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Drug Class Literature Scan: Oral and Parenteral Antipsychotics

Date of Review: September 2018

Date of Last Review: Oral: 3/2018; Parenteral: 9/2017
Literature Search: 4/1/17 – 5/31/18

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

Conclusions:

- Five recent systematic reviews are included in this literature scan of recent evidence for antipsychotic safety and efficacy. No new guidelines or Food and Drug Administration (FDA) safety alerts have been published since the last class update.
- Three separate Cochrane reviews evaluated evidence for the use of intramuscular haloperidol, intramuscular aripiprazole, and oral risperidone to manage psychosis-induced aggression or agitation for rapid tranquilization.[1-3] Outcomes of interest included tranquilization or time to sleep onset within 30 minutes, repeated need for rapid tranquilization within 24 hours, and adverse effects. In the 2 trials that compared haloperidol versus aripiprazole, people in the haloperidol group required fewer injections; this difference was statistically significant (pooled Relative Risk (RR) 0.78, 95% Confidence Interval (CI) 0.62 to 0.99).[1] More people in the haloperidol group experienced dystonia compared to aripiprazole (pooled RR 6.63, 95% CI 1.52 to 28.86). The risperidone review found risperidone was no better or worse than haloperidol or olanzapine for calming aggression within 24 hours.[3]
- Limited data from small studies assessing treatments for tardive dyskinesia (TD) including antipsychotic reduction, antipsychotic discontinuation, or specific antipsychotic drugs did not provide convincing evidence of the value of these approaches in alleviating dyskinesia.[4]
- A 2017 systematic review and meta-analysis analyzed randomized control trial (RCT) data comparing long-acting injectable antipsychotics (LAI) to the oral formulation of the same medication to determine if route of administration impacted efficacy or tolerability.[5] The primary outcome was the overall dropout rate for any reason from antipsychotic therapy. For risperidone, olanzapine, fluphenazine, and haloperidol the number of overall dropouts did not differ between oral or LAI formulations.[5] A small effect in favor of LAI aripiprazole was observed in 2 trials (RR 0.78; 95% CI 0.64 to 0.95; Absolute Risk Reduction (ARR) 7%; Number Needed to Treat (NNT) 14).[5] No differences between oral and LAI formulations emerged in terms of dropouts for specific reasons including adverse events, extrapyramidal symptoms, prolactin increase, weight gain, non-response rate, or relapse rate.[5]
- Latuda (lurasidone) received an expanded indication in 10 to 17 year olds with major depressive episode associated with bipolar 1 disorder (bipolar depression) as of March 2018.[6] The efficacy of lurasidone in pediatric patients aged 10 to 17 years was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of patients who met Diagnostic and Statistical Manual (DSM)-5 criteria for a major depressive episode associated with bipolar I disorder.[7] The primary efficacy endpoint used to assess depressive symptoms, the mean change in Children's Depression Rating Scale, Revised (CDRS-R) total score (range 17 to 113 points) at 6 weeks, was significantly greater in the lurasidone group compared to placebo (-21.0 versus -15.3; $p < 0.0001$; effect size 0.45).[7]
- The November 1, 2017 ISMP Quarter Watch publication summarized reported adverse events (AEs) for pimavanserin through March 2017.[8] Of the 2236 reported events with pimavanserin, the most frequently reported AEs were: hallucinations (21.8%), ineffective drug (14.9%), confusional state (11.5%), and

death (10.9%).[8] Further analysis indicated pimavanserin may be making some psychosis worse, or in other instances, was not providing the expected benefit.[8] The FDA is continuing to monitor these reports, but has not revised labeling for pimavanserin to date.

- A new formulation of long-acting aripiprazole lauroxil, Aristada Initio™, designed for administration as a one-time injection at the start of LAI antipsychotic therapy received FDA approval in July 2018. Aristada Initio™ is designed to provide an extended-release formulation using a smaller particle size of aripiprazole lauroxil compared to Aristada®, thereby enabling faster dissolution and leading to more rapid achievement of therapeutic levels of aripiprazole.[9] Previously, the standard initiation regimen for long acting aripiprazole injection included 21 consecutive days of oral aripiprazole starting with the first long acting injection of Aristada®. According to the manufacturer, the Aristada Initio™ regimen provides patients with relevant levels of aripiprazole within four days of initiation.[9]
- The FDA approved a new once-monthly subcutaneous formulation of risperidone (Perseris™) for the treatment of schizophrenia in adults in July 2018. Perseris™ uses an extended-release delivery system to form a subcutaneous depot that provides sustained levels of risperidone over 1 month.[10] According to the manufacturer, clinically relevant levels of the drug are reached after the first 90 mg or 120 mg injection without use of a loading dose or any supplemental oral dose of risperidone.[10] The efficacy of once-monthly subcutaneous risperidone injection was demonstrated in a phase 3 randomized, double-blind, placebo-controlled, 8-week study of 354 patients.[10]

Recommendations:

- No changes to the PDL are recommended for oral or parenteral antipsychotics based on efficacy or safety data.
- After evaluation of comparative costs in executive session, make injectable formulations of aripiprazole, paliperidone palmitate, and risperidone preferred on the PDL. Also make cariprazine capsules preferred on the PDL.

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**. The majority of antipsychotic use in the Oregon Medicaid population is for oral second generation antipsychotics (SGA) including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 4% of antipsychotic medication claims are for parenteral formulations. Paliperidone, aripiprazole, and haloperidol are the most frequently prescribed injectable agents in this class. Each quarter, approximately 25,000 patients receive a prescription for a SGA and 1700 patients have claims for a first generation antipsychotic. The antipsychotics included on the Oregon PDL are presented in **Appendix 1**.

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence 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, 21 systematic reviews were excluded due to poor quality, wrong study design of included trials (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Haloperidol, aripiprazole and risperidone for emergent use in patients with agitation due to psychosis
Three separate Cochrane reviews evaluated evidence for the use of intramuscular haloperidol, intramuscular aripiprazole, and oral risperidone to manage psychosis-induced aggression or agitation for rapid tranquilization.[1-3] Outcomes of interest included tranquilized or asleep by 30 minutes, repeated need for rapid tranquilization within 24 hours, and adverse effects. The 2017 haloperidol review was an update of a 2012 Cochrane publication and identified nine new RCTs.[1] Most of the trials were small and carried considerable risk of bias.[1] The authors reported no conflicts of interest. In the 2 trials that compared haloperidol versus aripiprazole, people in the haloperidol group required fewer injections; this difference was statistically significant(2 RCTS, n=473, pooled RR 0.78, 95% CI 0.62 to 0.99).[1] However, more people in the haloperidol group experienced dystonia compared to aripiprazole (2 RCTs, pooled RR 6.63, 95% CI 1.52 to 28.86).[1] In trials that compared haloperidol with lorazepam, no significant differences were found with regard to number of participants asleep at one hour (1 RCT, n=60, RR 1.05, 95% CI 0.76 to 1.44) or those requiring additional injections (1 RCT, n=66, RR 1.14, 95% CI 0.91 to 1.43).[1] The adverse effects of haloperidol (e.g. dystonia) were not offset by the addition of lorazepam (1 RCT, n=67, RR 8.25, 95% CI 0.46 to 147.45).[1] In comparative trials of haloperidol and olanzapine, significantly more people in the olanzapine group were asleep in 2 hours compared with those allocated haloperidol (1 RCT, n = 257, RR 1.16, 95% CI 1.02 to 1.32).[1] Addition of promethazine to haloperidol was investigated in two trials (n=376).[1] More people in the haloperidol group compared to the combination group were not tranquilized or asleep by 20 minutes (1 RCT, n=316, RR 1.60, 95% CI 1.18 to 2.16).[1] Acute dystonia was too common in the haloperidol alone group for the trial to continue beyond the interim analysis (1 RCT, n=316, RR 19.48, 95% CI 1.14 to 331.92).[1] Evidence for rapid tranquilization in agitated patients supports the use of haloperidol combined with promethazine; the 2015 update of United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines on short term management of aggression recommends this strategy as well.[11]

The aripiprazole review was based on a literature search from December 2014 through April 2017. Three trials (n=707) were included in this systematic review. The evidence was graded as low quality due to limited comparisons and small size of trials.[3] No trials reported useful data for the primary outcomes of tranquilized or time to sleep onset by 30 minutes. The aripiprazole versus haloperidol trials were previously described in the haloperidol summary. Compared to aripiprazole, olanzapine was better at reducing agitation based on the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score (1 RCT, n=80, RR 0.77, 95% CI 0.60 to 0.99) at two hours.[2] No differences were found between aripiprazole and olanzapine in the number of people experiencing at least one adverse effect within 24 hours of treatment (1 RCT, n=80, RR 0.75, 95% CI 0.45 to 1.24).[2] However, participants allocated to aripiprazole experienced less somnolence compared to olanzapine (1 RCT, n=80, RR 0.25, 95% CI 0.08 to 0.82).[2]

The literature search for the oral risperidone review was compiled through April 2017.[3] This systematic review contains data from five trials (total n=221) comparing risperidone to haloperidol, olanzapine, and quetiapine.[3] None of the included studies provided useable data on the primary outcome tranquilization or asleep by 30 minutes, or repeated need for tranquilization.[3] Data were available for the other main outcomes of agitation or aggression, needing restraint, and incidence of adverse effects.[3] Due to risk of bias, small size of trials, and indirectness of outcome measures, evidence was graded as low quality.[3] No clear difference was found between oral risperidone and haloperidol (oral or intramuscular) for reduction of agitation, measured as at least 50% reduction in the Positive and Negative Syndrome Scale-Psychotic Agitation Sub-score (PANSS-PAS) (RR 1.04, 95% CI 0.86 to 1.26; n=124), and no effect was observed for the need to use restraints (RR

2.00, 95% CI 0.43 to 9.21; n=28).[3] Incidence of adverse effects was similar between treatment groups (RR 0.94, 95% CI 0.54 to 1.66; n=124).[3] One small trial (n=29) compared oral risperidone to oral olanzapine. No difference was observed between risperidone or olanzapine for either agitation measured as PANSS-PAS endpoint score at two hours MD 2.50, 95% CI -2.46 to 7.46); the need to use restraints at four days (RR 1.43, 95% CI 0.39 to 5.28); or specific movement disorders measured as Behavioral Activity Rating Scale endpoint score at four days (MD 0.20, 95% CI -0.43 to 0.83).[3] There was no difference between risperidone and quetiapine for incidence of akathisia after 24 hours (RR 1.67, 95% CI 0.46 to 6.06).[3] In summary, this Cochrane review found risperidone was no better or worse than haloperidol or olanzapine for calming aggression within 24 hours, and two weeks after treatment, people receiving risperidone had worse scores on scales measuring levels of aggression than those receiving quetiapine.[3]

Treatment strategies for tardive dyskinesia

Some proposed strategies for alleviating tardive dyskinesia (TD) include antipsychotic cessation, dose reduction, or switch to a different medication. The focus of a 2018 Cochrane update evaluated evidence from 8 RCTs for the management of TD using these 3 strategies.[4] Due to small sample sizes and short trial duration most outcomes were rated as low quality evidence.[4] No clinically important improvement in TD severity was associated with antipsychotic dose reduction versus antipsychotic maintenance at 44 to 48 weeks (2 RCTs, n=17, RR 0.42 95% CI 0.17 to 1.04).[4] None of the 5 trials (n=140) that evaluated switching to another antipsychotic found a clinically important difference in improving TD symptoms.[4] Specifically, there was no evidence of a difference in TD symptoms for switch to risperidone or haloperidol compared with antipsychotic cessation (RR 1 RCT, n=48, RR 2.08 95% CI 0.74 to 5.86) or switch to risperidone compared with switch to haloperidol (RR 1 RCT, n=37, RR 0.68 95% CI 0.34 to 1.35).[4] Limited data from small studies using antipsychotic reduction or specific antipsychotic drugs as treatments for TD did not provide any convincing evidence of the value of these approaches.[4]

Safety and efficacy of oral antipsychotics compared to long-acting injectable antipsychotics

A 2017 systematic review and meta-analysis analyzed RCT data from long-acting injectable antipsychotics (LAI) compared to the oral formulation of the same medication to determine if route of administration had an impact on efficacy or tolerability.[5] Literature was searched through July 2016. Twenty studies were included in the review and data from 17 RCTs contributed to the meta-analysis for the following antipsychotics: risperidone (n=6), olanzapine (n=2), aripiprazole (n=3), fluphenazine (n=7) and haloperidol (n=2).[5] For the primary outcome of overall treatment discontinuation, quality of evidence was high for aripiprazole, moderate for risperidone, low for haloperidol, and very low for olanzapine and fluphenazine.[5] For all drugs, the number of dropouts for any reason did not differ between the two formulations, except for a small effect in favor of LAI aripiprazole (2 RCTs; 986 patients; RR 0.78; 95% CI 0.64 to 0.95; ARR 7%; NNT 14).[5] Similarly, no differences between oral and LAI formulations emerged in terms of dropouts for adverse events, extrapyramidal symptoms, prolactin increase, weight gain, non-response rate, and relapse rate.[5]

New Guidelines: No new guidelines have been published since the last class update.

New Formulations or Indications:

1.Latuda (lurasidone) received an expanded indication to 10-17 year olds with major depressive episode associated with bipolar 1 disorder (bipolar depression) as of March 2018.[6] Previously, lurasidone was only FDA approved for use in adults with bipolar depression. The efficacy of lurasidone in pediatric patients aged 10 to 17 years was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of patients who met DSM-5 criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=343).[7] Patients were randomized to flexibly dosed lurasidone 20 to 80 mg/day or placebo. At the end of the clinical study, most patients (67%) received 20 mg/day or 40 mg/day.[7] The primary rating scale used to assess depressive symptoms in this study was the CDRS-R total score. The CDRS-R is a 17-item clinician rated scale with total scores ranging from 17 to 113.[12] A score of greater than 40 is indicative of depression, whereas a score less than 28 is often used to define remission (minimal or no symptoms).[12] The

primary endpoint was the mean change from baseline in CDRS-R score to week 6.[7] The least squares mean change in CDRS-R total score was significantly greater in the lurasidone group compared to the placebo group (-21.0 versus -15.3; p < 0.0001; effect size 0.45) at week 6.[7] Treatment response was defined as ≥50% reduction from baseline to week 6 in CDRS-R total score (after subtracting 17 points from the total score to adjust for the scale range).[7] The percent of participants meeting a priori response criteria was significantly larger in the lurasidone group compared with the placebo group at week 6 (59.5% versus 36.5%; $p < .0001$; NNT = 5).[7] The 2 most common adverse events observed in patients taking lurasidone were nausea and somnolence.[7] Least squares mean change at week 6 in body weight was similar for the lurasidone and placebo groups (+0.74 versus +0.44 kg), and a similar percent of patients on lurasidone versus placebo had at least 7% weight gain (4.0% versus 5.3%).[7] There were no clinically meaningful differences between lurasidone and placebo groups in change in lipid, glucose, and prolactin levels.[7]

2. Alkermes, Inc. developed a new formulation of long-acting aripiprazole lauroxil, Aristada Initio™, designed for administration as a one-time injection at the start of LAI antipsychotic therapy which received FDA approval in July 2018. Aristada Initio™ uses proprietary NanoCrystal® technology and is designed to provide an extended-release formulation using a smaller particle size of aripiprazole lauroxil compared to Aristada®, thereby enabling faster dissolution and leading to more rapid achievement of therapeutic levels of aripiprazole.[13] Previously, the standard initiation regimen for long acting aripiprazole injection included 21 consecutive days of oral aripiprazole starting with the first long acting injection of Aristada®. According to the manufacturer, the Aristada Initio™ regimen provides patients with relevant levels of aripiprazole within four days of initiation.[13] Therapy is started with aripiprazole lauroxil extended-release 675 mg intramuscular injection administered by a health care professional in conjunction with aripiprazole 30mg orally as a one-time dose.[13] For patients naïve to aripiprazole, tolerability to the drug should be established with oral therapy before transitioning to LAI formulations.[13] Aristada Initio™ is not interchangeable with other aripiprazole LAI formulations due to different pharmacokinetic profiles and is not approved for repeated dosing.[13] Aristada Initio™ may also be administered as a single dose for patients re-starting therapy after missing a dose of Aristada®.[13] The first Aristada® injection (441 mg, 662 mg, 8821 mg or 1064 mg) may be administered on the same day as an Aristada Initio™ dose at different injection sites or 10 days afterwards.[13] A pharmacokinetic bridging study demonstrated that an intramuscular injection of Aristada®, a 30 mg dose of oral aripiprazole, and a single 675 mg dose of Aristada Initio™ resulted in aripiprazole concentrations comparable to Aristada® treatment initiated with 21 days of oral aripiprazole.[13] A single strength of Aristada Initio (i.e., 675 mg) was adequate for all dose levels of oral aripiprazole and Aristada LAI.[13] Aristada Initio™ was evaluated for safety in 170 adult patients with schizophrenia and was found to have similar side effects to Aristada®.[13] The efficacy of Aristada Initio™ was based on previous trials of the aripiprazole LAI formulation (Aristada®).[13]

3. The FDA approved a new once-monthly subcutaneous formulation of risperidone (Perseris™) for the treatment of schizophrenia in adults. Perseris™ uses an extended-release delivery system to form a subcutaneous depot that provides sustained levels of risperidone over 1 month.[10] According to the manufacturer, clinically relevant levels of the drug are reached after the first 90 mg or 120 mg injection without use of a loading dose or any supplemental oral dose of risperidone.[10] The efficacy of once-monthly subcutaneous risperidone injection was demonstrated in a phase 3 randomized, double-blind, placebo-controlled, 8-week study of 354 patients.[10] The study showed a statistically significant improvement in the Positive and Negative Syndrome Scale total score and the Clinical Global Impression Severity of Illness at day 57.[10] The clinical trials of Perseris™ were designed for the antipsychotic to be started without a loading dose or any supplemental risperidone. The systemic safety profile of Perseris was consistent with the known safety profile of oral risperidone.[10] The most common systemic adverse reactions were increased weight, sedation/somnolence, and musculoskeletal pain. The most common injection site reactions were injection site pain and reddening of the skin. Perseris™ has a boxed warning noting that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk for death.[10] Perseris is not approved for use in patients with dementia-related psychosis. This new formulation is not scheduled to arrive in pharmacies until the fourth quarter of 2018.

New Safety Alerts:

Food and Drug Administration: No new FDA safety alerts have been reported.

Institute for Safe Medication Practices (ISMP)

The November 1, 2017 ISMP Quarter Watch publication summarized reported adverse events (AEs) for pimavanserin through March 2017.[8] Of the 2236 reported events with pimavanserin, the most frequently reported AEs were: hallucinations (21.8%), ineffective drug (14.9%), confusional state (11.5%), and death (10.9%).[8] Further analysis indicated that the drug may make some psychosis worse, or in other instances, may not providing the expected benefit.[8] The number of reports of hallucinations was large (n=487), with 73% of incidents observed by health professionals, who could be expected to understand that hallucinations occur in 20-70% of Parkinson's patients.[8] The numerous reports that the drug was ineffective are consistent with the limited benefits observed in the clinical trials.[8] This first substantial group of pimavanserin adverse event reports disclosed an additional safety issue: ISMP identified 318 cases where pimavanserin, which blocks serotonin signaling, was combined with quetiapine or other antipsychotics that block dopamine signaling.[8] Antipsychotics are not recommended for use in the elderly, and are not approved for use in Parkinson's Disease.[8] In the clinical trials for pimavanserin, use of quetiapine or other antipsychotics was one of the exclusion criteria.[14] The FDA is continuing to monitor these reports, but has not revised labeling for pimavanserin to date.

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Appendix 1: Current Preferred Drug List

Oral Antipsychotics, 1st Generation

Route	Formulation	Brand	Generic	PDL	Carveout
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	PERPHENAZINE	perphenazine	Y	Y
ORAL	TABLET	TRIFLUOPERAZINE HCL	trifluoperazine HCl	Y	Y
ORAL	TABLET	THIORIDAZINE HCL	thioridazine HCl	Y	Y
ORAL	ORAL CONC	HALOPERIDOL LACTATE	haloperidol lactate	Y	Y
ORAL	TABLET	HALOPERIDOL	haloperidol	Y	Y
ORAL	CAPSULE	THIOTHIXENE	thiothixene	Y	Y
ORAL	CAPSULE	LOXAPINE	loxapine succinate	Y	Y
ORAL	TABLET	CHLORPROMAZINE HCL	chlorpromazine HCl	V	Y
ORAL	TABLET	ORAP	pimozide	V	Y
ORAL	TABLET	PIMOZIDE	pimozide	V	Y
INHALATION	AER POW BA	ADASUVE	loxapine	V	Y

Oral Antipsychotics, 2nd Generation

Route	Formulation	Brand	Generic	PDL	Carveout
ORAL	TABLET	CLOZAPINE	clozapine	Y	Y
ORAL	TABLET	CLOZARIL	clozapine	Y	Y
ORAL	TABLET	RISPERDAL	risperidone	Y	Y
ORAL	TABLET	RISPERIDONE	risperidone	Y	Y
ORAL	SOLUTION	RISPERDAL	risperidone	Y	Y
ORAL	SOLUTION	RISPERIDONE	risperidone	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
SUBLINGUAL	TAB SUBL	SAPHRIS	asenapine maleate	Y	Y
ORAL	TABLET	LATUDA	lurasidone HCl	Y	Y
ORAL	TAB RAPDIS	CLOZAPINE ODT	clozapine	V	Y
ORAL	TAB RAPDIS	FAZACLO	clozapine	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	risperidone	V	Y
ORAL	TAB RAPDIS	OLANZAPINE ODT	olanzapine	V	Y
ORAL	TAB RAPDIS	ZYPREXA ZYDIS	olanzapine	V	Y
ORAL	TAB ER 24H	QUETIAPINE FUMARATE ER	quetiapine fumarate	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	quetiapine fumarate	V	Y

ORAL	CAPSULE	GEODON	ziprasidone HCl	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ziprasidone HCl	V	Y
ORAL	TAB ER 24	INVEGA	paliperidone	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	paliperidone	V	Y
ORAL	TABLET	ABILIFY	aripiprazole	V	Y
ORAL	TABLET	ARIPIPRAZOLE	aripiprazole	V	Y
ORAL	SOLUTION	ARIPIPRAZOLE	aripiprazole	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	aripiprazole	V	Y
ORAL	TABLET	REXULTI	brexpiprazole	V	Y
ORAL	CAPSULE	VRAYLAR	cariprazine HCl	V	Y
ORAL	CAP DS PK	VRAYLAR	cariprazine HCl	V	Y

Parenteral Antipsychotics

Route	Formulation	Brand	Generic	PDL	Carveout
INJECTION	AMPUL	CHLORPROMAZINE HCL	chlorpromazine HCl	Y	Y
INJECTION	VIAL	FLUPHENAZINE DECANOATE	fluphenazine decanoate	Y	Y
INJECTION	VIAL	FLUPHENAZINE HCL	fluphenazine HCl	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 50	haloperidol decanoate	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE	haloperidol decanoate	Y	Y
INTRAMUSC	VIAL	HALOPERIDOL DECANOATE	haloperidol decanoate	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 100	haloperidol decanoate	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE 100	haloperidol decanoate	Y	Y
INJECTION	AMPUL	HALDOL	haloperidol lactate	Y	Y
INJECTION	AMPUL	HALOPERIDOL	haloperidol lactate	Y	Y
INJECTION	VIAL	HALOPERIDOL LACTATE	haloperidol lactate	Y	Y
INTRAMUSC	SYRINGE	RISPERDAL CONSTA	risperidone microspheres	Y	Y
INTRAMUSC	SUSER VIAL	ABILIFY MAINTENA	aripiprazole	Y	Y
INTRAMUSC	SUSER SYR	ABILIFY MAINTENA	aripiprazole	Y	Y
INTRAMUSC	SUSER SYR	ARISTADA	aripiprazole lauroxil	Y	Y
INTRAMUSC	VIAL	OLANZAPINE	olanzapine	V	Y
INTRAMUSC	VIAL	ZYPREXA	olanzapine	V	Y
INTRAMUSC	VIAL	GEODON	ziprasidone mesylate	V	Y
INTRAMUSC	SYRINGE	INVEGA SUSTENNA	paliperidone palmitate	V	Y
INTRAMUSC	SYRINGE	INVEGA TRINZA	paliperidone palmitate	V	Y
INTRAMUSC	VIAL	ZYPREXA RELPREVV	olanzapine pamoate	V	Y
INTRAMUSC	SYRINGE	ARISTADA INITIO	aripiprazole lauroxil, submicronized, ER	V	Y

Appendix 2: New Comparative Clinical Trials

A total of 249 citations were manually reviewed from the initial literature search. After further review, 247 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 trials are summarized in the table below. The full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr><td>Nemeth G, et al.[15]

DB, MC, RCT

n = 460

Duration: 32 weeks</td><td>1.Cariprazine 3mg, 4.5 mg, or 6mg per day

vs.

2.Risperidone 3mg, 4mg, or 6mg per day

4 week lead-in period followed by 26 week DB treatment and 2 week safety follow-up</td><td>Adults aged 18-65 years with stable schizophrenia (> 2 years) with predominant negative symptoms (> 6 months)</td><td>Change from baseline to week 26 on the PANSS-FSNS</td><td>Least squares mean change in PANSS-FSNS:
1. Cariprazine -8.90 points (n=230)
2. Risperidone -7.44 points (n=230)

Least squares mean difference −1.46; 95% CI −2.39 to −0.53; p=0.0022</td></tr>
<tr><td>Nicol G, et al.[16]

OL, RCT

N = 144

Duration: 12 weeks</td><td>1.Aripiprazole 6 mg po (mean dose)

Vs.

2. Olanzapine 6 mg po (mean dose)

Vs.

3.Risperidone 1 mg po (mean dose)</td><td>Antipsychotic-naive youths aged 6 to 18 years
with 1 or more Axis I DSM IV diagnosis and clinically significant aggression defined by a score of at least 18 on the Irritability subscale of the Aberrant Behavior Checklist</td><td>Treatment effects over 12 weeks on total body fat (mean DXA percentage)
as well as insulin sensitivity at muscle</td><td>
<table>
<tr><th>Variable</th><th>Risperidone</th><th>Olanzapine</th><th>Aripiprazole</th></tr>
<tr><td>Change in DXA Body Fat from Week 0 to Week 12</td><td>1.81%

95% CI 0.91 to 2.71</td><td>4.12%

95% CI 3.16 to 5.08</td><td>1.66 %

95% CI 0.86 to 2.46</td></tr>
<tr><td>p value</td><td>< 0.001</td><td><0.001</td><td><0.001</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Insulin-stimulated change in glucose rate of disappearance</td><td>2.30%

95% CI -24.04 to 28.64</td><td>-29.34%

95% CI -58.53 to -0.15</td><td>-30.26

95% CI -50.5 to -9.97</td></tr>
<tr><td>p value</td><td>0.87</td><td>0.06</td><td>0.006</td></tr>
</table>
</td></tr>
</table>

Abbreviations: CI = Confidence Interval; DB =Double Blind; MC = Multi-Center, OL = Open Label; PANSS-FSNS = Positive and Negative Syndrome Scale Factor Score for Negative Symptoms; PO = Oral; RCT = Randomized Clinical Trial

Appendix 3: Abstract of Comparative Clinical Trials

1.Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet.389 (10074):1103-1113.

BACKGROUND: Although predominant negative symptoms of schizophrenia can be severe enough to cause persistent impairment, effective treatment options are lacking. We aimed to assess the new generation antipsychotic cariprazine in adult patients with predominant negative symptoms.
METHODS: In this randomised, double-blind, phase 3b trial, we enrolled adults aged 18-65 years with long-term (>2 year), stable schizophrenia and predominant negative symptoms (>6 months) at 66 study centres (mainly hospitals and university clinics, with a small number of private practices) in 11 European countries. Patients were randomly assigned (1:1) by an interactive web response system to 26 weeks of monotherapy with fixed-dose oral cariprazine (3 mg, 4·5 mg [target dose], or 6 mg per day) or risperidone (3 mg, 4 mg [target dose], or 6 mg per day); previous medication was discontinued over 2 weeks. The primary outcome was change from baseline to week 26 or end of treatment on the Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) analysed in a modified intention-to-treat population of patients who had follow-up assessments within 5 days after last receipt of study drugs with a mixed-effects model for repeated measures. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with EudraCT, number 2012-005485-36.
FINDINGS: Between May 27, 2013, and Nov 17, 2014, 533 patients were screened and 461 (86%) patients were randomised to treatment (230 for cariprazine and 231 for risperidone); 460 were included in the safety population (one patient discontinued before study drug intake). 227 (99%) of 230 patients in the cariprazine group and 229 (99%) of 230 patients in the risperidone group were included in the modified intention-to-treat population (178 [77%] in each group completed 26 weeks of treatment). Mean daily doses were 4·2 mg (SD 0·6) for cariprazine and 3·8 mg (0·4) for risperidone. Treatment-emergent adverse events (eg, insomnia, akathisia, worsening of schizophrenia, headache, and anxiety) were reported in 123 (54%) patients treated with cariprazine and 131 (57%) patients treated with risperidone. Use of cariprazine led to a greater least squares mean change in PANSS-FSNS from baseline to week 26 than did risperidone (-8·90 points for cariprazine vs -7.44 points for risperidone; least squares mean difference -1.46, 95% CI -2.39 to -0.53; p=0.0022; effect size 0.31). One patient in the risperidone group died of a cause regarded as unrelated to treatment.
INTERPRETATION: Our results support the efficacy of cariprazine in the treatment of predominant negative symptoms of schizophrenia.
FUNDING: Gedeon Richter Plc.

2. 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.

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.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2018, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 31, 2018

1 exp CHLORPROMAZINE/	17141
2 exp HALOPERIDOL/	15380
3 exp FLUPHENAZINE/	2391
4 exp ARIPIPRAZOLE/	2032
5 exp Paliperidone Palmitate/	700
6 exp RISPERIDONE/	5844
7 olanzapine.mp.	7479
8 exp PERPHENAZINE/	1560
9 exp Trifluoperazine/	3554
10 exp Thioridazine/	2348
11 exp THIOTHIXENE/	333
12 exp LOXAPINE/	604
13 exp PIMOZIDE/	1687
14 exp CLOZAPINE/	7648
15 exp Quetiapine Fumarate/	2528
16 asenapine maleate.mp.	15
17 exp Lurasidone Hydrochloride/	177
18 ziprasidone HCl.mp.	5
19 brexpiprazole.mp.	70
20 cariprazine.mp.	79
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	59162

22 limit 22 to (english language and humans and yr="2017 -Current" and (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))
248

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;	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 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: *9/18 (DM); 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: *9/18 (DM); 3/18; 01/17*
Implementation: *4/1/17*

Risperdal® Consta® Quantity Limit

Goal(s):

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

Length of Authorization:

- Date of service or 12 months, depending on criteria

Requires PA:

Risperdal® Consta®

Approval Criteria		
11. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	**Yes:** Go to #2	**No:** Have pharmacy correct to number of syringes instead of number of mL.
12. Is the amount requested above 2 syringes per 18 days for one of the following reasons? • Medication lost • Medication dose contaminated • Increase in dose or decrease in dose • Medication stolen • Admission to a long term care facility • Any other reasonable explanation?	**Yes:** Approve for date of service only (use appropriate PA reason)	**No:** Go to #3
13. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	**Yes:** Approve for 1 year (use appropriate PA reason)	Note: This medication should NOT be denied for clinical reasons.

P&T Review: *9/18 (DM); 9/17; 9/16; 5/05*
Implementation: *10/13/16; 11/18/04*