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## Is there a role for the depot clinic in the modern management of schizophrenia?

The value of antipsychotic medication in preventing relapse in schizophrenia has been apparent since soon after its introduction (National Institute of Mental Health, Psychopharmacology Service Centre Study Group, 1964) but non-compliance remains a problem. Failure to take prescribed medication is a challenge in general medicine but presents special difficulties when treating mental illness; residual symptoms of psychosis and impaired insight after discharge increase the likelihood that a patient will stop taking antipsychotic medication, thereby contributing to higher relapse rates. The development of depot antipsychotic medication that could be administered intramuscularly at intervals of several weeks raised treatment and outcome expectations for patients who were felt to be at higher risk of non-compliance when in the community. The need for regular administration and monitoring of patients receiving depot medication led to depot and maintenance medication clinics. Today, with increasing numbers of patients who would previously have been receiving depot medication now taking atypical oral antipsychotics, is there still a need for the depot clinic?

### Development and pharmacology

Depot antipsychotic medication is produced by esterifying the classical antipsychotic agent with a long-chain fatty acid and injecting it in an oily solution. The resulting esters have a high oil-to-water ratio and are slowly released from the depot administration site into the circulation. Esterases are present in many tissues and once the ester has been released into the circulation it is rapidly split by these enzymes, thereby making the parent compound available.

It is recommended that patients who are candidates for depot medication should first be stabilised on the oral form of the medication. Plasma concentrations have been used to justify the use of loading doses to achieve earlier steady states after initiation of depot treatment (Ershefsky *et al*, 1990) but there is wide inter-patient variability in plasma concentration after depot administration. There is little convincing support from controlled

studies for therapeutic drug monitoring of plasma concentration during treatments. Depot antipsychotic adverse effects are related to the active antipsychotic agent and are therefore comparable to oral agents. One significant difference, however, relates specifically to the long half-life associated with depot medication; an adverse event such as neuroleptic malignant syndrome, although rare (Addonizio & Susman, 1991), may be much more difficult to manage in a patient receiving a depot medication with an extended elimination time. The literature review by Gerlach (1995) does not support the view that depot antipsychotics are associated with a greater risk of major side-effects than the oral equivalent.

Concerns have been raised (particularly during the first 10 years of use) about the ethics of depot use; critics have associated administering medication in this form with coercive or forced treatment. Certain patients may indeed have persistent feelings of loss of control over their treatment, necessitating the change to oral medication. Others may develop a more positive outlook if lowest effective dose strategies are used early in treatment, allowing symptom control and insight improvement to take place while minimising distressing side-effects. The subjective experience of side-effects to medication is a critical factor in the development of negative feelings towards antipsychotic medication (Gerlach & Larsen, 1999). A systematic review of patient attitude to depot antipsychotic medication by Walburn *et al* (2001) indicates that patients on depot antipsychotics prefer this route of administration. However, the authors acknowledge that the evidence base for this finding is limited.

Differing approaches to these concerns may partly explain some of the wide variations in depot antipsychotic use between countries: it has been consistently lower in the US and France than in some northern European countries (UK, Sweden and Denmark) (Dencker & Axelsson, 1996), although this may also be related to the relatively limited selection of typical depots (haloperidol and fluphenazine) available in the US.

Particular management difficulties are presented by patients with a history of poor compliance who are sensitive to the extrapyramidal side-effects of conventional antipsychotics. This group would seem to



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be particularly suited to atypical depot preparations. There are, however, no clear indications at present as to when these new depots might become available (although more than one is expected to be launched within the next 3 years). Their exact place in therapy will only become clear when information about cost, dose intervals and relative efficacy are available.

## Efficacy

Early attempts at assessing the efficacy of depot antipsychotics in preventing relapse in schizophrenia (mirror image studies) were criticised for methodological shortcomings. In the mirror image studies, patients receiving depot antipsychotics were followed up for a set period of time and the number and length of relapses were recorded. This result was compared to the number of relapses or days in hospital for an equal period of time before the depot medication was commenced. Six of these mirror image studies were examined by Davis *et al* (1994), who noted that the studies had failed to statistically analyse days in hospital or oral medication before or after days on depot medication. When these analyses were carried out, a statistically significant decrease in the number of hospitalised days was detected (see Table 1). For example, Denham and Adamson (1973) followed up 103 patients after they commenced depot antipsychotic medication. The mean duration of follow up was 24.8 months. The number of days in hospital during this period was compared to an equal amount of time on oral medication before commencement of the depot. The number of days in hospital was reduced from 8719 to 1335, and the number of relapses from 191 to 50. Eleven of the 50 relapses occurred after a patient had failed to attend at a depot clinic.

A major limitation of the mirror image design is that it is unclear how much of the detected benefit can be attributed to a pharmacological effect and how much may have been due to spontaneous improvement independent of treatment or to extra support and supervision provided by the staff in the clinic where

the depot medication was administered. Controlled comparisons of oral and depot forms of antipsychotic medication have not shown a clear compliance benefit for depot forms (Rifkin *et al*, 1977; Schooler *et al*, 1980) but this has been linked to the assumption that patients with schizophrenia who enrol in clinical trials may have higher compliance rates than the general population with schizophrenia (Kane & Kissling, 1991).

It must also be borne in mind when attempting to critically evaluate these studies or other work looking at depot medication, that the very nature of the patient group who may benefit most from depot medication and depot clinics tends to contain uncooperative, poorly compliant patients. Research with such a group is fraught with difficulty but the patient sample studied must be representative of those attending depot clinics. Once the limitations of the early studies are acknowledged, there is still valuable information to be gleaned from them.

## Compliance and indications for depot use

Carpenter *et al* (1990) have examined the intervals at which depot antipsychotic medication should be administered to help prevent relapse. The study attempted dose reduction through lengthening the time between injections rather than a reduction of the dose per administration. He detected no differences between patients with schizophrenia receiving 25 mg fluphenazine every 2 weeks and those receiving the same dose every 6 weeks. The patients were, however, only followed up for 54 weeks, so delayed effects associated with an overall reduction in antipsychotic dose may have been missed. All participants attended at 2-week intervals and those in the 6-week group received placebo at times when their dose was not due, thereby ensuring that there was little difference in the intensity of care delivered to the two groups.

The use of depot medication requires compliance on the part of the patient, although attending for administration of medication once every 2 or 3 weeks may be preferable to taking medication every day or several times

**Table 1. Mirror image studies comparing number of hospital days on depot and oral medication**

Study	Number of patients	Duration of study (years)	Hospital days		P value
			On oral medication	On depot medication	
Denham & Adamson (1973)	103	12–40 (months)	8719	1335	<0.0001
Gottfries & Green (1974)	36	2–6	12390	2940	<0.0001
Marriott & Hiep (1976)	131	1	12434	5619	<0.0001
Devito <i>et al</i> (1978)	122	1	3329	314	<0.01
Freeman (1980)	143	12	19510	4376	<0.0001
Tegeler & Lehmann (1981)	78	5	19110	3276	<0.0001

Based on Davis *et al*, 1994.

1. P value derived by Davis *et al* (1994) from number of admissions – not from original paper.

2. P value from original paper.

3. P value calculated by Davis *et al* (1994) using number of hospital days given in original paper.



a day. In a review of medication compliance in schizophrenia, Falloon (1984) reported 80% compliance with depot medication and 60% with oral antipsychotics. This is comparable to compliance rates among other medical out-patients. Increasing the complexity of the regime has been shown to cause decreased compliance (Hulka *et al*, 1976). The seriousness of the disorder (as perceived by the patient) is also linked to compliance and this has particular importance in the treatment of schizophrenia. Appointments can best be seen as part of an educative process using negotiation to develop and maintain compliance.

In order to reduce non-compliance associated with non-attendance at depot clinic, it is important to be able to identify the group of patients who are at risk of dropping out of clinic attendance. Heyscue *et al* (1998) looked at groups of patients attending urban and rural out-patient clinics to have depot antipsychotic medication administered. Clinic attendance was high in both groups, averaging 95%. This compliance rate is higher than that reported in previous depot medication studies and may be owing to reportedly thorough follow-up on missed appointments at both sites. The patient was understood to be compliant if the depot dose was administered within 4 days of the scheduled date. The only characteristic associated with a decreased compliance rate was a history of substance misuse. Substance misuse has previously been linked to poor compliance in other studies. Focusing on those with a history of substance misuse and reacting quickly to early signs of their defaulting from treatment may be important in increasing overall compliance rates at the depot clinic.

Although switching to a depot medication has been used as an attempt to increase compliance, it is important to recognise that there are other methods of helping to achieve this. Turner and Vernon (1976) reported on using telephone prompting to boost attendance at the first out-patient appointment after discharge. Considerable success was reported in this study in increasing the percentage of patients who attend a first appointment through the use of telephone prompting. The advantages of assigning staff to this prompting were stressed. A long waiting period was associated with non-attendance, as was chronic illness and poverty. Burgoyne *et al* (1983), however, were unable to replicate these results and concluded that earlier apparent improvement caused by telephone prompting may in fact have been related to socioeconomic factors (having a telephone). Better compliance with aftercare in general after admission to a psychiatric unit is associated with an increased number of previous hospitalisations, a longer stay and less denial of need for medication and other treatments.

Patients not meeting these criteria, especially those with a history of substance misuse, may be best served at discharge with a referral to a depot medication clinic. Increasingly, however, patients are receiving oral atypical antipsychotic medication as first-line treatment. Is there a case to be made for greater use of depot typical medication in patients at higher risk of non-compliance

or is the non-compliance associated with troublesome side-effects and cognitive deficits that may respond better to atypical medication?

## Cost–benefit analysis

Using a decision tree analysis model Glazer and Ereshefsky (1996) have looked at treatment selection for 'revolving door' patients with schizophrenia. In the analysis, the example of a 29-year-old with schizophrenia, hospitalised for 30 days after a relapse, is taken. Three pharmacological options were considered before discharge: typical oral drug, typical depot drug and atypical oral drug. Five sets of cost and outcome combinations were considered. The results suggested that switching to the depot route in a patient with a history of relapses and readmissions could reduce total direct treatment costs by US\$650–2500/year compared with an atypical oral drug and by US\$460–1150/year when compared with an oral typical drug. However, a sixth set of assumptions was also considered: in this scenario a compliance rate of 80% was selected for the atypical oral drug (equal to depot) (in the five earlier scenarios the compliance rate for the atypical oral agent had been set at 65% as against 55% for the typical oral agent). A 25% reduction in wholesale price of the atypical agent was also assumed. In this scenario, treatment with the atypical oral agent would cost US\$700 less than with depot medication and US\$1860 less than with a typical oral agent. There are, however, several limitations associated with a model like this. Primarily, the model rests on assumptions about a 'typical patient'. Although different combinations of costs and outcome were factored into the model, it cannot of course represent the full range of variables associated with outcome. There are also some questions as to whether findings from a cost–benefit analysis can be generalised from one country to another, given the differences between health care systems (including differences in the threshold at which readmission is considered and differences in admission duration rates). The cost–benefit outlined above of switching to an oral typical drug is dependent on an assumed increase in compliance.

## Running a depot clinic

With a better side-effect profile than traditional drugs and the capacity to improve the cognitive deficits associated with schizophrenia it is reasonable to assume, however, that compliance rates will improve with atypical antipsychotics. It may be possible to increase compliance rates still further if some of the lessons learned in depot clinics are applied to the administration of atypical oral medication. Delays to first appointment after discharge should be administered. Efforts should be made to limit frequent changes of staff at the clinic to allow relationships to be built up and to facilitate early detection of impending relapse. The development of an outreach service with a clear response policy to non-attendance or other possible signs of deterioration should



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be attempted. Enquiries and examination for medication side-effects should be conducted at each assessment and the use of structured scales such as the Abnormal Involuntary Movement Scale (AIMS, Guy, 1976) should be considered. It is important that appointment intervals should not be solely dictated by medication administration. This is especially important if longer dosage intervals are being used. Finally, prompt medical review should be available for those patients who are relapsing or expressing dissatisfaction with their treatment. Medical review should also be arranged for those patients showing an inadequate response to treatment (including refractory negative symptoms, cognitive deficits and poor quality of life).

## Conclusions

It is clear that some patients fare poorly on oral antipsychotic medication and the future introduction of depot atypical antipsychotics will be a significant addition to treatment options. At present, typical antipsychotic depots retain their place in the armamentarium but increasing numbers of patients are being switched to oral antipsychotic agents. Important lessons have been learned through the use of depot clinics and there are several ways in which the service provided can be improved. The skills and experience associated with these clinics can be put to best use by incorporating them into maintenance medication clinics, thereby helping to maintain compliance and reduce relapse rates for those taking oral atypical medication as well as those continuing to take depot medication.

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