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Drug Class Literature Scan: Antipsychotics

Date of Review: March 2019

Date of Last Review: September 2018
Literature Search: 01/01/2018 – 01/8/2019

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- Two systematic reviews are included in this literature scan of recent evidence for antipsychotic safety and efficacy.
- The Agency for Healthcare Research and Quality (AHRQ) published a systematic review to assess the effectiveness of drug and non-drug therapies for treating acute mania or depression symptoms and preventing relapse in adults with bipolar disorder (BD) diagnoses.[1] No high- or moderate-strength evidence was identified for any intervention to effectively treat any phase or type of BD versus placebo or an active comparator.[1] When compared to placebo, pooled data from low strength evidence showed asenapine, cariprazine, olanzapine, and quetiapine improved acute mania symptoms in Bipolar Disorder Type I (BD-I).[1] Data from the specific trials is outlined in **Table 2**. Lithium was the only mood stabilizer that improved acute mania in the short-term and prolonged time to relapse in the long term compared to placebo (low-strength evidence).[1] Evidence was largely insufficient to draw conclusions for all other non-approved FDA drugs for BD-I for the primary outcomes of interest (response, symptom scores, and function).[1]
- A 2018 Cochrane review evaluated the evidence to support the efficacy and safety of oral olanzapine when used as an antiemetic in the prevention and treatment of nausea and vomiting related to cancer in adults.[2] Currently the use of olanzapine to mitigate nausea and vomiting associated with chemotherapy is off-label, as olanzapine is not FDA-approved for this indication. There is moderate-quality evidence that oral olanzapine decreases the likelihood of nausea or vomiting during chemotherapy from 50% to 25% in adults with solid tumors, in addition to standard therapy, compared to placebo or no treatment (risk ratio 1.98, 95% confidence interval (CI) 1.59 to 2.4).[2] Number needed to treat for additional beneficial outcome (NNTB) was 5 (95% CI 3.3 to 6.6).[2] It is uncertain if olanzapine increases the risk of serious adverse events (absolute risk difference 0.7% more, 95% CI 0.2 to 5.2; relative risk (RR) 2.46, 95% CI 0.48 to 12.55, low-quality evidence).[2]
- The FDA published a new safety alert for ziprasidone advising against use in elderly patients with dementia due to the increased risk of death in these patients when administered ziprasidone.[3]
- Warnings about dosing errors were added to Aristada Initio® extended-release injection labeling. Aristada Initio® is for single administration in contrast to Aristada® which is administered monthly, every 6 weeks, or every 8 weeks.[4]

Recommendations:

- No further review or research needed at this time.
- No changes to the PDL are recommended for oral or parenteral antipsychotics based on efficacy or safety data.
- After evaluation of costs in executive session, no PDL changes were recommended.

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Summary of Prior Reviews and Current Policy

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 PA criteria for these safety edits are outlined in **Appendix 5**. Injectable formulations of aripiprazole, haloperidol, chlorpromazine, fluphenazine, trifluoperazine, paliperidone palmitate, and risperidone are preferred on the Preferred Drug List (PDL). Oral antipsychotics that are preferred on the PDL include chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, thiothixene, trifluoperazine, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, and risperidone. The majority of antipsychotic use in the Oregon Medicaid population is for oral second generation antipsychotics (SGA) including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 10% of antipsychotic medication claims are for parenteral formulations. Paliperidone, aripiprazole, and haloperidol are the most frequently prescribed injectable agents in this class. The antipsychotics included on the Oregon PDL are presented in **Appendix 1**.

Previous reviews have found insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy, effectiveness, or harms between antipsychotic agents for schizophrenia, bipolar mania or major depressive disorder (MDD). There is insufficient evidence from randomized controlled trials or high quality systematic reviews 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.

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. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:

After review, 4 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[5-8]

<u>Agency for Healthcare Research and Quality</u>

In 2018, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review completed by the Minnesota Evidence-based Practice Center.[1] The purpose of the review was to assess the effectiveness of drug and non-drug therapies for treating acute mania or depression symptoms and preventing relapse in adults with bipolar disorder (BD) diagnoses.[1] The literature search evaluated trials published from 1994 through May 2017. Eligible studies included randomized controlled trials and prospective cohort studies with comparator arms in adults with BD of any type with 3 weeks follow up for acute mania, 3 months for depression, and 6 months for maintenance treatments.[1] One hundred fifty-seven studies were included in the review; 108 studies for 28 drugs and 49 studies for

non-drug interventions.[1] Trials with greater than 50 percent attrition rates were excluded from the systematic review because of potential systematic differences between patients who complete a study and those who do not.[1] Study findings were interpreted using published minimally important differences (MIDs) for the Young Mania Rating Scale (YMRS) (MID=6) and the Clinical Global Impressions (CGI) scale (MID=1).[9] Drug treatments approved by the Food and Drug Administration (FDA) for bipolar treatment are summarized in **Table 1**. No high- or moderate-strength evidence was identified for any intervention to effectively treat any phase or type of BD versus placebo or an active comparator.[1] Evidence was largely insufficient to draw conclusions regarding the effects of drug treatments for depression in adults with BD for the primary outcomes of interest (relapse, symptom scores, and function).[1]

Table 1. FDA-approved medications for bipolar disorder[1]

Drug Type	Generic Name (Date Approved)	Brand Name	Manic	Mixed (Mania/Depression)	Maintenance	Depression
Salts	Lithium (1970)	Lithobid®	X	X	X	
Atypical Antipsychotics	Aripiprazole (2004)	Abilify®	X	X	X	
	Asenapine (2015)	Saphris®	X	X	X	
	Cariprazine (2015)	Vraylar®	X	X		
	Lurasidone (2013)	Latuda®				X
	Olanzapine (2000)	Zyprexa®	X	X	X	
	Quetiapine (2004)	Seroquel®	X		X	X
	Risperidone (2003)	Risperdal®	X	X	X	
	Ziprasidone (2004)	Geodon®	X	X	X	
Anticonvulsants	Carbamazepine (2004)	Equetro®	X	X		
	Lamotrigine (2003)	Lamictal®			X	
	Divalproex Sodium (1995)	Depakote®	X	X		

Antipsychotics to treat acute mania in bipolar disorder

When compared to placebo, pooled data showed asenapine, cariprazine, olanzapine, and quetiapine improved acute mania symptoms (low-strength evidence).[1] However, improvements were of modest clinical significance, with values that were less than the MID, but still large enough that a reasonable proportion of participants likely received a benefit.[1] Unpooled evidence indicated an overall beneficial effect of risperidone and ziprasidone on acute mania symptoms compared to placebo (low-strength evidence).[1] Specific findings for the atypical antipsychotics in managing acute mania are summarized in **Table 2.** Evidence was insufficient for all outcomes to address whether aripiprazole or haloperidol was better than placebo for acute mania in adults with BD-I, due to high study limitations and imprecise data.[1] Participants using atypical antipsychotics, except quetiapine, reported more extrapyramidal symptoms compared to placebo (specific rates not specified by the authors).[1] Patients using olanzapine reported more clinically significant weight gain (at least a 7 percent increase) compared to placebo.[1]

Table 2. Summary of findings with at least low-strength evidence for antipsychotic drug treatments for acute mania[1]

Intervention	Number of Studies (number of patients) Timing	Findings	Strength of Evidence
Asenapine vs. placebo	3 RCTs (n=936) 3 weeks	Response/Remission Rates: No difference YMRS: Favors Asenapine, MD 4.37 (95% CI 1.27, 7.47; MID 6) CGI-BP-S: Favors Asenapine, MD 0.5 (95% CI 0.29, 0.71; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference	Low (moderate study limitations, imprecise)
Cariprazine vs. placebo	3 RCTs (n=1,047) 3 weeks	Response Rate: Favors Cariprazine, OR 2.14 (95% CI 1.08, 4.23); NNT 6 Remission Rate: Favors Cariprazine, OR 1.95 (95% CI 1.45, 2.63); NNT 7 YMRS: Favors Cariprazine, MD 5.38 (95% CI 1.84, 8.92; MID 6) CGI-BP-S: Favors Cariprazine, MD 0.54 (95% CI 0.35, 0.73; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference	Low (moderate study limitations, imprecise)
Olanzapine vs. placebo	5 RCTs (n=1,199) 3 weeks	Response Rate: Favors Olanzapine, OR 1.99 (95% CI 1.29, 3.08); NNT 6 Remission Rate: Favors Olanzapine, OR 1.75 (95% CI 1.19, 2.58); NNT 8 YMRS: Favors Olanzapine, MD 4.9 (95% CI 2.34, 7.45; MID 6) Withdrawal (Lack of Efficacy, Overall): Favors Olanzapine, MD 0.42 (95% CI 0.29, 0.61); NNH 2	Low (moderate study limitations, imprecise)
Quetiapine vs. placebo	4 RCTs (n=1,007) 3 weeks 5 RCTs (n=699) 3 weeks	Response Rate: Favors Quetiapine, OR 2.07 (95% CI 1.39, 3.09); NNT 7 Withdrawal (Lack of Efficacy): Favors Quetiapine, MD 0.38 (95% CI 0.23, 0.63); NNH 2 YMRS: Favors Quetiapine, MD 4.92 (95% CI 0.31, 9.53; MID 6)	Low (moderate study limitations, imprecise)
Risperidone vs. placebo	2 RCT (n=584) 3 weeks	Response Rate, YMRS, and CGI: Favors Risperidone (not pooled)	Low (moderate study limitations, imprecise)
Ziprasidone vs. placebo	2 RCT (n=402) 3 weeks	Response Rate, YMRS, and CGI: Favors Ziprasidone (not pooled)	Low (moderate study limitations, imprecise)

Abbreviations: AE=adverse events; CGI =Clinical global impression; CGI-BP=Clinical global impression scale, bipolar edition; CI=confidence interval; MD=mean difference; MID=minimally important difference; n=number; NNH = Number needed to harm; NNT=number needed to treat; OR=odds ratio; RCT=randomized controlled trial; YMRS=Young mania rating scale

Mood stabilizers to treat acute mania in bipolar disorder

Four mood stabilizers, all FDA approved for use in patients with bipolar disorder experiencing mania, were evaluated as single drugs: carbamazepine, divalproex/valproate, lamotrigine, and lithium. All studies enrolled adults with BD-I. Only one study (for lithium) also included adults with BD Type II (BD-II). Low-strength evidence showed lithium increased response rates, remission rates, and manic symptom improvement in BD-I participants with acute mania compared to placebo.[1] The data from these trials is summarized in **Table 3**. Lithium improved acute mania in the short-term and prolonged time to relapse in the long-term

compared to placebo (low-strength evidence).[1] All other drug comparisons to placebo or active controls had insufficient evidence for acute mania, depression, and maintenance treatment outcomes.[1] No difference was found between olanzapine and divalproex/valproate for acute mania (low-strength evidence).[1]

Table 3. Summary of findings with at least low-strength evidence for lithium for acute mania[1]

Intervention	Number of Studies (number of patients) Timing	Findings	Strength of Evidence
Lithium vs. placebo	1 RCT + 1 IPD (n=325) 3 weeks 3 RCTs (n=325) 3 weeks	Remission and Response Rates: Favors Lithium (not pooled) YMRS: Favors Lithium, MD 5.81 (95% CI 2.21, 9.4; MID=6) Withdrawal (Overall): No difference	Low (moderate study limitations, imprecise)

Abbreviations: AE=adverse events; CI=confidence interval; IPD=Individual patient data; MD=mean difference; MID=minimally important difference; n=number; RCT=randomized controlled trial; YMRS=Young mania rating scale

Drugs Not FDA-approved for acute mania in bipolar disorder

Ten drugs not FDA approved for BD were examined for acute mania: allopurinol, celecoxib, donepezil, dipyridamole, endoxifen, gabapentin, paliperidone, tamoxifen, topiramate, and oxcarbazepine, some in combination with mood stabilizers.[1] Low-strength evidence showed paliperidone improved manic symptoms over placebo in adults with BD-I, although the improvement was not a clinically important difference (n=763).[1] Low-strength evidence showed topiramate was not significantly different from placebo for symptom improvement, and participants using placebo withdrew less for adverse events (n=876) in adults with BD-I.[1] Low-strength evidence showed allopurinol plus mood stabilizers/other psychotropic medications did not differ significantly from mood stabilizers alone for manic symptom, CGI improvement, or overall withdrawals (n=355) in adults with BD-I.[1] Evidence was largely insufficient to draw conclusions for all other non-approved FDA drugs for BD-I for the primary outcomes of interest (response, symptom scores, and function).[1]

Non-drug studies examined eight therapy approaches, seven of which were psychosocial intervention types: 1) psychoeducation, 2) cognitive behavioral therapy (CBT), 3) systematic/collaborative care, 4) family/partner interventions, 5) interpersonal and social rhythm therapy (IPSRT), 6) combination treatments (treatments that combined two or more psychosocial interventions, and 7) other psychosocial treatments (e.g. self-management via phone application support).[1] For psychosocial interventions, CBT was no better for depression or mania symptoms than psychoeducation or other active psychosocial comparators (low-strength evidence).[1] Systematic/collaborative care had no effect on relapse compared to inactive comparators (low-strength evidence).[1] Evidence for other non-drug interventions was insufficient.[1]

Cochrane Collaborative

A 2018 Cochrane review evaluated the evidence to support the efficacy and safety of oral olanzapine when used as an antiemetic in the prevention and treatment of cancer-related nausea and vomiting in adults.[2] Currently the use of olanzapine to mitigate nausea and vomiting associated with chemotherapy is off-label, as olanzapine is not FDA-approved for this indication. Thirteen RCTs at high risk of bias due to inadequate blinding were included in the Cochrane systematic review. Most of the RCTs enrolled less than 50 subjects per treatment arm and compared olanzapine to placebo. Olanzapine may double the likelihood of no nausea or vomiting during chemotherapy from 25% to 50% (risk ratio 1.98, 95% CI 1.59 to 2.47; 561 participants; 3 studies; moderate-quality evidence) when added to

standard therapy.[2] Number needed to treat for additional beneficial outcome was 5 (95% CI 3.3 to 6.6).[2] It is uncertain if olanzapine increases the risk of serious adverse events (absolute risk difference 0.7% more, 95% CI 0.2 to 5.2; RR2.46, 95% CI 0.48 to 12.55; 7 studies, 889 participants, low-quality evidence).[2]

One study (20 participants) compared olanzapine versus neurokinin 1 (NK1) antagonists and no difference in any reported outcomes was observed.[2] One study (112 participants) compared olanzapine versus metoclopramide and reported that olanzapine may increase freedom from overall nausea (RR 2.95, 95% CI 1.73 to 5.02) and overall vomiting (RR 3.03, 95% CI 1.78 to 5.14).[2] Absolute risk reduction was not reported for this trial. Another study (62 participants) examined olanzapine versus 5-hydroxytryptamine (5-HT3) antagonists, reporting olanzapine may increase the likelihood of 50% or greater reduction in nausea or vomiting at 48 hours (RR 1.82, 95% CI 1.11 to 2.97), but not at 24 hours (RR 1.36, 95% CI 0.80 to 2.34).[2] One study (229 participants) compared olanzapine versus dexamethasone, reporting that olanzapine may reduce overall nausea (RR 1.73, 95% CI 1.37 to 2.18), overall vomiting (RR 1.27, 95% CI 1.10 to 1.48), delayed nausea (RR 1.66, 95% CI 1.33 to 2.08), and delayed vomiting (RR 1.25, 95% CI 1.07 to 1.45).[2] All of the data comparing olanzapine to an active comparator was rated as low quality or very low quality evidence.[2]

In summary, there is moderate-quality evidence that oral olanzapine may increase the likelihood of not being nauseous or vomiting during chemotherapy from 25% to 50% in adults with solid tumors, in addition to standard therapy, compared to placebo or no treatment.[2] There is uncertainty whether it increases serious adverse events.[2]

New Guidelines: No new guidelines have been published since the last literature scan.

New Formulations: No new formulations have been FDA-approved since the last literature scan.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ziprasidone	Geodon	11/2018	Boxed Warning and Warnings/Precautions	Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Geodon® is not approved for elderly patients with dementia related psychosis.[3]
Aripiprazole Extended Release Injection	Aristada	11/2018	Dosage and Administration and Warnings/Precautions	Medication errors, including substitution and dispensing errors, between Aristada® and Aristada Initio® could occur. Aristada Initio is for single administration in contrast to Aristada® which is administered monthly, every 6 weeks, or every 8 weeks.[4] Do not substitute Aristada Initio® for Aristada® because of differing pharmacokinetic profiles.[4]

References:

1. Butler M, Urosevic S, Desai P, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. Comparative Effectiveness Review No. 208. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 18-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2018.
2. Sutherland A, Naessens K, Plugge E, et al. Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. Cochrane Database Syst Rev. 2018; 9.
3. Geodon (ziprasidone) Prescribing Information. New York, NY; Pfizer. 11/2018.
4. Aristada (aripiprazole lauroxil) Extended Release Injectable Prescribing Information. Waltham, MA; Alkermes, Inc. 11/2018.
5. Ali SN, Bazzano LA. Hyponatremia in Association With Second-Generation Antipsychotics: A Systematic Review of Case Reports. Ochsner Journal.18 (3):230-235.
6. Channing J, Mitchell M, Cortese S. Lurasidone in Children and Adolescents: Systematic Review and Case Report. Journal of Child & Adolescent Psychopharmacology.28 (7):428-436.
7. Cuomo A, Goracci A, Fagiolini A. Aripiprazole use during pregnancy, peripartum and lactation. A systematic literature search and review to inform clinical practice. Journal of Affective Disorders.228:229-237.
8. Lally J, Al Kalbani H, Krivoy A, Murphy KC, Gaughran F, MacCabe JH. Hepatitis, Interstitial Nephritis, and Pancreatitis in Association With Clozapine Treatment: A Systematic Review of Case Series and Reports. Journal of Clinical Psychopharmacology.38 (5):520-527.
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. Nicol GE, Yingling MD, Flavin KS, et al. Metabolic Effects of Antipsychotics on Adiposity and Insulin Sensitivity in Youths: A Randomized Clinical Trial. JAMA psychiatry. 2018; 75(8):788-796.
11. Calabrese JR, Sanchez R, Jin N, et al. Symptoms and functioning with aripiprazole once-monthly injection as maintenance treatment for bipolar I disorder. Journal of Affective Disorders.227:649-656.

Appendix 1: Current Preferred Drug List

Second Generation Antipsychotics

Generic	Brand	Form	PDL
asenapine maleate	SAPHRIS	TAB SUBL	Y
cariprazine HCl	VRAYLAR	CAP DS PK	Y
cariprazine HCl	VRAYLAR	CAPSULE	Y
clozapine	CLOZAPINE	TABLET	Y
clozapine	CLOZARIL	TABLET	Y
lurasidone HCl	LATUDA	TABLET	Y
olanzapine	OLANZAPINE	TABLET	Y
olanzapine	ZYPREXA	TABLET	Y
quetiapine fumarate	QUETIAPINE FUMARATE	TABLET	Y
quetiapine fumarate	SEROQUEL	TABLET	Y
risperidone	RISPERDAL	SOLUTION	Y
risperidone	RISPERIDONE	SOLUTION	Y
risperidone	RISPERDAL	TABLET	Y
risperidone	RISPERIDONE	TABLET	Y
aripiprazole	ARIPIPRAZOLE	SOLUTION	V
aripiprazole	ARIPIPRAZOLE ODT	TAB RAPDIS	V
aripiprazole	ABILIFY MYCITE	TAB SENSPT	V
aripiprazole	ABILIFY	TABLET	V
aripiprazole	ARIPIPRAZOLE	TABLET	V
brexpiprazole	REXULTI	TABLET	V
clozapine	VERSACLOZ	ORAL SUSP	V
clozapine	CLOZAPINE ODT	TAB RAPDIS	V
clozapine	FAZACLO	TAB RAPDIS	V
olanzapine	OLANZAPINE ODT	TAB RAPDIS	V
olanzapine	ZYPREXA ZYDIS	TAB RAPDIS	V
paliperidone	INVEGA	TAB ER 24	V
paliperidone	PALIPERIDONE ER	TAB ER 24	V
pimavanserin tartrate	NUPLAZID	CAPSULE	V
pimavanserin tartrate	NUPLAZID	TABLET	V
quetiapine fumarate	QUETIAPINE FUMARATE ER	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	TAB ER 24H	V
quetiapine fumarate	SEROQUEL XR	TAB24HDSPK	V
risperidone	RISPERIDONE ODT	TAB RAPDIS	V
ziprasidone HCl	GEODON	CAPSULE	V
ziprasidone HCl	ZIPRASIDONE HCL	CAPSULE	V

First Generation Antipsychotics

Generic	Brand	Form	PDL
chlorpromazine HCl	CHLORPROMAZINE HCL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	ELIXIR	Y
fluphenazine HCl	FLUPHENAZINE HCL	ORAL CONC	Y
fluphenazine HCl	FLUPHENAZINE HCL	TABLET	Y
fluphenazine HCl	PROLIXIN	TABLET	Y
haloperidol	HALOPERIDOL	TABLET	Y
haloperidol lactate	HALOPERIDOL LACTATE	ORAL CONC	Y
loxapine succinate	LOXAPINE	CAPSULE	Y
perphenazine	PERPHENAZINE	TABLET	Y
thioridazine HCl	THIORIDAZINE HCL	ORAL CONC	Y
thioridazine HCl	THIORIDAZINE HCL	TABLET	Y
thiothixene	THIOTHIXENE	CAPSULE	Y
thiothixene HCl	THIOTHIXENE HCL	ORAL CONC	Y
trifluoperazine HCl	STELAZINE	TABLET	Y
trifluoperazine HCl	TRIFLUOPERAZINE HCL	TABLET	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	TABLET	V
chlorpromazine HCl	THORAZINE	TABLET	V
loxapine	ADASUVE	AER POW BA	V
pimozide	ORAP	TABLET	V
pimozide	PIMOZIDE	TABLET	V

Parenteral Antipsychotics

Generic	Brand	Form	PDL
aripiprazole	ABILIFY MAINTENA	SUSER SYR	Y
aripiprazole	ABILIFY MAINTENA	SUSER VIAL	Y
aripiprazole lauroxil	ARISTADA	SUSER SYR	Y
aripiprazole lauroxil,submicr.	ARISTADA INITIO	SUSER SYR	Y
chlorpromazine HCl	CHLORPROMAZINE HCL	AMPUL	Y
chlorpromazine HCl	THORAZINE	AMPUL	Y
fluphenazine decanoate	FLUPHENAZINE DECANOATE	VIAL	Y
fluphenazine HCl	FLUPHENAZINE HCL	VIAL	Y
haloperidol decanoate	HALDOL DECANOATE 100	AMPUL	Y
haloperidol decanoate	HALDOL DECANOATE 50	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE 100	AMPUL	Y
haloperidol decanoate	HALOPERIDOL DECANOATE	VIAL	Y
haloperidol lactate	HALDOL	AMPUL	Y
haloperidol lactate	HALOPERIDOL LACTATE	AMPUL	Y

haloperidol lactate	HALOPERIDOL LACTATE	SYRINGE	Y
haloperidol lactate	HALOPERIDOL LACTATE	VIAL	Y
risperidone	PERSERIS	SUSER SYKT	Y
risperidone microspheres	RISPERDAL CONSTA	SYRINGE	Y
paliperidone palmitate	INVEGA SUSTENNA	SYRINGE	Y
paliperidone palmitate	INVEGA TRINZA	SYRINGE	Y
trifluoperazine HCl	STELAZINE	VIAL	Y
olanzapine	OLANZAPINE	VIAL	V
olanzapine	ZYPREXA	VIAL	V
olanzapine pamoate	ZYPREXA RELPREVV	VIAL	V
ziprasidone mesylate	GEODON	VIAL	V

Appendix 2: New Comparative Clinical Trials

A total of 70 citations were manually reviewed from the initial literature search. After further review, 68 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Nicol et al.[10]	Oral aripiprazole vs. oral olanzapine vs. oral risperidone	Anti-psychotic-naïve youths aged 6 to 18 years diagnosed with 1 or more psychiatric disorders and clinically significant aggression n=144	Percentage of total body fat measured by DXA and insulin sensitivity in muscle measured via hyperinsulinemic clamps with stable isotopically labeled tracers over 12 weeks.	From baseline to week 12, DXA percentage total body fat increased by 1.81% (95% CI 0.91 to 2.71; p <0.001) for risperidone, 4.12% (95% CI 3.16 to 5.08; p<0.001) for olanzapine, and 1.66% (95% CI 0.86 to 2.46; p <0.001) for aripiprazole. Increased in total body fat was significantly greater for olanzapine than risperidone or aripiprazole. From baseline to week 12, insulin-stimulated change in glucose rate of disappearance increased by 2.30% (95% CI -24.04 to 28.64; p=0.87) for risperidone and decreased by 29.34% for olanzapine (95% CI -58.53 to -0.15; p=0.06) and 30.26% (95% CI -50.55 to -9.97; p=0.006) for aripiprazole, with no significant difference across medications.
Calabrese et al.[11]	Aripiprazole 400mg IM once monthly vs. placebo	Adults with bipolar I disorder stabilized on oral aripiprazole N=266	Time to recurrence of any hospitalization over 52 weeks.	AOM 400 significantly delayed the time to hospitalization for any mood episode compared with placebo (log-rank test, P=0.0002) with a recurrence rate of 2.3% (n=3) for the AOM 400 group versus 13.5% (n=18) for placebo. AOM 400 treatment led to more than 85% reduction in risk of recurrence defined by hospitalization over 1 year compared with placebo (HR 0.14; 95% CI 0.04–0.47; p=0.0002).

Abbreviations: AOM = Aripiprazole once a month; CI = Confidence Interval; DXA= dual-energy x-ray absorptiometry; HR = hazard ratio

Appendix 3: Abstracts of Comparative Clinical Trials

Nicol GE, Yingling MD, Flavin KS, et al. Metabolic Effects of Antipsychotics on Adiposity and Insulin Sensitivity in Youths: A Randomized Clinical Trial. JAMA psychiatry. 2018;75(8):788-796.

Objective: To characterize the metabolic effects of first exposure to antipsychotics in youths using criterion standard assessments of body composition and insulin sensitivity.
Design, Setting, and Participants: This randomized clinical trial recruited antipsychotic-naive youths aged 6 to 18 years in the St Louis, Missouri, metropolitan area who were diagnosed with 1 or more psychiatric disorders and clinically significant aggression and in whom antipsychotic treatment was considered. Participants were enrolled from June 12, 2006, through November 10, 2010. Enrolled participants were randomized (1:1:1) to 1 of 3 antipsychotics commonly used in children with disruptive behavioral disorders and evaluated for 12 weeks. Data were analyzed from January 17, 2011, through August 9, 2017.
Interventions: Twelve weeks of treatment with oral aripiprazole (n = 49), olanzapine (n = 46), or risperidone (n = 49).
Main Outcomes and Measures: Primary outcomes included percentage total body fat measured by dual-energy x-ray absorptiometry (DXA) and insulin sensitivity in muscle measured via hyperinsulinemic clamps with stable isotopically labeled tracers. Secondary outcomes included abdominal adiposity measured by magnetic resonance imaging (MRI) and adipose and hepatic tissue insulin sensitivity measured via clamps with tracers.
Results: The intention-to-treat sample included 144 participants (98 males [68.1%]; mean [SD] age, 11.3 [2.8] years); 74 (51.4%) were African American, and 43 (29.9%) were overweight or obese at baseline. For the primary outcomes, from baseline to week 12, DXA percentage total body fat increased by 1.18% for risperidone, 4.12% for olanzapine, and 1.66% for aripiprazole and was significantly greater for olanzapine than risperidone or aripiprazole (time by treatment interaction $P < .001$). From baseline to week 12, insulin-stimulated change in glucose rate of disappearance increased by 2.30% for risperidone and decreased by 29.34% for olanzapine and 30.26% for aripiprazole, with no significant difference across medications (time by treatment interaction, $P < .07$). This primary measure of insulin sensitivity decreased significantly during 12 weeks in the pooled study sample (effect of time, $F = 17.38$; $P < .001$). For the secondary outcomes from baseline to week 12, MRI measured abdominal fat increased, with subcutaneous fat increase significantly greater for olanzapine than risperidone or aripiprazole (time by treatment, $P = .003$). Behavioral improvements occurred with all treatments.
Conclusions and Relevance: Adverse changes in adiposity and insulin sensitivity were observed during 12 weeks of antipsychotic treatment in youths, with the greatest fat increases on olanzapine. Such changes, likely attributable to treatment, may be associated with risk for premature cardiometabolic morbidity and mortality. The results inform risk-benefit considerations for antipsychotic use in youths.

Calabrese JR, Sanchez R, Jin N, et al. Symptoms and functioning with aripiprazole once-monthly injection as maintenance treatment for bipolar I disorder. Journal of Affective Disorders.227:649-656.

Background: Effects of maintenance treatment with aripiprazole once-monthly 400 mg (AOM 400) on symptoms and functioning were assessed in adults with bipolar I disorder (BP-I) after a manic episode.
Methods: Patients were stabilized on oral aripiprazole, cross-titrated to AOM 400, then randomized in a 52-week, double-blind, placebo-controlled, withdrawal phase. Prespecified secondary outcomes are reported: time to hospitalization for mood episode, Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression–Bipolar scale, Functioning Assessment Short Test (FAST), and Brief Quality of Life in Bipolar Disorder questionnaire. Time to hospitalization for mood episode was analyzed using log-rank test and changes from baseline using mixed model for repeated measures or analysis of covariance.
Results: AOM 400 significantly increased time to hospitalization for any mood episode versus placebo ($P=0.0002$). YMRS total scores decreased with oral aripiprazole; improvements were maintained with AOM 400. After randomization, YMRS scores changed little with AOM 400 but worsened with placebo ($P=0.0016$), and MADRS scores, already low at trial initiation, did not differ between groups. FAST score improvements were maintained with AOM 400 but not placebo ($P=0.0287$).
Limitations: Results are generalizable to patients with BP-I stabilized on aripiprazole following a manic episode.
Conclusions: Patients with BP-I experiencing an acute manic episode exhibited symptomatic and functional improvements during stabilization with oral aripiprazole and AOM 400 that were maintained with continued AOM 400 treatment but not placebo. AOM 400 is the first once-monthly long-acting injectable antipsychotic to demonstrate efficacy in maintenance treatment of the manic phase of BP-I.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 4 2018 & Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 8, 2019

1 exp CHLORPROMAZINE/	1567
2 exp HALOPERIDOL/	5577
3 exp FLUPHENAZINE/	285
4 exp ARIPIPRAZOLE/	1984
5 exp Paliperidone Palmitate/	663
6 exp RISPERIDONE/	5334
7 olanzapine.mp.	7991
8 exp PERPHENAZINE/	243
9 exp Trifluoperazine/	573
10 exp Thioridazine/	392
11 exp THIOTHIXENE/	17
12 exp LOXAPINE/	188
13 exp PIMOZIDE/	271
14 exp CLOZAPINE/	5533
15 exp Quetiapine Fumarate/	2435
16 asenapine maleate.mp.	15
17 exp Lurasidone Hydrochloride/	170
18 ziprasidone HCl.mp.	6
19 brexpiprazole.mp.	101
20 cariprazine.mp.	118
21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	26144
22 limit 21 to (English language and full text and last year)	237
23 limit 22 to clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	70

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	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 or equal to 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: *3/19 (DM); 9/18; 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		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. 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
4. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
5. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
6. 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: *3/19 (DM); 9/18; 3/18; 01/17*
Implementation: *4/1/17*
Author: Moretz
March 2019