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Abbreviated Class Review: Long-Acting Injectable Antipsychotics

Month/Year of Review: November 2014 **End date of literature search:** September 2014
Current PDL Class: First Generation Antipsychotics and Second Generation Antipsychotics

Drugs Included in Review

Generic	Brand
Fluphenazine decanoate	Prolixin Decanoate
Haloperidol decanoate	Haldol Decanoate
Olanzapine pamoate	Zyprexa Relprevv
Paliperidone palmitate	Invega Sustenna
Risperidone LAI	Risperdal Consta
Aripiprazole LAI	Abilify Maintena

Research Questions:

- Are there differences in efficacy or safety between the LAI antipsychotic agents?
- Are there subpopulations that certain LAI antipsychotics are more effective or safer than others?
- Is there evidence that long-acting injectable antipsychotics are more efficacious or safer than oral antipsychotic agents?
- Is there evidence that long acting injectable (LAI) antipsychotics prevent relapse or improve adherence?

Conclusions:

- There is moderate quality evidence of no difference in relapse prevention between long-acting injectables (LAI) antipsychotics and oral antipsychotics in adults with schizophrenia (21 studies; RR = 0.93, 95% CI: 0.80-1.08; p=0.35).[1,2] There is low quality evidence that fluphenazine decanoate is superior to oral antipsychotics in preventing hospitalizations (4 studies, RR = 0.82, 95% CI: 0.67-0.99, p=0.04).[1] There is low quality evidence of no significant differences between LAI antipsychotics and placebo or oral antipsychotics with respect to death, overall number of treatment-adverse events, insomnia, or injection site pain.[2]
- There is insufficient evidence on the comparative efficacy between fluphenazine, olanzapine, risperidone and aripiprazole LAIs.
- There is low quality evidence of no difference in efficacy between paliperidone palmitate and haloperidol deconoate.[3]

- There is insufficient evidence data available for this class in regards to mortality and serious harms.
- There is low quality evidence of more weight gain with paliperidone palmitate compared to haloperidol decanoate (2.17 kg vs -0.96 kg) and more akathisia with haloperidol decanoate compared to paliperidone palmitate.[3]
- There is insufficient evidence to determine a meaningful difference in efficacy or harms between LAI antipsychotics in any subgroup population.
- Guidelines consistently include LAI antipsychotics as a treatment option for patients but are not consistent about stabilizing patients on oral medication before starting a LAI.[4–6]

Recommendations:

- Create a new voluntary PDL class for the Long Acting Injectable Antipsychotics.
- Make risperidone microspheres (Risperdal Consta®) preferred.

Background:

Antipsychotic medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder and are divided into conventional, first generation antipsychotics and the second generation (or atypical) antipsychotics. There are currently ten second generation antipsychotics available in the US. Antipsychotics are available in many dosage forms (tablets, orally disintegrating tablets, and injectable), have an assortment of FDA-approved indications (ranging from the irritability associated with autistic disorder in children and adolescents to the maintenance treatment of schizophrenia in adults), and are commonly used off-label for various psychiatric conditions. Side effect profiles between agents vary and are often an important factor in treatment selection. These side effects include extrapyramidal symptoms, autonomic effects, increased prolactin levels, metabolic effects, and cardiac risks including risk of ventricular arrhythmias.

Commonly used outcomes in clinical trials for assessing patients with schizophrenia include the Positive and Negative Syndrome Scale (PANSS) which is a validated 30-item rating scale used to assess the effects of drug treatment in schizophrenia, and the Clinical Global Impression Severity Scale (CGI-S) which measures the subject's current severity of illness. Data from the CATIE trial, a large, multicenter trial for patients with schizophrenia, suggests a minimal clinically important difference in the PANSS Scale is 15 points, but will vary according to a patient's baseline PANSS score.[7]

Long-acting injection (LAI) depot preparations of antipsychotics are widely used, especially for treating patients who show non-adherence or partial adherence to oral therapy. The proposed benefits of LAI's are their relapse-preventing properties, patient convenience, and improved compliance. Drug adherence is essential in improving clinical and social outcomes in schizophrenia. First generation antipsychotics LAIs (fluphenazine and haloperidol) have been available since the late 1960s, and more recently second generation antipsychotic LAI formulations have become available (olanzapine pamoate, paliperidone palmitate, risperidone LAI, and aripiprazole LAI). Data on the safety and efficacy of second generation antipsychotic LAI formulations is lacking, particularly head-to-head data.[8] There is some controversy over the most appropriate patient to select the LAI antipsychotics in, as some clinicians claim that depots would cause more adverse effects or patients would not accept injections.

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The primary indication for using LAI antipsychotics is for patients with schizophrenia who have poor adherence to oral medication leading to relapse. They are commonly used in chronically ill patients with significant compliance issues. They are also used less frequently for patients how become symptomatic after stopping antipsychotics with behaviors leading to highly adverse consequences, when dose-related adverse events are experienced, or when patients are considered treatment resistant except for a question of medication nonadherence.[9]

The adverse effect profile of LAI antipsychotics is not yet fully understood. Olanzipine pamoate causes dose-dependent weight gain and adversely effects lipid and glucose metabolism, and may increase prolactin levels even in at low doses.[8] Postinjection syndrome, due to accidental intravascular injection of olanzapine pamoate, is characterized by delirium and/or excessive sedation (incidence 1.2%).[8] Hyperprolactinemia, extrapyramidal side effects, cardiovascular events (i.e. tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone LAI and paliperidone palmitate.[8] Risperidone LAI may also increase the risk of QT prolongation, although this may not be clinically significant.[8] The most common adverse event associated with paliperidone palmitate is worsening of psychotic symptoms (incidence between 3.5% and 16%).[8] There has only been one study of aripiprazole LAI; the most common adverse reactions were worsening of psychotic symptoms, extrapyramidal side effects, and weight gain.[8]

Reason for Review:
Currently, all antidepressants are available without prior authorization for non-preferred placement. Oregon law prohibits traditional methods of PDL enforcement on mental health drugs. First and second generation antipsychotics have been reviewed for clinical efficacy and safety and specific oral agents were chosen as clinically preferred; this eliminates a copayment. Oregon's Medicaid program does not currently charge a copayment for preferred PDL drugs.
The Oregon P&T Committee has reviewed both first and second generation oral antipsychotic medications (November 2013 and January 2014). Aripiprazole LAI was reviewed during the second generation class update in January 2014, but there has not been a review conducted comparing both generations of long-acting injectable antipsychotics for placement on the PDL.

Methods:
A Medline literature search ending September 2014 for new systematic reviews, clinical guidelines, and head-to-head randomized controlled trials (RCTs) comparing LAI antipsychotic agents fluphenazine decanoate, haloperidol decanoate, olanzapine pamoate, paliperidone palmitate, risperidone or aripiprazole. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Care Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and 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 for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Kishimoto et al[1] conducted a systematic review to evaluate the efficacy of LAI antipsychotics and oral antipsychotics (OAPs). The review included 21 randomized controlled trials that lasted ≥6 months comparing LAIs and OAPs; 10 included first generation antipsychotics while 11 included second generation antipsychotics. LAIs were similar to OAPs for relapse prevention at the longest time point (21 studies; RR = 0.93, 95% confidence interval (CI): 0.80-1.08; p=0.35). When

restricting the analysis to outpatient studies lasting one year or longer, the finding was the same (12 studies, RR=0.93; 95% CI 0.71-1.07; p = 0.031). When comparing relapse rates at different time points (3, 6, 12, 18 and 24 months), pooled LAIs did not separate from OAPs. Neither individual LAI nor pooled LAIs separated from OAPs regarding all-cause discontinuation (21 studies, RR= 1.00; 95% CI: 0.89-1.13, p=0.99) or discontinuation due to adverse events (19 studies, RR = 1.10, 95% CI: 0.74-1.64, p=0.65). Among individual LAIs, only fluphenazine was superior to OAPs in drug efficacy (8 studies, RR = 0.78, 95% CI: 0.66-0.91, p=0.02). Among individual LAIs, only fluphenazine was superior to OAPs in preventing hospitalization (4 studies, RR = 0.82, 95% CI: 0.67-0.99, p=0.04). The authors concluded more studies in real-world settings are needed.

A systematic review and meta-analysis of second-generation LAIs in patients with schizophrenia was conducted.[2] Thirteen studies were included comparing second-generation LAIs to placebo and oral antipsychotics. LAI antipsychotics were associated with a statistically significant decrease in the Positive and Negative Syndrome Scale (PANSS) total score from baseline to the end of the study period compared to placebo injections (Hedges's *g*=0.336, 95% CI 0.246–0.426, *Z*=7.325, *P*<0.001), but not significantly different from oral antipsychotics (Hedges's *g*=0.072, 95% CI -0.072 to 0.217, *Z*=0.983, *P*=0.326). No significant differences between LAI antipsychotics and placebo or OAPs were observed with respect to the number of deaths, overall number of treatment-adverse events, insomnia, or pain at the injection site. There was a greater risk of developing extrapyramidal symptoms (EPS) with LAI therapy than in both control groups (vs. placebo, RR=2.037, *P*<0.001; vs. OAPs, RR=1.451, *P*=0.048).

Guidelines:

American Psychiatric Association (APA) [4]

The APA guidelines were first released in 2004, and the 2009 updated literature search did not address LAI use specifically. The guidelines recommend using LAI antipsychotics in patients with recurrent relapses related to nonadherence and patients who prefer LAIs over oral medications. Patients may transition from an OAP to LAI; however, LAIs should not be initiated for acute psychotic episodes because LAIs can take months to reach stable steady state and are eliminated slowly, making it difficult to titrate the dose to control therapeutic effects and side effects.

Canadian Psychiatric Association [5,10]

Guidelines on LAI antipsychotics were released by the CPA in May 2013. The following were recommendations made based on medical evidence and consensus data solicited on LAI use in Canada:

- The overall evidence was not convincing of the superiority of LAIs compared with oral medications, suggesting equal effectiveness and some benefits of using LAIs in patients who are or who are likely to be nonadherent, irrespective of the phase of their illness.
- The use of LAIs may not prevent nonadherence but may allow for earlier recognition of nonadherence when a dose is missed and may help identify patients with poor or no response from those who are non- or partially adherent.
- For patients who are clearly adherent to OPAs, there may not be reason or evidence to switch to a LAI.
- In case of overt or impending nonadherence to medication, serious consideration should be given to using LAIs as one of the choices for addressing nonadherence.

- It is preferable to initiate treatment with an OAP, but not necessary to achieve stabilization with an OAP prior to initiating an LAI as long as the patient has been exposed to a test dose. This is particularly relevant for patients refusing to take oral medication or who are unlikely to take it during the acute phase of psychosis.

The National Institute for Health and Care Excellence (NICE): [6]

An update to NICE Psychosis and Schizophrenia in Adults evidence-based guidelines was released in February 2014. The recommendations for use of LAI antipsychotics are given:

- Consider offering depot/LAI antipsychotics to people with psychosis or schizophrenia who would prefer such treatment after an acute episode or to patients where avoiding covert nonadherence (either intentional or unintentional) is a clinical priority within the treatment plan.
- When initiating depot/LAI medication, take into account patient preference and attitudes, as well as risks and benefits of the drug regimen, and use a small initial test dose before injecting (not necessary to stabilize on oral medication).

Randomized Controlled Trials:

- In the ACLAIMS (A Comparison of Long-Acting Medications for Schizophrenia) trial, McEvoy et al[3] compared first-generation haloperidol decanoate to paliperidone palmitate in 311 adults with schizophrenia or schizoaffective disorder judged to be at risk for relapse for up to 24 months. The primary outcome was efficacy failure, which included psychiatric hospitalization; a need for crisis stabilization; a clinically meaningful increase in outpatient visits; a clinician's decision to discontinue the LAI antipsychotic agent due to inadequate benefit; or ongoing need for adjunctive OAP therapy. Approximately one-third of patients in both groups reported efficacy failure (defined as a psychiatric hospitalization, an increase in outpatient visits, or other clinical intervention). There was no difference between the two groups (adjusted hazard ratio, 0.98; 95% CI, 0.65-1.47). Side effect profiles between the two LAIs did differ. Patients experienced statistically significant more weight gain at 6 months in the paliperidone group (2.17 kg; 95% CI, 1.25-3.09) compared to those taking haloperidol (-0.96 kg; 95% CI, -1.88 to -0.04). This difference in weight change widened at 24 months between the two groups. Patients in the paliperidone group also experienced more moderate or severe adverse events than patients in the haloperidol decanoate group, including significantly higher serum prolactin levels among men and women; however, haloperidol decanoate was associated with more akathisia.

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