Atypical and conventional depot medications

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The introduction of atypical antipsychotics created a therapeutic dilemma between choosing the oral novel antipsychotic or the conventional depot form. Clinicians want the advantages of both, resulting in higher levels of polypharmacy. Modern psychiatry is probably in a transitional stage from the depot culture to safer oral medications or even to a safer depot culture.

The lack of psychophysiological parameters makes diagnosis and treatment of psychotic illness complex. Making matters worse, there are many ambivalent ideas in psychiatry compared to other specialities. This hinders the study and evaluation of psychotropic drugs.

The side effects of the novel antipsychotics (clozapine, risperidone, olanzapine, amisulpiride, quetiapine) are more acceptable for most patients. Since the introduction of the novel antipsychotic drugs patients seldom say that the side effect is more unbearable than the illness. Atypicals are not free from side effects but have different, more tolerable side effects. When anxiety and depression are contributing to, or exacerbating the onset of psychosis, the mood-stabilizing and anxiolytic properties of atypicals have an added therapeutic value in early intervention in cases of psychosis.

ORAL ATYPICAL ANTIPSYCHOTICS *VS* DEPOT MEDICATIONS

One US study (Ayd, 1999) comparing rehospitalization rates among patients discharged from hospital receiving clozapine, risperidone or depot antipsychotics found the probability of readmission within the first year after discharge was 17% for risperidone, 13% for clozapine, and 26% for haloperidol and fluphenazine decanoate depot formulations. These highlight that atypical antipsychotics have lower readmission rates than depot injections. It has been suggested that the superiority of atypical preparations in preventing rehospitalizations may be a result of both improved compliance and better antipsychotic effect. There has not been much research in this area.

When atypical antipsychotics were introduced, clinicians started many patients who were already on depot injections on the newer drugs, allowing the depot drug to continue as well. Eventually the doses of the depots were reduced but most clinicians, carers and patients were reluctant to stop the depot altogether in case this resulted in relapse. Even though reduction of the dose of depot drug has some advantages, this has resulted in polypharmacy. Good practice dictates that patients should receive only one antipsychotic drug, preferably in a single formulation (Taylor, 1999; British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2001).

A number of double blind trials have indicated that chronic schizophrenic patients can be equally well maintained on oral and depot medications (Schooler et al, 1980). The use of atypical antipsychotics as an add-on therapy while patients are on depot or other antipsychotic medications has been questioned, particularly in the case of risperidone, by suggesting that the balance between dopamine (D_2) and serotonin ($5HT_2$) blockade of risperidone would be disturbed by concurrent treatment with a conventional antipsychotic which has potent D_2 blockade properties (Livingston, 1994).

Polypharmacy is not desirable but is common either because of overenthusiasm of clinicians or pressure from patients for speedier recovery. It is important that psychiatrists and patients allow the drug time to work properly. Polypharmacy causes confusion between therapeutic efficacy, side effects and the risk of drug interactions. Sometimes it is used with patients with more than one diagnosis, to enhance a specific therapeutic action (*Table 1*). Concomitant use of two antipsychotics while switching from depot medication to atypical is justifiable but only for a short period.

A high prevalence of combining depot antipsychotics and novel antipsychotics in forensic patients has been reported without theoretical validation but this reflects the hands-on problems

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of this subspecialty (Bains and Nielssen, 2003). There may be circumstances, as there are in treatment of most illnesses, when rational, evidence-based combination therapy can be advantageous.

Anticholinergic medications

Use of anticholinergic drugs to counteract the side effects of conventional depot antipsychotics is another drawback and they are sometimes inappropriately prescribed for every single case. Short-term prescription of anticholinergic medications has some advantages (*Table 2*).

Anticholinergic drugs have their own side effects, which include dry mouth, blurred vision, hot dry skin, hyperpyrexia, changes in behaviour (aggression and paranoid ideas), changes in cognition (impairment of recent memory to acute confusional states, inattention, slowness of thought process), and less commonly tactile hallucinations, urinary retention and decreased gut mobility. Anticholinergics can slow or reduce the benefits of antipsychotics and have been blamed for influencing drug absorption from the gut. Anticholinergic drugs are also thought to lower the plasma levels of phenothiazines (Loga et al, 1975). They may also uncover latent cases of tardive dyskinesia (TD) or exacerbate existing conditions (Casey, 1978), and they may also produce a choreiform dyskinesia (DeSilva, 1977) (*Table 2*).

Patients prescribed the novel antipsychotics do not require anticholinergic medications so often and thereby are spared their side effects. Atypical antipsychotics are not totally free from side effects. Clozapine is associated with agranulocytosis and seizures. Olanzapine is linked to weight gain, amisulpiride with hyperprolactinaemia and risperidone at a higher dose causes extrapyramidal side effects (EPS). There are several case reports of severe hypertriglyceridaemia with olanzapine, quetiapine and clozapine (Meyer, 2001).

It is well-recognized that depressive symptoms may co-exist with schizophrenia (Docherty et al, 1978). Antipsychotic agents including certain depot preparations were alleged to have a depressant effect (Falloon et al, 1978). Antiparkinsonian drugs also cause depressive symptoms and if a patient is taking both depot and anticholinergic drugs the diagnosis is more difficult (Ayd, 1975). Depression is reported to be more common in patients on a high dose of depot medication and/or who showed EPS (Johnson, 1981). One of the atypical features of the novel antipsychotics is their favourable effect on mood symptoms, which prompts clinicians to prefer them over the long-established ones. The merits of atypical drugs over standard depots are listed in *Table 3*.

THE ATYPICAL LONG-ACTING ANTIPSYCHOTIC INJECTION

Within Europe, depot is most popular in the UK, particularly in community psychiatry. Depots are more widely used in the UK than the USA. Depot medications are rejected by some patients; one of the reasons for this has been their unwanted drug effects (Carney and Sheffield, 1976). It was thought that the lack of a depot formulation may limit the use of atypical drugs to compliant patients or those who could readily be supervised. The need for an atypical antipsychotic depot was satisfied by the introduction of Risperdal Consta (Janssen Cilag, High Wycombe, Bucks) which has filled a therapeutic gap.

TABLE 1.
Factors leading to psychiatric polypharmacy

Concurrent treatment of multiple symptoms
Treatment of multiple illnesses
Strong biological views of mental illnesses
Involvement of more than one prescriber with different clinical views
Adjunctive treatment of side effects
Management of co-existing mood symptoms
Augmentation therapies
Availability of multiple drugs

TABLE 2.
Anticholinergic drugs

Benefits	Prevention and treatment of extrapyramidal side effects
	Facilitates compliance
	Might help relieve negative symptoms
	Help differential diagnosis between negative and residual symptoms of schizophrenia and extrapyramidal side effects
Problems	Anticholinergic side effects
	Side effects in turn endangering therapeutic alliance
	May worsen positive symptoms
	May interact with other psychotropic medications
	Abuse potential
	Procyclidine causes insomnia
	Lower the plasma levels of phenothiazines
	Antagonize or slow the therapeutic effects of neuroleptics
	Influence the absorption of drugs from the gut
	May mask the objective monitoring (hypokinesia and rigidity) of neuroleptic administration
	May produce choreiform dyskinesia
	Uncover latent cases of tardive dyskinesia
	Exacerbate existing tardive dyskinesia
	Added cost

Clinical monitoring of any new drug is paramount, and is derived from three sources:

1. Mandatory monitoring required by the regulatory authorities
2. Special monitoring procedures suggested based on the knowledge of a drug's adverse effects
3. Monitoring implicit in good clinical management when using a new drug.

Risperdal Consta should be subjected to these monitoring policies and demands fairly intensive observations even though the oral form of risperidone has been available for nearly 8 years.

Risperidone has a cleaner side-effect profile than the conventional antipsychotics at reduced doses (6 mg or under), and was introduced in 1994. It is a benzisoxazole derivative with selective balanced antagonism of $5HT_2$ and D_2 receptors (Janssen et al, 1988). Unwanted dopaminergic blockade in the nigrostriatal tract is partially overcome through blockade of 5HT receptors, thereby lessening EPS. Potent dopaminergic blockade in the mesolimbic area attenuates positive symptoms.

Hypodopaminergia in the prefrontal cortex, which underlies negative symptoms, responds to a net increase in dopaminergic activity as a result of D_2 and $5HT_2$ receptor antagonism (Leysen et al, 1994). The possible thymoleptic action of $5HT_2$ receptor antagonism may benefit patients with prominent affective symptoms (Keck et al, 1996). The metabolite of risperidone is 9-hydroxyrisperidone which has the same pharmacological profile. Risperidone is rapidly absorbed and plasma concentration peaks about 2 hours post-injection. Pharmacokinetics for doses of 0.5–25 mg/day are linear (Mesotten et al, 1989). Risperidone is effective for both positive and negative symptoms of schizophrenia (Marder and Meibach, 1994).

TABLE 3.
Comparison of atypical oral and classical depot antipsychotics

Atypical oral antipsychotics	Favourable side-effect profile
	Rarely require anticholinergic drugs
	Better efficacy against positive and negative symptoms
	Better efficacy in treatment-resistant patients
	Mood symptoms are benefited
	Fewer affective side effects
	Negligible effect on prolactin level
	Better adherence
	Not perceived as invasive
	Enhances participation in psychosocial treatments, augmenting the overall clinical effectiveness
	Drug effects can be stopped by withdrawal of the drug
	Less impact on fecundity, but their use in pregnancy and lactation needs further investigation
	Less stigma
	Perceived as more modern
Classical depot antipsychotics	Pervasive, unpleasant, disabling and dangerous side effects
	Require anticholinergic drugs which have their own side effects
	Minimal efficacy on negative symptoms Might contribute to negative symptoms
	Ineffective
	No favourable effect on mood symptoms
	Can cause depressive mood symptoms
	Adverse effect on prolactin level
	Forced adherence and a sense of being overly controlled
	Too invasive
	Negative symptoms are an impediment to social rehabilitation
	Drug effects cannot be stopped immediately
	More stigma
	Perceived as old fashioned

Side effects

Risperidone is believed to carry a lower risk of EPS and TD (Owens, 1996). However, risperidone-induced EPS have been reported including dystonia, akathisia, rigidity and TD (Faulk et al, 1996), and one study showed comparable incidence and severity of EPS to haloperidol (Rosebush and Mazurek, 1999). More side effects of risperidone are being reported and clinicians should be aware of this when patients are given risperidone (Vasudevan et al, 2002).

There are sporadic reports of TD in patients on long-term treatment with risperidone (Buzan, 1996). The incidence of TD in patients treated with risperidone for at least 1 year has been estimated at around 0.3% (Brecher, 1996). Even though risperidone is feared to produce TD, there is a claim that it may improve TD (Chouinard and Jones, 1993), which needs thorough evaluation.

Risperidone requires upward titration. The dose should be gradually increased from 1 mg to avoid postural hypotension. A dose above 10 mg has no clinical advantage but the movement disorder profile resembles that of haloperidol (Janssen Cilag, data on file, 1991, 1992). Weight gain is also reported (Cardoni, 1995). In open-label long-term studies weight gain averaged 2.3 kg (C Mertens, unpublished data, 1992).

Risperidone is associated with antipsychotic malignant syndrome (Sharma et al, 1996). A dose-related rise in prolactin is seen which could cause menstrual upset, diminished libido, galactorrhoea, gynaecomastia and osteoporosis. Risperidone shares some adverse effects with standard antipsychotics (Taylor, 1997). Hepatotoxicity is occasionally reported (Fuller et al, 1996) and agranulocytosis is extremely rare (Godleski and Sernyak, 1996). Risperidone-induced pseudomyasthenic

syndrome has been reported (Hadjikoutis and Fish, 2002). Blood monitoring is not essential but periodic tests are advisable.

Formulation

In Risperdal Consta, risperidone is encapsulated in biodegradable polymer microspheres, which slowly dissolve inside the muscle. A small amount is released in the first 3 weeks; the main drug release starts in week 4 and peaks in weeks 5–6. Owing to this time lag in onset of its effect, clinical benefit may not be observed for 3 weeks from initiating treatment. Intramuscular (IM) risperidone is available in the UK, Germany, Austria, New Zealand and Mexico and is under review in a number of other countries. The Food and Drug Administration has not authorized its use in the USA because of concern about increased risk of cancer found when testing the drug in rodents.

IM risperidone has not been studied in patients younger than 18 years or those with hepatic and renal impairment and should be used with caution in these groups. The price of 1 year's treatment with risperidone IM formulation is £2156 for 25 mg dose fortnightly, £3012 for 37.5 mg fortnightly, £3862 for 50 mg fortnightly and £940 for oral risperidone 4 mg per day. One disadvantage of IM risperidone is that its dosing interval is not flexible. This is similar to the classical depots except for fluspiriline which has a dose interval of 1 week. Risperdal Consta has only a limited range of formulations (25 mg, 37.5 mg and 50 mg). If IM risperidone causes injection site reactions (as cautioned in the British National Formulary) like the fluspiriline depot, its use would be restricted.

THE CONVENTIONAL DEPOTS

Conventional depot preparations in the UK include fluphenazine enanthate (Moditen, Sanofi-Synthelabo, Guildford), fluphenazine decanoate (Modecate, Sanofi-Synthelabo, Guildford), flupenthixol decanoate (Depixol, Lundbeck, Milton Keynes), fluspiriline (Redeptin, Janssen Cilag, Berchem, Belgium), pipothiazine palmitate (Piportil, JHC Healthcare Ltd, Hitchin), haloperidol decanoate (Haldol, Janssen Cilag, High Wycombe), zuclopenthixol decanoate (Clopixol, Lundbeck, Milton Keynes), zuclopenthixol acetate (Clopixol-Acuphase, Lundbeck, Milton Keynes).

Fluphenazine

Fluphenazine enanthate was introduced in UK in 1966 and decanoate in 1968. Enanthate and decanoate have different pharmacokinetics; the former is rapidly released into the bloodstream and so requires frequent administration, resulting in severe EPS. Fluphenazine decanoate is intrinsically long acting and is esterified with decanoic acid and then dissolved in sesame oil. It is a potent phenothiazine which can be given once every 4 weeks as a depot. It is the most commonly prescribed depot and is often given above the maximum British National Formulary limit, running the risk of causing TD. It is used to treat agitated or aggressive patients with schizophrenia and is contraindicated in severely depressed states.

Flupenthixol

Flupenthixol decanoate, introduced in 1970, is a dopamine-specific thioxanthene antipsychotic with potentially activating and/or stimulating effects at low dose. It can be given weekly but fortnightly is usually more appropriate. It is useful in treating retarded or withdrawn schizophrenia sufferers as it has an apparent alerting quality. It may be the antipsychotic drug of choice in patients with bipolar affective disorder as it is likely to protect against depressive relapse. Flupenthixol is not recommended in agitated or aggressive patients with schizophrenia because of its alerting nature.

Fluspiriline

Fluspiriline is a diphenylbutylpiperidine antipsychotic available only on a named-patient basis as a water-based microcrystalline injection. It often leads to tissue damage when fluspiriline precipitates out in the muscle. This preparation has been reported to cause subcutaneous nodules resulting in local irritation and necrosis.

Pipothiazine

Pipothiazine palmitate can be administered in a 4-weekly dosage regimen.

Haloperidol

Haloperidol decanoate is a longer-acting depot. A 4-weekly interval between injections is possible but dose titration can be difficult. It is best reserved for patients who respond to haloperidol.

Zuclopenthixol

Zuclopenthixol is a well-established depot in the UK. It has been used in high doses in aggression, particularly in patients with learning disabilities and forensic patients in view of its sedative nature. It is more sedative than fluphenazine decanoate. As it may exacerbate psychomotor retardation, zuclopenthixol is not preferred in these patients. Zuclopenthixol acetate, as a single dose of between 50 and 150 mg, provides rapid and effective symptom reduction in acute psychotic conditions over about 78 hours. It is really a specialist short-acting depot for emergency situations. It has replaced the use of phenothiazines in acute psychi-

atric emergencies. Zuclopenthixol reaches a peak blood level about 32 hours after a 100 mg dose.

It is also an alternative to haloperidol to control an acutely disturbed patient as it is more sedative than haloperidol. It is suggested that treatment should not exceed 2 weeks with a maximum of 400 mg for each injection and should not be used more than twice in a row. Clinical experience suggests that all depot preparations have similar efficacy and toxicity, different patients having idiosyncratic responses to them.

Long-acting medications are useful for prophylaxis of bipolar affective disorder in patients who have poor compliance with oral medication. Depot medication protects against hypomanic relapse and it may protect against subsequent depressive relapse. Low-dose antipsychotics, including depots, have a broad spectrum of efficacy in acute use, with effects against symptom severity of depressed mood and impulsivity, as well as anger, hostility and psychotic symptoms (Cowdry and Gardner, 1988). *Tables 4* and *5* detail the depot antipsychotic formulations and their prices.

DISCUSSION

Non-compliance is overt rather than covert and depot medication does not guarantee cooperation, but makes it easier to monitor compliance. Once non-compliance is detected, the clinician can address this. Ideally, adherence to medication should be achieved through compliance therapy (psychoeducation and cognitive therapy), not through invasive treatment methods. Assertive outreach is promising for existing patients who are non-compliant and relapse repeatedly.

Depot formulations encourage regular contact between patient and management team, simplifying and assuring medication delivery. If a patient misses an injection, there is no abrupt discontinuation. One disadvantage of depot medication is potential negligence by prescribers, as once a depot is commenced the same dose of medication is carried on indefinitely, even after recovery from illness. This can be avoided if drugs are reviewed frequently and a proper understanding is established between prescribers, carers and recipients.

Side effects, labelling and stigmatization apply to all psychotropic drugs. Social dignity of psychiatric patients is important; both psychotic symptoms and EPS cause social stigma. Clinicians must weigh the consequences of mental illness against the stigmatization of treatment. Only time will tell whether the novel antipsychotics also carry the risk of TD, a dreaded side effect of antipsychotics. It has been suggested that TD is a neuropathological feature associated with schizophrenia, and it has been reported to occur independently of antipsychotic drugs (McCreadie et al, 2002).

Although depot antipsychotics were introduced to control both positive and negative symptoms of schizophrenia, the depot itself produces negative symptoms at high doses. Biological and forensic psychiatrists are more adventurous with high doses of depot antipsychotics. There is no evidence that large loading doses of antipsychotic enhance response. Mega-doses of antipsychotic have been associated with sudden death and such practice has been challenged (Hirsch and Barnes, 1994). Some biological psychiatrists believe that the only advantage of atypical antipsychotics is improved tolerability (Mattes, 1997). Some feel that depot injections may sometimes be appropriate for short-term therapies, just as oral drugs have a place in longer duration treatments. Some practitioners prefer to use depots to win patients' confidence during initial treatment and then change to oral preparations. Depot medications may reduce the risk of relapse in the maintenance phase for some patients.

TABLE 4.
Classical depot formulations

Generic name	Proprietary name	Equivalent doses (mg)	BNF maximum (mg/week)	Preferred interval
Fluphenazine enanthate	Moditen	25	50	2 weeks
Fluphenazine decanoate	Modecate	25	50	2–5 weeks
Flupenthixol decanoate	Depixol	40	400	2–4 weeks
Fluspiriline	Redeptin	2	10	1 week
Pipothiazine palmitate	Piportil	25	50	4 weeks
Haloperidol decanoate	Haldol	50	75	2–4 weeks
Zuclopenthixol decanoate	Clopixol	200	600	2–4 weeks

BNF = British National Formulary

TABLE 5.
Cost of depot formulations

Generic name	Strength	Cost
Fluspiriline	2 mg	£30
Flupenthixol decanoate	300 mg	£55.41
	400 mg	£167.92
Fluphenazine decanoate	12.5 mg	£1.35
	100 mg	£18.20
Haloperidol decanoate	50 mg	£4.35
	300 mg	£17.30
Zuclopenthixol decanoate	200 mg	£3.38
	500 mg	£31.98
Zuclopenthixol decanoate concentrate	500 mg	£45.50
Risperidone	25 mg	£82.93
	37.5 mg	£115.84
	50 mg	£148.55

The National Institute for Clinical Excellence (NICE) (2002) has authorized the use of atypical antipsychotics. No advice on IM formulations was given as no such products were available at that point. The guidelines suggest that relapse prevention is the main aim of treatment of schizophrenia. Patients taking novel antipsychotics who develop side effects may have to try standard antipsychotics. A certain drug may be found to be superior at a specific time with a certain patient. Risperdal Consta is expensive but it is claimed to be cost effective as it might prevent relapses and reduce readmissions. Risperdal Consta may be the first of a new series of novel depot formulations.

There is a vast literature on depot medications but only a few data assess patient satisfaction or their attitude towards depot drugs. These data do not look at outcomes such as user satisfaction, quality of life and economic variables. Future research should also compare depot *vs* atypical antipsychotic drugs. Social and environmental factors in the treatment of schizophrenia should not be ignored and all relapsing patients should have their needs for drug and psychological therapy assessed.

Depot preparations were initially indicated only for actively suicidal and violent patients but they came to be seen as valuable for maintenance treatment. Newer oral antipsychotic agents mean that their use could now be reserved for such patients. The depot medication is a highly dynamic treatment with psychological and social benefits. **HM**

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KEY POINTS

- Atypical oral antipsychotics are superior to depot medications in treatment of compliant patients.
- Polypharmacy is an undesirable practice
- Compliance therapy should be tried before initiating depot medications.
- The advantages and disadvantages of intramuscular risperidone require further research. It is too early to comment on the incidence of tardive dyskinesia with risperidone.