

# Long-acting injectable antipsychotics

## Review and recent developments

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### ABSTRACT

Long-acting injectable antipsychotics, also known as "depots", were developed in the late 1960s as an attempt to improve compliance and long-term management of schizophrenia. Despite their availability for over 30 years, guidelines for their use and data on patients for whom long-acting injectable antipsychotics are most indicated are sparse and vary considerably. A review of the perceived advantages and disadvantages of using long-acting injectable antipsychotics is provided in this article, as well as a review of the literature to update clinicians on the current advances of this therapeutic option to optimize compliance and long-term management of chronic schizophrenia.

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Schizophrenia is a chronic disorder for which it is well recognized that lifelong treatment with antipsychotics is necessary. Although quite successful in treating and preventing relapses,<sup>1,2</sup> antipsychotics are not readily accepted by patients, thus, non-compliance is common.<sup>3,4</sup> Thus, long-acting injectable forms of these medications were developed in an attempt to help medication compliance especially during the maintenance phase of this chronic condition.<sup>5</sup> They are considered a useful therapeutic option in patients with psychosis who lack insight or are known to adhere poorly to oral medication.<sup>1,2,5-8</sup> Long-acting injectable antipsychotics, also known as "depot" formulations, are traditionally manufactured as alcohols, which by esterification, form highly hydrophobic esters which are only sparingly soluble in aqueous fluids such as blood.<sup>2</sup> These esters are dissolved in a variety of oils (sesame seed, coconut or other vegetable oil such as Viscoleo®).<sup>9</sup> Once injected into a muscle, these formulations form a reservoir or depots of drug that is slowly dissolved in the surrounding blood where endogenous plasma esterases

hydrolyze the esterified compound and liberates the parent antipsychotic.<sup>2,9,10</sup> Although depot antipsychotics have been available for over 30 years, guidelines for their use and data on patients for whom long-acting injectables are most indicated are sparse and vary considerably. In addition, despite the fact that the use of depot antipsychotics has been extensively promoted to overcome patient non-compliance with medications,<sup>8,10</sup> their acceptance by prescribers and patients remains variable.<sup>11</sup> A review of the perceived advantages and disadvantages of using long-acting injectable antipsychotics is provided in this article, as well as a review of the literature to update clinicians on the current advances of this therapeutic option to optimize compliance in chronic schizophrenia.

**Advantages of long-acting injectable antipsychotics.** Assured compliance, with associated and proven reduction in relapses, re-hospitalization and severity of relapse.<sup>1,2,5-7</sup> Reduction in bio-availability problems. It is widely known that some people metabolize antipsychotics extensively via the first-pass effect.<sup>6,12-14</sup> Compared

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to oral medication, long-acting injectable administration produces a more stable plasma concentration, without the daily oscillations related to the repeated ingestion required for oral medications.<sup>6,7,13,14</sup> By being sure that the doses are received, using long-acting injectable antipsychotics should be able to facilitate better downward titration of doses to reduce the potential for side effects.<sup>7</sup> Increased contact with the treatment team facilitates initiation of efforts to deal timely with arising problems the patient may be going through.<sup>7,15,16</sup> Generally, patients have shown positive attitudes toward long-acting injectable antipsychotics, even favoring this route of administration over the oral route.<sup>16,17</sup>

**Disadvantages of long-acting injectable antipsychotics.** Difficulty in altering a dose if side effects develop (such as tardive dystonia or neuroleptic malignant syndrome),<sup>6,7,10</sup> Local complications with the administration technique, or when high doses are injected (pain, bleeding, hematoma, leakage, inflammatory nodules) may discourage patient compliance.<sup>6,10,13,18-20</sup> Some patients may not like the feeling of being under control.<sup>7,13</sup>

**Long-acting injectable atypical antipsychotics.** Atypical antipsychotics have been reported to have numerous advantages over typical agents, and have become the standard of care in managing schizophrenia and related psychosis.<sup>21</sup> Until recently, all marketed atypical antipsychotics were only available orally; thus, the depot formulations were all for first-generation (or typical) high-potency antipsychotic agents. It was hypothesized that having a long-acting injectable atypical antipsychotic would ideally combine the benefits provided by this dosage form (improved compliance) with the benefits of using atypical agents (improved tolerability). In October 2003, the US Food and Drug Administration (FDA) agency approved the intramuscular, long-acting preparation of risperidone (Risperdal® Consta®, Janssen-Cilag Inc),<sup>1,3,22</sup> becoming the first long-acting injectable atypical antipsychotic, now available in several other countries. The formulation of long-acting injectable risperidone differs significantly from the ones described above for typical depot antipsychotic formulations, as its final presentation is an aqueous suspension rather than an esterified drug suspended in oil. This novel formulation incorporates risperidone inside a glycolide/lactide matrix and is available as powder microspheres which are reconstituted to the aqueous suspension. After injection, the microspheres undergo gradual hydrolysis, resulting in a slow release of risperidone into the blood stream.<sup>3,22</sup>

**"Short-acting" depot?** Zuclophenixol acetate is a unique injectable antipsychotic agent. Although it is considered a depot formulation, it has a duration

of action of only 48-72 hours.<sup>23,24</sup> This short-acting depot appears to be particularly effective in the treatment of manic relapse, drug-induced psychosis, aggressive psychotic episodes and acute relapse symptoms of chronic schizophrenia.<sup>25</sup> Its use in emergency psychiatry or acute psychotic states is popular, as it obviates the need for repeated intramuscular administration of other injectable antipsychotics or benzodiazepines which have a significantly shorter duration of action, usually requiring administration every 4-6 hours. Clinical guidelines for the use of zuclophenixol acetate injection have suggested that it should be considered for patients who are not neuroleptic-naïve, and recommend it to be prescribed as a treatment course rather than simply an "as required" (prn) medication for acute psychotic symptoms.<sup>26</sup>

**Administration of long-acting injectable antipsychotics.** Long-acting injectable

antipsychotics are administered by deep intramuscular (IM) injection and are usually considered to be quite painful.<sup>19,23</sup> Thus, the need for a meticulous injection technique and using the most appropriate preparation and dose for an individual patient are essential for long-term success. Because injections are painful, less-frequent administration is also desirable.<sup>10</sup> Injections of long-acting risperidone are water based; thus they appear to be less painful than the traditional depot antipsychotic injections.<sup>16,27</sup> This may be useful when reassuring some patients, particularly those who have experienced pain with other depots.<sup>15</sup> The following tips may be used to minimize the pain associated with the administration of long-acting injectable antipsychotic formulations.<sup>20,23,28-31</sup> a) Massage the muscle area overlying the injection site for about 10 seconds before injecting will help in relaxing the muscle. However, do not massage it after the injection.<sup>31</sup> b) Not more than 2-3 ml should be administered at any one site. Also, post-injection muscular discomfort is more commonly associated with more concentrated drugs. Thus, whenever possible, use the preparation with the lowest concentration per ml (for example, Fluphenazine 25 mg/ml or Haloperidol 50 mg/ml preparations). It has been suggested that haloperidol decanoate is probably the most viscous of the depot preparations and, therefore, should not be given in volumes exceeding 3 ml.<sup>15</sup> c) Inject slowly, about 30 seconds per ml is adequate. A faster injection can increase pain.<sup>31</sup> d) Rotate the injection sites. The deltoid's posterior aspect (latitudinally about 1 cm behind the deltoid midline and longitudinally about 5 cm below the acromioclavicular joint) and the lateral gluteus (to avoid stimulating the sciatic nerve that runs down the medial gluteus) are suitable injection sites.<sup>20,27,31</sup> e) Z-track injection technique has been recommended as the most suitable for depot antipsychotics<sup>20,23</sup> as with this method, skin and

subcutaneous tissue are retracted to avoid creating a straight-line needle tract that would allow the ready backflow of injected material. However, this technique may not be essential as the decanoate preparations are viscous enough to prevent significant backflow, provided the injection is slowly administered.<sup>27</sup> f) Consider subcutaneous (SC) administration rather than IM, as it is less painful. Subcutaneous administration may be suitable for fluphenazine decanoate by using a 5/8-inch, 22-gauge needle for patients who fear long needles or are particularly sensitive to pain. Haloperidol decanoate, however, is only suitable for IM administration.<sup>27,31</sup> It is important to note that this route of administration for fluphenazine decanoate is licensed only in the US, Canada, and some European countries.

**General recommendations for the use of long-acting injectable antipsychotics.** Once the decision to prescribe long-acting injectable antipsychotic therapy has been made, following the recommendations outlined below has been suggested in order to achieve optimal therapeutic outcomes. In addition, **Table 1** has been compiled as a guide for clinicians on various aspects of long-acting injectable antipsychotic medications.

**Typical depot antipsychotics.** Prior to initiating treatment with a depot antipsychotic, the patient should first be stabilized on an antipsychotic drug administered orally, following which the transition to depot medication can be made with a decreased potential for side effects. Although no reliable formula yet exists to convert the dose of orally administered neuroleptic to the amount of depot medication that should be administered, the "oral to depot dosing equivalency" proposed in **Table 1** may be used as reference. Consider a test dose if the patient has never been on a depot formulation before.<sup>17</sup> This may help to avoid severe, prolonged adverse effects. However, some extrapyramidal reactions may occur even after several doses have been given.<sup>2,15,18</sup> Some patients may require intermittent short-term use of orally administered anticholinergic medication during the first week following a depot injection. As patients may be at an increased risk of developing extrapyramidal side effects (EPSE) at the time the drug concentration reaches its peak.<sup>13</sup> In general, side effects of depot antipsychotic treatment are comparable to those experienced by patients receiving effective doses of orally administered high-potency neuroleptics.<sup>1,9,13,16,23</sup>

**Long-acting injectable risperidone.** Administration by gluteal injection, using a customized needle (external diameter of 22 gauge, internal diameter of 20 gauge).<sup>32</sup> No test dose is required for patients who have taken oral risperidone in the past. For patients who have never taken oral risperidone, a hypersensitivity challenge

with a test dose of 1-2 mg/day of oral risperidone for 2 consecutive days is recommended before the first injection.<sup>15,33</sup> Ideally, the patient would have been stabilized on oral risperidone first; however, it has been suggested that this approach may not be necessary with long-acting injectable risperidone. A starting dose of 25 mg every 2 weeks is recommended in this population.<sup>16,33,34</sup> If the patient is being switched from an oral antipsychotic which caused EPSE, the anticholinergic agent used to treat the EPSE should be continued until the oral antipsychotic is cleared from the body (in general, about 2-3 weeks), but at a reduced dose. Discontinue the anticholinergic if EPSE are no longer present.<sup>15,33</sup> If the patient is being switched from a typical depot antipsychotic, the anticholinergic medication should be tapered and discontinued over at least one month after depot antipsychotic has been discontinued.<sup>33</sup> Risperidone-naïve patients should be monitored for EPSE, and anticholinergic medication started if deemed necessary.<sup>33</sup> Full release of long-acting injectable risperidone from the gradually hydrolyzing microspheres starts about 3 weeks after the injection. Thus, supplemental oral risperidone is recommended to cover for at least the first 3 weeks of IM injections.<sup>15,33,34</sup>

**Zuclophenixol acetate.** Zuclophenixol acetate is administered by IM injection into the upper outer quadrant of the gluteal region.<sup>25</sup> First dose varies between 25-150 mg, but it is usually recommended to start with 100 mg. The elderly, patients with small stature or neuroleptic-naïve may be started at 25-50 mg. Large young males may require up to 150 mg.<sup>24</sup> A course of injections (100 mg every 48-72 hours) is usually required to settle the patient. At least 24 hours must elapse between injections.<sup>23-25</sup> The recommended maximum dose is 400 mg over 2 weeks or 4 injections (whichever comes first). Then, change to oral medication or to a long-acting injectable antipsychotic.<sup>23-25</sup> Patients should be monitored for common side effects, such as EPSE, sedation and hypotension. All other parenteral antipsychotics should be ceased when patients are receiving a course of zuclophenixol acetate, including all "as required" medications. If extra sedation is required, intramuscular lorazepam or midazolam may be given, but they cannot be mixed in the same syringe.<sup>24</sup> If other parenteral antipsychotics have been administered, it is recommended to wait at least 15 minutes after IV, or 60 minutes after IM injections before commencing the course of zuclophenixol acetate. This time frame will allow adequate assessment of the full response of the parenteral antipsychotic.<sup>25</sup> Zuclophenixol acetate may be mixed in the same syringe with the first dose of fluphenazine decanoate or zuclophenixol decanoate if the depot formulation for these antipsychotics is to be initiated.<sup>24,36</sup>

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Table 1 - A guide for the use of long-acting injectable antipsychotics<sup>2,5,8-10,12,13,22,23,31,33,35-38</sup>

| Characteristics   | Flupenthixol decanoate  | Fluphenazine decanoate   | Haloperidol decanoate  | Pipothiazine palmitate   | Zuclopentixol decanoate   | Risperidone   |
|---|---|--|--|--|---|---|
| Common commercial name  | Fluanxol  | Moderate   | Haldol, Haldol Concentrate   | Piporitl   | Clopixol  | Risperdal Consta  |
| Chemical class  | Thioxanthene  | Piperazine phenothiazine   | Butyrophenone  | Piperidine phenothiazine   | Thioxanthene  | Benzisoxazole derivative  |
| Form  | Dissolved in vegetable oil. Must be hydrolyzed to free flupenthixol. Inactive metabolites | Dissolved in sesame oil. Must be hydrolyzed to free fluphenazine.                      | Dissolved in sesame oil. Must be hydrolyzed to free haloperidol                    | Esterified with palmitic acid in sesame oil (coconut oil). Must be hydrolyzed to free to pipothiazine. | Dissolved in thin vegetable oil (Viscoleo®)   | Free-flowing powder composed of risperidone micro-encapsulated in 7525 polylactide-coglycolide at a concentration of 381 mg risperidone per gram of microspheres. |
| Common strengths supplied   | 20 mg/ml, 1 ml<br>20 mg/ml, 2 ml<br>100 mg/ml, 1 ml                                       | 12.5 mg/0.5 ml<br>25 mg/ml, 1 ml<br>25 mg/ml, 2 ml<br>100 mg/ml, 1 ml                  | 50 mg/ml, 1 ml<br>100 mg/ml, 1 ml  | 50 mg/ml, 1 ml<br>50 mg/ml, 2 ml   | 100 mg/ml   | 25 mg/vial<br>37.5 mg/vial<br>50 mg/vial  |
| Usual dose range  | 20-80 mg  | 12.5-50 mg   | 50-300 mg  | 50-300 mg  | 200-400 mg  | 25-50 mg  |
| Usual duration of action  | 3-4 weeks   | 4 weeks  | 4 weeks  | 4 weeks  | 2-4 weeks   | 2 weeks   |
| Dose equivalency to 100 mg CPZ (approximate)*   | 1.8 mg<br>(40 mg q2/52)   | 0.46 mg<br>(25 mg q2/52)   | 1.1 mg<br>(100 mg q4/52)   | 0.85 mg<br>(24 mg q4/52)   | 2.8 mg<br>(200 mg q2/52)  | Not applicable  |
| Oral to long-acting injectable dosing equivalency   | 10 mg/day = 40 mg every 2 weeks   | 1.2 x total daily oral dose every 1-2 weeks<br>OR: 10 mg/day = 12.5 mg every 1-2 weeks | 20 x total daily oral dose every 4 weeks<br>OR: 10 mg/day = 100-150 mg every month | 17 x total daily oral dose every 4 weeks   | 8 x total daily oral dose every 2 weeks<br>OR: 20 mg/day = 100-200 mg every 2 weeks | Approximately†; 2 mg = 25 mg IM<br>4 mg = 50 mg IM  |
| Onset of action   | 24-72 hours   | 4 hours  | 48-72 hours  | 24-72 hours  | First week after injection  | Approximately 3 weeks after initial injection‡  |
| Peak plasma level   | 4-7 days  | 6-48 hours   | 3-9 days   | 9-10 days  | 4-9 days  | 4-6 weeks   |
| Elimination half-life   | 8 days (after single injection)<br>17 days (multiple dosing)                              | 6-10 days (single injection)<br>14-100 days (multiple dosing)                          | 18-21 days (multiple dosing)   | 15-16 days   | 17-21 days (multiple dosing)  | 3 - 6 days (single dosing)  |
| Time to steady state  | 2 months (10-12 weeks)  | 2 months (6-12 weeks)  | 3 months (10-12 weeks)   | 2-3 months   | 2 months (10-12 weeks)  | About 8 weeks after the first injection   |
| * - Equivalencies must not be extrapolated beyond the maximum dose for the drug, †-No studies available, ‡-Requires oral supplementation for a minimum of 3 weeks after the injection, CPZ - chlorpromazine |   |  |  |  |   |   |

In conclusion, as schizophrenia is a chronic illness, non-adherence to medications is a potential problem that may lead to higher relapse rates which in turn worsens long-term outcomes and leads to poor prognosis. Long-acting injectable antipsychotics are particularly important as they may improve medication adherence and therefore reduce relapse rates and improve long-term outcomes in patients suffering with this chronic condition. When using appropriate doses, long-acting injectable-release formulations have the advantage of causing less variable plasma concentrations and possibly decreased side effects as compared to oral agents. The recent availability of long-acting injectable risperidone is providing patients with the advantage of combining all the benefits of using an atypical antipsychotic in a long-acting formulation. It also provides an alternative treatment for those patients who are hesitant to receive an injection because of the pain involved. As injections of long-acting injectable risperidone are water based, they appear to be less painful than the traditional oil-based formulations. This may be useful when reassuring some patients, particularly those who have experienced pain with other long-acting injectable antipsychotics. Pharmacists have a significant role in facilitating medication adherence. As long-acting injectable antipsychotic use may partially address the issue of non-compliance among schizophrenics, pharmacists need to be knowledgeable to encourage their safe and effective prescribing, and to promote adherence by maintaining patients, their families and caregivers, well informed on this type of antipsychotic therapy.

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