Why aren’t depot antipsychotics prescribed more often and what can be done about it?

Maxine X. Patel & Anthony S. David

Abstract
Long-acting depot antipsychotics were developed specifically to promote treatment adherence (compliance) and they are a valuable option for patients requiring maintenance medication for schizophrenia. Depot use has fallen in recent years, perhaps owing to the introduction of oral atypical antipsychotics. Psychiatrist and patient acceptance of depot medication is variable. The depot formulation and the traditional ‘depot clinic’ seem to have an image problem, although many patients already receiving depot medication like it. Some psychiatrists may not adequately consider the risks and benefits when contemplating prescribing depot medication. Further, public opinion and planning forces in psychiatric health services may have a negative influence on the use of long-acting treatments. This review considers possible reasons for underutilisation of depot antipsychotics in maintenance treatment of schizophrenia and highlights the potential benefits and future role of depot drugs.

The role of antipsychotic maintenance medication in symptom control and the prevention of relapse in schizophrenia is well established. However, the success of antipsychotic treatment is reduced by patients’ partial or total non-adherence to medication regimens (Lindstrom & Bingefors, 2000). Non-adherence in schizophrenia is a major, preventable cause of morbidity, with significant personal, social and economic costs. Long-acting depot antipsychotics were developed in the 1960s and were specifically aimed at promoting treatment adherence (compliance) in people with chronic illness, thereby enhancing relapse prevention (Davis et al., 1994; Weiden & Glazer, 1997). Depot antipsychotics generally consist of an ester of the antipsychotic drug injected intramuscularly in an oily solution every 1–6 weeks (Davis et al., 1994). Here we examine the reasons why long-acting antipsychotics are currently underutilised for maintenance treatment and highlight why they are potentially beneficial to patients with schizophrenia. We also consider the future role of depot antipsychotics in the psychiatrist’s armamentarium.

Reasons for non-adherence
The reasons for non-adherence are complex but include such factors as beliefs about the illness and medication. The theoretical framework of the ‘health belief model’ indicates that health behaviour is determined by beliefs that fall into four main categories: benefits, costs, susceptibility to relapse and secondary benefits of medication and treatment adherence (Hughes et al., 1997). Even within a relatively compliant group of patients, widely varying degrees of insight and a large range of health beliefs will exist, which, in turn, are important contributors to treatment adherence. Smith et al. (1999) suggest that non-adherence is significantly associated with patients’ perception that they have a low susceptibility to relapse (a component of poor insight) and that this is therefore more important than their perceptions and beliefs about potential side-effects.

For patients with schizophrenia, Cramer & Rosenheck (1998) reported an average adherence rate for all antipsychotics of 58% (range 24–90%). Two reviews on depot medication suggest a non-adherence rate of 24% (range 0–54%) (Young et al., 1986, 1999). Hogan et al. (1983) demonstrated that patients’ experience of and adherence to...
antipsychotic regimens depended on how they felt on medication, rather than what they knew or believed about it. Awad (1993) found a correlation between altered subjective state on antipsychotics and medication adherence. Factors implicated in the genesis of such altered states included the patients’ values and attitudes towards health and illness, as well as demographics, psychiatric characteristics, type and dose of antipsychotic, depressive states and extrapyramidal symptoms (Gerlach, 1995; Patel & David, 2004). In other words, people who are not well disposed towards a particular treatment may be more alert to possible side-effects and more inclined to report them. Weiden et al (1994) suggested, however, that patients’ attitudes to medication may be completely different from their actual medication-taking behaviour.

Improving treatment adherence has rightly become an important area of clinical research (Lindstrom & Bingefors, 2000; Zygmunet al, 2002; Patel & David, 2004). In general, simple psycho-educative methods in isolation are not effective, whereas cognitive–behavioural techniques are more likely to succeed (Kemp et al, 1998). Kissling (1994, 1997) suggested that depot antipsychotics should be considered for relapse prevention but that it is neither ethically nor economically defensible to perform relapse prevention of schizophrenic psychosis without measures aimed at improving treatment adherence. However, dedicated time and resources for this remain rare.

The role of long-acting depot antipsychotics

With the relatively recent introduction of the oral atypical antipsychotics, there has been a shift away from depot typicals. The main driving force for this was the reduction in side-effects and the presumed lowered risk of tardive dyskinesia with the atypicals. Nevertheless, until the guidelines on antipsychotic prescribing were released by the National Institute for Clinical Excellence (Box 1), some psychiatrists remained reluctant to prescribe atypicals and, in some cases, had been restricted by pharmacy or health authority directives, owing to cost (Taylor et al, 1999).

However, many clinicians continue to promote the use of depot antipsychotics (Glazer & Kane, 1992; Gerlach, 1995; Kane et al, 1998). The relative efficacy and adverse effects of the various depot preparations have been examined and are summarised in a meta-review by Adams et al (2001). Overall analysis of the many randomised controlled trials (RCTs) included in the review showed only a modest benefit for depot over oral antipsychotics. Such trials may not provide a complete picture; few were of a duration sufficient to obtain the maximum benefit in terms of relapse prevention. Reassuringly, there was little evidence that people receiving depot medication experienced greater side-effects than those taking oral preparations. However, acceptance

Box 1 Summary of NICE guidelines (2002)

- The choice of antipsychotic drug should be made jointly by the patient and responsible clinician, on the basis of an informed discussion of benefits and side-effects
- Oral atypical antipsychotics are recommended as first-line treatment for patients with newly diagnosed schizophrenia
- If a patient on oral typical antipsychotics has adequate symptom control but is experiencing unacceptable side-effects, an oral atypical should be considered
- If a patient on an oral typical has good symptom control and no unacceptable side-effects, a routine switch to an atypical preparation is not recommended
- Clozapine should be used at the earliest opportunity for patients with evidence of treatment-resistant schizophrenia
- A risk assessment should be performed regarding treatment adherence, and depot preparations should be prescribed when appropriate
- Where more than one atypical drug is considered appropriate, the drug with the lowest purchase cost (allowing for daily required dose) should be prescribed
- Where full discussion between the patient and responsible clinician is not possible, oral atypicals should be the treatment of choice because of the lower potential risk of extrapyramidal symptoms
- Antipsychotic therapy should be initiated as part of a comprehensive package of care that addresses the patient’s clinical, emotional and social needs
- Atypical and typical antipsychotics should not be prescribed concurrently, except for short periods to cover changeover of medication

1. These guidelines were written before the first atypical antipsychotic long-acting injection was licensed.
of depot typical antipsychotics by patients and clinicians is variable and the mode of delivery seems to be a major stumbling block (Walburn et al, 2001).

**Underutilisation: clinicians’ fears and expectations**

The main indication for depot antipsychotics is in maintenance treatment for people with schizophrenia for whom relapse prevention is indicated. For this target population it has been found that 50% are not treated prophylactically at all or only for an inadequate duration (Kissling, 1994, 1997). Prescribing practices for depot antipsychotics differ significantly between countries, with higher rates of depot prescribing in Denmark, Sweden and the UK, and lower rates in France and the USA (Dencker & Axelsson, 1996). Prescribing habits can also vary greatly within a region and between regions of one country (Taylor et al, 1999). Further, the prescribing practice of an individual psychiatrist is subject to a multitude of influences, including the psychiatrist’s beliefs about adverse side-effects, the patient’s acceptance of depot, stigma, involvement of nursing staff, external forces in healthcare systems, prescribing knowledge and experience (Box 2).

**Adverse side-effects**

In comparison with conventional oral antipsychotics, some clinicians perceive depot preparations to be associated with an increased risk of certain adverse side-effects (Kane et al, 1998) and neuroleptic malignant syndrome. The risk of the latter, however, has not been found to be higher for depot drugs, although the evidence base is weak (Glazer & Kane, 1992). Further, Glazer & Kane stated that there are no data to suggest that a prior history of neuroleptic malignant syndrome is a contraindication to the use of depot antipsychotics.

Depot preparations are thought by some clinicians to cause tardive dyskinesia more frequently than oral preparations (Kissling, 1994; Kane et al, 1998). Adams et al (2001) did not confirm a greater risk of tardive dyskinesia in individuals receiving depot medication in RCTs, although this may be because adequate long-term studies have seldom been reported.

There is, perhaps, more of a consensus on extra-pyramidal symptoms. It is generally agreed that typical antipsychotics (oral or depot) cause such symptoms more frequently and more severely than atypical antipsychotics. However, when comparing existing depot typical preparations with oral preparations of the same drug, there was no conclusive evidence of a difference (Adams et al, 2001).

<table>
<thead>
<tr>
<th>Box 2 Tackling myths about depot drugs</th>
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<tbody>
<tr>
<td>• The risk of neuroleptic malignant syndrome is not higher for depot than oral drugs</td>
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<tr>
<td>• There is no evidence to suggest that neuroleptic malignant syndrome is a contraindication for subsequent depot use</td>
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<tr>
<td>• For the same drug, the risk of tardive dyskinesia is not higher for depot than oral formulations</td>
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<td>• Patients already on depot like this formulation and many prefer depot to oral drugs</td>
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<tr>
<td>• Although depots are sometimes associated with coercion and reduced patient autonomy, coercion is not very common</td>
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<tr>
<td>• Clinicians perceive a stigma to be associated with depots but this may be based on the worst characteristics of typical drugs (e.g. unacceptable side-effects) rather than on intramuscular long-acting injections per se</td>
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<td>• Most nursing staff are aware of the benefits of depots but their training experiences and pressure of time may adversely affect systematic monitoring of potential side-effects</td>
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<tr>
<td>• Depot clinics are relatively cheap to run and the financial benefits of avoiding rehospitalisation are clear-cut but acute services currently have preference in terms of service planning and budgeting</td>
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<tr>
<td>• Prescriber knowledge about depots may be suboptimal, resulting in use of inadequate dose and/or premature discontinuation of treatment, with subsequent poor clinical outcomes</td>
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**Patient acceptance**

Some clinicians believe that the depot formulation is not a good treatment option because patients have negative attitudes towards parenteral administration. In a survey of out-patients by Pereira & Pinto (1997), 87% of those receiving depot antipsychotics (with or without oral augmentation) would, given a free choice, elect to continue with their present dose form. Similarly, Wistedt (1995) found that more than 60% of patients converted to depot medication preferred the injection to their previous tablet treatment and said that they felt better during the injection regimen. In a qualitative survey, patients on depot felt that ‘more normal lives’ are possible and that depots were a safety net protecting them from relapses and rehospitalisations (Svedberg et al, 2003). In The Netherlands, out-patients receiving oral or depot antipsychotics were compared and were found to have similar attitudes towards their disease and medication use.
(Hoencamp et al, 1995). However, the patients were clearly biased towards the medication that they were receiving at the time.

Some patients prefer depot medication because the injections are easier to remember than daily tablets (Wistedt, 1995). Indeed, patients who have a tendency to deny their illness may be more comfortable with monthly or fortnightly injections than having to remember to take tablets daily. Others, however, fear the pain of intramuscular injections or consider injections to be intrusive or degrading (Glazer & Kane, 1992). Walburn et al (2001) conducted a systematic review of satisfaction with depot antipsychotic medication. In total, twelve main studies were considered: in ten of these, a positive opinion towards depot antipsychotics was expressed, in one a neutral opinion and in one a negative opinion. Five out of six studies that compared depot with oral antipsychotics showed patient preference for depots, although again, patients tended to state a preference for the formulation that they were taking at the time. Furthermore, in all of these studies it is only possible to present the opinions of patients who are willing to engage in the research process; as non-adherent patients rarely participate, their opinions are not necessarily represented. In this age of increasing consumer choice and decreasing medical paternalism, where concordance is preferred over compliance, the real issue is to ensure that a representative view of patients is obtained.

Stigma

A generally negative attitude towards ‘chemical’ treatments of mental diseases is sometimes found among patients’ families and friends (Gerlach, 1995; Kissling, 1997). When considering depot antipsychotics, Pereira & Pinto (1997) stated that

“Consumer advocates” concentrate on the undeniable adverse effects of antipsychotic drugs and upon the accusation that depot treatments involve an element of coercion’. 

In society at large, both public opinion and the media often support these views and throw suspicion on professions who use somatic means, especially depot injections, in their treatment of mental diseases. Much more information is needed for patients, relatives and the public to engender more balanced attitudes (Gerlach, 1995).

Some psychiatrists associate depot antipsychotics with ‘non-compliant’ or ‘bad’ patients (Glazer & Kane, 1992), but non-adherence to prophylactic or maintenance treatments is not unique to schizophrenia and is seen in many medical specialities (Cramer & Rosenheck, 1998). Unfortunately, there are few published data on psychiatrists’ attitudes to depot medication in the era of oral atypical antipsychotics. Further, it is not known how many clinicians feel that there is a stigma attached to depot medication and that they do indeed represent a more coercive form of treatment. As noted above, prescribing practices for depots vary, and in the USA it has been reported that White patients are less likely to receive depot medication than Black and Hispanic patients (Valenstein et al, 2001). This is either evidence of bias against people from minority ethnic groups or preferential treatment, depending on one’s point of view. There is also the possibility that, given the wide and successful publicity promoting the atypical agents – at the expense of the typicals (oral and depot) – depots have taken on the supposed worst characteristics of typical antipsychotics, namely unacceptable side-effects and even ineffectiveness. On the other hand, other clinicians will have experienced the disappointment of having a patient respond well to oral atypicals only to discontinue them and relapse.

Nursing staff involvement

In their systematic review, Walburn et al (2001) identified only a handful of studies that specifically investigated the nursing staff’s opinion of depot antipsychotics. Bennett et al (1995) suggested that community psychiatric nurses (CPNs) had a positive attitude towards their involvement with medication, but they were monitoring their patients for only three or four side-effects. The Royal College of Nursing’s guidelines now advocate the use of systematic assessment tools for side-effect monitoring (Royal College of Nursing, 1994). Further investigation of nursing staff involvement in the administration of depot drugs found that treatment and care planning involving both patients and nurses is essential to enhance patients’ autonomy (and empowerment), which is a precondition for satisfactory nurse–patient interactions (Marland & Sharkey, 1999). The authors further commented that the method of drug administration should not influence the patient’s right to information. Thus, the role of nursing staff in depot administration should also include advocacy and education.

For primary care practice nurses (who, in general, receive little training in depot administration), knowledge of schizophrenia, its treatment and medication side-effects are often poor. Practice nurses in one survey reported avoiding asking patients questions for fear of ‘opening a can of worms’. One nurse commented, ‘If they can’t be bothered to turn up, I can’t be bothered to chase them’ (Kendrick et al, 1998). It is hoped that specific training may lead to more positive attitudes.
External forces in healthcare systems: the plight of the depot clinic

Maintenance therapy is usually regarded as secondary to treatment of acute symptoms in terms of planning and financial budgeting, to the detriment of maintenance and prophylactic services. Indeed, Anderson et al (1989) reported that the depot clinic was perceived as being ‘out of date, not geared to the needs of the patient, inaccessible and unable to provide personalised care’. The financial incentives of preventing rehospitalisation, however, are self-evident and maintenance services such as depot clinics are comparatively cheap to run (Remington & Adams, 1995). O’Ceallaigh & Fahy (2001) suggested that the currently less fashionable depot clinic be renamed ‘maintenance medication clinic’ and include patients receiving oral atypical maintenance medication. Systematic economic studies should be undertaken to evaluate maintenance treatments such as depot antipsychotics and associated services to guide future planning.

The impact of prescribing knowledge and experience

Owing to the large variety of antipsychotics now available, the choice of maintenance medication has become more complicated. In a naturalistic study conducted in Slovenia, the best predictor for prescription of depot antipsychotics was previous use of depot formulations by the individual patient (Tavcar et al, 2000). So there is a positive cycle of familiarity and continued use. Depot medication is often regarded as useful only in those patients who are at high risk of non-adherence to treatment (Barnes & Curson, 1994; Davis et al, 1994). Some clinicians may be largely unfamiliar with current prescribing guidelines for depot antipsychotics (Kissling, 1994; Dencker & Axelsson, 1996) and therefore use inadequate doses or discontinue treatment too rapidly, or even prematurely, resulting in unfavourable outcomes in terms of relapse prevention.

Advantages of depot medication

Depot antipsychotics have several advantages over oral medication, including improved treatment adherence and hence reduced treatment failures, guaranteed and consistent delivery of the drug and reduced risk of side-effects and overdose (Box 3).

Improved treatment adherence and relapse prevention

Depot antipsychotics are generally considered to improve overall rates of treatment adherence with regard to consistency between the drug prescription and drug delivery, and the necessary addition of recordable and regular staff–patient contact. Patients not managed under a compulsory treatment order, however, may accept or refuse depot medication in the same way as any other treatment. Depot formulations do not overcome the problem of a patient failing or refusing to attend the clinic for their medication (Glazer & Kane, 1992; Barnes & Curson, 1994; Gerlach, 1995). In such cases, the clinical team can respond appropriately to reduce the risk of relapse by actively trying to re-engage the patient (Weiden & Glazer, 1997). Hence, depot antipsychotic medication largely overcomes the problem of covert non-adherence and enhances clinical management for overt non-adherence. Further, it should be noted that poor treatment adherence can in itself be a sign of impending relapse rather than a consequence (Curson et al, 1985). Depot antipsychotics are unable to prevent relapse completely; even in clinical trials there is an irreducible 20–25% of patients who relapse, despite receiving depots (Adams et al, 2001). If a patient discontinues depot treatment their risk of relapse increases, but if a patient relapses despite regular depot injections then non-adherence can be safely excluded as the cause (Barnes & Curson, 1994).

While it might be assumed that improved adherence to medication regimens will inevitably lead to reduced rates of relapse, demonstrating this in rigorous RCTs is not simple (Adams et al, 2001). Yet evidence from other study designs, such as ‘mirror image’ studies – which may or may not

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**Box 3 Advantages of depot antipsychotics over oral preparations**

- Improved treatment adherence, especially by overcoming covert non-adherence
- Easier early detection of relapse, improved relapse prevention and reduced rehospitalisation rates
- Enhanced consistency between the drug prescription and drug delivery
- More predictable and stable serum concentrations of the active drug
- Less variability between patients in steady-state blood levels for a given dose
- Lowest effective dose principle more safely achieved with depots (step-wise reduction)
- Reduced risk of accidental or deliberate self-poisoning (overdose)
involve random allocation to treatment – and in which outcomes are compared within individuals before and after introduction of depot medication, seems unequivocally in favour of depots (Davis et al, 1994).

**Consistent drug delivery**

Depot formulations allow more predictable and stable serum concentrations of the active drug than do oral formulations and may increase the likelihood that the blood levels remain in the therapeutic range over long periods (Glazer & Kane, 1992; Barnes & Curson, 1994; Remington & Adams 1995). Owing, it is presumed, to the avoidance of first-pass metabolism by the gastrointestinal system and liver, depot antipsychotics are also associated with less variability between patients in steady-state blood serum levels for a given dose than are oral formulations (Glazer & Kane, 1992; Gerlach, 1995; Darby et al, 1995). Notably, slight peaks in serum levels of the active drug have been observed shortly after depot administration and patients report an increase in side-effects (e.g. sedation) during the first few days after receiving their injections. However, the overall long-term benefits in avoiding daily oscillations related to the repeated ingestion of oral medication have to be balanced against this.

**Reduced risk of side-effects**

Clinicians are familiar with the concept of risk–benefit analysis when considering which dose to prescribe. At low depot drug doses, the clinical benefits are reduced and the risk of relapse is higher, whereas at high doses the probability of disabling side-effects is increased with limited benefits in terms of symptom improvement. Moderate doses are effective for most patients. Indeed, depot formulations are considered to provide a better and safer way to use the lowest effective dose principle to reduce the frequency of side-effects, as a gradual step-wise reduction can be achieved without incurring a significant risk of severe relapse. Lengthening the injection interval is also a safe, alternative method for reducing the overall dose of depot atypical antipsychotics (Baldessarini et al, 1988; Gerlach, 1995; Carpenter et al, 1999).

**Reduced risk of overdose**

It should also be remembered that deliberate or accidental self-poisoning with antipsychotic medication is avoided by depot prescription (Dencker & Axelsson, 1996). This important outcome measure is seldom investigated in clinical trials.

What will encourage physicians to prescribe depot antipsychotics?

In our surveys of attitudes to depot typical antipsychotic treatment held by psychiatrists and CPNs in the south-east of England, we found that a substantial minority believe that depots are old-fashioned (40% and 34% respectively), stigmatising (48% and 44%) and produce more side-effects than the oral typical antipsychotics (38% and 54%). The majority believe that depots are less acceptable to patients (69% and 61%) and their relatives (66% and 49%), but are better for monitoring treatment adherence (81% and 99%) and relapse prevention (94% and 89%) (Patel et al, 2003a,b, 2005). Compared with psychiatrists, significantly more CPNs felt that a patient’s autonomy was more compromised if they received a depot and also believed that prescribing depots was more coercive. Alternatively, psychiatrists were much more likely than CPNs to consider local inflammation at the injection site to be a rare event.

Psychiatrists also reported they could be persuaded to prescribe depot antipsychotics if they were associated with fewer side-effects, in patients where treatment adherence is an issue and if depot atypical antipsychotics were available. With the anticipated change in legislation in the UK to allow for community treatment orders, a significant majority of psychiatrists surveyed would use the legislation to continue depot administration with the aim of preventing further morbidity. Certainly the need for depot formulations continues and the first depot atypical (risperidone long-acting injection) shows promise, with efficacy equivalent to that of oral risperidone and a similar side-effect profile (Altamura et al, 2003; Fleischhacker et al, 2003; Kane et al, 2003). Depot risperidone uses microsphere technology rather than the traditional esterification. Risperidone microspheres have different pharmacokinetics, requiring two or three fortnightly injections before therapeutic levels are reached.

A recent Australian survey highlighted that the lack of depot atypical preparations was the major reason for the common but generally frowned-upon practice of concurrent depot-plus-oral atypical prescribing in forensic patients (Bains et al, 2003). Now that the first of the depot atypicals is available, these drugs may simplify the formulation dichotomy between typicals and atypicals (Tavcar et al, 2000; O’Ceallaigh & Fahy, 2001) (Box 4).

In our studies we found significant correlations between attitudes to depot medication and knowledge about depots. General knowledge was associated with more favourable attitudes (psychiatrists: $r = 0.39$, $P<0.001$; CPNs: $r = 0.33$, $P = 0.006$) (Patel...
Why aren’t depot antipsychotics prescribed more often?

Box 4 Antipsychotic drugs – class, formulation and characteristics

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<th>Class</th>
<th>Typical</th>
<th>Atypical</th>
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<tr>
<td>Formulation</td>
<td>Typical</td>
<td>Atypical</td>
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<tr>
<td>Oral (tablets)</td>
<td>Non-adherence more difficult to detect</td>
<td>Many types available</td>
</tr>
<tr>
<td></td>
<td>Worse relapse prevention over time</td>
<td>Several types available (since 1990s)</td>
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<td></td>
<td>Higher rehospitalisation rates</td>
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<td></td>
<td>Less-invasive delivery</td>
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<tr>
<td>Long-acting depot injections</td>
<td>Non-adherence more easily detected</td>
<td>Many types available</td>
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<tr>
<td></td>
<td>Better relapse prevention</td>
<td>Only one currently available</td>
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<tr>
<td></td>
<td>Reduced rehospitalisation rates</td>
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<td>More-invasive delivery</td>
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et al, 2003a, 2005). These associations do not necessarily show causality. However, Lambert et al (2003), in their survey of Australian mental health professionals, noted that potential barriers for switching to depot antipsychotics included fear of relapse as well as uncertainty of switching method, both of which could be addressed by augmenting clinicians’ knowledge about depots. To date, suggestions to improve this state of affairs, for example using publications, conferences and continued medical education, have had little impact.

Conclusions

At present, depot antipsychotics have an image problem, even though patients already receiving depots like them, as do many psychiatrists, and with good reason. The depot formulation has several advantages over oral medication, including improved treatment adherence and consistent drug delivery. Glazer & Kane (1992) stated that if psychiatrists ‘want depot medication to work, they must weigh the negative aspects against the positive ones and believe in what they are doing’. We would add that this must be a collaborative process with patients and carers. Updating psychiatrists’ knowledge about depot formulations may lead to more positive attitudes. Similarly, educating patients’ relatives, friends and the general public may result in a more balanced attitude to antipsychotic medication in general, as well as to depot injections in particular. This may result in pressure on psychiatric healthcare systems to re-evaluate their maintenance therapy services in terms of both planning and budgeting. However, with the likely impact of the community treatment order on depot use, it is perhaps inevitable that the parenteral route of administration will always have associations with coercion. Future research should therefore address the issues of coercion, stigma and patient autonomy.

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Why indeed?

INVITED COMMENTARY ON... WHY AREN’T DEPOT ANTI PSYCHOTICS PRESCRIBED MORE OFTEN AND WHAT CAN BE DONE ABOUT IT?

Thomas R. E. Barnes

A recent review concluded that replicated, evidence-based studies have demonstrated several areas of advantage for long-acting antipsychotics over oral antipsychotics. These include improved global outcome and reduced risk of rehospitalisation, psychopharmacological benefits such as more consistent bioavailability and more predictable dose–blood level correlations, an improved pharmacokinetic profile allowing lower dosages to be used with a consequent reduced likelihood of side-effects, and a reduced burden of care when injections are required only every 2–6 weeks (Robert & Geppert, 2004). Further, if a patient relapses despite receiving uninterrupted depot treatment, this indicates the need to consider reasons for deterioration other than poor adherence. However, perhaps the critical advantage over oral preparations is the avoidance of covert non-adherence (Barnes & Curson, 1994).

With depot treatment, any decision by the patient not to continue medication will be signalled by failure to attend for, or refusal of, injection. The clinical team can therefore act to intervene appropriately,
bearing in mind that non-adherence may be both a cause and consequence of worsening of illness. Lastly, with depot preparations the risk of self-poisoning is reduced.

The disadvantages relate to the relatively stable plasma drug concentrations, leading to a lack of flexibility should side-effects develop or when titrating the dose clinically. However, clinical experience suggests that long-acting formulations in standard dosage have a relatively low side-effect burden, and specific notions that such preparations are associated with an increased risk of neuroleptic malignant syndrome and extrapyramidal side-effects, particularly tardive dyskinesia, have not been supported by reviews of the published evidence (Glazer & Kane, 1992).

An image problem

Given the apparent benefits of depot preparations, why, as Patel & David (2005, this issue) ask, are they not used as often as they used to be? These authors essentially give two main reasons. First, they refer to an ‘image problem’: clinicians believe that patients and the wider community have negative attitudes to depot. Patel & David argue that this is a misapprehension, and adduce results from a host of studies that suggest that at least a proportion of people with severe, enduring mental illness prefer depot administration of antipsychotics, because of its perceived efficacy, its function as a ‘safety net’ protecting them from risk of relapse and hospitalisation (Svedberg et al., 2003) and its usefulness in obviating the need to remember to take tablets on a daily basis. Nevertheless, despite such positive reports, people switched from a depot first-generation antipsychotic to an oral second-generation drug may favour the latter (Desai et al., 1999; Godleski et al., 2003).

Demonstrating that some patients are satisfied with their current treatment does not address what is perhaps a broader image problem for depot medication. Clinicians may have a lingering concern that, in the public perception, the parenteral route of administration is associated with the patient as a passive recipient at best, and with coercion at worst. The use of the depot route may be seen as the cautious choice for clinicians faced with cultural, ethnic or communication barriers (Ziguras et al., 1999). There is also the awareness that, with their long half-lives, depot preparations inevitably delay the opportunity for a patient to reverse any decision about continuing with medication. Thus, clinicians may fear that the process of the regular administration of injections, apart from having the potential to be rather ignominious and painful, might symbolise a relationship between prescriber and patient that is incompatible with a clinical culture that seeks to approach patients in a respectful and empathic manner and encourage communication of any treatment concerns. But it is precisely in the context of such a culture of concordance, involving informed choice and unbiased discussion of the treatment options available, that the ethical and clinical issues surrounding depot treatment can be adequately addressed, and the restrictive notion of depot as a ‘treatment of last resort’ dispelled (Robert & Geppert, 2004).

The restricted evidence

The second main reason propounded by Patel & David for the reduction in depot use is that clinicians may not adequately consider the risk–benefit balance with depot antipsychotics. This may partly reflect the nature and amount of relevant evidence available. For example, the studies comparing depot and oral medication in terms of risk of relapse that show only modest differences may for two reasons underestimate the value of depot in clinical practice. First, as Patel & David point out, in most cases the trial period was too short to reveal the longer-term benefits of depot treatment. In one of the longer studies comparing depot and oral antipsychotic treatment, Hogarty et al (1979) found no difference in the proportion relapsing within the first year, but a significant advantage for depot emerged in the second. Second, the patients for whom depot is commonly indicated, that is, those with a history of poor adherence, may be underrepresented in the studies. Recruitment seems to have been biased towards the inclusion of patients with a lower risk of non-adherence to treatment (Schooler, 2003), which would serve to diminish any advantage for depot compared with unreliable tablet-taking in the oral treatment group. That patients consenting to participate in clinical studies will tend to be more treatment adherent than those failing to consent is a problem relating to generalisability of results that may be ubiquitous in trials in schizophrenia (Bowen & Barnes, 1994).

Clinicians will face a similar lack of robust evidence if they try to weigh the possible risks and benefits of traditional depot drugs, all of which are first-generation antipsychotics, against those of a second-generation drug, only one of which, risperidone, is as yet available as a long-acting injection. There is accumulating evidence that the second-generation drugs may have advantages over those of the first-generation in terms of efficacy, including relapse prevention (Leucht et al., 2003), and safety, with a lower liability for extrapyramidal side-effects, including tardive dyskinesia (Correll et al,
2004), but these findings predominantly relate to comparisons of oral first- and second-generation antipsychotics. At present, there is a paucity of long-term trials systematically comparing depot formulations and oral second-generation drugs on key clinical outcome measures.

References


Thomn Barnes is Professor of Clinical Psychiatry at Imperial College (Department of Psychiatry, Imperial College Charing Cross Campus, Reynolds Building, St Dunstan’s Road, London W6 8RP, UK. E-mail: t.r.barnes@imperial.ac.uk). He has a long-standing interest in the evidence base for the rational prescribing of antipsychotic drugs. Professor Barnes has received consultation fees from the pharmaceutical industry and recent funding from Sanofi-Synthélabo for an investigator-initiated clinical trial.
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Thomas R.E. Barnes

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