**Introduction**

Non-adherence to antipsychotic medications is a leading cause of preventable morbidity in patients with schizophrenia in the community. It is estimated that 40-60% of patients with schizophrenia are partially or totally non-compliant with oral antipsychotic medication.

Oral administration of antipsychotics results in a higher risk of relapse than long-acting injections (LAIs). LAIs have been developed to promote adherence and improve treatment outcomes. Non-adherence is associated with poor treatment outcomes including poor symptom control, loss of insight, decreased functioning, relapse and admission into hospital. LAIs guarantee the delivery of the prescribed medication, and thereby reduce the risk of relapse due to non-adherence.

LAIs, or depot antipsychotics, are recommended as maintenance treatment for patients with a history of non-adherence to oral antipsychotics. The decision to initiate a LAI should be based on a clinical assessment of the risks and consequences of medication non-adherence.

**Utilisation rates**

Approximately 30% of patients with schizophrenia in Australia are prescribed a LAI. An audit of Graylands Hospital usage in October 2009 showed that 41% of inpatients were prescribed a LAI.

**Advantages**

The decision to use LAIs instead of oral medications is usually based on compliance, however there are other advantages to choosing this route of administration.

LAIs eliminate bioavailability problems associated with absorption and first-pass metabolism. Oral antipsychotics are converted to inactive metabolites in the gut wall and during ‘first pass’ metabolism in the liver, leaving only a portion of the dose available to reach systemic circulation.

In addition, the risk of overdose of medications due to suicidal ideation is reduced when patients are prescribed LAIs. Suicide is a common cause of death in mental health patients, so may be relevant when considering treatment options.

Due to the guaranteed delivery associated with LAIs, there is evidence to suggest that LAIs provide better relapse prevention than oral antipsychotics. Re-hospitalisation rates are also lower in patients on LAIs compared to oral formulations.

Although the delivery system itself does not prevent non-adherence, as patients may not present for their scheduled injection, it readily identifies non-adherence. The regular scheduled contact between patients and clinicians allows for early, effective follow-up and can identify impending relapse.

Plasma drug concentrations are relatively stable and predictable in patients treated with LAIs. This increases the likelihood that plasma concentrations will remain within the therapeutic range over long periods.

**Disadvantages**

The stable plasma concentrations also represent a disadvantage because of the lack of flexibility in dosing. If an adverse effect occurs, the medication cannot be rapidly withdrawn, as is the case with oral preparations.

These injections can be painful which can have a negative effect on patient attitude towards the medication. They may fear the injection, consider it intrusive and degrading, or see LAI administration as a way of “being controlled”.

An increased incidence of extrapyramidal side effects (EPSE) with first-generation antipsychotic (FGA) LAIs has been reported in some trials. However, this data is controversial, as some reports show no difference between oral and LAI antipsychotics.

**Patient preference**

Studies show that the percentage of LAI users who prefer this route of administration ranges from 23-93%. The acceptance of LAI treatment generally increases with experience and duration of treatment. Research also shows patients tend to prefer the current formulation of their antipsychotic.

Reasons for not preferring LAI administration include embarrassment surrounding the need to attend the clinic for medication and the perception of forced treatment. Possible reasons for patients preferring LAIs is that they find it easier than taking oral medication once or twice daily.

Educating staff, patients, carers and family members
about the positive and negative aspects of LAI medication may help address the stigma associated with this route of administration.\textsuperscript{9}

**Prescribing Long-Acting Injections**

**Test doses**

Test doses of the FGA LAIs are recommended prior to therapy. This ensures the patient can tolerate the medication and is not allergic to the oily vehicle.\textsuperscript{4} A test dose helps to avoid severe, prolonged adverse effects, however some EPSE can occur only after several doses.\textsuperscript{11}

The usual test doses of the FGAs are outlined in Table 1. Regular dosing of the FGA LAI should commence approximately 7 days after the test dose.\textsuperscript{12}

The second-generation antipsychotics (SGAs), risperidone and olanzapine, do not require a test dose of the LAI as the drug in these preparations is suspended in an aqueous base.\textsuperscript{13} A test dose of the corresponding oral antipsychotic is recommended to ensure the patient does not adversely react to the medication.\textsuperscript{13}

**Use lowest therapeutic dose**

There is limited data available indicating a clear dose-response effect for LAIs, but there is some information indicating that lower doses are at least as effective as higher doses.\textsuperscript{11, 14} Low doses are likely to be better tolerated and are less expensive.\textsuperscript{11, 14}

**Administer at longest possible licensed interval**

Less frequent administration is desirable for many patients as it also means fewer potentially painful injections.\textsuperscript{11, 14} There is no current evidence to suggest shortening the interval improves efficacy.\textsuperscript{11, 14}

**Adjust dose only after adequate period of assessment**

Peak plasma levels, therapeutic effect and steady state are all delayed with LAIs.\textsuperscript{11, 14} Doses may be reduced if adverse effects occur, but should only be increased after careful assessment over at least 1 month (preferably longer).\textsuperscript{11, 14}

**Initiation**

FGA LAI therapy is usually started during the administration of oral therapy, followed by a gradual tapering of the oral dose.\textsuperscript{4} For SGAs, oral risperidone is required for at least 3 weeks after risperidone LAI initiation.\textsuperscript{13} Long-acting olanzapine does not require oral supplementation.\textsuperscript{15}

**Administration**

The FGA LAIs should be administered using a 21-gauge needle.\textsuperscript{16} Risperidone and olanzapine are supplied with needles. All LAIs are to be given via deep intramuscular injection.\textsuperscript{16} Do not massage the site after injection.\textsuperscript{16}

**First-Generation Antipsychotics**

All of the FGA LAI preparations are esters of the medication dissolved in an oily base (see Table 1).\textsuperscript{17} These compounds are highly oil-soluble, but are only sparingly soluble in aqueous fluids such as blood.\textsuperscript{11} When injected deeply into muscle, the ester slowly dissolves in the surrounding blood, is hydrolysed by enzymes and releases the parent antipsychotic compound.\textsuperscript{11} Some anecdotal evidence and comparisons between the FGA LAIs are listed in Table 2.

Pipotiazine is not registered in Australia\textsuperscript{19} and is therefore only available via the Special Access Scheme.\textsuperscript{20} A patient cannot be prescribed pipotiazine until approval is received from the Therapeutic Goods Administration.\textsuperscript{20}

Zuclopenthixol is also available in an oily injection as an acetate ester (Clopixol Acuphase\textsuperscript{®}) that is used in acute psychosis.\textsuperscript{13} This preparation has a much faster onset of action than the decanoate ester, with peak concentration reached after 24-36 hours.\textsuperscript{13} Zuclopenthixol acetate is not intended for long-term use and the duration of treatment should not exceed 2 weeks.\textsuperscript{13} The maximum accumulated dose in a course is 400mg and the total number of injections should not exceed four, preferably at intervals of two to three days.\textsuperscript{13, 21} Significant sedation occurs within 2 hours of injection,\textsuperscript{13, 22} therefore monitoring in an inpatient

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vehicle</th>
<th>Test dose (mg)</th>
<th>Dose range (mg/week)</th>
<th>Dosing interval (weeks)</th>
<th>Half life (days)</th>
<th>Time to max conc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupenthixol decanoate</td>
<td>Coconut oil</td>
<td>20</td>
<td>12.5-50</td>
<td>2-4</td>
<td>8 (single dose)</td>
<td>7-10 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 (multiple doses)</td>
<td></td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>Sesame oil</td>
<td>12.5</td>
<td>6.25-50</td>
<td>2-5</td>
<td>6-10 (single dose)</td>
<td>6-48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14-100 (multiple doses)</td>
<td></td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>Sesame oil</td>
<td>50</td>
<td>12.5-75</td>
<td>4</td>
<td>18-21</td>
<td>3-9 days</td>
</tr>
<tr>
<td>Pipotiazine palmitate*</td>
<td>Sesame oil</td>
<td>25</td>
<td>12.5-50</td>
<td>4</td>
<td>14-21</td>
<td>9-10 days</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate</td>
<td>Coconut oil</td>
<td>100</td>
<td>100-200</td>
<td>2-4</td>
<td>17-21</td>
<td>4-9 days</td>
</tr>
</tbody>
</table>

* not registered in Australia
facility is recommended.
These two different formulations of zuclopenthixol cannot be used interchangeably.

Table 2: Comparisons between FGA depots

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupenthixol</td>
<td>Standard doses appear to be as effective as high doses.</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>High incidence of EPSE.</td>
</tr>
<tr>
<td></td>
<td>Smoking significantly reduces plasma levels.</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>High incidence of EPSE, low incidence of sedation.</td>
</tr>
<tr>
<td></td>
<td>Smoking significantly reduces plasma levels.</td>
</tr>
<tr>
<td>Pipothiazine</td>
<td>Reports of lower incidence of EPSE, though this is unproven.</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>Has prominent sedative properties.</td>
</tr>
<tr>
<td></td>
<td>May be more effective at preventing relapse than other FGA LAIs.</td>
</tr>
<tr>
<td></td>
<td>but at the expense of increased side-effects.</td>
</tr>
</tbody>
</table>

Second-Generation Antipsychotics

There are currently two SGA LAIs available in Australia, risperidone and olanzapine, which are summarised below in Table 3. Both of these use an aqueous base, compared to the oily preparations used with the FGAs. Test doses of these injections are not required, but trials of the oral antipsychotic are recommended prior to the LAI being commenced to ensure the patient is tolerant to the medication.

The cost differential between first generation and second generation LAIs is large. For example, a 25mg risperidone LAI is more than 30 times more expensive than a 200mg zuclopenthixol decanoate injection.

Risperidone LAI consists of risperidone coated in a polymer to form microspheres, which are suspended in an aqueous base immediately prior to use. After intramuscular administration, a small initial release of drug (<1% of the dose) occurs, followed by a lag time of three weeks. The main release of the drug starts from week 3, is maintained from four to six weeks and subsides from week 7. Oral antipsychotic supplementation is therefore required for at least the first three weeks of risperidone LAI treatment. Risperidone LAI can now be administered into the gluteal or deltoid muscle. The product is supplied with two different size needles - a shorter 1-inch needle for deltoid administration and a longer 2-inch needle for gluteal administration. These needles cannot be interchanged. The medication and reconstitution remains unchanged.

Olanzapine

Olanzapine pamoate, the most recent LAI injection to become available in Australia, is reviewed on the last page of this bulletin. The Western Australian Therapeutic Advisory Group has not yet approved olanzapine pamoate for use in public hospitals or clinics.

Currently, no head-to-head comparison trials have been conducted between the SGA LAIs.

A number of other SGA LAIs are currently either in development or under review by regulatory agencies.

Adverse effects

Anecdotal evidence suggests LAI formulations are associated with a higher incidence of adverse reactions compared to oral preparations, particularly EPSE. Data on this issue is controversial, however it appears that the frequency of adverse effects of FGA LAIs is similar to those seen with oral FGAs.

Adverse effects observed with olanzapine pamoate are similar to those with oral olanzapine, apart from the risk of post-injection syndrome (see over). Risperidone LAI has a similar incidence of adverse effects to oral risperidone. Injection site pain leading to withdrawal is reported to be uncommon.

Conclusion

LAIs are a significant component in the maintenance care of patients with schizophrenia. Their popularity fell in the late 1990s and early 2000s after the introduction of oral SGAs, but is now rising. LAIs are a valuable tool for non-adherent patients in the management of psychosis and relapse prevention. Although patients may still be non-compliant with LAIs, relapse due to non-compliance can be easily identified from relapse due to ineffectiveness.

Table 3: Second-generation antipsychotic long-acting injections

<table>
<thead>
<tr>
<th>Drug</th>
<th>Test dose</th>
<th>Oral supplementation</th>
<th>Dose range (mg/fortnight)</th>
<th>Dosing interval (weeks)</th>
<th>Half life (days)</th>
<th>Time to max conc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Oral risperidone</td>
<td>For at least 3 weeks</td>
<td>25-50</td>
<td>2 weeks</td>
<td>4-6 days (once drug released)</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Oral olanzapine</td>
<td>Not required</td>
<td>150-300</td>
<td>2 or 4 weeks</td>
<td>30 days</td>
<td>2-4 days</td>
</tr>
</tbody>
</table>
Olanzapine Pamoate: new long-acting injection

Olanzapine pamoate (Zyprexa Relprevv®) is a new LAI indicated for the maintenance treatment of schizophrenia in adult patients sufficiently stabilised during acute treatment with oral olanzapine.15

Formulation
Olanzapine pamoate is a crystalline salt formulation composed of olanzapine and pamoic acid.27 The crystals are suspended in water and when injected, they slowly dissolve and dissociate, releasing the olanzapine.27

Availability
Olanzapine pamoate is available in 3 vial strengths - 210mg, 300mg and 405mg.15 Currently, the 210mg and 300mg strengths are available in Australia on the Pharmaceutical Benefits Scheme (PBS).24 The 405mg strength is currently unavailable in Australia and is expected to be listed on the PBS when it becomes available.

Pharmacokinetics
The peak plasma level of olanzapine is achieved within the first week after injection and the lowest trough level is immediately before the next injection.15 Reasonably consistent plasma levels are sustained during the injection interval.15

The half-life of olanzapine pamoate is 30 days (compared to 30 hours with oral olanzapine).15 Complete elimination of the drug is achieved 6 to 8 months after the last dose.15

Administration
Olanzapine pamoate is for deep gluteal intramuscular use.15 It should not be administered into the deltoid muscle, intravenously or subcutaneously.15

Each vial strength requires a different volume of diluent to be added so that once reconstituted all vial strengths have a concentration of 150mg/mL. Accordingly, each dose requires a different volume of suspension to be withdrawn and the entire contents of the vial are never used.28

Dose
The recommended dosing schemes between oral olanzapine and the LAI are listed below in Table 4.

Table 4: Recommended dosing of olanzapine pamoate15

<table>
<thead>
<tr>
<th>Target oral olanzapine dose</th>
<th>Recommended starting dose of olanzapine pamoate</th>
<th>Maintenance dose after 2 months of olanzapine pamoate treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg/day</td>
<td>210mg/2 weeks or 405mg/4 weeks</td>
<td>150mg/2 weeks or 300mg/4 weeks</td>
</tr>
<tr>
<td>15mg/day</td>
<td>300mg/2 weeks</td>
<td>210mg/2 weeks or 405mg/4 weeks</td>
</tr>
<tr>
<td>20mg/day</td>
<td>300mg/2 weeks</td>
<td>300mg/2 weeks</td>
</tr>
</tbody>
</table>

A higher dose of olanzapine pamoate is used initially as steady state is achieved only after several weeks, and plasma levels increase several-fold on repeated dosing.28 A loading dose is not used with any other depot medication. Prescribers must be vigilant and reduce the dose after this 2-month period to avoid patients remaining on higher than required doses.28

Post-injection syndrome
Post injection syndrome (PIS) is a rare side effect occurring in approximately 1% of patients.15 It produces signs and symptoms consistent with olanzapine overdose, including sedation (ranging from mild in severity up to coma) and delirium.15 PIS is thought to occur when olanzapine pamoate is inadvertently injected into the bloodstream, where it is more soluble compared to muscle.15 There is a risk of PIS after each injection.15

Initial signs of PIS generally appear within 1 hour, and rarely within 1-3 hours.15 There has been one case report of it occurring after 3 hours.15 No deaths have been reported and in all cases full recovery was reported within 24-72 hours.15

After each injection, appropriately trained personnel must monitor patients for at least 3 hours and actively monitor for alertness every 30 minutes.15 For the remainder of the day, patients must be vigilant for signs of PIS and should not drive a car or operate machinery.15

Efficacy
The efficacy of olanzapine pamoate was demonstrated in several placebo-controlled and open-labelled trials. It was non-inferior to oral olanzapine at a comparable dose, but has not been compared to other oral or LAIs.27

Side effects
The general safety profile of olanzapine pamoate is similar to that of oral olanzapine.27 There is, however, the risk of PIS and therefore a need to monitor patients for 3 hours.15

Metabolic effects occur at a similar rate with olanzapine pamoate compared to oral olanzapine.15 These effects may be prolonged even after olanzapine pamoate is ceased due to the long half-life and time needed for olanzapine to be cleared from the body.

Conclusion
Olanzapine pamoate appears to be an option to consider in patients who have previously responded to olanzapine, but for whom adherence may be difficult.27 The possibility of 4-weekly injections is an advantage, however the 3-hour observation period required due to the risk of PIS and the complicated dosing schedule may be problematic.

This Drug Bulletin was written by Katie Walker and was reviewed by the Graylands Pharmacy Department and Dr Joseph Lee

References available on request
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