

A review of the efficacy and tolerability of antipsychotic long-acting injections

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The formulation of long-acting injections (LAIs) as a method of delivering antipsychotics can be used to improve adherence, particularly in those unintentionally non-adherent. Here, the authors review the efficacy and tolerability of first-generation antipsychotic (FGA) and second-generation antipsychotic (SGA) LAIs, analyse drug cost, give guidance on initiation regimens for SGA LAIs and discuss the future for these drugs.

Antipsychotics are the mainstay of treatment in schizophrenia and are used to treat acute psychotic symptoms as well as protect against relapse. The National Institute for Health and Care Excellence (NICE) recommends that oral antipsychotics

should be offered first line to individuals with newly-diagnosed schizophrenia in conjunction with psychological interventions.¹

Non-adherence with antipsychotic medication remains high in those with schizophrenia; only 10 days after discharge from hospital up to 25% are partially or non-adherent, rising to 50% at one year and 75% at two years.² First-generation (typical) antipsychotic depots and second-generation (atypical) antipsychotic LAIs may be used to try to improve adherence and so to reduce the risk of relapse, although evidence for this is conflicting.

FGA depots are oil-based formulations consisting of the antipsychotic esterified to a decanoate, which is dissolved in an oily vehicle. Once injected into the muscle, it forms a depot from where it is slowly released. SGA LAIs are formulated differently in that they are all aqueous suspensions (not oil-based) that slowly dissolve over time following injection into the muscle. For the purposes of this article, both the FGA depots and SGA LAIs will be referred to as LAIs.

In 2011, a meta-analysis comparing LAIs with oral medication demonstrated that those treated with LAIs were 30% less likely to relapse compared to those on oral antipsychotics,³ and a further study demonstrated that LAIs significantly lowered the risk of rehospitalisation.⁴ More recent studies concluded that LAIs did not significantly reduce relapse rates or time to hospitalisation.^{5,6} However, methodological issues may have affected study results. Buckley *et al*⁶ noted that frequent contact with study participants, access to trial medication and patient selection may have contributed to the inability to detect differences between the LAI and oral antipsychotics in time to first relapse or hospitalisation. Despite conflicting evidence, LAIs play an important role in improving adherence with antipsychotics, preventing relapse and hospitalisation. NICE recommends depots/LAIs following an acute episode where this is the patient's preference or where avoiding covert non-adherence

Drug	Dosing regimen	Cost per 28 days	Annual cost
FGA LAIs*			
Flupentixol decanoate	60mg 2-weekly	£7.61	£98.98
	300mg 2-weekly	£19.52	£253.73
Fluphenazine decanoate	100mg 2-weekly	£8.75	£227.40
Haloperidol decanoate	200mg 4-weekly	£20.21	£262.70
Zuclopentixol decanoate	400mg 2-weekly	£11.90	£154.67
	600mg weekly	£17.85	£232.00
SGA LAIs			
Aripiprazole**	400mg monthly	£220	£2,645
Olanzapine pamoate	150mg–300mg 2-weekly	£223–£445	£2894–£5789
	300mg–405mg 4-weekly	£223–£286	£2894–£3712
Paliperidone palmitate**	25mg–150mg monthly	£184–£393	£2207–£4711
Risperidone	25mg–50mg 2-weekly	£153–£286	£2072–£3712

*First-generation antipsychotic (FGA) costs based on commonly prescribed doses in clinical practice

**Annual cost based on 12 injections per year (ie once-monthly dosing).

SGA = second-generation antipsychotic

NB 13 injections of paliperidone palmitate LAI are given in the first year (due to the two loading doses) adding to the cost

NB Paliperidone palmitate 25mg LAI is not available in the UK

Table 1. Cost comparison of antipsychotic long-acting injections (LAIs)¹²

to antipsychotic medication is a clinical priority.¹ LAIs also have some clear advantages due to assurance that medication will be administered and the opportunity for health-care professionals to step in immediately if patients stop treatment.³ NICE does not make specific recommendations on the choice of LAI.¹ The patient's preference and attitudes towards the mode of administration and organisational procedures should be taken into account alongside consideration of likely benefits and possible side-effects, including metabolic (weight gain, diabetes), extrapyramidal (akathisia, dystonia, dyskinesia), cardiovascular (prolonged QT interval) and hormonal (hyperprolactinaemia).¹

Comparison of efficacy and tolerability of first- and second-generation LAIs

Several studies have shown that there are not many important differences between oral FGAs and SGAs in terms of efficacy and tolerability.^{7,8} Few studies have compared first- and second-generation LAIs in schizophrenia and related disorders. Lammers *et al*⁹ found no significant difference between risperidone LAI and first-generation LAIs and a comparison study of the effectiveness of depot antipsychotics in routine clinical practice found no LAI was superior in all outcomes measured.¹⁰ More recently, the ACLAIMS study¹¹ compared the effectiveness of paliperidone palmitate LAI (second generation) with haloperidol decanoate LAI (first generation) in 311 patients. The study concluded that there was no evidence that paliperidone palmitate was superior to haloperidol decanoate in terms of preventing efficacy failure, however, there was a difference in adverse effects.

Paliperidone palmitate was associated with more weight gain and higher mean prolactin levels. There was no statistically significant difference in the ratings of the severity of abnormal involuntary movements and parkinsonism or in the incidence of tardive dyskinesia. However, haloperidol was associated with significantly larger increases in ratings of the severity of akathisia. More medications to manage akathisia and parkinsonism were used in the haloperidol decanoate group.

Although there are few advantages of one LAI over another in terms of efficacy and tolerability the second-generation LAIs are significantly more expensive. See Table 1 for cost comparisons.¹²

First-generation antipsychotic LAIs

FGA LAIs were developed in the 1960s and are generally given as intramuscular (IM) injections, usually into the gluteal muscle, every two to five weeks. There are few clear advantages of one FGA LAI over another in terms of efficacy and tolerability, with the exception of zuclopenthixol decanoate which may be slightly more efficacious in preventing relapses.¹³ There are now four FGA LAIs available in the UK, including flupentixol decanoate, zuclopenthixol decanoate, haloperidol decanoate and fluphenazine decanoate (Table 2). Pipotiazine palmitate was discontinued in 2015 due to a worldwide shortage of the active ingredient. For all FGA LAIs a small test dose should be given initially to assess for sensitivity to extrapyramidal side-effects (EPSEs) (*eg* acute dystonic reactions) as well as possible adverse reactions to the base oil. Doses and dosing intervals should be adjusted and individualised to the patient after an

FGA LAI	Formulation	Test dose for adults*	Usual dose range**	Usual dosing interval	Licensed injection site (IM)***
Flupentixol decanoate (Depixol®)	Oily injection (vegetable oil)	20mg	12.5–400mg weekly	Every 2–4 weeks	Outer buttock or lateral thigh
Fluphenazine decanoate (Modecate®)	Oily injection (sesame oil)	12.5mg	6.25–50mg weekly	Every 2–5 weeks	Gluteal
Haloperidol decanoate (Haldol®)	Oily injection (sesame oil)	25mg****	12.5–75mg weekly	Every 4 weeks	Gluteal
Zuclopenthixol decanoate (Clopixol®)	Oily injection (vegetable oil)	100mg	100–600mg weekly	Every 2–4 weeks	Outer buttock or lateral thigh

*After the test dose, wait 4–10 days before giving the next dose
 **Doses stated are for adults, lower doses may be required for older adults
 ***See Figure 1
 ****Not stated by manufacturers

Table 2. First-generation antipsychotic long-acting injections (FGA LAI)^{12,14}

adequate period of assessment of efficacy and tolerability, allowing sufficient time to reach steady state (approximately 8–12 weeks). FGA LAIs are significantly cheaper in comparison with the newer SGA LAIs (Table 1).

Second-generation antipsychotic LAIs

There are now four SGA LAIs available (Table 3), and in the UK three are given monthly, including paliperidone palmitate, aripiprazole and olanzapine pamoate. The fourth, risperidone LAI, is a fortnightly LAI. However, it is now used less frequently in practice due to the practical advantages that paliperidone palmitate (an active metabolite of risperidone) offers.

Risperidone LAI (Risperdal Consta®)

Risperidone LAI was the first SGA LAI to be developed, in 2002. It is indicated for maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics.¹⁵ It is a complex pharmaceutical formulation consisting of risperidone coated in a polymer; immediately prior to use this powder is mixed with an aqueous solution to form a suspension of microspheres for injection. After the first injection is given there is a very small initial release of risperidone (<1%) followed by a lag phase of three weeks.¹⁵ The main release does not start until three weeks, therefore requiring oral antipsychotic supplementation for at least the first three

SGA LAI	Initiation regimen	Dose and range frequency*	Licensed injection site (IM)**	Time to peak (days) ¹⁴	Half-life (days) ¹⁴	Time to steady state (weeks) ¹⁴	Advantages	Disadvantages
Risperidone (Risperdal Consta®)	Tolerability and response to oral risperidone required. Initial dose based on oral risperidone dose. Requires oral supplementation for at least 3 weeks	25–50mg 2-weekly	Deltoid or gluteal	35	4	~8	Prefilled syringe	Requires refrigeration. 3-week time lag until drug released (requires oral supplementation at initiation) 2-weekly administration
Paliperidone palmitate (Xeplion®)	Tolerability and response to oral risperidone required. Two loading doses required: Day 1 and Day 8	25–150mg monthly	Loading doses: deltoid only Maintenance doses: deltoid or gluteal	13	29–45	~20	Prefilled syringe Flexibility in dosing to avoid missed doses Monthly Oral supplementation not required	Loading doses – deltoid route only (must be stable)
Olanzapine pamoate (ZypAdhera®)	Tolerability and response to oral olanzapine required. Initial dose based on equivalent oral olanzapine dose	150–300mg 2-weekly or 300–405mg 4-weekly	Gluteal only	2–3	30	~12	Can be given 4-weekly (unless max dose required) Oral supplementation not required	Requires reconstitution Post-injection syndrome 3 hours post-injection monitoring 2-weekly administration required for maximum dose (~20mg daily)
Aripiprazole (Abilify Maintena®)	Tolerability and response to oral aripiprazole required. Continue oral aripiprazole for 14 days after first injection	400mg monthly	Deltoid or gluteal	7	30–46	~20	Monthly Prefilled syringe (400mg dose only)	Requires oral supplementation at initiation Prefilled syringe not available for doses less than 400mg Doses less than 400mg require reconstitution

*Doses stated are for adults, lower doses may be required for older adults

**See Figure 1

NB Paliperidone palmitate 25mg LAI and aripiprazole 300mg prefilled syringe LAI are not available in the UK

Table 3. Second-generation antipsychotic long-acting injections (SGA LAIs)^{12,14}

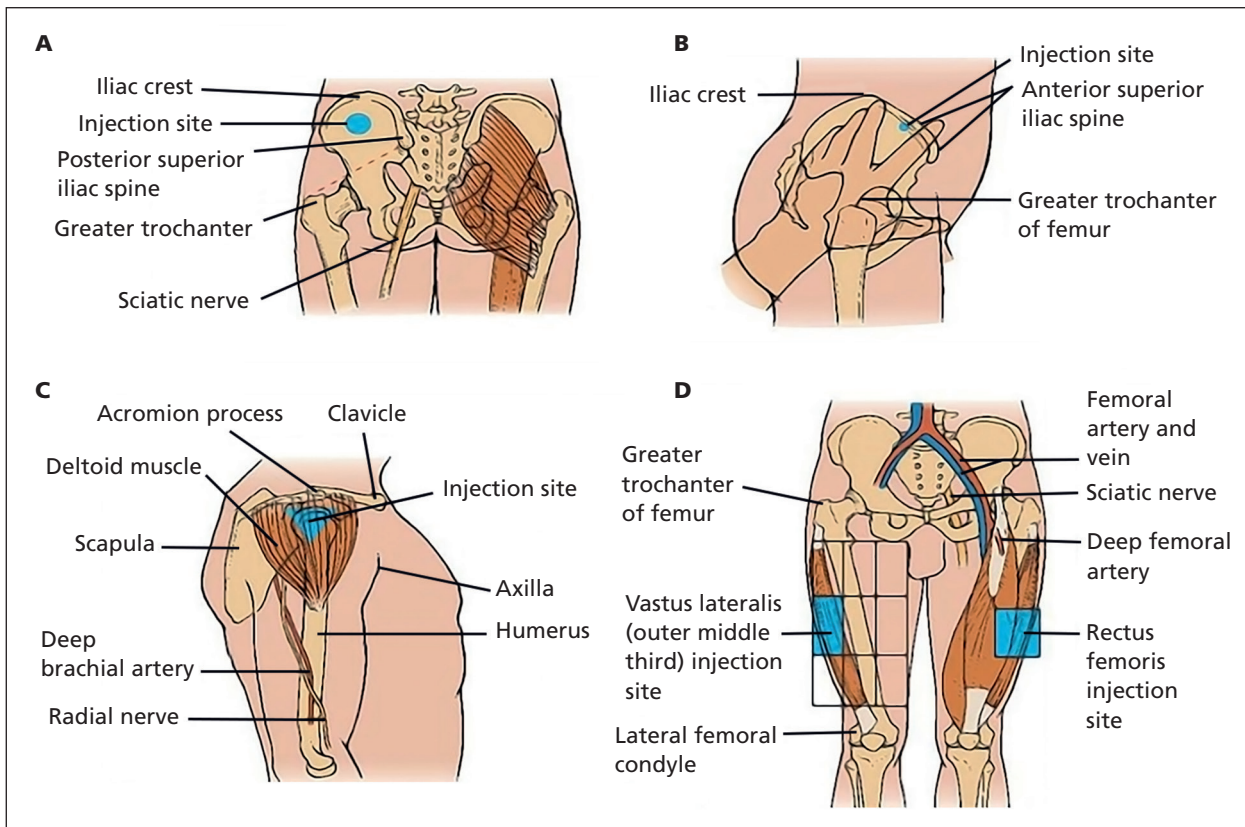


Figure 1. Location of intramuscular injection sites (deltoid and gluteal)

weeks of treatment,¹⁵ and sometimes longer.¹⁴ The initial dose of risperidone LAI is based on the dose of oral risperidone. For example, if a patient is taking oral risperidone 4mg per day then they should be initiated on risperidone LAI 50mg every two weeks.¹⁴ Ideally patients should be stabilised on an oral dose of risperidone before initiation of the LAI to allow for a more effective way of predicting response. Risperidone LAI should be administered every two weeks by IM injection into the deltoid or gluteal muscle, requiring more frequent injections than the other SGA LAIs.

Risperidone LAI also requires refrigeration, making it potentially less convenient for staff and increasing the risk of financial implications in the event of a break in the cold chain. In recent years there has been a decline in the use of risperidone LAI in practice as paliperidone palmitate LAI has been formulated in a way that it has several practical advantages for patients and staff.

Paliperidone palmitate LAI (Xeplion®)

Paliperidone palmitate is the active metabolite of risperidone. This LAI formulation was launched in 2011 as a maintenance treatment of schizophrenia in adults stabilised on oral paliperidone or risperidone.¹⁶ For those with a previous response to oral

paliperidone or risperidone, paliperidone palmitate LAI may be used without prior stabilisation with oral treatment as long as psychotic symptoms are mild to moderate and an LAI is needed.¹⁶ Paliperidone palmitate has demonstrated non-inferiority when compared with risperidone LAI¹⁷ and a Cochrane review concluded that in short-term studies paliperidone palmitate was more efficacious than placebo.¹⁸ As discussed above, paliperidone palmitate LAI was compared with haloperidol decanoate in the ACLAIMS study,¹¹ which demonstrated comparable efficacy between the two LAIs.

Paliperidone palmitate initiation consists of two loading doses of 150mg on Day 1 and 100mg on Day 8.¹⁶ Both doses should be administered by IM injection into the deltoid muscle in order to achieve rapid therapeutic concentrations. Following a single deltoid IM injection, concentrations are approximately 28% higher than those achieved via gluteal IM injection. Peak plasma levels are obtained within 13 days, therefore co-administration of oral paliperidone or risperidone is not necessary during the initiation phase.^{14,16} Following paliperidone initiation, the first monthly maintenance dose should be given one month later, administered into either the deltoid or gluteal muscle. The usual recommended maintenance dose is 75mg, however, the dosing range is

25–150mg, based on individual patient efficacy and tolerability.¹⁶ When making dose adjustments, the long half-life of paliperidone palmitate and time to reach steady state (approximately 20 weeks)¹⁴ should be considered. Previous response and tolerability to oral risperidone or paliperidone should help guide the monthly maintenance dose. For example, if a patient is taking oral risperidone 4mg per day then the monthly maintenance dose of paliperidone palmitate should be 100mg.¹⁴ In order to avoid missed doses the manufacturer allows some flexibility in the dosing regimen. The second loading dose may be given four days before or after Day 8 and each maintenance dose may be given seven days before or after its monthly due date. The summary of product characteristics (SPC) also provides detailed instructions on how to manage missed doses.¹⁶

A Cochrane review¹⁸ demonstrated that the adverse effects of paliperidone palmitate LAI were similar to those of its related compounds, oral paliperidone and risperidone (oral and LAI), with EPSEs, weight gain and tachycardia all more common with paliperidone palmitate LAI compared with placebo. While no difference was found in the incidence of sexual side-effects, paliperidone palmitate LAI was found to be associated with substantial increases in prolactin levels. In the ACLAIMS study,¹¹ although there were no statistically significant differences in rating scores for parkinsonism, fewer patients on paliperidone palmitate required treatment to manage these adverse effects.

Olanzapine pamoate LAI (ZypAdhera®)

Olanzapine pamoate LAI was approved for use in the EU in 2008 and available in the UK from 2010 for the maintenance treatment of adults with schizophrenia who have been sufficiently stabilised with oral olanzapine.¹⁹ Olanzapine pamoate LAI has been shown to have comparable efficacy to oral olanzapine in preventing relapse.¹⁹ There have been no direct head-to-head clinical trials comparing the efficacy and tolerability of olanzapine pamoate LAI with other antipsychotic LAIs.

One of the main issues with olanzapine LAI is post-injection syndrome, occurring in <0.1% of injections and approximately 2% of patients during clinical trials.¹⁹ Signs and symptoms are consistent with olanzapine overdose, ranging from mild (*eg* sedation) to serious (unconsciousness or coma). Other symptoms include those of delirium and extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsions. In approximately 80% of cases, mild symptoms appeared within one hour of the injection and progressed to more severe

symptoms, full recovery occurred within 24–72 hours post-injection.^{19,20} Postmarketing reports appear consistent with those seen in clinical trials.¹⁹ Post-injection syndrome appears to be related to high peak olanzapine levels. However, it remains unpredictable and is not thought to be related to the dose or dosing frequency or number of doses administered, or patient or medical factors (*eg* injection technique).^{14,21}

If it is to be used, olanzapine pamoate LAI should be initiated only for patients who have demonstrated response and tolerability to oral olanzapine. The SPC clearly states that the recommended starting doses and maintenance doses (after two months of treatment) of olanzapine LAI should be based on equivalent doses of oral olanzapine. For example, if the patient is taking oral olanzapine 15mg per day then the loading dose of olanzapine pamoate LAI should be 300mg every two weeks and a maintenance dose of 210mg every two weeks or 405mg every four weeks.¹⁶ It should be administered only by IM injection into the gluteal muscle.¹⁹ In most cases, olanzapine pamoate can be administered every four weeks. However, two-weekly administration is required when the highest dose is prescribed (300mg every two weeks, equivalent to olanzapine 20mg daily).¹⁹ Oral supplementation with olanzapine is not required following the first injection.¹⁹

Other adverse effects of olanzapine LAI are similar to those with oral olanzapine (sedation, weight gain, metabolic effects)^{19,22} plus injection site-related adverse effects consistent with those reported for other IM injections.²²

As a result of the major safety issue of post-injection syndrome, olanzapine pamoate injection should be administered only in a health-care facility where access to medical care can be assured and patients can be observed for three hours post-injection by suitably trained staff.¹⁹ After three hours, patients should not travel home alone, drive or operate machinery and should be vigilant for any signs and symptoms of post-injection syndrome. They must be able to obtain help if required.¹⁹ These risk management requirements hamper the clinical utility of this formulation of olanzapine.

Aripiprazole LAI (Abilify Maintena®)

Aripiprazole LAI was launched in the UK in January 2014; of the LAIs currently in use this is the most recently launched SGA LAI. It is licensed for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.²³ The effectiveness of aripiprazole LAI has been demonstrated in two double-blind randomised controlled trials (RCT). One RCT (n=403) compared it with placebo and concluded that aripiprazole LAI statistically sig-

nificantly delayed time to impending relapse ($p < 0.0001$).²⁴ The other RCT demonstrated that aripiprazole LAI (400mg) was non-inferior to oral aripiprazole (10–30mg daily) in preventing relapse in adult patients with stabilised schizophrenia.²⁵ Authors could not find any RCTs directly comparing aripiprazole LAI with other antipsychotic LAIs.

Aripiprazole LAI should be initiated only for patients who have demonstrated response and tolerability to therapeutic doses of oral aripiprazole. The recommended starting dose of aripiprazole LAI is 400mg administered as a single IM injection into the gluteal or deltoid muscle.²³ After the first injection, oral aripiprazole should be continued for 14 days at a dose of 10–20mg daily to maintain therapeutic concentrations of aripiprazole during the initiation phase.²³ The maintenance dose of aripiprazole LAI is 400mg monthly (no sooner than 26 days after the previous injection). Peak plasma levels are obtained within one to two weeks after the first injection with the lowest trough at four weeks.²⁶ Steady-state concentrations are reached after approximately 20 weeks, at which point peak plasma levels are up to 50% higher than the first-dose peak, and trough levels are only slightly below those of the first-dose peak.^{14,26} If maintenance doses are missed, the SPC provides clear instructions on subsequent dosing regimens.²³

Adverse effects of aripiprazole LAI are similar to those of oral aripiprazole, with the exception of injection site reactions. Commonly reported adverse effects from the RCTs include weight gain (9%), akathisia (7.9%), insomnia (5.8%) and injection site pain (5.1%).^{25,27} If aripiprazole LAI 400mg is not tolerated the dose may be reduced to 300mg monthly.²³ Dose reductions are also required for those who are also taking strong CYP2D6 inhibitors (eg fluoxetine) and/or strong CYP3A4 inhibitors (eg HIV protease inhibitors). Dose reductions depend on each patient's monthly maintenance dose and concomitant interacting drugs.²³

Missed doses

In the short term, missing or delaying a dose of a LAI by a few days is generally not problematic. However, repeated patterns of missed doses of a LAI will begin to affect the pharmacokinetics of the antipsychotic and may result in the emergence of psychotic symptoms or relapse. In order to manage missed doses of LAIs, the SPC should be consulted and the pharmacokinetics of the drug should be borne in mind. The manufacturer of paliperidone palmitate LAI allows some flexibility in the dosing regimen to avoid missed doses and the manufacturers of paliperidone palmitate

and aripiprazole LAI provide clear guidance on how to manage missed doses if they occur.

Switching to second-generation antipsychotic LAIs

When switching to a SGA LAI from an oral antipsychotic or another LAI, the general principles and pharmacokinetic profiles of both antipsychotics should be considered and the SPC should be referred to. A period of crossover between the two antipsychotics is likely to be needed. In general, the first antipsychotic should not be stopped abruptly, but the dose should be reduced and the LAI started. Thereafter, the first antipsychotic should be reduced further and stopped. Care should be taken to avoid underdosing or using excessive doses together, and to minimise polypharmacy and the burden of side-effects. The Royal College of Psychiatrists recommends that high dose antipsychotic prescribing (*ie* when the BNF percentages of each antipsychotic combined exceeds 100%) should be avoided.²⁸ For further detailed recommendations on switching from one antipsychotic to a specific LAI readers are referred to guidance detailed in *The Maudsley Prescribing Guidelines in Psychiatry* and the *Psychotropic Drug Directory*.

The future

Given that LAIs were developed to help improve adherence with antipsychotics and therefore improve patient outcomes and prognosis, there is now interest in developing formulations with longer durations of action. In June 2016, in the UK, a three-monthly formulation of paliperidone palmitate (Trevicta®) launched for the treatment of schizophrenia.^{29,30} At the time of writing, most organisations and trusts have not yet determined its place in therapy.

Summary

The formulation of LAIs as a method of delivering antipsychotics can be used to improve adherence, particularly in those unintentionally non-adherent. Therefore these formulations can decrease the chance of a patient's illness relapsing, and improve their recovery. Additionally, some patients prefer to choose this type of formulation over having to take tablets on a daily basis.

Contrary to the previous emphases to give greater credence to the SGAs, several recent large trials do not show greater efficacy compared with FGAs (with the exception of clozapine). Therefore when choosing to use a LAI formulation, consideration should be given to all eight available LAIs. The choice of LAI should be individualised to each patient, taking into account both efficacy and tolerability specific to the patient, practicalities, patient preference and cost.

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Declaration of interests

No conflicts of interest were declared.

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