 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. Recommendations for specific medications are discussed here. Haloperidol is not recommended as a first-line nonemergency medication in patients with dementia and without delirium (strong recommendation; moderate quality evidence).[40] In addition, long-acting injectable antipsychotic medications are not recommended unless used for patients with concomitant chronic psychotic disorders (strong recommendation; moderate quality evidence).[40]

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.

In November 2017, the FDA approved Abilify Mycite®, a new formulation of aripiprazole oral tablets with a sensor.[41] This formulation is a drug-device combination product with an ingestible event marker sensor which is intended to track whether the tablet is consumed.[41] Approval was based on prior efficacy and safety analysis of aripiprazole tablets. Abilify Mycite is indicated for treatment of adults with schizophrenia, adjunct treatment of adults with MDD, and acute or maintenance treatment of bipolar I disorder (as monotherapy or in combination with lithium or valproate).[41] The sensor embedded in the tablet activates upon contact with gastric fluid and sends a signal to a Mycite® Patch which is worn by the patient.[41] This patch then transmits the data to a smartphone app for the patient and/or web-based portal for healthcare providers. Labeling specifies that improved compliance with this formulation has not been

established, and that tracking drug ingestion in "real-time" or during an emergency is not recommended because detection of sensors may be delayed or not occur.[41]

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.[4]

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.[4]

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.[4]

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.[4]

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 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Mohamed S, et al.[42] AC, single-blind, MC, PG, RCT N=1522 Duration: 36 weeks	1. Switch to bupropion 150-400 mg daily 2. Add bupropion 150-400 mg daily 3. Add aripiprazole 5-15 mg daily Doses titrated based on tolerability and treatment effect	Veterans with MDD unresponsive to at least one antidepressant	Remission at 12 weeks defined as a score of ≤5 on the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C16) score	1. 114/511 (22.3%) 2. 136/506 (26.9%) 3. 146/505 (28.9%) 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.[43] 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.[44] 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.[45] OL, RCT N=44 Duration: 24 weeks	1. Risperidone 0.25 to 3 mg daily 2. Aripiprazole 1.25 to 15 mg daily Dose titrated based on clinical response	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 CGI-I at 24 weeks 1. 2.7 (SD 0.7) 2. 3.0 (SD 1.2) P=0.356

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

References:

1. McDonagh MS DT, Selph S, Devine EB, Cantor A, Bougatsos C, Blazina I, Grusing S, Fu R, Kopelovich SL, Monroe-DeVita M, Haupt DW. Treatments for Schizophrenia in Adults: A Systematic Review. Comparative Effectiveness Review No. 198. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 17(18)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality; October 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. DOI: https://doi.org/10.23970/AHRQEPCCER198.
2. Pillay J BK, Carrey N, Newton A, Vandermeer B, Nuspl M, MacGregor T, Ahmed Jafri SH, Featherstone R, Hartling L. . First- and Second-Generation Antipsychotics in Children and Young Adults: Systematic Review Update. Comparative Effectiveness Review No. 184. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2015-00001-I.) AHRQ Publication No. 17-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017. www.effectivehealthcare.ahrq.gov/reports/final/cfm. doi: https://doi.org/10.23970/AHRQEPCCER184.
3. Treatment for Bipolar Disorder in Adults: A Systematic Review Comparative Effectiveness Review No. (Prepared by the Pacific Northwest Evidence-based Practice Center) AHRQ Publication No. Rockville, MD: Agency for Healthcare Research and Quality; October 2017.
4. Food and Drug Administration. Medical Product Safety Information. http://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/ Accessed .
5. Micromedex Healthcare Series [internet database]. Greenwood Village, CO: Truven Health Analytics, Inc. Updated periodically. Accessed October 23, 2017.
6. Ortiz-Orendain J, Castiello-de Obeso S, Colunga-Lozano LE, Hu Y, Maayan N, Adams CE. Antipsychotic combinations for schizophrenia. *The Cochrane database of systematic reviews.* 2017;6:CD009005.
7. Bipolar Disorder. In: Dynamed [internet database]. Ipswich, MA: EBSCO Publishing. Updated September 27, 2017. Accessed November 18, 2017.
8. Samara MT, Dold M, Gianatsi M, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. *JAMA Psychiatry.* 2016;73(3):199-210.
9. Lukasiewicz M, Gerard S, Besnard A, et al. Young Mania Rating Scale: how to interpret the numbers? Determination of a severity threshold and of the minimal clinically significant difference in the EMBLEM cohort. *International journal of methods in psychiatric research.* 2013;22(1):46-58.
10. Abou-Setta AM, Mousavi SS, Spooner C, et al. AHRQ Comparative Effectiveness Reviews. In: *First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
11. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry.* 2003;60(1):82-91.
12. Combination Atypical Antipsychotics in Adolescents or Adults with Schizophrenia: A Review of Clinical and Cost-Effectiveness and Guidelines. Rapid Response Report: Summary with Critical Appraisal. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Sep 6.
13. Barber S, Olotu U, Corsi M, Cipriani A. Clozapine combined with different antipsychotic drugs for treatment-resistant schizophrenia. *The Cochrane database of systematic reviews.* 2017;3:CD006324.
14. Aripiprazole for Patients with Bipolar Disorder: A Review of the Clinical Effectiveness, Cost-effectiveness and Guidelines. CADTH Rapid Response Reports. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 May 25. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0088612/. Accessed 10/27/17.
15. Combination Atypical Antipsychotics in Adolescents or Adults with Bipolar Disorder with Psychotic Features: A Review of Clinical and Cost-Effectiveness and Guidelines. Rapid Response Report: Summary with Critical Appraisal. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Sep 6. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089735/. Accessed 10/27/17.
16. Williamson E SN, Andrews JC, Krishnaswami S, McPheeters ML, Fonnesbeck C, Sanders K, Weitlauf A, Warren Z. Medical Therapies for Children With Autism Spectrum Disorder—An Update. Comparative Effectiveness Review No. 189. (Prepared by the Vanderbilt Evidence-based Practice Center under

Contract No. 290-2015-00003-I.) AHRQ Publication No. 17-EHC009-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. doi: https://doi.org/10.23970/AHRQEPCCER189.
17. Antipsychotics for Pediatric Patients: A Review of the Clinical Effectiveness, Safety, and Guidelines. CADTH Rapid Response Reports. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; Nov 2016. https://www.ncbi.nlm.nih.gov/pubmed/28121104. Accessed 11/2/17.
18. Aripiprazole for Borderline Personality Disorder: A Review of the Clinical Effectiveness. CADTH Rapid Response Reports. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; Feb 2017. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0096409/. Accessed 11/2/17.
19. Khushu A, Powney MJ. Haloperidol for long-term aggression in psychosis. *The Cochrane database of systematic reviews.* 2016;11:CD009830.
20. Saha KB, Bo L, Zhao S, Xia J, Sampson S, Zaman RU. Chlorpromazine versus atypical antipsychotic drugs for schizophrenia. *The Cochrane database of systematic reviews.* 2016;4:CD010631.
21. Sampford JR, Sampson S, Li BG, Zhao S, Xia J, Furtado VA. Fluphenazine (oral) versus atypical antipsychotics for schizophrenia. *The Cochrane database of systematic reviews.* 2016;7:CD010832.
22. Land R, Siskind D, McArdle P, Kisely S, Winckel K, Hollingworth SA. The impact of clozapine on hospital use: a systematic review and meta-analysis. *Acta psychiatrica Scandinavica.* 2017;135(4):296-309.
23. Citrome L. Activating and Sedating Adverse Effects of Second-Generation Antipsychotics in the Treatment of Schizophrenia and Major Depressive Disorder: Absolute Risk Increase and Number Needed to Harm. *Journal of clinical psychopharmacology.* 2017;37(2):138-147.
24. Chiu L, Chow R, Popovic M, et al. Efficacy of olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2016;24(5):2381-2392.
25. Chow R, Chiu L, Navari R, et al. Efficacy and safety of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV) as reported in phase I and II studies: a systematic review. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* 2016;24(2):1001-1008.
26. Dold M, Tardy M, Samara MT, Li C, Kasper S, Leucht S. Are all first-generation antipsychotics equally effective in treating schizophrenia? A meta-analysis of randomised, haloperidol-controlled trials. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry.* 2016;17(3):210-220.
27. Forcen FE, Matsoukas K, Alici Y. Antipsychotic-induced akathisia in delirium: A systematic review. *Palliative & supportive care.* 2016;14(1):77-84.
28. Galling B, Roldan A, Nielsen RE, et al. Type 2 Diabetes Mellitus in Youth Exposed to Antipsychotics: A Systematic Review and Meta-analysis. *JAMA Psychiatry.* 2016;73(3):247-259.
29. Kishi T, Hirota T, Matsunaga S, Iwata N. Antipsychotic medications for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. *Journal of neurology, neurosurgery, and psychiatry.* 2016;87(7):767-774.
30. Meduri M, Gregoraci G, Baglivo V, Balestrieri M, Isola M, Brambilla P. A meta-analysis of efficacy and safety of aripiprazole in adult and pediatric bipolar disorder in randomized controlled trials and observational studies. *Journal of affective disorders.* 2016;191:187-208.
31. Murru A, Hidalgo D, Bernardo M, et al. Antipsychotic switching in schizoaffective disorder: A systematic review. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry.* 2016;17(7):495-513.
32. Tarraf C, Naja WJ. Aripiprazole-Induced Hyperlipidemia: An Update. *The primary care companion for CNS disorders.* 2016;18(4).
33. Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. *Early intervention in psychiatry.* 2016;10(3):193-202.
34. Wilson RP, Bhattacharyya S. Antipsychotic efficacy in psychosis with co-morbid cannabis misuse: A systematic review. *Journal of psychopharmacology (Oxford, England).* 2016;30(2):99-111.

35. Yoodee J, Permsuwan U, Nimworapan M. Efficacy and safety of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: A systematic review and meta-analysis. *Critical reviews in oncology/hematology.* 2017;112:113-125.
36. Zheng W, Zheng Y-J, Li X-B, et al. Efficacy and Safety of Adjunctive Aripiprazole in Schizophrenia: Meta-Analysis of Randomized Controlled Trials. *Journal of clinical psychopharmacology.* 2016;36(6):628-636.
37. Freire RC, Zugliani MM, Garcia RF, Nardi AE. Treatment-resistant panic disorder: a systematic review. *Expert Opin Pharmacother.* 2016;17(2):159-168.
38. Management of Major Depressive Disorder Work Group. VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Version 3.0. Washington, DC: Veterans Health Administration and Department of Defense. 2016.
39. Management of Posttraumatic Stress Disorder Work Group. VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Version 3.0. Washington, DC: Veterans Health Administration and Department of Defense. 2017.
40. National Guideline Clearinghouse. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. 2016.
41. Abilify Mycite (aripiprazole oral tablet with sensor) [product labeling]. Rockville, MD: Otsuka America Pharmaceutical, Inc. November 2017.
42. 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.
43. 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.
44. Deckersbach T, Nierenberg AA, McInnis MG, et al. Baseline disability and poor functioning in bipolar disorder predict worse outcomes: results from the Bipolar CHOICE study. *The Journal of clinical psychiatry.* 2016;77(1):100-108.
45. 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.

Appendix 1: Current Preferred Drug List

ROUTE	FORM	BRAND	GENERIC	PDL	CARVEOUT
FIRST GENERATION ORAL ANTIPSYCHOTICS					
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
SECOND GENERATION ORAL ANTIPSYCHOTICS					
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	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ABILIFY	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TABLET	REXULTI	BREXPIPRAZOLE	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	TABLET	FANAPT	ILOPEIDONE	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

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 (>=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

Author: Servid

Date: March 2018

Appendix 4: Safety Edits

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: • 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: *3/18 (SS); 11/17; 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: *3/18 (SS); 01/2017*
Implementation: *4/1/17*