Effectiveness of long-acting injectable antipsychotics: a clinical perspective
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INTRODUCTION
The personal and societal costs of schizophrenia spectrum disorders are immense. Affected individuals may experience positive, negative, and mood symptoms; medical and substance use comorbidities; and cognitive impairment that significantly impair social and occupational functioning. Globally, schizophrenia is a leading cause of years lost to disability, with a particularly large burden among adolescents and young adults.1 Treatment of schizophrenia spectrum disorders aims at improved functioning and recovery across the lifespan, but symptom reduction and relapse prevention are important interim goals. Although antipsychotic medications reduce psychotic symptoms and greatly decrease the risk of relapse, their effectiveness in real-world practice is decreased by non-adherence.2 A meta-analysis of studies that used trained personnel to measure antipsychotic medication adherence found that not ‘regularly taking medications as prescribed’ is prevalent in an average of 41% of participants across 10 studies.3 Despite this high prevalence, providers are often unaware of this issue and generally overestimate medication adherence in their patients.4

Long-acting injectable (LAI) formulations of antipsychotic medications were developed to improve adherence. The first LAIs, fluphenazine enanthate and decanoate, were introduced in 1966 in the context of large-scale deinstitutionalisation of patients with serious mental illnesses and the consequent need for effective community-based treatment. Numerous LAI antipsychotics have been developed and marketed in the meantime. Table 1 lists the LAI antipsychotic medications currently available in the USA and the UK.5 6

LAIs reduce the frequency at which a patient has to decide whether to take medication. Rather than deciding to take a medication once or twice daily, the patient must only decide to have an injection administered once or twice monthly. Pharmacokinetically, LAIs provide a more stable steady-state concentration of medication in the blood compared with daily oral dosing. Clinicians who are considered using LAIs in their practice want to know: Do LAIs improve patient outcomes compared with oral antipsychotics and if so, which outcomes? Are newer LAIs more effective than older ones? Who should receive LAIs? This review will draw lessons from decades of research that compares the effectiveness of LAIs to oral medications and to other LAIs.

LAIS VERSUS ORAL ANTIPSYCHOTIC MEDICATIONS: ADHERENCE
Numerous researchers have examined whether LAIs improve adherence as compared with oral medications, but there is no definitive answer. While LAIs decrease how often a patient has to decide whether to take a medication, they do not eradicate adherence issues, as patients may choose to discontinue the monthly or bimonthly injections.

Observational studies, though subject to confounding, provide suggestive evidence that LAIs improve medication adherence in routine practice.7–11 For example, Brnabic et al12 conducted a post hoc analysis of a prospective observational study that collected data at 31 international sites. The study matched 40 participants taking an LAI to an equal number taking an oral antipsychotic medication. The study found that compared to those treated with LAIs, twice as many on oral medications switched, augmented or discontinued their medications.

Randomised controlled trials (RCTs), however, have not found improved adherence with LAIs.13–19 A systematic review and meta-analysis by Leucht et al20 identified five RCTs that reported results on adherence and found no significant difference in adherence between those on LAIs and those on oral medications, although adherence was typically not measured rigorously. The methodological differences between observational studies and RCTs that may explain these conflicting findings are described below.

LAIS VERSUS ORAL MEDICATIONS: EFFECTIVENESS
The literature on LAIs and relapse prevention is also conflicting, as illustrated by two meta-analyses by the same research group. The first meta-analysis in 2011 collected outpatient RCTs that compared LAIs with oral antipsychotic medications and lasted for at least 12 months (10 studies, n=1700).20 The analysis found that patients on LAIs are 30% less likely to relapse compared with those on oral antipsychotic medications. This translates to a number needed to treat of 10. The second meta-analysis in 2014 used a broader set of inclusion criteria, including inpatient and outpatient studies of at least 6-month duration, and included two new large studies that did not find an overall advantage for LAIs over oral medications. This will be discussed below.21 Contrary to the earlier study, this second meta-analysis (21 studies, n=5176) concluded that LAIs did not significantly reduce rates of

Table 1 Long-acting antipsychotic injectable medications available in the USA and the UK5 6

<table>
<thead>
<tr>
<th>Medication</th>
<th>Half-life (days)</th>
<th>Starting dose (mg)</th>
<th>Second dose (mg)</th>
<th>Maintenance dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole extended release</td>
<td>29.9–46.5</td>
<td>400</td>
<td>400 (4 weeks later)</td>
<td>300–400 every 4 weeks</td>
</tr>
<tr>
<td>Flupenthixol decanoate</td>
<td>21</td>
<td>20 mg</td>
<td>20–40 mg (7 days later)</td>
<td>50–300 every 2–4 weeks</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>6–10</td>
<td>12.5</td>
<td>12.5–25 (6–14 days later)</td>
<td>12.5–50 every 2–3 weeks</td>
</tr>
<tr>
<td>Haloperidol decanoate</td>
<td>21</td>
<td>50</td>
<td>50–100 (3–28 days later)</td>
<td>50–200 every 3–4 weeks</td>
</tr>
<tr>
<td>Olanzapine pamoate/embonate</td>
<td>30</td>
<td>210–300</td>
<td>210–300 (2 weeks later)</td>
<td>150–300 every 2 weeks or 300–405 every 4 weeks</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>25–49</td>
<td>234</td>
<td>156 (7 days later)</td>
<td>39–234 every 4 weeks</td>
</tr>
<tr>
<td>Pipotiazine palmitate</td>
<td>15</td>
<td>25 mg</td>
<td>25–50 mg (4–7 days later)</td>
<td>50–100 every 4 weeks</td>
</tr>
<tr>
<td>Risperidone microspheres</td>
<td>3–6</td>
<td>25</td>
<td>25–50 (2 weeks later)</td>
<td>25–50 every 2 weeks</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate</td>
<td>19</td>
<td>100 mg</td>
<td>200–500 mg (7 days later)</td>
<td>200–500 mg every 1–4 weeks</td>
</tr>
</tbody>
</table>
relapse compared with oral antipsychotic medications, except in studies that used ‘first-generation’ antipsychotic LAIs and in studies published in 1991 or earlier. The authors postulate a number of reasons for the superiority of LAIs in these two subgroups, including changes over the decades in definitions and thresholds for relapse, differences between older and newer medications, and recent trends towards the use of lower doses of antipsychotic medications. Since there are striking differences in results between the two meta-analyses, the authors reanalysed the newer data using the same criteria as the first study. By now including the two large additional trials that lasted for more than 12 months and found no advantage for LAIs, this updated analysis showed no significant difference in relapse rates between LAIs and oral medications.

The two recent RCTs that were added to the earlier meta-analysis used slightly different approaches to compare the effectiveness of LAIs with oral medications in preventing relapse. The PROACTIVE study was a double-blind RCT at eight clinical sites that randomised 305 patients with schizophrenia or schizoaffective disorder and a history of an exacerbation in the past year to LAI risperidone or to a newer oral antipsychotic medication of their physician’s choice. The primary outcomes were rates of relapse and hospitalisation over 30 months. In this broad sample of patients, the PROACTIVE trial found no significant difference between the LAI and oral groups in the primary outcomes of time to first relapse or time to first hospitalisation. Secondary analyses found that patients in the LAI group had greater improvements in some types of psychiatric symptoms.

In their discussion of the PROACTIVE study, Buckley et al highlighted methodological issues that may affect the comparative effectiveness research on LAIs versus oral antipsychotics. The authors noted that frequent study contacts, access to free study medications, implicit or explicit efforts to monitor adherence, and patient selection may lead to improved adherence to all medications in these studies. These factors, which are present in RCTs but not in routine practice, could diminish differences between LAIs and oral medications with respect to adherence and relapse prevention compared with what would be expected in usual community care.

The issue of patient selection deserves special focus. Clinical trials, due to the importance of informed consent, select patients who are willing to be enrolled in a clinical trial that involves medications, to have their adherence monitored, and to attend frequent appointments. This population may have greater insight into their illness, greater engagement with their providers, and less non-adherence than the usual patients whom providers would consider for LAI medications. In short, if LAI clinical trials select patients who are relatively adherent and stable, then it is possible that LAIs might have a different effect in the real-world patients with unstable illness who are often prescribed LAIs.

To address the issue of patient selection, Rosenheck et al conducted a 2-year study in the US Veterans Health Affairs system that specifically selected patients with unstable illness by including only those deemed at risk of psychiatric hospitalisation. The double-blind RCT included 369 individuals with schizophrenia who were assigned to LAI risperidone or the clinician’s choice of oral antipsychotic medication. Similar to the PROACTIVE study, this study found no significant differences between LAIs and oral drugs in rates of psychiatric hospitalisations, psychotic symptoms, quality of life or social functioning. Kirson et al used meta-analyses to examine the influence of study design on the results of LAI versus oral antipsychotic medication comparative effectiveness research. The authors examined 12 studies that included 19 different LAI–oral medication combinations. They found no superiority of LAIs over oral medications in RCTs, but found significant benefits of LAIs over oral formulations in observational studies. To explain these findings, the authors highlight the tension between methodological rigour and real-world generalisability in RCTs and observational studies, respectively. RCTs include methods to standardise the conditions between the LAI and oral medication arms such as adherence monitoring and frequent appointments. Kirson et al also describe a possible ‘Hawthorne effect’—where behaviour is affected by the awareness of being observed—that would lead study subjects to have greater adherence to oral medications than they would have in real-world practice because of their knowledge that their adherence is being monitored. The authors conclude that these aspects of RCTs attenuate the advantages of LAIs over oral medications that are seen in observational studies.

Another issue is stage of illness. Some have argued that LAIs may be most beneficial when used for people experiencing a first episode of psychosis, when knowledge about the illness is low and ambivalence about medications is high. A large-scale study, using Finnish national health registries of 2588 participants after a first hospitalisation for schizophrenia, compared LAIs with oral antipsychotic medications in routine practice conditions. The authors found that those on LAI haloperidol, risperidone or perphenazine were significantly less likely to discontinue their medication compared to those on oral versions of these medications. When these results were pooled, they found that those on LAIs were 59% less likely to discontinue their medication up to 7 years of follow-up and 36% less likely to be hospitalised within 2 years. Interestingly, these benefits have also been recently reported in a single-site RCT (n = 83) that compared oral with LAI risperidone among those with recent-onset schizophrenia. In this study, those treated with the LAI had significantly lower rates of relapse (5% vs 33%) and were four times less likely to be hospitalised compared with those on the oral formulation. These two studies, a large-scale naturalistic study and an RCT, agree in their observations of substantial benefits of LAIs over oral medications in those with recent-onset schizophrenia.

OLDER LAIS VERSUS NEWER LAIS

Beginning with clozapine in 1989, a new wave of oral antipsychotic medications that came to be known as second-generation or atypical antipsychotics was released. The initial hope was that the newer medications would be more efficacious than the older antipsychotic medications. However, a considerable amount of research has called into question this initial assumption. For example, the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) schizophrenia trial found that several newer antipsychotic medications were not more effective than the older antipsychotic medication perphenazine. Other comparative effectiveness trials and meta-analyses comparing newer with oral antipsychotic medications have shown similar results. Research has shown that some of the newer antipsychotics are associated with a lower incidence of neurological side effects as well as high rates of metabolic adverse effects compared with older medications. Additionally, increasing evidence suggests that there is considerable variability among the older and newer drugs, which calls into question the validity of the ‘generation’ categories.

Few studies have looked at how newer LAIs are compared with older LAIs. Rubio et al examined the effects of the drugs on substance use outcomes in an RCT of 115 individuals with schizophrenia and a substance use disorder. Participants were randomly assigned to risperidone LAI or zuclopenthixol LAI on an open-label basis for 6 months. The authors found those on LAI risperidone to have significantly fewer positive urine drug tests and significantly lower ratings on a psychotic symptom scale (positive and negative syndrome scale, PANSS) compared with those on zuclopenthixol LAI.

In contrast, a 2013 study by Lammers et al found no significant difference between LAI risperidone and ‘first-generation’ LAIs. The authors conducted a single-site, outpatient retrospective comparative effectiveness study comparing those with schizophrenia spectrum illness on
risperidone LAI (n=70) versus ‘first-generation’ LAIs (n=102). Lammers et al found no significant differences between the groups for the primary outcomes of time to treatment discontinuation or hospitalisation, but did find that a higher incidence of extrapyramidal symptoms in patients on ‘first-generation’ LAIs.

Two recent multisite RCTs have taken on this question of newer versus older LAIs. A small trial by Covell et al enrolled patients on haloperidol decanoate (n=40) or fluphenazine decanoate (n=22), and then randomised these patients to remain on their current LAI or switch to risperidone LAI. The study period was for 12 months, six of which followed a study protocol followed by 6 months of more naturalistic observation. The primary outcome was time to treatment discontinuation, with a number of secondary outcomes. The authors found that those randomised to switch to risperidone LAI had higher rates of treatment discontinuation and significantly greater increases in weight and prolactin levels.

McEvoy et al conducted a large prospective comparative effectiveness trial of the newer LAI paliperidone palmitate to haloperidol decanoate. A Comparison of LAI Medications (ACLAIMS) was a double-blind RCT at 22 clinical sites. The patients (n=311) received LAI paliperidone or haloperidol monthly for as long as 24 months. Inclusion criteria explicitly required a history of medication non-adherence and/or substance use, both of which are risk factors for the primary outcome of efficacy failure. The authors defined efficacy failure as “a psychiatric hospitalisation, a need for crisis stabilisation, a substantial increase in frequency of outpatient visits, a clinician’s decision that oral antipsychotic could not be discontinued within 8 weeks after starting the long-acting injectable antipsychotics, or a clinician’s decision to discontinued the assigned long-acting injectable due to inadequate therapeutic benefit.” The ACLAIMS trial found no significant difference in efficacy failure between those taking paliperidone palmitate and haloperidol decanoate. However, those in the paliperidone palmitate group had higher serum prolactin levels and gained weight, while the haloperidol decanoate group experienced more akathisia, used more antiparkinsonian medications and lost weight. In summary, ACLAIMS did not find that the newer LAI was superior to the older LAI, but found significant differences in side effects.

CONCLUSIONS

While researchers debate the most appropriate research design (RCTs vs observational studies) and whether to focus on all-comers or those with risk factors for medication non-adherence, clinicians still need answers to the questions posed earlier: Do LAIs improve patient outcomes compared to oral antipsychotics and if so, which outcomes? Are certain LAIs more effective than others? Who should receive LAIs? (Box 1).

Although the evidence is conflicting and weaker than expected, we believe LAIs can play an important role in improving adherence and preventing hospitalisations. LAIs should be considered in those with risk factors for medication non-adherence, for example a history of non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medications and poor insight. By decreasing the number of times a patient has to decide to take a medication, and by promptly alerting clinicians and other providers to the onset of non-adherence when a patient misses a scheduled injection, LAIs are a useful part of the antipsychotic formulary.

Research to date is clear in showing no efficacy or overall effectiveness advantage of newer LAIs (risperidone and paliperidone) over older LAIs. We recommend that clinicians consider each patient’s preferences, prior experience with antipsychotics, health status and the specific side-effect profiles of the medications when selecting an LAI antipsychotic.

Box 1: Summary of clinical perspective on long-acting injectable (LAI) antipsychotic medications

- Consider LAIs for patients with recent-onset schizophrenia and those with risk factors for medication non-adherence: history of non-adherence, severe symptoms, comorbid substance use, cognitive impairment, ambivalence or negative attitudes towards medications, and poor insight.
- When selecting an LAI, consider a patient’s preferences, health status, experience with prior antipsychotic medication trials, and the side-effect profiles of different medications.
- The effectiveness of newer LAIs and older LAIs is similar.
- Clozapine rather than LAIs should be tried for those whose clinical instability is due to treatment-resistant illness rather than medication non-adherence.

Since recent-onset psychosis is an important opportunity to prevent relapses and clinical deterioration, LAIs may have an important role to play in this situation. However, we caution that this is also a time to use medications judiciously to help ensure that an individual’s early encounters with medications are positive. For example, because the dosages of LAI antipsychotics are not immediately changeable, they are less convenient than oral medications when a dose reduction is indicated due to side effects. As people experiencing recent-onset psychosis are particularly sensitive to side effects, this is a disadvantage of LAIs in this situation.

Should LAIs be used for those with treatment-resistant schizophrenia? If medication non-adherence is not known or suspected, then the answer is no. For true treatment resistance, in which patients take but do not adequately benefit from antipsychotics, clozapine is the evidence-based choice.

In summary, in spite of equivocal evidence to support any advantages over oral medications, LAIs have a legitimate and potentially important role in clinical practice. We strongly recommend that clinicians include LAI antipsychotics in their armamentarium and offer them to patients with known or suspected poor adherence, and consider them for patients with recent-onset psychosis. However, in all the cases medications and medication adherence are only part of a comprehensive treatment plan to help patients achieve their goals.

Competing interests None.

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