NHS Greater Glasgow & Clyde
Prescribing Management Group – Mental Health

Effective use of First-Generation Antipsychotic Depot Injections

Aim

To provide guidance to clinicians on gaining optimum benefit for patients in use of first-generation depots. It should be read in conjunction with the Mental Health Service Good Practice Statement for the use of Depot and Long-Acting Antipsychotic Injections.

Background

Antipsychotic depot injections (also known as long-acting injections (LAIs)) are commonly prescribed in mental health services. Their use is recommended in national guidance.[1] Over the last 10 years the growth in the use of second-generation antipsychotic long-acting injections has seen them inadvertently perceived as the preferred option when considering depot treatment.

There is a growing body of evidence that is questioning if second generation LAIs truly offer a significant clinical advantage over the older first-generation depots.[2,3,4] This suggests that the first-generation depots are as effective as the second generation LAIs and may be better tolerated.

Due to the prominence of second-generation LAIs many current clinicians will be less familiar with the properties of the first-generation depots and consequently maybe reluctant to prescribe them.

Drug choice[5,6,7,8,9,10]

There are three first generation antipsychotic depot antipsychotic injections available in the UK. Table 1 below lists the preparations available.

Drug	Brand name	Strengths available
Flupentixol decanoate	Psytixol, Depixol	20mg/ml as both 1ml & 2ml ampoules, 100mg/ml as both 0.5ml & 1ml ampoules and 200mg/ml as 1ml ampoules
Haloperidol decanoate	Haldol	50mg/ml and 100mg/ml as 1ml ampoules
Zuclopenthixol decanoate	Clopixol	200mg/ml and 500mg/ml as 1ml ampoules

Clinical differences

All first-generation depot antipsychotics are esterified long chain fatty acids contained in a base oil. Once injected the ester bond is gradually broken down releasing active drug into the blood stream.

There is little evidence to suggest any significant differences in efficacy between the three available drugs. The main differences are in relative side effects. Haloperidol is more commonly associated with extra-pyramidal side effects (EPSE), acute dystonic reactions (torticollis, facial grimacing, trismus, tongue protrusion, and abnormal eye movements, including oculogyric crisis) can occur within the first few days of treatment and may necessitate stopping treatment. Zuclopenthixol may be more effective at preventing relapse than the others.[11] Flupentixol is probably less sedating.[10]

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Test doses

When prescribing first generation depot antipsychotics, administering a test dose is essential for two reasons. Firstly, to determine the sensitivity of the patient to extrapyramidal side effects (EPSE) and secondly, to test sensitivity to the base oil. The next table lists the recommended test dose for each drug.

Drug	Test dose (mg)
Flupentixol decanoate	20
Haloperidol decanoate	25[a]
Zuclopenthixol decanoate	100

a. The SPC for haloperidol does not recommend a test dose therefore a test dose of 25mg is suggested.

After giving the test dose monitor the patient closely over the next 4 – 10 days for any reaction to the base oil and the emergence of EPSE. If any reaction or side effects occur do not proceed with treatment doses. Note: hypersensitivity and anaphylaxis are rare side effects of depot antipsychotics.[7,8,9]

Titration/maintenance doses

If the test dose is tolerated, active treatment can then commence. The following principles should be applied:

1. **Begin with the lowest therapeutic dose and titrate slowly to the minimum effective dose.** Lower doses may be as effective as the higher end of the dose range and are likely to be better tolerated. This is especially true with flupentixol decanoate where standard doses are as effective as high doses.[12]
2. **Administer at the longest possible licensed interval to begin with** as this reduces the potential medicine burden and minimises the number of injections required.
3. **Adjust doses only after an adequate period of assessment**. Clearly with depot antipsychotics the pharmacokinetics of the drug is significantly altered due to the sustained action. Peak plasma levels, therapeutic effect and steady state plasma levels are all delayed. At the start of treatment the plasma levels of the antipsychotic released from a depot increase over several weeks or months without increasing the given dose due to accumulation. Steady state therefore may take up to 12 weeks to achieve. Dose increases during this period are therefore illogical but may be driven by practical necessity. It is recommended that after the initial treatment dose a minimum of 2 further doses should be administered before any dose increase is considered. During this period the patient should be assessed for response, side effects and physical health impact.

The following table illustrates the dose range and time to steady state for the first-generation depot antipsychotics.

Drug	Dose range	Dosing interval	Time to steady state
Flupentixol decanoate	50mg every 4 weeks to 400mg a week	1 – 4 weeks	6 – 12 weeks
Haloperidol decanoate	50 – 300mg every 4 weeks	4 weeks	10 – 12 weeks
Zuclopenthixol decanoate	200mg every 3 weeks to 600mg a week	1 – 4 weeks	10 – 12 weeks

The time delays with depot treatment can cause practical management difficulties but pressures to increase doses more rapidly should be resisted in the interest of achieving treatment with the lowest possible effective dose at the maximum possible interval.

Side effects

In addition to the known side effects associated with phenothiazine and thioxanthene antipsychotics (EPSE, sedation, antimuscarinic effects, sexual dysfunction) injection site reactions are possible. Long term use can lead to scarring and nodule formation however this can be minimised by good injection technique and rotation of the injection site.

Swapping and stopping

Discontinuation of depot antipsychotics is straightforward. Withdrawal reactions are unlikely as active drug persists in the body for 3 – 6 months after discontinuation.

Changing antipsychotic is more problematic. The extended half-life of these preparations means the potential for significant interactions when swapping treatments needs careful consideration. Whether it involves swapping from one depot to another or from a depot to an oral treatment, factors to consider include:

- The dose and frequency of administration of the current drug.
- The length of time on treatment
- If swapping from a first-generation depot to oral treatment, titrate up to an approximately equivalent oral dose when the depot is next due.
- When swapping from one first generation depot to another, there is still the requirement to administer a test dose. The test dose should be administered on the day the previous depot was due. The dose should then be titrated cautiously bearing in mind the previous depot will still be present.
- Please contact mental health clinical pharmacy services for advice regarding switches.
- It is important to be aware of the potential for cumulative side effects with the delayed clearance of the original depot and the introduction of the new antipsychotic.

Patient education

It is important to provide patients with appropriate information prior to and throughout treatment with first generation depot antipsychotics. The specific drug leaflets from the Choice and Medication website are recommended. https://www.choiceandmedication.org/nhs24/

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