The long-acting depot antipsychotic drugs

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The novel antipsychotics have reduced the use of depot medications, but the introduction of the atypical depot antipsychotic has rekindled an interest in the long-acting antipsychotic formulations. The use of atypical antipsychotics is recommended, except where patients are otherwise stable on classical antipsychotics without unwanted side effects.

Frequent relapses tend to shorten symptom-free periods for patients with schizophrenia, leading to more disabilities and increased refractoriness to future treatment (Wyatt, 1991). Maintenance treatment with antipsychotic medication appears to be the best method of averting relapse. Non-compliance with medication by patients with schizophrenia is a significant avoidable cause of treatment resistance (Kane, 1985; Fenton et al, 1997). About 50% of patients with schizophrenia are non-adherent to medication. Rehospitalization is one consequence of therapeutic failure, not to mention other intensive interventions.

To make matters worse, some patients suffering from schizophrenia also display aggression during periods of psychosis (Lindquist and Allebeck, 1990; Tam et al, 1996; Mitchell, 1999). Schizophrenia also carries a high suicidal risk: almost 50% of patients will attempt suicide in their lifetime (Planasky and Johnson, 1971). This figure is 20–50 times higher than that seen among the general population (Meltzer and Okayili, 1995). Thanks to diverse antipsychotic formulations, the severely deteriorated 'chronic dement' is no longer seen so frequently.

The incidence of schizophrenia in developed countries appears to be on the decline but changing diagnostic criteria and the clearer clinical definition of schizophrenia may partially explain this decrease (Nicole et al, 1992; Suvisaari et al, 1999). Management of schizophrenia places a huge economic burden on the NHS and much of the cost is a result of the consequences of psychotic relapse (Weiden and Olfson, 1995). The average treatment cost of schizophrenia in 1987 was £1670 per individual patient (Davies and Drummond, 1990). The direct drug cost to the NHS for treatment of schizophrenia has been estimated at £396 million (Davies and Drummond, 1994). However, when all health services are taken into account, estimates add up to more than £1 billion, with the indirect cost of lost production estimated at £1 billion (Rice and Miller, 1996). Frequently relapsing patients who require acute inpatient care are responsible for most of the total treatment costs.

Although the first antipsychotic drug was introduced in 1952 (Delay et al, 1952), it was some years before the prophylactic usefulness of antipsychotics in psychiatry was recognized (Pasamanick et al, 1967; Leff and Wing, 1971). Depot preparations were initially intended only for patients with suicidal tendencies or violent patients, but they became a valuable method of achieving maintenance treatment. This should change in future because of the availability of oral drugs with cleaner side-effect profiles. The atypical drugs have higher compliance rates than other forms of antipsychotic medication, so should be given initially in their oral formulation.

The National Institute for Clinical Excellence (NICE) guidelines (2002) recommend that oral atypical antipsychotics should be considered for patients on conventional drugs if they experience intolerable side effects even when their symptoms are under control, and depot medications may be continued if patients are well maintained without unpleasant side effects. Nevertheless, use of depot medications should be scrutinized.

It was expected that the novel antipsychotic drugs would mark the beginning of the end of the classical depots, but they are still being used. Atypical drugs have not revolutionized the treatment of schizophrenia and there is much that we still do not know. The aetiology of schizophrenia is still debatable, so depots will continue to be used until drugs with better antipsychotic efficacy and fewer side effects are available. Although concordance with atypical drugs is promising, some patients insist on continuing depot medication.

DEPOT MEDICATIONS

Depot antipsychotics are so called because medications are stored in the muscles and slowly

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released over several weeks to achieve sustained pharmacological action. There are two ways of achieving prolonged pharmacological action:

1. If a drug has a very long plasma half-life, its action will be extended (plasma half-life is the time taken for the plasma concentration of a drug to fall by half). Pimozide is an example, with a plasma half-life of 53 hours.
2. By dispensing the drug in a slow release form, prolonged pharmacological action can be achieved.

There are two types of depot: absorption and conversion depots. Absorption depots retain the active substance, releasing it gradually. The atypical antipsychotic Risperdal Consta (Janssen Cilag, High Wycombe, Bucks) is an example of an absorption depot.

In conversion depots the active substance is made available as a derivative that slowly converts to the active substance. Typical antipsychotics use this principle of storage and conversion to provide the extended effect of the drug. Conventional antipsychotics may be manufactured as alcohols which react with carboxylic acids to form esters or organic salts which are highly oil soluble. They do not dissolve easily in aqueous solutions such as blood, thus an oily solution of the antipsychotic medicine forms a depot when injected into the muscle. The oil is slowly absorbed into the systemic circulation or the lymph system to create numerous secondary deposits in other muscles and adipose tissue.

Once the ester form of the drug is released into the blood, it is de-esterified to the original drug by endogenous esterase enzymes. De-esterification can occur at secondary sites or during passage through the liver, resulting in the release of the free base that is pharmacologically active.

Depot antipsychotics have long biological half-lives. The pharmacological half-life is also significant. Serum prolactin concentration can provide a marker for pharmacological concentrations of antipsychotics. However, plasma prolactin concentration is useful only as a guide to compliance. Hyperprolactinaemia has been reported as long as 6 months after the last depot injection of fluphenazine decanoate in patients who have been receiving the drug for more than 1 year.

TABLE 1.
Reasons for non-compliance

Poor or fluctuating insight
Disturbing side effects of medication
Paranoid delusions
A poor doctor–patient relationship
A general scepticism towards chemical treatment of mental symptoms
Inhibition of sexual functions
Stigma of antipsychotic drugs and schizophrenia
Lack of information and understanding about illness
Problems in managing complex regimens
Denial
Forgetfulness
Expense of medications
Lack of active symptoms
Fear of long-term harm and addiction
Substance misuse
Fear of loss of one's autonomy
Younger age and male gender
Mistaking the initial artificial improvement for true improvement
Severe warnings of side effects by prescribers, print and electronic media

Advantages

Depot medications are now used only for maintenance therapy in schizophrenia and are assumed to provide stability. The major advantage of depot formulations is the assurance of compliance leading to fewer relapses and rehospitalizations. It has been estimated that non-compliance occurs in 30–40% of patients during 1 year (Kane, 1995).

Clinical trials of the effects of compliance are difficult to conduct because patients who participate in clinical trials are generally compliant and willing to take treatment. Non-compliance may be a result of poor or fluctuating insight, disturbing side effects of medication or paranoid delusions. A poor doctor–patient relationship or scepticism towards chemical treatment of mental symptoms can also result in non-compliance. Patients may give up medications that reduce sexual function. Antipsychotic medications add to the existing stigma surrounding schizophrenia. Other factors which may contribute to non-compliance are listed in *Table 1*.

Patients may forget medications or intentionally miss doses. They sometimes feel they do not need medication because of a transient improvement of symptoms, and discontinue the medication entirely. A number of factors may influence absorption of oral medications, including physiological variants and concomitant use of other drugs, e.g. anticholinergic drugs. The side-effect profiles of depot and oral antipsychotics are similar (Glazer and Kane, 1992); intramuscular (IM) administration lowers the dosing and guarantees steady-state serum levels. The hypothetical advantage of depot administration is that the drug initially bypasses deactivation in the liver, resulting in an unaltered drug selectively reaching the CNS. This can enhance antipsychotic efficiency while

reducing drug exposure and tolerance. Depot antipsychotics use the lowest effective dose, reducing the frequency of side effects, e.g. akathisia, dysphoria and antipsychotic-induced deficit syndrome, and enhancing the patient's quality of life. A patient taking oral medication is reminded that he/she is mentally ill several times a day, which in itself has a counter-therapeutic effect. Oral medications give patients the opportunity to overdose, whereas depots reduce this risk.

Depot medications also help avoid bioavailability problems related to absorption and first-pass metabolism and give stable plasma concentration, although Tunninger and Levander (1996) claim that depot antipsychotics do not eliminate clinically unwanted and sometimes marked variation in plasma levels. Once on depot medications, patients receive regular attention because they are periodically supervised by the nursing staff administering the depot for the development of side effects and also for dose titration.

Community psychiatric nurses are in the forefront of depot therapy, and an increasing body of knowledge demonstrates the efficacy of nursing approaches to drug therapy which seek to empower the patient (Marland and Sharkey, 1999). Patients who have no insight into their mental state refuse medication and pose difficulties in the administration of oral medication. Another advantage is that depot medication saves staff time within inpatient settings and minimizes the medication struggle (*Table 2*).

Disadvantages

Many patients get a false feeling of being controlled or, worse still, of being punished when they are on a depot preparation. Delayed disappearance of side effects after discontinuation of the medication compared to the tablet form is a major shortcoming of this treatment.

It is well recognized that antipsychotic drugs cause extrapyramidal side effects, the prevalence of which may be around 40% (Kennedy et al, 1971). Tardive dyskinesia has an incidence of approximately 15% in those taking antipsychotic medications and is as high as 70% in those on depot medication for over 20 years. Involuntary orofacial and buccal-lingual movements and choreo-athetoid movements of the limbs can occur. Tardive dyskinesia can be made worse by cholinergic medication, but it often appears if antipsychotics are suddenly withdrawn.

Weight gain is an important side effect of antipsychotic depot medication but is generally less talked about (Chouinard et al, 1978). It does not appear to be dose related or a result of concomitant use of anticholinergic drugs. The hypothalamic–pituitary axis is innervated by dopaminergic receptors, which inhibit the release of prolactin. Classical antipsychotics block this inhibition, elevating prolactin levels and resulting in galactorrhoea and sexual dysfunction.

Local tissue reactions at the site of injection can also be discouraging for certain patients (*Table 3*). This is particularly important for elderly patients treated with high doses (Hay, 1995).

Techniques of administration

One cause of complication of depot is some degree of fault in the IM injection administration technique. There are two accepted techniques of depot administration: the 'air bubble' and 'Z track' (*Figure 1*).

In the air bubble technique (Pritchard and Mallett, 1992), a small amount of air is drawn up into the syringe along with the drug, which is injected into the muscle following the medication. The air lock formed in the muscle depot stops the drug from seeping out along the needle tract into other subcutaneous tissue or the skin.

TABLE 2.
Advantages of depot medications

Assures compliance leading to fewer relapses and rehospitalizations
Patients do not need reminding of medication
Depot lowers the dosing, guaranteeing steady-state serum levels
Enhanced antipsychotic efficiency with reduced drug exposure and tolerance
Better and safer possibilities using the lowest effective dose, reducing the frequency of side effects
Oral drugs remind the patient that he/she is mentally ill, several times daily
Reduces the risk of overdose
Avoids bioavailability problems
Patients get regular attention with more staff–patient contact
Saves staff time within inpatient settings
Minimizes the medication struggle at home

TABLE 3.
Disadvantages of depot medications

Feeling of being controlled
Delayed disappearance of potentially irreversible and distressing side effects after discontinuation of the medication
Side effects mistaken for core psychotic symptoms, resulting in increase of antipsychotic dose which further exacerbate side effects
Higher incidence of tardive dyskinesia
Anticholinergic medication making tardive dyskinesia worse
Weight gain
Unpleasant local tissue reactions at the site of injection

In the Z track technique (Belanger, 1985), the skin is drawn away from the site. When skin and subcutaneous tissues are released, they return to their original position which breaks the needle track into the muscle and keeps the medication locked in the muscle depot. Air bubble techniques are popular in the USA while variants of Z track tend to prevail in the UK (Taylor et al, 1993).

GUIDELINES FOR USE OF DEPOT

At present, Risperdal Consta is the only atypical antipsychotic available in a depot formulation. Risperdal Consta is presented as vials of dry powder containing risperidone 25 mg, 37.5 mg, or 50 mg, which require suspension before injection, and is administered by deep IM injection every 2 weeks. Risperdal Consta should not be used by patients who are resistant to atypical antipsychotics because the depot form has the same antipsychotic efficacy as the oral form. It may be considered for patients who have been treated successfully with atypical antipsychotics but are non-compliant, or who have a history of responding to conventional depot preparations, but suffer from unwanted drug effects. A secondary care consultant should be involved before initiating IM risperidone, but this can continue under primary care or be transferred to primary care after stabilization under secondary care.

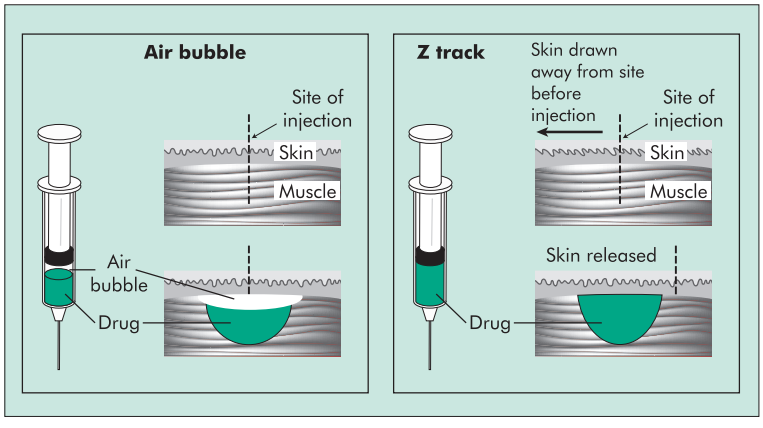
Patients should be pre-treated with oral risperidone to test tolerability and the IM form started after 3 weeks. All patients should be started on 25 mg fortnightly. Any existing antipsychotic should be withdrawn slowly. At least three 25 mg doses should be given before increasing the dose to 37.5 mg where necessary. The main drug release starts in the fourth week and peaks in the fifth and sixth weeks. If oral psychotropic supplements are required in the interim period, low dose benzodiazepines should be given rather than conventional antipsychotic drugs to avoid drug interactions. Patients may require extra medication for symptom control until the depot produces the desired effect. By being sure of the dose received, depots should facilitate downward titration of doses to reduce the incidence of side effects. Patients, families and carers should be educated about the pros and cons of depot administration.

In the event of unavailability of refrigeration, packs should be used within 7 days and once reconstituted, the suspension should be used within 6 hours. Multidose vials are not to be used. Mixing different strengths of the same preparation or mixing different drugs in the same syringe is not acceptable. The maximum volume of depot given in one site should normally be 2 ml but should not exceed 3 ml.

There are four muscles used for IM injections, the gluteus medius (buttock – dorsogluteal site), vastus lateralis (outer aspect of upper thigh), deltoid (upper arm) and ventrogluteal muscle (gluteus medius lying on minimus; side of the hip). The gluteus medius is used for administering depot preparations because it has a greater capacity for holding fluids. The upper outer quadrant of buttock is the preferred dorsogluteal site; the gluteus maximus is spared as the needle can damage the sciatic nerve and superior gluteal artery. Most patients are used to receiving injections in the upper arm and, to avoid embarrassment, reasons for using the gluteus medius should be explained to the patient. If a patient has developed injection site reactions in the buttock, the upper thigh (vastus lateralis) is used for flupenthixol decanoate, fluspiriline and zuclopenthixol decanoate. The arm is not an acceptable site for depot injection.

To increase dose awareness among colleagues, depot prescription cards should have the maximum dose recommended in the British National Formulary written in bold at the top. Maintenance therapy is indicated from the second episode of psychosis and the use of depot medication becomes relevant from then onwards. Patients should be given the lowest therapeutic dose at the longest possible licensed dose (*Table 4*).

Figure 1. Techniques of depot administration.



ETHNICITY AND DEPOT MEDICATION

A patient's ethnicity and culture influences the response to psychotropic medications. Antipsychotic medications interact with ethnicity in multiple ways; the response to the same medication and dose varying with a patient's ethnicity (Frackiewicz et al, 1997). Pharmacokinetic and pharmacodynamic profiles of antipsychotics vary from race to race and are influenced by many biological and non-biological factors (Lin and Shen, 1991). Racial and ethnic variations are likely to stem from a combination of genetic and psycho-

social factors, such as diet and health behaviour (Lin et al, 1995), or be the result of an underlying biological mechanism of mental illness related to ethnicity, culture and gender variations. The effect of psychotropic drugs may be interpreted differently by different cultures (Lewis et al, 1980).

Indian patients tend to be more susceptible to extrapyramidal side effects (Kumar et al, 2001). Parenteral administration of any drug carries an additional placebo effect and bodily tremor has superstitious connotations among the rural population of the Indian subcontinent. Asian patients appear to need lower doses of most psychotropic medications than Caucasians (Lin and Anathan, 1982; Lin and Finder, 1983; Price et al, 1985; Collazo et al, 1996; Jeste et al, 1996; Ramirez, 1996) which affects the dose of depot.

Ethnopsychopharmacology will be highly relevant in future as today's transcultural psychiatry will become tomorrow's social psychiatry. In the UK, patients of non-English speaking background are more likely to receive a depot monotherapy than the indigenous population, reflecting communication problems; it is seen as safer to put patients on a depot to ensure compliance. Indigenous patients tend to receive higher doses of depot.

Transient psychotic or psychosis-like reactions are reported particularly frequently among Africans and Afro-Caribbeans (Jilek and Jilek-Aall, 1970) and these most often self-limiting psychiatric conditions have been given various diagnostic labels. These transient psychotic reactions have sociocultural factors and are a reaction to stress resulting from imposed acculturation and marginalization through rapid sociocultural change (Guinness, 1991). It is also reported that in the UK, among patients of English-speaking background, Afro-Caribbeans who suffer from atypical psychosis run the risk of being inappropriately prescribed depot medications because they are sometimes misdiagnosed as suffering from schizophrenia. Studies in the USA have concluded that African Americans are more likely than other ethnic groups to be misdiagnosed and overmedicated (Adebimpe, 1981; Baker and Carlo, 1999).

ETHICAL CONCERNS

Clinicians should respect the autonomy of patients unless there are compelling reasons not to do so (Gillon, 1986). The process of consulting patients for informed consent can serve as psychotherapy. Patients feel respected when they are involved in decision making about treatment which can promote compliance (Tyrer et al, 1994).

Practitioners are sometimes reluctant to inform patients of the side effects of antipsychotics for fear that this may lead to non-compliance. Quaid et al (1990) showed that informing patients about untoward effects of medications for obtaining informed consent does not usually reduce compliance. Informed choice has more positive results than pressurized treatment. Depot medications are often used under the Mental Health Act 1983 to ensure compliance, particularly in at-risk patients. Depot medication can be given to a patient under sections 3(37) and 3(41) of the Mental Health Act with or without their consent for up to 3 months. Thereafter 'consent to treatment' as outlined in the Mental Health Act 1983 guidelines must be followed. Informed consent to drug treatment may be difficult to obtain from patients with dementia. Under UK law, staff and relatives have no right to give consent on behalf of the patient (Department of Health, 2001). However, if a person is not capable of giving or refusing consent, and has not validly refused such care in advance, treatment may still be given lawfully if it is deemed to be in the patient's best interests.

FUTURE PERSPECTIVES

The most controversial future development could be the introduction of antipsychotic implants. Surgically implantable formulations might be a viable approach for long-term delivery of antipsychotic medication (Siegel et al, 2002). Implants might give superior medication adherence, with symptomatic improvement for many months. These may be safer in the event of adverse side effects because implants could be removed, offering a degree of reversibility.

A surgically implantable formulation of haloperidol has been created using biodegradable polymers and animal experiments have been successful. Haloperidol implants demonstrate steady release of drug for 5 months. Rodents in

TABLE 4.
Guidelines for use of depot medications

Administer via deep intramuscular injection using the correct injection technique
Rotate the site of injection
Pretreat with a test dose of the depot
Use the lowest therapeutic dose with longest interval
Never extrapolate beyond the British National Formulary maximum limits
Adjust dose only after an adequate period of assessment
Reduce dose in the event of side effects
Review the dose of depot and the need for anticholinergic drugs and their dose periodically
Titrate upwards for all depots
Never stop abruptly; titrate downwards before discontinuing depot

experiments have displayed increased striatal D2 receptor expression as well as increased apomorphine-stimulated locomotion. Further tests in other species and humans are required to confirm potential clinical uses.

Implantable pellets lasting months to years may be a distant possibility. Use of antipsychotic implants would require patients to be able to provide informed consent because of the invasive nature of the procedure. These would become the last option in antipsychotic treatment and should be limited to cases where there is an active suicidal or homicidal risk. HM

Conflict of interest: none.

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KEY POINTS

- The first-line treatment strategy of schizophrenia should involve use of oral atypical antipsychotic drugs.
- Depot formulations are highly useful for maintenance therapy of non-compliant patients and they are assumed to provide stability.
- Depot formulations have obvious advantages and disadvantages.
- Informed consent should be sought before initiating depot medication.

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