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Literature Scan: Parenteral Antipsychotics

Date of Review: September 2016

Date of Last Review: May 2016 (all antipsychotics)
End Date of Literature Search: August 2016

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

Conclusions:
- One new high quality systematic review was published since the parenteral antipsychotic agents were last reviewed in May 2016. Otherwise, no new clinical practice guidelines, formulations, indications, or safety alerts were identified.
- One systematic review with meta-analysis specifically evaluated long-acting injectable risperidone. Evidence shows the drug may have similar efficacy and harms as oral second-generation antipsychotics and other long-acting parenteral antipsychotics.

Recommendations:
- No further review or research needed at this time.
- After comparison of drug costs in the executive session, add Abilify Maintenna (aripiprazole) extended-release injectable suspension and Aristada (aripiprazole lauroxil) extended-release injectable suspension to the Oregon Health Plan fee-for-service Preferred Drug List contingent upon executed supplemental rebates.

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

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- After executive session, make Latuda (lurasidone), Saphris (asenapine) and Abilify Maintenna (aripiprazole) preferred and make chlorpromazine voluntary non-preferred (no PA required).

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

The primary focus of the evidence 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.

Systematic Reviews:
The Cochrane Collaboration conducted a systematic review with meta-analysis to critically appraise the current evidence for risperidone by long-acting intramuscular injection for the treatment of schizophrenia or related psychoses.[1] The long-acting injectable formulation contains risperidone encapsulated within biodegradable polymer microspheres and suspended in an aqueous solution.[1] The polymers break down after intramuscular administration and the drug is released at a set rate that occurs over several weeks, with the highest plasma concentrations occurring at about one month after injection.[1] Randomized controlled trials that compared the long-acting risperidone injectable product with placebo, no treatment, or other oral or long-acting injectable formulations of antipsychotic agents in these populations were eligible for inclusion.[1] For dichotomous data, the risk ratio (RR) with 95% confidence intervals (CI) was calculated. For continuous data, mean difference (MD) was calculated. The GRADE approach was used to interpret the evidence after risk of bias was assessed. Primary outcomes included long-term relapse and long-term clinically important changes in mental state.[1] Several pre-specified secondary outcomes were also assessed, including early study withdrawal, severe adverse effects, and any adverse effects related to movement disorder, weight gain, prolactin levels and glucose metabolism.[1] All outcomes were reported for the short-term (up to 12 weeks), medium term (13-26 weeks), and long-term (>26 weeks).[1] Twelve studies (n=5723; mean age ~40 years) were included in the final analysis.[1] The prescribing of risperidone was consistent across all studies; 25 mg, 37.5 mg and 50 mg injections every 2 weeks were the most common dosages, with participants typically initiated on 25 mg every 2 weeks, which was then titrated by 12.5 mg increments if symptoms worsened.[1] All studies used the Diagnostic and Statistical Manual version 1V (DSM-IV) to define schizophrenia.[1] Exclusion criteria for all studies were fairly consistent: patients with a history of violence to themselves or others, recent suicide attempts, substance use disorders, or general ill health were all excluded.[1]

It is uncertain if long-acting injectable risperidone is any more effective than placebo in controlling symptoms of schizophrenia because outcomes of relapse and improvement in mental state were neither measured nor reported in placebo-controlled trials.[1] Compared to placebo, less patients who received risperidone withdrew from the study early by 12 weeks (RR 0.74; 95% CI, 0.63 to 0.88) and less risperidone-treated patients experienced severe short-term adverse events (RR 0.59; 95% CI, 0.38 to 0.93) based on low quality evidence.[1] However, low quality evidence suggests no difference in weight gain between long-acting injectable risperidone and placebo (RR 2.11; 95%CI, 0.48 to 9.18).[1]

Outcomes of improvement in mental state could not be reported when long-acting injectable risperidone was compared to oral antipsychotics because trials had such high attrition rates.[1] Most primary outcomes of these studies did not show a difference between treatment groups, including in trials that compared injectable to oral risperidone.[1] However, more patients who received long-acting injectable risperidone experience nervous system disorders long-term compared to oral antipsychotics (RR 1.34; 95% CI, 1.13 to 1.58) based on low-quality evidence.[1]

In comparisons with other long-acting injectable second-generation antipsychotics, risperidone was primarily studied against paliperidone palmitate.[1] Relapse rates were not reported and rates of response using total Positive and Negative Syndrome Scale (PANSS), weight increase, prolactin-related adverse events and glucose-related adverse events were similar between groups.[1] Fewer patients in the risperidone group withdrew early due to lack of efficacy in one long-term study (RR 0.60; 95% CI, 0.45 to 0.81) based on low quality evidence, but more patients in the risperidone group required use of medications to manage extrapyramidal symptoms (RR 1.46; 95% CI, 1.18 to 1.8) based on moderate quality evidence.[1]

Outcomes of relapse, severe adverse events or movement disorders were not reported in trials that compared long-acting injectable risperidone to first-generation long-acting injectable antipsychotics.[1] Outcomes relating to improvement in mental state demonstrated no difference between groups based on low quality evidence.[1] However, more patients who received risperidone withdrew early in long-term studies compared to first-generation long-acting injectable antipsychotics (RR 3.05; 95% CI, 1.12 to 8.31) based on low quality evidence.[1]

New Guidelines:
None identified.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:
1. Sampson S, Hosalli P, Furtado VA, Davis JM. Risperidone (depot) for schizophrenia. *Cochrane Database of Systematic* Reviews. 2016, Issue 4. Art. No.: CD004161. DOI: 10.1002/14651858.CD004161.pub2.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVEOUT
ANTIPSYCHOTICS, PARENTERAL					
INJECTION	AMPUL	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	Y	Y
INJECTION	AMPUL	HALDOL	HALOPERIDOL LACTATE	Y	Y
INJECTION	AMPUL	HALOPERIDOL	HALOPERIDOL LACTATE	Y	Y
INJECTION	VIAL	FLUPHENAZINE DECANOATE	FLUPHENAZINE DECANOATE	Y	Y
INJECTION	VIAL	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
INJECTION	VIAL	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 100	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 50	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE 100	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	SUSER SYR	ABILIFY MAINTENA	ARIPIPRAZOLE	V	Y
INTRAMUSC	SUSER SYR	ARISTADA	ARIPIPRAZOLE LAUROXIL	V	Y
INTRAMUSC	SUSER VIAL	ABILIFY MAINTENA	ARIPIPRAZOLE	V	Y
INTRAMUSC	SYRINGE	INVEGA SUSTENNA	PALIPERIDONE PALMITATE	V	Y
INTRAMUSC	SYRINGE	INVEGA TRINZA	PALIPERIDONE PALMITATE	V	Y
INTRAMUSC	SYRINGE	RISPERDAL CONSTA	RISPERIDONE MICROSPHERES	Y	Y
INTRAMUSC	VIAL	GEODON	ZIPRASIDONE MESYLATE	V	Y
INTRAMUSC	VIAL	HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	VIAL	OLANZAPINE	OLANZAPINE	V	Y
INTRAMUSC	VIAL	ZYPREXA	OLANZAPINE	V	Y
INTRAMUSC	VIAL	ZYPREXA RELPREVV	OLANZAPINE PAMOATE	V	Y

Appendix 2: New Clinical Trials

A total of 4 citations were manually reviewed from the literature search. After manual review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). Full abstracts are included in **Appendix 3**.

Appendix 3: Abstracts of Clinical Trials
Not applicable.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 2 2016

1 exp Chlorpromazine/ 1537
2 exp Haloperidol/ 5473
3 exp Fluphenazine/ 283
4 exp Aripiprazole/ 1773
5 exp Paliperidone Palmitate/ 523
6 exp Risperidone/ 5185
7 olanzapine.mp. 6908
8 1 or 2 or 3 or 4 or 5 or 6 or 7 17907
9 parent*.mp. 222873
10 inject*.mp. 403022
11 intramusc*.mp. 29455
12 intravenou*.mp. 198274
13 9 or 10 or 11 or 12 755591
14 8 and 13 2296
15 limit 14 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 4

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		
1. 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.
2. 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
3. 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: *9/16; 5/05*
Implementation: *11/18/04*

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