

Editorial

Antipsychotic long-acting injections: mind the gap

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Summary

Long-acting injections of antipsychotic medication (or depots) were developed specifically to promote treatment adherence and are a valuable option for maintenance medication in psychotic illnesses. Approximately 40–60% of patients with schizophrenia are partially or totally non-adherent to their antipsychotic regimen, but only 30% or less are prescribed a long-acting injection. The use of such injections has declined in recent years after the introduction of second-generation (atypical) oral antipsychotic drugs. Research shows that possible reasons for this decline include concerns that may be based on suboptimal knowledge, as well as an erroneous assumption that one's own patient group is more adherent than those of one's colleagues. Research on attitudes has also revealed that psychiatrists feel that long-acting injections

have an 'image' problem. This editorial addresses the gaps in knowledge and behaviour associated with possible underutilisation of these formulations, highlighting the role of stigma and the need for more research.

Declaration of interest

M.X.P. and A.S.D. have been reimbursed for attendance at scientific conferences and have received consultation fees from Janssen-Cilag and Eli Lilly. They have also received investigator-initiated grants from Janssen-Cilag and Eli Lilly and have previously worked on two clinical drug trials for Janssen-Cilag. M.T. has received hospitality and advisory or speaker fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Janssen-Cilag within the past 5 years.

First-generation antipsychotic (FGA) long-acting injections or depots were developed in the 1960s and were specifically aimed at promoting treatment adherence in people with chronic schizophrenia, thereby enhancing relapse prevention.^{1–4} Most patients with schizophrenia (about 80%) recover from their first episode of illness. Of these, approximately 80% then go on to relapse within 5 years.^{5,6} Worse still, approximately 5–10% of people with schizophrenia are thought to complete suicide.^{7,8}

It is timely to examine the issues around the use of long-acting injections (LAIs) in the maintenance treatment of schizophrenia, as we now have sufficient experience of the first second-generation antipsychotic LAI – risperidone LAI – which has been available since 2002. Another second-generation LAI has been licensed and a third is in process.⁹ This supplement contains the first systematic review of the data surrounding the use of injectable risperidone,⁹ as well as providing valuable critical updates on diverse LAI-related areas such as pharmacology, attitudes to LAIs, FGA–LAIs compared with oral FGA medications, LAIs and community compulsion, the nursing perspective and a snapshot of English prescribing patterns.

Utilisation rates

Long-acting injection utilisation rates vary greatly internationally, with lower rates seen in France and the USA.¹⁰ In countries such as Australia and the UK, the higher rates of use are currently approximately 30% of patients with schizophrenia,⁶ and only a minority of these individuals are subjected to compulsory treatment. This is confirmed by recent data from Scotland, which revealed that of 2323 patients with schizophrenia, 34% were prescribed an LAI, of whom 15% were detained (further information available on request). However, even in these countries, the rate of use declined considerably following the introduction of the oral second-generation antipsychotics (SGA–orals) in the 1990s.^{11–15} Subsequently the knowledge base and skills associated with prescribing FGA–LAIs arguably declined, leaving a younger generation of psychiatrists at risk of diminished experience. In turn this may further add to the decline in LAI utilisation. For SGA–LAIs there are other restraints, and perhaps the most common of these is their high purchase cost. The cost differential between FGA–LAIs and SGA–LAIs is large. Financial cost does

remain an important concern and in certain areas, use has been restricted by those holding the medication budget. Even if others consider depot utilisation rates in the UK to be at a reasonable level already, it remains true that evidence of regional variation exists.

According to systematic reviews approximately 40–60% of patients with schizophrenia are known to be partially or totally non-adherent to oral antipsychotic medication.^{16–18} Long-acting injections are indicated where medication adherence is a cause for concern. Thus it is argued by some that it might seem reasonable to consider such injections for approximately half of patients with schizophrenia, and Valenstein *et al* reported that 61% of patients with schizophrenia had difficulties with adherence at some point over a 4-year period.¹⁹ However, the dearth of long-term studies comparing outcomes between oral medication and long-acting injections remains an important cautionary note. The studies that do exist are old, of poor methodological quality, short in follow-up duration and usually underpowered. When an LAI is prescribed, attendance in clinic for a regular injection every 1–6 weeks guarantees delivery of medication and assists in the process of regular review.²⁰ Covert non-adherence can be overcome as it is immediately obvious to the clinician when the patient has not been given an injection.²¹ This early detection of non-adherence also facilitates the opportunity for early contact with the patient, and discussion about the reasons for non-adherence, including unintentional forgetfulness and disorganisation.

Intentional and overt non-adherence with LAIs does, of course, also occur. However, findings of two systematic reviews on LAIs suggested a non-adherence rate of only 24% (range 0–54%).^{22,23} Three subsequent studies investigated patients who remained on LAIs for 12 months. Heyscuse *et al* reported an overall 'adherence proportion' of 0.96 (the adherence proportion is the ratio of kept appointments to scheduled appointments for LAI administration).²⁴ In a later study 26% were reported to have poor adherence, based on the duration of missed injections.²⁵ Most recently, Shi *et al* calculated the mean medication possession ratio (cumulative number of days covered by depot divided by 365 days) to be 91% for patients receiving FGA–LAIs.²⁶ This implies that adherence rates are better with LAIs than with oral formulations. However, it seems that LAIs have lower than

expected prescribing rates, i.e. 28–36% of patients with schizophrenia,^{27–29} but the prescribing practice of an individual psychiatrist is subject to many factors (see Appendix).^{2,30,31}

Allowing for the differences between FGA–LAIs and SGA–LAIs, some believe that LAIs as a group are underused.^{32–34} It should be noted that LAIs are unable to prevent relapse completely; even in clinical trials there is an irreducible 20–25% of patients who relapse despite receiving an LAI.³⁵ If patients discontinue LAI treatment their risk of relapse increases, but if a patient relapses despite regular injections then non-adherence can be safely excluded as the cause.¹⁴ Although the evidence base for examining the potential gains of LAI use over oral preparations remains inadequate,^{29,4,35} clinicians can use this as a legitimate reason for not increasing LAI usage. Furthermore, the relative merits of prescribing an SGA–LAI over an FGA–LAI are unknown. Perhaps surprisingly, no prospective head-to-head double-blind randomised controlled study has been conducted to date, although recent evidence and debate have suggested that the efficacy of SGA–orals is not superior to that of FGA–orals.^{36–38} That said, a good study of LAIs would be of long duration since the most salient outcomes go beyond efficacy in terms of symptom control and extend to relapse prevention, rehospitalisation and mortality. Until such studies are done, clinicians are likely to choose one LAI over another according to preference of side-effect profile for each individual patient, and perhaps cost.

Long-acting injections and polypharmacy

A recurring theme in this supplement is antipsychotic polypharmacy and the use of LAIs.^{3,6,39} We note that antipsychotic polypharmacy is more common in those prescribed an LAI.⁶ Is such polypharmacy always a ‘bad thing’, and are there circumstances in which it makes good pharmacological sense to use this approach?⁴⁰ Certainly it is a part of our prescribing heritage,¹¹ and the practice is common in many countries.

There may be a perception that the side-effects of LAIs are worse than those of oral preparations of the same drug, contrary to the available evidence,^{2,4,33,39} and this belief may be fuelled by the use of polypharmacy. It may also be that when clozapine fails, owing to lack of efficacy or non-adherence, prescribers look to LAIs to provide adherence and then add another oral antipsychotic (i.e. polypharmacy) to attempt to compensate for single-agent lack of efficacy in known treatment resistance.

Stigma and LAIs: what’s in a name?

It has been noted that LAIs may have an ‘image problem’.³³ This is especially true for FGA–LAIs. Many proponents of SGA–LAIs have attempted to dodge this by rejecting the term ‘depot’, which was perceived to be stigmatising, in favour of ‘long-acting injection’, although some have argued that a new word had to be used anyway because of the different nature of the drug, implying that it was not a ‘true’ depot. In 2002 the belief that second-generation antipsychotics were superior in all ways – including efficacy, adherence and side-effect profile – was common.^{37,41,42} Those with a vested interest seemed to work hard to deter prescribers from associating SGA–LAIs with their older FGA–LAI counterparts. Choosing a collective term for this group of medications was difficult. Underpinning this whole argument was the debate about how to overcome the potential for discrimination associated with the word ‘depot’, as it was felt that it was perceived by some (but not all) clinicians as stigmatising. After debate, the collective term ‘long-acting injection’ was chosen to cover both first- and second-generation antipsychotics in this formulation, with the

subcategories of FGA–LAI and SGA–LAI. This was partly an attempt to move away from stigmatising stereotypes, and also to promote therapeutic optimism for a population for whom hope can be all too scarce.

Conclusion

The problems facing psychiatrists, patients and their carers 40 years ago, when FGA–LAIs were first introduced,³ remain observable today. Non-adherence to antipsychotic medication is still a key concern, particularly with regard to relapse prevention. Approximately 50% of patients with schizophrenia are partially or totally non-adherent to their antipsychotic regimen but only 30% or less are prescribed an LAI, although of course injections only have a chance to work if they are accepted. Heres *et al* inform us that, as psychiatrists, we grossly underestimate the numbers of our own patients who are non-adherent,⁴³ and anxieties about LAIs are in some cases based on suboptimal knowledge.^{30,33} Thus, psychiatrists may not even think to consider discussing with their patients the option of prescribing an LAI. This situation is complicated by the fact that LAIs are unable to prevent relapse completely,³⁵ and there is also a virtual absence of high-quality head-to-head comparisons of oral and LAI antipsychotic formulations. Naturalistic studies of risperidone LAI report attrition rates higher than those seen in randomised controlled trials and the reasons for this are not fully understood. These are gaps in knowledge and behaviour that should concern us.

Long-acting injection prescribing will evolve in the future, and associated clinical guidelines will require regular updates,⁴⁴ as seen in the recent update of the National Institute for Health and Clinical Excellence (NICE) guidelines for schizophrenia.⁴⁵ This guidance states that LAIs should be considered for those who prefer such treatment, and when avoidance of covert non-adherence is a clinical priority. It is conceivable that LAI prescribing will increase in the coming years as more SGA–LAIs will be made available, and the increasing use of compulsory community treatment orders may contribute to this.⁴⁶ The evidence base supporting (or otherwise) LAIs needs to be substantially updated and improved so that the ‘gaps’ will diminish and more appropriate use of LAIs can occur. Perhaps the most critical issue to be addressed is the need for definitive evidence from randomised controlled trials as to whether or not SGA–LAIs are superior, in terms of clinical outcomes, to their respective oral formulations. This needs to be considered particularly in those who have a history of prior oral non-adherence. Surprisingly, these studies have still not been conducted for risperidone LAI, and we urge industry and other funding bodies to consider this a true priority. Other new studies might address FGA–LAIs *v.* SGA–LAIs (efficacy and tolerability), the use of ‘real world’ outcomes such as mortality and relapse rates, and the nature of the clinician–patient interaction when LAIs are used.

We also hope that the use of long-acting injections occurs within the context of a therapeutic relationship, where both clinician and patient are working in collaboration, and the option of an LAI is discussed openly and not merely as a last resort. Thus, informed patient choice for LAIs may truly occur and the adverse image and associated stigma of this formulation can be reduced.

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Appendix

Long-acting injections v. oral formulations

Advantages of long-acting injections over oral formulations

- Easier early detection of relapse, improved relapse prevention and reduced rehospitalisation rates
- More predictable and stable serum concentrations for first-generation antipsychotic long-acting injections (FGA-LAIs)
- Enhanced consistency between the drug prescription and drug delivery of the active drug
- Less steady-state interpatient blood level variability for a given dose
- Reduced risk of accidental or deliberate self-poisoning
- Facilitated differentiation between lack of efficacy and poor adherence

Advantages of oral formulations over LAIs

- Possibility of rapid discontinuation enables rapid response to serious adverse side-effects
- Patient has enhanced sense of autonomy
- Patient perceived as being at less risk of stigma and discrimination
- Less frequent attendance at clinic is possible (as can self-administer medication)

Clinicians' fears and expectations

- Psychiatrists' beliefs that LAIs are associated with worse side-effects than the equivalent drug in its oral preparation, despite lack of evidence to suggest this
- Concerns regarding patients' acceptance of LAIs, yet patients already on this formulation often prefer it
- Concerns regarding stigmatising effect of prescribing an LAI, although overcoming stigma and discrimination is not best dealt with by avoidance
- Concerns regarding reduced patient autonomy in the context of LAI utilisation, but this could be more to do with the fact that patients are less involved in decision-making at the point that LAIs are prescribed and it is this that needs to be addressed rather than the use of LAIs *per se*
- Concerns regarding nursing staff involvement in administering LAIs and updating training and reducing time pressures on staff so that they can adequately and routinely monitor symptoms and side-effects
- Budget holders giving preferential treatment to more fashionable early intervention services and medication rather than maintenance services and medication
- Prescriber knowledge and experience about LAIs may be suboptimal, resulting in use of inadequate dose and/or premature discontinuation of treatment with subsequent poor clinical outcomes

(Adapted from Patel & David.²)

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