

Depot antipsychotics revisited

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Many typical antipsychotic drugs may be manufactured as alcohols, which react with carboxylic acids to form esters (organic salts). These compounds are highly oil-soluble, but are only sparingly soluble in aqueous fluids such as blood. Thus, an oily solution of an antipsychotic can be injected into a muscle, where it forms a reservoir or 'depot' of drug that is slowly dissolved in the surrounding blood. Once released into the blood, drug esters are rapidly hydrolysed by endogenous esterase enzymes to produce the parent antipsychotic. Stable serum concentrations of antipsychotics are usually engendered (although this is not always observed in practice (Tuninger & Levander, 1996)), and administration need only take place every few weeks or so. Adherence can be assured and relapse rates are reduced (Groves & Mandel, 1975; Davis *et al.*, 1994).

Disadvantages of depot injections include a suspected (see Ayd, 1975) higher incidence of extrapyramidal adverse effects (and perhaps tardive dyskinesia), the prolonged nature of all adverse effects and the difficulty in adjusting the dose regimen to suit patient needs (the pharmacokinetics of depot preparations are extremely complex). Local complications can also occur, especially in older patients and when high doses are injected (Hay, 1995).

Depots are widely used in UK clinical practice. Doses used seem to vary substantially, as do the choice of drug and the co-prescription of oral antipsychotics. This article briefly reviews the rather sparse and largely dated evidence base for the use of depots and gives some practical guidance for clinical practice.

Depots available in the UK

Flupenthixol decanoate

Flupenthixol decanoate dissolved in thin vegetable oil has been available since 1972. Peak plasma levels are reached approximately one week after intramuscular administration and the plasma half-life is around 17 days after multiple administrations (Jørgensen, 1978; Davis *et al.*, 1994). Flupenthixol decanoate may be given every two to four weeks; it is said to improve mood and cause fewer extrapyramidal effects than fluphenazine decanoate (Carney &

Sheffield, 1976), although this is not universally accepted.

Fluphenazine (Table 1)

Fluphenazine is available in some countries as the enanthate and, more widely, as the decanoate ester. The decanoate compound is longer acting and better tolerated (Van Praag & Dols, 1973). In the UK, fluphenazine decanoate in sesame oil may be administered every two to five weeks, although shorter intervals are licensed in other countries. The plasma half-life as a single dose is around eight days and in multiple dosing is around 20 days (Ereshefsky *et al.*, 1984). When first used widely, fluphenazine depots were associated with depressive reactions. A true association has been contested (Ayd, 1975), but it is probably best to avoid fluphenazine in those with a history of depression.

Haloperidol decanoate

Haloperidol decanoate may be administered every four weeks but, with an apparent plasma half-life of three weeks (Reyntjens *et al.*, 1982), steady-state plasma levels are not reached for around three months. Doses of up to 300 mg/month are licensed but are often exceeded; the optimal dose appears to be around 150 mg/month (Marr & Batchelor, 1982). Indeed, much lower doses (30–50 mg/month) have been shown to be effective (Nyberg *et al.*, 1995). Minor differences in efficacy and tolerability occasionally have been detected between haloperidol decanoate and other depot formulations (Beresford & Ward, 1987). These observed differences

Table 1. Fluphenazine decanoate, 50 mg weekly ($n=7$): resultant plasma levels of fluphenazine (from Ereshefsky *et al.*, 1984)

	Time (weeks)				
	0	1	2-3	4-5	6 or more
Mean fluphenazine plasma level (ng/ml)	0	0.58	1.09	1.73	1.99

Note how the mean plasma levels increase without an increase in dosage and that the percentage increase is highest at the start of therapy and lowest as steady state is approached.

are probably a result of the use of poorly matched doses or dose schedules.

Pipothiazine palmitate

Pipothiazine palmitate is a piperidine phenothiazine ester used in the UK and Europe. A lower incidence of extrapyramidal effects might be predicted from the drug's chemistry, but there are no unequivocal, practical data to support this. Pipothiazine palmitate is suitable for administration at four-week intervals. Peak plasma levels are reached only in the second week following injection (Girard *et al*, 1984).

Zuclopenthixol

Zuclopenthixol (cis-Z-clopenthixol) is available as two esters with very different pharmacokinetic properties. Zuclopenthixol acetate is a short-acting depot used in the acute treatment of psychosis. Peak plasma levels are reached after around 30 hours (Amdisen *et al*, 1986) and decline fairly quickly thereafter. A sedative effect is apparent around two hours after injection, but significant changes in psychotic symptoms are apparent only after eight hours, with the effect persisting for at least 72 hours (Chakravarti *et al*, 1990). Firm evidence for the superior therapeutic efficacy of this preparation over simple injections is lacking (Coutinho *et al*, 1997). Zuclopenthixol decanoate is longer acting and may be administered every two to four weeks, with good therapeutic effects (Dom *et al*, 1978).

Table 2 gives details of all the above-mentioned depot antipsychotics.

Prescribing depots

Depot medication is a useful therapeutic option in patients with psychosis who lack insight or who are known to adhere poorly with oral medication. However, their use is made complicated by the complex and varied

pharmacokinetic profiles of different depot preparations. For example, peak plasma levels are reached only after a long period (which varies from one depot to another); antipsychotic response is also delayed; and steady-state plasma levels are reached only after several weeks or months of continuous therapy.

In an attempt to assure optimal evidence-based prescribing of depot medications, the following guidance is suggested.

Give a test dose

Depots are long-lasting, so any adverse effects that result from injection are likely to be long-lived. Thus, a small test dose is essential to help avoid severe, prolonged adverse effects. Note, however, that some extrapyramidal reactions occur only after several doses (Warner & Wyman, 1975).

Continue with the lowest therapeutic dose

In general, there are few data showing clear dose-response effects for depot preparations throughout their licensed dosage range. There is some information that indicates that low doses are at least as effective as higher doses. Low doses are likely to be better tolerated and are certainly less expensive.

Administered at the longest possible licensed interval

All depots can be administered safely at their maximum licensed dosing intervals. There is no evidence to suggest that shortening the dose interval improves efficacy. Moreover, injections are painful, so less-frequent administration is desirable. The 'observation' that some patients deteriorate in the days before the next depot is due is probably fallacious. For some hours (or even days with some preparations) plasma levels of antipsychotics may continue to fall, albeit slowly, after the next injection has been given.

Table 2. Depot antipsychotic preparations

Drug	Time to peak plasma levels (days)	Approximate time to steady state (months)	Licensed frequency of administration (weeks)
Flupenthixol decanoate	7-10	2	2-4
Fluphenazine decanoate	1-2	2	2-5
Haloperidol decanoate	3-9	3	2-4
Pipothiazine palmitate	9-10	2-3	4
Zuclopenthixol decanoate	4-7	2	2-4
Zuclopenthixol acetate	1-2	N/A (acute use only)	As required, but not less than 24 hours apart

(From Currey *et al*, 1979; Davis *et al*, 1994; Ereshfsky *et al*, 1984; Association of British Pharmaceutical Industry, 1996; Reynolds, 1996.)

Thus patients are most at risk of deterioration immediately after a depot injection and not before it. Note also that, at steady state, plasma drug levels, even before each dose, are several times greater than levels during early 'acute' treatment (Ereshefsky *et al*, 1984). Moreover, in trials, true relapse seems only to occur three to six months after withdrawing depot therapy (Taylor, 1997).

Adjust doses only after an adequate period of assessment

Attainment of peak plasma levels, therapeutic effect and steady-state plasma levels are all delayed with depot injections. Doses obviously should be *reduced* if adverse effects occur, but should be *increased* only after careful assessment over at least one month, preferably longer. The use of adjunctive oral medication to assess depot requirements may be helpful, but it too is complicated by the slow emergence of antipsychotic effects. Remember that, at the start of therapy, plasma levels of antipsychotic released from a depot increase over several weeks without increasing the given dose (see Table 1). Dose increases during this time to steady-state plasma levels are thus illogical and impossible to evaluate properly.

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