Long-Acting Injectable Antipsychotic Medications in Schizophrenia Management

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ABSTRACT
Antipsychotic medications are indicated for the treatment of schizophrenia and other psychiatric disorders including bipolar disorder. However, oral antipsychotics are associated with a number of issues including poor treatment adherence. Long Acting Injectable (LAI) antipsychotics were designed to address these issues with oral antipsychotics. LAI antipsychotics offer several advantages including less frequent dose administration, better adherence and tolerability, and relapse prevention, which in turn help in improving patients’ quality of life. Recent development of atypical antipsychotics has the advantages over typical antipsychotics in terms of improved efficacy and tolerability. This review highlights the advantages and disadvantages of LAI antipsychotics, outlines the currently available LAIs and their indications, and real-world evidence for LAIs based on the observational studies.

KEYWORDS: Antipsychotics; Injectables; efficacy; tolerability; quality of life.

Introduction
Long-acting injectable antipsychotics (LAIs) such as risperidone, paliperidone, aripiprazole, and risperidone are commonly used in the treatment of psychotic disorders, particularly schizophrenia (Jarema et al., 2015). The goals of schizophrenia treatment include improved function and recovery across lifespan, with symptom reduction and relapse prevention. LAIs were developed in order to overcome the drawbacks associated with oral antipsychotics such as poor medication adherence (Sacchetti et al., 2015). However, they are not solely used to improve patient’s compliance, but also have other advantages including better tolerability, reduced frequency of administration, and maintenance of stable level of antipsychotics which assures better bioavailability. LAIs provide a persistent and effective blockade of dopaminergic D2 receptors in a range that is required to control psychotic symptoms, and also reduce the risk of abrupt treatment discontinuation (Jarema et al., 2015). Despite their widespread use, there are some concerns of LAIs due to slow dose titration, less flexibility of dose adjustment, longer time to achieve steady state levels, pain at injection site, and burden of frequent travel to outpatient clinics (Brissos et al., 2014).

Historical Background of LAI Development
The initial LAIs were based on first-generation antipsychotics or typical antipsychotics. Fluphenazine enanthate was developed as injectable in 1966 followed by development of fluphenazine decanoate, to address the issue of poor adherence to oral antipsychotics. Haloperidol decanoate became available in USA in 1986 (Brissos et al., 2014). The LAIs of second generation or atypical antipsychotics were recently developed to avail the advantages of both, improved efficacy and tolerability of atypical antipsychotics and increased compliance and better bioavailability of LAIs (Nahata and Saini, 2009; Offord et al., 2013; Brissos et al., 2014; Pesa 2015).

Available LAI Products
Currently, there are six LAI antipsychotics available for treatment of schizophrenia and other psychotic disorders. These include first-generation antipsychotics (Fluphenazine decanoate, and Haloperidol decanoate) and second-generation antipsychotics (Aripiprazole, Risperidone, Paliperidone and Olanzapine) (Jarema et al., 2015; Brissos et al., 2014). Table 1 outlines the characteristics of various LAIs.

Indications for LAI use
Current guidelines recommend the use of LAI antipsychotics for the maintenance treatment of schizophrenia among other available treatment options and when there is a need to improve patient’s medication adherence (Jaskelainen et al., 2013; Leucht et al., 2012; CG, 2005). Several guidelines recommend that LAI antipsychotics should be used only in patients with recurrent relapses related to partial or full non-adherence (Lehman et al., 2004; Lindenmayer, 2010; Mauri et al., 2014; LAIA, 2015; Marcus et al., 2015; McEvan et al., 2016).

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**Fluphenazine**

Fluphenazine mainly acts as a dopamine antagonist. Fluphenazine LAI is indicated in the management of patients requiring prolonged parenteral neuroleptic therapy (e.g., chronic schizophrenia). It is not intended for use in children under 12 years of age. Fluphenazine may be administered as a maintenance therapy in patients who have been stabilized on a fixed daily dosage of oral fluphenazine. Fluphenazine LAI is administered at a dose of 12.5-100 mg at 1-4 weeks interval (AAP, 2010).

**Haloperidol**

Haloperidol blocks the dopamine receptors; however, its exact mechanism of action is not known. Haloperidol LAI is indicated for treatment of schizophrenic patients who require prolonged parenteral antipsychotic therapy. Haloperidol is not indicated in patients with severe toxic central nervous system depression, comatose patients, and in individuals hypersensitive to this drug or having Parkinson’s disease. Haloperidol LAI should be administered in patients who have been previously stabilized with an oral antipsychotic, preferably oral haloperidol. The maintenance dose of haloperidol LAI must be individualized with titration and the usual maintenance dose range is 10 to 15 times the previous daily oral dose. It is administered in the dose range of 50-400 mg every four weeks (LAIA, 2015).

**Risperidone**

Risperidone blocks the serotonin 5-HT_{2A} and 5-HT_{7} receptors as well as dopamine D2 receptors. Risperidone LAI is indicated for the treatment of schizophrenia in patients presently treated with oral antipsychotics. It should be used with caution in patients with dementia and cerebrovascular disorders and is not indicated for patients below 18 years of age. Risperidone LAI should be administered to patients who have been treated with an antipsychotic, preferably oral risperidone. The period of oral risperidone treatment should be no shorter than 2 weeks. The maximum dosage of risperidone LAI is 50 mg every two weeks (JP, 2016; Mauri et al., 2014).

**Aripiprazole**

Aripiprazole is an antipsychotic agent that is sometimes referred to as the third-generation antipsychotic drug due to its unique mechanism of action; it is serotoninergic 5-HT_{2} antagonist as well as 5-HT_{1A} and D_{2} partial agonist. Aripiprazole LAI is indicated for maintenance treatment of patients with schizophrenia who have been initially prescribed oral antipsychotics. It is not indicated in elderly patients with dementia and in patients under 18 years of age. It is associated with an increased risk of death, mainly due to cardiovascular causes. In patients who have been treated with oral aripiprazole, 400 mg of Aripiprazole LAI should be administered with simultaneous continuation of oral aripiprazole for 14 days in order to maintain stable serum aripiprazole levels. After 14 days, oral aripiprazole should be discontinued, and aripiprazole LAI should be given every four weeks (Jarema 2015; AW, 2014).

**Paliperidone**

Paliperidone blocks the monoamine activity with a strong affinity to serotonin 5-HT_{2A} and dopaminergic D2 receptors. In addition, it also blocks the α-1, H1 and α-2 receptors, but does not bind to cholinergic receptors. Its central antagonistic action may be the reason for the lower incidence of extrapyramidal side-effects. Paliperidone LAI is indicated in adult schizophrenia patients after at least one relapse or exacerbation of symptoms due to non-adherence to treatment; and should be used in patients who have been stabilized using risperidone or paliperidone treatment. If the patient is treated with another antipsychotic, they should first be switched to oral risperidone or paliperidone followed by paliperidone LAI. Paliperidone LAI is administered at a dose of 25-150 mg at every four weeks interval (Mauri et al., 2014; JP, 2016 (a)).

**TABLE 1**

Characteristics of LAI antipsychotics

<table>
<thead>
<tr>
<th>Name</th>
<th>Year of approval</th>
<th>Formulation</th>
<th>Dose range (mg)</th>
<th>Administration interval (weeks)</th>
<th>Injection Site</th>
<th>Half-life (days) (multiple dose)</th>
<th>Time to reach peak plasma concentration (days)</th>
<th>Monitoring post injection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine decanoate</td>
<td>1967</td>
<td>Sesame oil solution</td>
<td>12.5-100</td>
<td>1-4</td>
<td>Gluteal muscle</td>
<td>14</td>
<td>0.3-1.5</td>
<td>No</td>
<td>(Sacchetti et al., 2015; Curry et al., 1979)</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>1986</td>
<td>Sesame oil solution</td>
<td>50-400</td>
<td>4</td>
<td>Gluteal muscle</td>
<td>21</td>
<td>3-9</td>
<td>No</td>
<td>(Sacchetti et al., 2015; Reyntjens et al., 1982; Kissling et al., 1991)</td>
</tr>
<tr>
<td>Risperidone long-acting</td>
<td>2001</td>
<td>Aqueous suspension, risperidone encapsulated into biodegradable microspheres</td>
<td>25-50</td>
<td>2</td>
<td>Gluteal or deltoid muscle</td>
<td>4-6</td>
<td>28</td>
<td>No</td>
<td>(Sacchetti et al., 2015; Agid et al., 2010; Gefvert et al., 2005; Thyssen et al., 2010)</td>
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</thead>
<tbody>
<tr>
<td>Paliperidone palmitate</td>
<td>2009</td>
<td>Aqueous suspension of nanoparticles</td>
<td>25-150</td>
<td>4</td>
<td>Gluteal or deltoid muscle</td>
<td>25-49</td>
<td>13</td>
<td>No</td>
<td>(Sacchetti et al., 2015; Gilday and Nasrallah, 2012)</td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>2009</td>
<td>Aqueous microcrystalline suspension</td>
<td>150-300</td>
<td>2-4</td>
<td>Gluteal muscle</td>
<td>14-30</td>
<td>8-12</td>
<td>Yes</td>
<td>(Sacchetti et al., 2015; Agid et al., 2010; Rosaria and Alice, 2010)</td>
</tr>
<tr>
<td>Aripiprazole long-acting</td>
<td>2009-10</td>
<td>Aqueous suspension microparticles</td>
<td>300-400</td>
<td>4</td>
<td>Gluteal muscle</td>
<td>29-46</td>
<td>5-7</td>
<td>No</td>
<td>(Sacchetti et al., 2015; Nahata and Saini, 2009)</td>
</tr>
</tbody>
</table>

**Olanzapine**

Olanzapine is an antipsychotic that has affinity towards multiple receptors including serotonergic 5-HT₂A and 5-HT₆, 5-HT₃, 5-HT₄ dopaminergic D1-D5, muscarinic M1-M5, adrenergic α-1 and histaminergic H1 receptors. This multi-receptor affinity is probably associated with its antipsychotic effectiveness. Olanzapine LAI is indicated for maintenance treatment of adult schizophrenia patients who have been stabilized by oral olanzapine. They are not recommended for patients aged 65 years or older, or for children and adolescents. They are also not indicated for patients with renal and liver failure. Olanzapine LAI should be administered in patients already stabilized on oral olanzapine, usually 150-300 mg at four weeks interval (Jarema et al., 2015; Lindenmayer, 2010).

**Real World Evidence of LAIs**

**LAI**s and Hospital Re-admission Rates

In a retrospective cohort study conducted by McEvans et al., lower probability (adjusted OR = 0.60, 95% CI = 0.41-0.90) of re-hospitalization was observed for LAIs compared to oral antipsychotics for schizophrenia patients (McEvans et al., 2016). Similar results were observed in a study by Marcus et al. in adult schizophrenia patients with a recent history of non-adherence. Patients who were initiated LAIs, had lower odds (adjusted OR = 0.73, 95% CI = 0.54-0.99) of re-hospitalization compared to those receiving oral antipsychotics (Marcus et al., 2015). Another study evaluated the risk of re-hospitalization among patients with schizophrenia and LAIs. In this study, the adjusted odds ratio for re-hospitalization risk was 0.80 (95% CI = 0.65-0.98), compared to the oral antipsychotics group (Ju 2014). Also, in a study evaluating the association between second generation antipsychotic medication half-life and hospitalization in adult schizophrenia, a significantly lower rate of hospitalization was evident for long half-life (0.74/patient-year) compared to short half-life (1.06/patient-year) antipsychotics (Broder et al., 2012).

**LAI**s Cost and Resource Utilization

Schizophrenia represents 1.5-3% of national healthcare expenditures, hence cost-effective treatment is essential to ensure reduction in disease burden and efficient resource utilization (Brisos et al., 2014). Many retrospective studies have been conducted to determine the cost and resource utilization in patients using LAI antipsychotics. A study by Pesa et al., found that schizophrenia patients who were prescribed paliperidone palmitate had higher per-month mental-health prescription costs, however they had lower inpatient and outpatient care costs. Use of paliperidone palmitate resulted in 0.44 times reduction in all-cause hospitalizations and 0.47 times reduction in the odds of mental-health-related hospitalizations, compared to oral atypical antipsychotics, over a twelve-month follow-up period (Pesa et al., 2015). Similar results were observed in a study conducted by Baser et al., where schizophrenia patients from Veterans Health Administration treated with paliperidone palmitate had lower inpatient costs ($18,560 vs. $31,505, p=0.002) and lower frequency of hospitalization (34% vs. 53%, p<0.001) compared to patients with oral atypical antipsychotics (Baser et al., 2015). Lin et al. observed that among schizophrenia patients, LAI users had lower schizophrenia-related hospital costs during the follow-up period compared to the pre-index period, but oral antipsychotic users had increased costs ($5,981 ± $16,554 vs. $758 ± $14,328, p<0.001) (Lin et al., 2013). Offord et al. observed that schizophrenia patients initiating LAI vs oral antipsychotics, showed significantly greater reduction in the average number of all-cause hospitalizations (-0.90 ± 1.77 vs. 0.02 ± 1.49, p < 0.001), length of stay (-10.3 ± 23.2 vs. 0.7 ± 16.7 days, p < 0.001) and schizophrenia-related hospitalizations (-0.60 ± 1.37 vs. 0.05 ± 0.99, p < 0.001) (Offord et al., 2013).

**Comparative Effectiveness of LAIs**

In a Medicaid claims database study, patients who switched from risperidone LAI to paliperidone palmitate had fewer events (schizophrenia-related hospitalization) (26 vs. 32), longer time to event (mean 70 vs. 47 days), and lower risk of relapse (HR= 0.54, 95% CI= 0.32-0.92)
compared to those who switched from risperidone LAI to oral antipsychotics (Voss et al., 2015). In another study comparing risperidone and paliperidone LAIs, significantly lower discontinuation rates (36.5% vs. 53.3%, p<0.001) and longer days of LAI coverage (233.6 vs. 131.7 days, p<0.001) were associated with paliperidone. Also, patients treated with paliperidone palmitate were 12.5 times (95% CI= 9.0-17.8) more likely to be adherent based on medication possession ratio and 11.7 times (95% CI= 8.0-17.4) more likely to be adherent based on proportion of days covered (Joshi et al., 2016).

Conclusions

Based on the findings of observational studies, compared to oral antipsychotics, LAIs were found to be associated with significantly lower re-hospitalizations, better medication adherence, and lower all-cause and schizophrenia-related costs of hospitalizations; thus ensuring effective resource utilization, reduced disease burden and pharmaceutical costs of schizophrenia (Reyntjens et al., 1982; Rosaria and Alice, 2010; Sacchetti et al., 2015; Thyssen et al., 2010).

LAIs antipsychotics provide a valuable treatment option for individualized and personalized treatment of schizophrenia. LAIs have shown to be associated with reduced hospital readmissions, improved treatment adherence, and reducing the costs and burden of the disease. Although there has been recent emergence of LAI atypical antipsychotics, there is a need to evaluate comparative effectiveness and safety for patients with schizophrenia due to cost and quality of care concerns. Also, well-designed long-term studies are needed to evaluate its role in other psychiatric disorders.

References


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