

Intramuscular Preparations of Antipsychotics

Uses and Relevance in Clinical Practice

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Abstract

Intramuscular formulations of antipsychotics can be sub-divided into two groups on the basis of their pharmacokinetic features: short-acting preparations and long-acting or depot preparations. Short-acting intramuscular formulations are used to manage acute psychotic episodes. On the other hand, long-acting compounds, also called 'depot', are administered as antipsychotic maintenance treatment to ensure compliance and to eliminate bioavailability problems related to absorption and first pass metabolism.

Adverse effects of antipsychotics have been studied with particular respect to oral versus short- and long-acting intramuscular formulations of the different compounds. For short-term intramuscular preparations the main risk with classi-

cal compounds are hypotension and extrapyramidal side effects (EPS). Data on the incidence of EPS with depot formulations are controversial: some studies point out that the incidence of EPS is significantly higher in patients receiving depot preparations, whereas others show no difference between oral and depot antipsychotics.

Studies on the strategies for switching patients from oral to depot treatment suggest that this procedure is reasonably well tolerated, so that in clinical practice depot antipsychotic therapy is usually begun while the oral treatment is still being administered, with gradual tapering of the oral dose.

Efficacy, pharmacodynamics and clinical pharmacokinetics of haloperidol decanoate, fluphenazine enanthate and decanoate, clopenthixol decanoate, zuclopenthixol decanoate and acutard, flupenthixol decanoate, perphenazine enanthate, pipothiazine palmitate and undecylenate, and fluspirilene are reviewed. In addition, the intramuscular preparations of atypical antipsychotics and clinical uses are reviewed. Olanzapine and ziprasidone are available only as short-acting preparations, while risperidone is to date the only novel antipsychotic available as depot formulation.

To date, acutely ill, agitated psychotic patients have been treated with high parenteral doses of typical antipsychotics, which often cause serious EPS, especially dystonic reactions. Intramuscular formulations of novel antipsychotics (olanzapine and ziprasidone), which appear to have a better tolerability profile than typical compounds, showed an equivalent efficacy to parenteral typical agents in the acute treatment of psychoses. However, parenteral or depot formulations of atypical antipsychotics are not yet widely available.

1. Different Antipsychotic Formulations: Mechanisms of Action and General Pharmacokinetic Considerations

Antipsychotic drug treatment was introduced into clinical psychiatry in the 1950s with chlorpromazine. Since then, molecules of different chemical structures, ranging from tricyclic phenothiazines to thioxanthenes, butyrophenones, dibenzoxazepines, substituted benzamides, and benzisoxazole derivatives have been used in the treatment of psychotic disorders. In addition, the new 'atypical' antipsychotics, developed after the successful re-introduction of clozapine, have been developed and employed widely for the treatment of major psychoses.

These drugs were developed to overcome limitations mainly due to extrapyramidal side-effects (EPS) of typical antipsychotics which are dopamine D₂ antagonists. They are a heterogeneous group of compounds (amisulpride, clozapine,

risperidone, olanzapine, quetiapine and ziprasidone) with high affinity for 5-HT_{2A} receptors, but also for D₁ and D₂ receptors.^[1] These pharmacodynamic properties are likely to be responsible for their higher efficacy particularly on the negative/anergic/depressive dimension of schizophrenia.^[2,3] On the other hand, it should be noted that a meta-analysis completed on 52 randomised trials comparing atypical with conventional antipsychotics suggested that when the dose was less than 13 mg/day of haloperidol (or equivalent), atypical antipsychotics had no benefits in terms of efficacy or overall tolerability^[4] compared with typical compounds.

Antipsychotics have been always available in both oral and parenteral formulations. In the 1960s long-acting or 'depot' formulations of typical antipsychotic drugs were added for clinical use by parenteral route. Depot antipsychotics are effective and can be safely used, and they may confer a

small benefit over oral compounds on the global outcome of the patient.^[5] Most of them are synthesised by esterification of the active drug to a long chain fatty acid and are subsequently dissolved in a vegetable oil.^[6] Depot treatment of psychotic outpatients offered some advantages when compared with conventional formulations of the same compounds, that is better compliance and bioavailability,^[7,8] and they may be used in the maintenance treatment of psychotic patients, usually after clinical stabilisation with oral treatment.^[9]

The attitudes of long-term psychiatric patients towards depot antipsychotic medication is generally positive, although future randomised, controlled trials should include satisfaction as an outcome measure.^[10,11] The pharmacokinetic profiles show prolonged times to reach peak plasma concentrations, as well as extended elimination half-lives especially after multiple injections.^[12] However, even when the active molecule is the same, there can still be differences in reaching the peak concentration depending on the vehicle of esterification used, as in the case of fluphenazine enanthate and decanoate.^[13-15]

Short-acting intramuscular preparations of antipsychotics are particularly suitable for the management of acute psychotic symptoms, agitation and aggressive behaviour or delirium.^[16] This indication is supported by the fact that intramuscular formulations bypass the gastrointestinal tract and the first-pass metabolism, being immediately active. Rapid tranquillisation with intramuscular

preparations is preferred over oral medication when patients are not co-operative and require medication with a faster onset of action and good bioavailability.^[15]

In this article we review the uses and advantages of short- and long-acting intramuscular preparations of antipsychotics, taking into account recent advances in this field, such as the development intramuscular preparations for the atypical antipsychotics risperidone, olanzapine and ziprasidone.

It should be noted that in the more recent literature there is paucity of data on depot formulations of typical antipsychotics. This is probably because of the growing interest in novel compounds seen as a more effective treatment in the long-term management of psychotic disorders, with a favourable tolerability profile.^[17]

2. Long and Short Acting Intramuscular Preparations

2.1 Types of Preparations and Therapeutic Indications

Intramuscular formulations of antipsychotics can be subdivided into two groups on the basis of their pharmacokinetic features:

- short-acting preparations (time to peak plasma concentration 30 minutes);
- long-acting or depot preparations (half-life ranging from 3.5 to 21 days) [see table I].

Table I. Summary of the pharmacokinetic properties of depot intramuscular antipsychotics

Drug	Doses (mg)	Administration interval	$t_{1/2}$	t_{max}
Clophenxol decanoate	50–600	2–4 weeks	19 days	4–7 days
Perphenazine enanthate	25–200	2 weeks	4–6 days	2–3 days
Pipothiazine palmitate	25–400	4 weeks	15–16 days	12–24 hours
Haloperidol decanoate	20–400	4 weeks	21 days	3–9 days
Flupentixol decanoate	10–50	4 weeks	8 days	3–7 days
Fluspirilene	2–6	1 week	7 days	24–72 hours
Fluphenazine decanoate	12.5–100	6 weeks	14.3 days	8–10 hours
Fluphenazine enanthate	12.5–100	6 weeks	3.5–4 days	2–3 days
Zuclophenxol decanoate	50–800	2–4 weeks	19 days	1 week
Risperidone	25–75	2 weeks		

$t_{1/2}$ = elimination half-life; t_{max} = time to peak-plasma concentration.

Short-acting intramuscular formulations are used to manage a variety of acute psychotic states and symptoms. Short-acting formulations are particularly suitable in rapid tranquillisation, when the priority objective is to acutely control agitation and violent behaviour rather than to treat the overall psychotic picture.^[18] The strategy implies the administration of intramuscular antipsychotics alone, or the combination of intramuscular antipsychotics and benzodiazepines. For example, short-acting intramuscular haloperidol can be a useful tool for the management of agitation of several aetiologies (i.e. acute psychosis or acute intoxication with ethanol).^[19] When compared with oral concentrate, intramuscular haloperidol shows a significantly shorter time to reach peak plasma concentrations.^[20,21] However, the combination of intramuscular haloperidol and intramuscular lorazepam appears to have a better clinical efficacy than either treatment alone, assuring also a more rapid effect.^[22-24] The most commonly used regimen is haloperidol 2–5mg combined with lorazepam 2mg injected every 30–60 minutes for up to three doses.^[25]

When treating a patient with rapid tranquillisation, the risk of severe adverse events needs to be taken into consideration, particularly in patients with medical or neurological problems. Although the incidence of adverse effects from rapid tranquillisation is low,^[26] there are relative contraindications for this procedure, that is, central nervous system depression, unstable epilepsy, clinically significant hypo- or hypertension, recent head injury, recent drug overdose or serious haematological, cardiovascular, renal or liver function impairment.^[26]

Rapid tranquillisation should not be confused with rapid neuroleptisation, which implies the use of very high loading dosages of antipsychotics over the first weeks of treatment to produce a more rapid remission of psychotic symptoms. This strategy was studied during the late 1970s,^[27,28] but more recent observations suggest that rapid neuroleptisation leads to higher incidence of EPS without advantages on efficacy when compared with

the administration of lower doses of the same drug.^[29] On the basis of what has been reported in the literature and observed clinically, the strategy of rapid neuroleptisation should be avoided.

Long-acting or depot compounds are administered in the maintenance phase of treatment to ensure compliance and to eliminate bioavailability problems related to absorption and first pass metabolism.^[9,30,31]

The decision to use intramuscular instead of oral preparations is mainly based on compliance considerations. Intramuscular administration guarantees drug intake in both short-^[32] and long-term^[33] treatment, thus the prescription of depot antipsychotics is also an excellent method by which the clinician can monitor patient compliance. However, the use of an intramuscular preparation can only partially overcome compliance problems: while in acute psychosis the problem is successfully solved because often patients are inpatients, the use of depot antipsychotics does not guarantee good compliance for patients for whom maintenance therapy is indicated in an outpatient setting.^[34,35] Thus, conversion to depot medications before hospital discharge may facilitate medication compliance during transition to outpatient treatment, but other clinical interventions are needed to maintain compliance over time.^[36]

Another advantage of injectable depot antipsychotic medications is that they eliminate bioavailability problems related to absorption and 'first pass' metabolism, and maintain stable plasma concentrations.^[30,31] Oral antipsychotics are converted to inactive metabolites by non-specified enzymes in the gut wall and rapidly metabolised during the 'first pass' through the liver. Thus, only a small portion of the dose reaches the systemic circulation. These bioavailability difficulties can be successfully overcome by the parenteral administration of the drug.^[37,38]

Furthermore, the risk of overdose of medications in suicidal intention is significantly reduced using injectable depot formulations, and this is relevant when considering that suicide is a relatively common cause of death in psychotic patients (10–

20% lifetime risk in those with schizophrenia),^[39,40] and that most of the suicide attempts are with medication overdose.^[41]

It should also be noted that depot formulations, when compared with oral formulations in the maintenance treatment of psychoses, provide better relapse prevention,^[11] although this finding has been challenged by Schooler^[42] and by Soni et al.^[43] In terms of efficacy, patients maintained on long-acting antipsychotic medication showed a significantly lower re-hospitalisation rate than those on oral preparations.^[44]

Plasma drug concentrations are relatively stable when treating patients with depot antipsychotics, allowing administration every 2 or 4 weeks.^[6] However, this aspect also represents a potential disadvantage because of the lack of flexibility in doses. As an example, if adverse effects occur, depot medication cannot be as rapidly withdrawn as the oral preparation. It is for this reason that an oral or short-acting preparation should be administered before prescribing a depot treatment in order to test the susceptibility of the patient to adverse effects, especially when treating first episodes.

In conclusion, there are some clear advantages in using depot preparations over oral medication for long-term maintenance therapy with antipsychotics, not the least being that the intramuscular treatment represents a structured management of the patient, his/her illness and his/her treatment far beyond the simple administration of a drug.^[45,46]

2.2 Adverse Effect Profiles

Adverse effects of antipsychotics have been studied, in particular, with respect to oral versus depot formulations of the different compounds.

For short-acting intramuscular preparations the main risk with classical antipsychotics are hypotension (particularly with parenteral chlorpromazine)^[24] and EPS. The latter occur less frequently than with haloperidol alone with the combination of intramuscular haloperidol (2–5mg) plus lorazepam (2mg) or clonazepam in agitated patients.^[23,24,47] The rate of significant EPS observed in the treatment of acute psychosis with intra-

muscular antipsychotics not in association with benzodiazepines ranges from 20 to 50% even with low doses.^[48-50]

Depot formulations are usually believed to be associated with a much higher incidence of adverse reactions compared with oral formulations, particularly EPS. However, data on this issue are controversial: some studies point out that the incidence of EPS is significantly higher in patients receiving depot preparations,^[51-53] whereas other data showed no difference between oral and depot antipsychotics.^[54,55] There is also evidence supporting a better tolerability of depot compared with oral formulations of the same compound.^[56-58]

A comparative study of perphenazine decanoate versus perphenazine enanthate in two groups of 26 and 24 acutely psychotic patients showed more severe EPS in the group treated with the enanthate.^[59] This is probably due to the different pharmacokinetic profiles of the two compounds, which results in sustained plasma perphenazine concentration with the decanoate formulation. Similarly for fluphenazine esters, the decanoate provides an early high concentration of fluphenazine (8–10 hours after the injection), followed by a prolonged plateau.^[13] These peculiarities suggest a role for the fluphenazine decanoate not only in the treatment of chronic schizophrenia but also in the management of acute psychotic episodes.

Another study comparing haloperidol and fluphenazine decanoate reported that patients receiving haloperidol had a higher frequency of EPS. However, patients on haloperidol were receiving higher doses and thus, a generalisation of this result is not appropriate.^[60]

Early unwanted effects of fluphenazine decanoate have been related to early peaks of plasma fluphenazine concentration shortly after the intramuscular injection in schizophrenic patients.^[59] A higher incidence of unwanted EPS (akinesia, involuntary movement, autonomic disturbances, drowsiness, hypotension, tachycardia) occurred when plasma fluphenazine concentrations were maximal, although there were no further increases in prolactin levels.^[61]

Among the movement disorders induced by antipsychotics, the most difficult to manage is tardive dyskinesia, which may occur after months or years of treatment. This disabling adverse effect is often irreversible and there is no consensus about the proper treatment of this condition, which can persist even after the discontinuation of the antipsychotic treatment. However, depot antipsychotic therapy, when compared with oral treatment, does not appear to be associated with an increased risk of developing tardive dyskinesia.^[62]

In addition, published data on neuroleptic malignant syndrome and EPS do not demonstrate a higher incidence of adverse effects with the use of depot therapy, indicating that depot antipsychotics represent a valuable treatment option for many patients.^[62]

With respect to activity on cardiovascular system, the effect of haloperidol decanoate was studied in patients with chronic schizophrenia; no significant changes in heart rate, or PR, QRS or QTc interval and T-wave height, or blood pressure were found.^[63]

Local reactions at the injection site of depot formulations may appear, such as redness, oedema and palpable masses, or even abscess formation after repeated injections of large volumes (8ml or more) of decanoate or enanthate preparations.^[64] Thus, deep intramuscular rather than subcutaneous or intralipomatous injections are recommended (also ensuring that unwanted intravascular entry does not occur), as well as limiting the volume (less than 6ml) and encouraging the patient to exercise the limb after the injection.

2.3 Switching Patients from Oral to Depot Antipsychotic Therapy

Studies on the strategies for switching patients from oral to depot treatment suggest that this procedure can be reasonably safely performed. The British National Formulary^[65] recommend the administration of a test dose of intramuscular formulation in order to avoid allergic reactions to the oily vehicle. Some authors suggest a wash-out period between the discontinuation of the oral treatment

and starting the depot therapy to avoid the risk of precipitating acute EPS.^[56,66] However, in clinical practice depot antipsychotic therapy is usually begun during the administration of oral treatment, followed by gradual tapering of the oral dose.

The effects of switching patients on combined depot and oral antipsychotics to a single depot preparation were investigated in another study, which also assessed the effects of switching patients from one depot antipsychotic to another. Whereas changing the depot preparation (flupenthixol to fluphenazine) had no clear disadvantages for the patients, switching from a combined oral and depot regimen (fluphenazine) to equivalent doses of depot alone resulted in an unacceptably high rate of relapses.^[43]

A prospective evaluation for converting 21 patients from oral to depot treatment with haloperidol (100mg weekly for the first 4 weeks, then every 2 weeks and finally every 4 weeks) showed, from a pharmacokinetic point of view, that all patients completed the conversion trial during the first 4 weeks without significant adverse events. By the third week, mean plasma haloperidol concentrations from the decanoate injections were comparable to those from oral haloperidol treatment. Steady state conditions for the decanoate therapy were achieved by the fourth week.^[67]

The use of a loading-dose regimen for initiating treatment with haloperidol decanoate has been suggested. This strategy appears to be effective and can be safely used. It also may be useful in a clinical setting, as was shown when three groups of patients were compared in a clinical trial: the first group was given a loading dose of approximately 20 times the oral maintenance dose in divided injections, the second and the third groups received lower doses of depot medication - one with supplemental oral haloperidol, the other without. The group of patients receiving the loading-dose regimen had a statistically significant clinical improvement and reduced adverse effects over baseline by the end of the fourth week.^[68] This may be explained by the fact that the ratio between haloperidol plasma concentrations and administered dose (L/D

ratio) increases over the first 4–5 months after implementation of depot haloperidol, thus indicating that patients could actually be treated with lower doses in the early phase despite the use of standard monthly doses of depot haloperidol.^[69] This phenomenon could explain the higher relapse rate seen in the first months after hospital discharge when shifting from oral to long-acting haloperidol:^[9] in this period a dose reduction may significantly increase the risk of an early relapse. The 'threshold' plasma concentration for reducing the risk of relapse in schizophrenic patients on maintenance therapy with haloperidol decanoate has been estimated to be $\geq 4 \mu\text{g/L}$. The dose administered in this study ranged from 150 to 200mg monthly.^[70] Thus, a dose-reduction strategy of depot (and conventional) antipsychotics during the maintenance phase of treatment (particularly in the first 6 months), without taking into account important variables such as the frequency of relapses and the severity of adverse effects (particularly EPS), should be discouraged.^[70]

On the basis of these and other^[71] literature data, a dose reduction of the depot formulation could be cautiously envisaged only in selected cases (i.e. patients with a low relapse frequency or developing a medication-induced depressive state, or with a poor tolerance for unwanted adverse effects associated with haloperidol), and only after satisfactory clinical stabilisation has been reached.

3. Intramuscular Preparations of Typical Antipsychotics

3.1 Haloperidol Decanoate

Haloperidol decanoate is a commonly used butyrophenone derivative with central antidopaminergic activity. Because of its beneficial antipsychotic action, schizophrenic clinical conditions, and particularly paranoid states, constitute the major indication for this compound.^[72]

The pharmacokinetic properties of haloperidol have been widely studied. Plasma concentrations of the decanoate formulation peak on day 7 after intramuscular injection, the elimination half-life is

about 3 weeks and the time to reach the steady-state is about 3 months.^[73] A plasma haloperidol concentration over $4 \mu\text{g/L}$, as a result of a variety of doses (e.g. 20–400mg), produced a therapeutic response and a good clinical stability in a 3-year follow-up study. An indiscriminate dose-reduction strategy during long-term treatment of schizophrenic disorders with haloperidol decanoate should be discouraged, since it leads to an increase in the relapse rates.^[9] However, there is large inter-individual, but not intra-individual, variability in plasma haloperidol concentrations and in most of the pharmacokinetics parameters of this compound. This variability could be partially explained by the reversible oxidation/reduction metabolic pathway of haloperidol: the compound is metabolised via reduction to reduced haloperidol, which is biologically inactive. Different extents of enterohepatic recycling, and genetic differences in metabolism, could also account for the observed variability in haloperidol bioavailability.^[74]

A multicentre, double-blind study was conducted to determine rates of exacerbation in 105 schizophrenic patients assigned to four fixed doses of haloperidol decanoate. The results suggested that the 200mg per month dose when compared to 100mg or 50mg is associated with the lowest rate of symptomatic exacerbation (15%) with minimal increased risk of adverse effects. At the same time, the rates of worsening with 100mg (23%) and 50mg (25%) were not significantly greater than those seen with 200mg.^[75]

Several studies clearly support the clinical efficacy of haloperidol decanoate. In an open, multicentre study haloperidol decanoate administered every 4 weeks to 38 inpatients with chronic psychosis proved to be as well tolerated and therapeutically reliable as orally administered haloperidol.^[74] The same results were obtained by Gelders et al.^[76] in 239 patients who entered a 52-week, open study, and by a clinical trial which demonstrated that haloperidol decanoate injected every 4 weeks provided control of psychotic symptoms at least as effectively as daily oral haloperidol.^[43] When compared with flupenthixol decanoate^[77]

and to fluphenazine decanoate^[78] administered at fixed 4-week intervals, haloperidol decanoate provided a better control of schizophrenic symptoms and significantly less frequent relapses in the maintenance phase. A 5-year follow-up study on 62 psychotic patients^[79] showed that there were more relapses and hospitalisations for patients maintained on antipsychotics other than haloperidol decanoate.

Haloperidol decanoate has a substantial effect in improving psychotic symptoms associated with schizophrenia compared with placebo,^[80] in addition to being an effective maintenance therapy in preventing relapse. However, recent data suggest better efficacy for ziprasidone^[81] and olanzapine^[82] in the treatment of acute psychotic symptoms and agitation in schizophrenia (see section 4).

It should be noted that there are no definitive data on the relationship between the reduced haloperidol/haloperidol ratio or clinical improvement and EPS. Some authors suggest that this ratio does not interfere with the antipsychotic activity of haloperidol in the treatment of acute schizophrenia.^[83] On the other hand, before drawing any definitive conclusion a long-term study should be conducted during steady-state conditions in a diagnostically homogeneous sample.^[84]

3.2 Fluphenazine Enanthate and Decanoate

Fluphenazine is a phenothiazine and probably the most commonly administered depot antipsychotic, which is available in two preparations, the enanthate and decanoate ester.

The two preparations have different pharmacokinetics: fluphenazine decanoate provides an early high concentration of fluphenazine (8–10 hours after the injection), followed by a sustained plateau.^[12] This feature suggests a role for the fluphenazine decanoate not only in the treatment of chronic schizophrenia but also in the management of acute phases. On the other hand, the enanthate provides a slowly increasing fluphenazine concentration to a peak occurring after 2–3 days, followed by decline.^[13]

The elimination half-life of the enanthate ester after a single dose is only 3.5–4 days and the therapeutic action persists for only 1–3 weeks.^[85,86] In the case of the decanoate ester, the apparent mean half life is 14.3 days and the time to reach steady-state plasma concentrations approximates 4–6 weeks.

Both of the esters are usually administered at an average dose of 25mg. Dose-reduction strategies for the maintenance treatment of schizophrenia are designed to maintain the benefits of the antipsychotic effect while reducing the risks of developing adverse events. The most valid approach is the use of injections every 6 weeks instead of every 2 weeks. This strategy may increase the compliance and improve patients' comfort as well as decrease cumulative antipsychotic exposure, without increasing relapse rates or symptoms.^[87] Marder et al. evaluated the effectiveness and the adverse effects of what they defined as low (5mg) and conventional (25mg) doses of fluphenazine decanoate administered every 2 weeks in a double-blind comparison. Evaluation of the survival rates revealed no significant difference at 1 year, but significantly better survival was seen with the 25mg dose (64%) than with the 5mg dose (31%) at 2 years.^[88]

In a randomised clinical trial of haloperidol decanoate and fluphenazine decanoate in the treatment of outpatients with schizophrenia no statistically significant differences in therapeutic effect were found between the two compounds and both had a similar profile in terms of drug-induced parkinsonism.^[89]

3.3 Clopenthixol Decanoate

Clopenthixol belongs to the group of thioxanthenes and has a duration of effect ranging from 2 to 4 weeks. The elimination half-life of the decanoate preparation is 19 days and the doses employed vary from 50 to 600mg.

The clinical properties of clopenthixol decanoate have been investigated compared with perphenazine enanthate in a double-blind, multicentre trial including 172 patients with schizophrenia. Significant differences in the effect were seen only

in 'hostile-suspiciousness' and 'social interest' dimensions rated at the Brief Psychiatric Rating Scale (BPRS).^[90] For these items clopenthixol decanoate was found to be superior to perphenazine enanthate.^[91] However, no differences were detected between clopenthixol decanoate and flupenthixol decanoate in another comparative study.^[92] Long-term treatment (6 months) of 68 patients with chronic schizophrenia with clopenthixol decanoate showed a significant reduction in total BPRS score.^[93] Twenty-three patients with chronic schizophrenia were followed-up for 5 years while receiving treatment with depot injections of clopenthixol decanoate in doses ranging from 100 to 600mg every 2–4 weeks. Improvement in both positive and negative symptoms occurred over that time.^[94]

3.4 Zuclopenthixol Decanoate

Zuclopenthixol is the *cis*(Z) isomer of clopenthixol, an antipsychotic of the thioxanthene group, and it should be partly devoid of EPS compared with oral clopenthixol.

With doses ranging from 50 to 800mg, peak serum concentrations are obtained 1 week after the zuclopenthixol injection, with detectable amounts of the compound persisting after 28 days. A clinical effect lasting 2–4 weeks was reported.^[95]

The target symptoms that essentially call for the application of zuclopenthixol decanoate are hostility, suspiciousness and psychomotor agitation. However, a distinct therapeutic effect has also been observed in patients with hallucinatory-disorganised and manic syndromes.^[96] Significant improvement on thought disturbances, hostile-suspiciousness and anxious-depression symptoms were obtained in 70 patients treated with depot preparation of zuclopenthixol. Adverse effects were of low intensity and no secondary depression was observed.^[97]

Twenty-three schizophrenic outpatients in maintenance treatment with zuclopenthixol decanoate were included in a study which aimed to find the minimum effective dose and corresponding serum concentration of zuclopenthixol. The minimum

effective dose of zuclopenthixol was 200 mg/2 week (range 60–400), with a serum concentration of 22 nmol/L (range 7.1–69.7). There was a significant correlation between the administered dose and the corresponding serum drug concentration. A trend towards a positive correlation was found between the serum concentration at the minimum effective dose and the BPRS scores at the end of the treatment. No correlation was found between the serum concentration or duration of antipsychotic treatment and the adverse effects.^[98]

Nineteen patients with chronic schizophrenia were included in an open clinical trial to evaluate the efficacy of zuclopenthixol decanoate. A clear improvement was recorded both on the BPRS and the Hamilton Depression Scale. The frequency of adverse effects was low and decreased during the course of the treatment.^[99]

In patients with acute psychosis, including mania or exacerbation of chronic psychosis it may be helpful to use zuclopenthixol acetate in a viscolean solution. This formulation has a rapid effect and induces sedation with a mean of five injections, which is particularly helpful in patients with paranoid symptoms.^[100] An open, multicentre study showed that treatment with zuclopenthixol was rapidly effective in reducing the severity of psychotic symptoms combined with an advantageous non-specific sedation. The adverse effect profile was similar to that obtained with other antipsychotics.^[101]

3.5 Flupenthixol Decanoate

Flupenthixol decanoate is a thioxanthene derivative and it is usually administered at average intervals of 4 weeks. Its apparent elimination half-life is approximately 8 days after a single injection of 10–50mg.^[102]

A number of controlled and open studies^[103–105] indicate that flupenthixol in a low-dose regimen (10mg) is effective in treating syndromes with depression, anxiety and psychosomatic disorders. There are no significant therapeutic differences between flupenthixol decanoate and other depot antipsychotics in patients with schizophrenia^[106] but

there could be a specific indication for flupenthixol decanoate in individuals with prevalent negative symptoms.^[107] An open clinical trial carried out in 21 patients with schizophrenia concluded that a group of patients characterised by depressive symptoms might benefit from a switch to flupenthixol treatment.^[108] The efficacy of flupenthixol decanoate as a monotherapy in the management of schizoaffective disorder has been reported in another study.^[109]

Some studies suggest that flupenthixol decanoate is less likely to induce movement disorders than other depot antipsychotic drugs: in particular, EPS are rarely encountered if the dose is kept below 10mg, such as the depressed patients discussed in the previous paragraph.^[107]

3.6 Perphenazine Enanthate and Decanoate

Perphenazine belongs to the phenothiazine family and has a piperazine ethanol side chain. The enanthate ester is administered every 2 weeks, at doses ranging from 25 to 200mg. A comparative study of pharmacokinetic properties showed that at all dosages, the decanoate preparation induces significantly lower peak plasma concentrations of perphenazine and less pronounced extrapyramidal adverse effects^[110] than the enanthate preparation.

In a 6-week, randomised, double-blind study the efficacy and adverse effects of perphenazine enanthate and perphenazine decanoate were compared in 26 and 24 acutely psychotic patients, respectively,^[59] showing no statistically significant differences between the two compounds in terms of the overall antipsychotic efficacy. In addition, in this study the administration of perphenazine decanoate resulted in fewer fluctuations of plasma concentrations of perphenazine. More recent studies have supported this finding^[111,112] showing that EPS were more pronounced among the enanthate recipients.

In a comparative study of schizophrenic patients, the antipsychotic effects of perphenazine enanthate were similar to those of fluspirilene on paranoid, hallucinatory and catatonic symptoms.

According to a self-rating scale, anxiety and depressive symptoms were significantly lower in the perphenazine enanthate regimen. The more pronounced sedative effect is recommended in hostile and agitated schizophrenic patients, whereas fluspirilene was more effective in autistic patients.^[113]

The clinical properties of perphenazine enanthate have been investigated versus clopenthixol decanoate in a double-blind clinical trial including 172 patients with chronic schizophrenia.^[91] Clopenthixol decanoate was found to be superior to perphenazine enanthate only in reducing hostility and suspiciousness.

A long-term, crossover study comparing perphenazine decanoate with haloperidol decanoate in 29 patients with schizophrenia showed that there was no significant difference between these compounds in terms of antipsychotic efficacy or adverse effects.^[114]

3.7 Pipotiazine Palmitate and Undecylate

Pipotiazine palmitate (pipothiazine palmitate) and undecylate are members of the phenothiazine family and are characterised by a slow rate of absorption from the site of injection. The palmitate ester is administered, on average, at intervals of 4 weeks, whereas the undecylate ester is given at average intervals of 2 weeks.^[115]

A 10-year follow-up of schizophrenic patients receiving pipotiazine palmitate showed an improvement of the physical, mental and social state of these individuals: the drug was effective when administered at 4-week intervals, the incidence of adverse effects was low, and there was no evidence of unforeseen biological effects compared with continuous medication.^[116]

In a multicentre, double-blind trial, fluphenazine decanoate and pipotiazine palmitate were compared with respect to their antipsychotic efficacy and adverse effect profile: a comparison between the two groups of patients by means of analysis of covariance at the syndrome level showed no statistically significant differences.^[117] On the other hand, another study indicated that pipotiazine pal-

mitate was not as potent as fluphenazine enanthate in terms of antipsychotic properties.^[118]

Some controlled studies^[119-121] suggest that pipotiazine palmitate and undecylate are as efficacious in the control of psychotic symptoms as other depot antipsychotics and no differences were identified in the adverse effects.

When pipotiazine palmitate was compared with oral antipsychotics no differences were found for outcomes of mental state, study attrition and adverse events.^[121]

3.8 Fluspirilene

The diphenylbutylpiperidine derivative fluspirilene is a hydrophobic compound which is directly administered intramuscularly as a micronised aqueous suspension, allowing gradual absorption of the active compound from the injection site. Unlike other depot antipsychotics, its absorption and action are regular and reproducible from one injection to the next. The elimination half-life after a single dose is about 7 days, with about 70% of the drug excreted in 27 days.^[122]

Fluspirilene proved to be a depot antipsychotic with good effect in the treatment of paranoid psychoses in elderly outpatients, being effective for delusions, restlessness and excitement symptoms.^[123]

A retrospective evaluation of long-term fluspirilene treatment showed that the antipsychotic efficacy of the drug was well maintained, that the patient's social and professional functioning had improved significantly, and that the incidence of adverse effects remained low.^[124] In a study on 29 non-hospitalised outpatients, a significant improvement was found at 4 weeks in 20 patients and at the end of the 12-week trial in 24 patients.^[125]

Fluspirilene showed an efficacy comparable with that of fluphenazine decanoate and the same incidence of adverse effects in two groups of schizophrenic patients treated for 6 months.^[126] However, the choice of using fluspirilene as a depot medication for its advantages over other depots cannot be confirmed at present by controlled trial-derived data.^[127]

4. Intramuscular Preparations of Atypical Antipsychotics

To date, acute and agitated psychotic patients have been treated with high parenteral doses of typical antipsychotics. Despite the proven efficacy of these treatments, it is well known that high doses of typical antipsychotics, including haloperidol, cause serious EPS, especially dystonic reactions. The impact of these acute EPS on the clinical management of the psychotic patient is significant, as the tolerability profile is one of the main factors affecting compliance.^[36]

For these reasons, there is a growing interest in developing intramuscular formulations of novel antipsychotics, which have been shown to have a better tolerability profile than typical compounds, and comparable efficacy in the acute and long-term treatment of psychoses.

In clinical practice, the combination of intramuscular conventional antipsychotics and oral atypical compounds is sometimes observed. However, there is not much data in the literature suggesting efficacy advantages with this type of combination. Actually, a study by Carpenter et al.^[128] pointed out that the combined administration of typical compounds (fluphenazine or haloperidol) did not improve the efficacy of clozapine administered in combination.

4.1 Olanzapine

An intramuscular short-acting formulation of the atypical antipsychotic olanzapine has been developed for treatment of agitation in acutely psychotic patients. Fundamental pharmacokinetic characteristics are similar to those of oral olanzapine, including half-life, clearance and distribution volume. The key difference is the more rapid absorption rate of the intramuscular formulation, as noted by higher peak concentration (2- to 5-fold) and an earlier time to peak concentration (30 minutes vs 4 hours).^[129]

In a double-blind, multicentre, placebo-controlled clinical trial of intramuscular olanzapine versus intramuscular haloperidol in the treatment of

acute agitation in hospitalised patients with schizophrenia,^[82] a total of 311 agitated patients were randomly assigned in a 2 : 2 : 1 ratio to receive up to three injections of olanzapine (10mg per injection), haloperidol (7.5mg per injection) or placebo within 24 hours. Following the 24-hour intramuscular injection phase, 285 patients entered a 4-day oral treatment phase. A significantly greater improvement from baseline on BPRS positive subscale scores was found with intramuscular olanzapine and intramuscular haloperidol than intramuscular placebo; however, improvements with intramuscular olanzapine and intramuscular haloperidol did not differ significantly. Patients treated with intramuscular olanzapine experienced a further decrease in mean baseline to endpoint BPRS positive subscale scores by day 5, i.e. 4 days after switching from intramuscular olanzapine to oral olanzapine therapy. No significant difference was found when data on intramuscular olanzapine were compared with data on intramuscular haloperidol. Acute dystonia did not occur in intramuscular olanzapine-treated patients, while it occurred in 7% of those who were treated with intramuscular haloperidol. Changes in QTc intervals with active treatments were not significantly different from those with placebo.

The efficacy and safety of intramuscular olanzapine in patients meeting DSM-IV (Diagnostic and Statistical Manual of mental disorders – 4th edition) criteria for acute non-organic psychosis have been also investigated in two single-blind clinical trials.^[130,131] In the first trial, 26 male inpatients received intramuscular injections of 2.5, 5, 7.5 or 10mg of olanzapine (1–4 injections/day for 3 days) followed by oral olanzapine (10–20 mg/day for 2 days). In the second trial, 82 inpatients received intramuscular injections of 2.5, 5, 7.5 or 10.0mg of olanzapine (1–4 injections/day for up to 3 days) followed by oral olanzapine (10–20 mg/day for 2 days). In both open-label studies and across all dose groups, mean BPRS positive subscale scores decreased from baseline to endpoint for the 3-day period of intramuscular injections for patients treated with intramuscular

olanzapine. There was a further decrease in BPRS positive subscale scores from baseline to the day 5 endpoint, which was 2 days after the transition from intramuscular olanzapine to oral olanzapine.

The results of these clinical studies support the evidence that acutely agitated patients with positive symptoms of schizophrenia may be effectively treated with intramuscular olanzapine for rapid sedation and then successfully switched to oral olanzapine maintenance therapy.

Another double-blind trial was conducted to assess the efficacy and safety of intramuscular olanzapine compared with lorazepam or placebo in treating acutely agitated patients diagnosed with bipolar mania.^[129] A total of 201 patients were randomly assigned to receive an intramuscular treatment with olanzapine, lorazepam or placebo in a 2 : 1 : 1 ratio. All patients received from one to three intramuscular injections during a 24-hour treatment period. For olanzapine recipients, the first and second injections were 10mg each and the third was 5mg; for lorazepam recipients, the first and second injections were 2mg each and the third was 1mg; for placebo treated patients, the first and second injections were placebo, the third one was olanzapine 10mg. Only lithium and valproic acid were permitted as concomitant therapy. The results showed that olanzapine was superior to placebo and lorazepam in reducing agitation. Moreover, olanzapine-treated patients experienced a significantly earlier response time than those in the lorazepam and placebo treatment groups starting at 30 minutes and continuing throughout 2 hours after the first injection. Olanzapine also demonstrated a good safety profile. It is important to note that there were no differences in QTc interval between the treatment groups at either time point. With respect to EPS, there was no significant difference in the incidence of akathisia or parkinsonism across the different treatment groups. As opposed to with intramuscular typical antipsychotics, there were no reports of acute dystonia.

4.2 Risperidone

A new risperidone depot formulation for intramuscular administration is an aqueous suspension microencapsulated into polylactide-coglycolide polymers whose degradation at the injection site results in release of risperidone over several weeks.

Bioequivalence of oral and intramuscular depot risperidone was demonstrated in 86 stable patients with schizophrenia. They were divided into three groups and received oral risperidone (2, 4 or 6 mg/day) for the first 3 weeks and oral risperidone at half those doses during weeks 4–5. They were then switched to intramuscular risperidone (25, 50 or 75mg, respectively) administered every 2 weeks (five injections). Peak plasma concentrations were significantly lower (25–32%) after depot than oral dose administration and patients remained symptomatically stable when treatment was changed from the oral to the depot treatment. The most frequent adverse events were flu-like symptoms and there were no consistent, clinically relevant changes in vital signs, ECG or laboratory tests observed. Patients remained symptomatically stable when the treatment was switched from the oral to the depot regimen.^[132]

Long-acting risperidone was evaluated in 13 patients with schizophrenia, and plasma concentrations of the parent compound and its main active metabolites were determined by radioimmunoassays. The drug was administered every 2 weeks at variable doses of 25, 50 or 75mg. D₂ receptor binding was measured by positron emission tomography (PET) in eight patients at the steady state.^[133] Plasma concentration started to increase after injections two and three, and the steady-state was reached after injection four. This means that there should be an overlap between oral and intramuscular administration during the first 3 weeks of treatment to ensure adequate risperidone plasma exposure.^[133] Steady-state levels were maintained for 4–5 weeks after injection five and thereafter declined rapidly. D₂ receptor occupancies ranged from 25 to 48% after the 25mg dose, from 59 to 83% after the 50mg dose, and from 62 to 72% after

the 75mg dose. The curvilinear relationship between receptor occupancy and plasma concentrations of the risperidone active moiety was confirmed.^[133]

A 14-week, randomised, double-blind trial was designed to investigate the effect of long-acting risperidone microspheres intramuscular formulation in 370 patients with schizophrenia. Patients received injections of placebo or of long-acting risperidone (25, 50 or 75mg) every 2 weeks. Improvements on the Positive and Negative Symptoms Scale (PANSS)^[134] total scores were higher in all risperidone groups than in the placebo group and no further benefit of a long-acting risperidone dose above 50mg was shown. The incidence of EPS was similar in the placebo and in the risperidone 25mg groups. Cardiovascular and metabolic adverse event profiles were similar in all three risperidone groups and the placebo groups.^[133]

The long-term safety of intramuscular risperidone was also investigated in a large, multicentre study involving 725 patients with schizophrenia or schizoaffective disorder. The complete trial lasted 1 year and only 5% of the patients discontinued the treatment because of adverse events. The most frequently reported adverse events to treatment were anxiety (25%), insomnia (23%), psychosis (18%), depression (16%), headache (13%), hyperkinesia (12%) and rhinitis (11%). The overall reported rate of treatment emergent EPS-related adverse events was 25.7%. No clinically relevant QTc abnormalities were observed. The mean increase in weight was 2.7 kg at week 50 and fewer than 1% of patients reported glucose-related adverse events. Local injection site reactions were minimal and >70% of patients did not report pain.^[135]

Another multicentre study was conducted in 640 patients with schizophrenia to test the efficacy and safety of the long-acting intramuscular formulation against oral formulation. The trial lasted 20 weeks and the mean between-group difference in PANSS score change was small. No adverse events were recorded with long-acting risperidone; 4.7% of oral recipients and 5.6% of long-acting risperidone recipients discontinued the trial

because of adverse events. It is concluded that the two formulations were equally efficacious and well tolerated.^[136]

4.3 Ziprasidone

The development of an intramuscular formulation of ziprasidone, using sulfobutylether β -cyclodextrin to solubilise the drug by forming a complex, provides a means of administering ziprasidone to patients for whom intramuscular formulation is the preferred route because of acute symptoms of agitation associated with psychosis. Intramuscular ziprasidone attains peak exposure within approximately 30 minutes, exposure is dose-related and there is negligible drug accumulation with multiple dose administration.^[137]

A pilot study on tolerability and efficacy of intramuscular ziprasidone demonstrated that it rapidly reduces psychomotor agitation and other symptoms of acute psychosis. This trial involved 12 patients with acute episodes of disorganised, paranoid or undifferentiated schizophrenia. During the 5-day treatment period, fixed doses of intramuscular ziprasidone (2.5, 5, 10 or 20mg) were administered for the first 3 days; then the patients were switched to oral ziprasidone (dose range 40–160 mg/day). Intramuscular ziprasidone treatment resulted in a marked and rapid improvement in overall psychopathology. Anxiety, tension, hostility and excitement were reduced, and patients did not report excessive sedation. The switch to oral ziprasidone did not affect efficacy. Adverse events were generally of mild or moderate severity. No EPS, tachycardia, postural hypotension or ECG abnormalities were reported, while there was slight median increase in standing pulse rate and a slight median decrease in sitting systolic blood pressure. Only one patient experienced mild acathisia, which was already present at baseline.^[138]

These encouraging results stimulated a growing interest in comparing ziprasidone with other intramuscular preparations. A randomised, open-label, multicentre, international study has compared intramuscular ziprasidone with intramuscular haloperidol in the treatment for up to 3 days of inpatients

with acute agitation and psychosis. The transition from intramuscular to oral therapy with ziprasidone was also assessed up to 7 days after the start of intramuscular therapy. Patients received up to 3 days of flexible-dose intramuscular ziprasidone ($n = 90$) or haloperidol (42) followed by oral treatment to day 7. After an initial intramuscular ziprasidone dose of 10 mg, subsequent intramuscular doses of 5–20mg could be given every 4–6 hours (maximum daily dose 80mg) if needed, followed by oral ziprasidone 80–200 mg/day. Intramuscular haloperidol doses of 2.5–10mg were given on study entry, followed by 2.5–10mg intramuscular every 4–6 hours (maximum daily dose 40mg) if needed, then by oral haloperidol 10–80 mg/day.

Intramuscular ziprasidone treatment was significantly more effective in reducing the symptoms of acute psychosis, including agitation, than haloperidol. In addition, ziprasidone showed well defined advantages in terms of tolerability over haloperidol, and the results of the study also demonstrated that patients can successfully make the switch from intramuscular to oral ziprasidone with further reductions in symptoms and no increase in the burden of adverse effects. Ziprasidone was associated with a lower incidence of movement disorders, and a reduced requirement for anticholinergic drugs during both intramuscular and oral treatment than haloperidol. Mild vomiting occurred with ziprasidone in 3.3% of patients during the intramuscular treatment period and in 6.7% of patients during the oral treatment period. Cardiovascular adverse effects appeared in both groups but they were not clinically relevant. There was no evidence of hepatic or haematological toxicity.^[81]

A prospective, randomised, double-blind 24-hour study compared intramuscular ziprasidone 2mg ($n = 38$) and 20mg (41) in the acute and short-term management of agitated psychotic patients. Out of the 79 patients enrolled, over half had schizophrenia, one quarter had schizoaffective disorder and approximately 15% had bipolar disorder as their primary diagnosis. The results of this trial indicated that intramuscular ziprasidone 20mg was

effective in rapidly and substantially reducing the symptoms of acute agitation in patients with psychotic disorders and that it was well tolerated. Although there was a marked difference in efficacy between the 2 and the 20mg dose in this study, assessments of tolerability showed that the profile was very similar in both groups. Neither treatment was associated with EPS, akathisia, dystonia, respiratory depression or excessive sedation, although moderate somnolence was the most frequently reported adverse event associated with the 20mg intramuscular dose. No consistent pattern of changes in blood pressure or pulse rate was observed during the study. There was no evidence of clinically relevant changes in ECG. There was a mean increase in the QTc interval of 3.6ms in the 2mg group and a mean reduction of 1.3ms in the 20mg group.^[139]

Another 24-hour, double-blind, fixed-dose, clinical trial compared two doses of intramuscular ziprasidone for the treatment of acute psychosis. The two groups of patients received, respectively, up to four injections (every 2 hours) of 2mg (n = 54) or 10mg (n = 63) of ziprasidone. The authors conclude that for patients with more severe symptoms than those included in the study, higher doses up to 20mg may be required. Assessments of tolerability and safety indicate that intramuscular ziprasidone 10mg was well tolerated and, in this respect, not clinically significantly different from the ineffective 2mg dose.^[140]

5. Conclusions

Parenteral formulations of antipsychotics are of critical importance for the clinical management of psychotic disorders, particularly when dealing with acute psychotic symptoms, such as psychomotor agitation, excitement and aggressive behaviour. These symptoms are typical of acute exacerbation of schizophrenia or manic states. In these situations the patient is hardly willing to collaborate to a therapeutic plan, mainly because of the lack of insight.^[7,8] As a consequence, the clinical situation is very difficult to manage with oral

preparations and intramuscular short-acting formulations are preferred.

In addition, given that situations with psychotic patients are usually characterised by a chronic lack of insight with consequent poor or no compliance to pharmacotherapy, the use of long-acting formulations of antipsychotics appear to be a valuable tool for the long-term maintenance treatment of psychoses.^[9] The depot preparations available, such as haloperidol decanoate or fluphenazine esters play a pivotal role in the long-term management of patients with chronic psychoses. However, it should be emphasised that adverse effects occurring in the course of treatment with long-acting formulations are more difficult to manage than those occurring during oral treatment. On the other hand, risk/benefit ratio studies^[6] generally appear to support the use of depot medications. Furthermore, cost/benefit studies showed that the use of depot preparations is related to fewer relapse rates, more successful and less expensive care.^[141]

Another aspect to be considered is related to pharmacokinetic issues. The depot formulations avoid bioavailability problems that may be encountered during oral treatment.^[9,30] As it has been reported since the 1970s, the use of intramuscular formulations may be useful to overcome, in some cases, drug resistance problems due to pharmacokinetic variables (e.g. the 'first-pass' effect).

Some caution is recommended when treating elderly patients or individuals who have never received antipsychotic medications. In individuals who have never received antipsychotics, the use of intramuscular long-acting preparations as first choice compounds should be avoided, as the tolerability profile in that particular patient first needs to be confirmed with oral compounds.

In general, parenteral formulations do not induce higher rates of adverse effects than oral preparations^[54,55] and, although there are no unequivocal data on this issue, there is no clear evidence that the tolerability profile of oral preparations is better than that of parenteral ones.^[53,58]

With respect to the novel antipsychotics, it should be noted that parenteral or depot formula-

tions are not yet widely available. On the other hand, it has been shown that they have a better tolerability profile than typical antipsychotics and, in most cases, a higher efficacy in some symptom dimensions (e.g. negative and depressive symptoms) that have been shown to be resistant to conventional antipsychotics.^[17] In clinical conditions where negative or depressive symptoms represent the primary target for the pharmacological treatment the use of compounds with a broader pharmacodynamic profile is suggested.

There are few data on efficacy and safety of intramuscular preparations of atypical antipsychotics. Olanzapine and ziprasidone are available only as short-acting preparations, while risperidone is to date the only novel antipsychotic available as depot formulation. However, given that intramuscular formulations for atypical compounds are not widely available yet, intramuscular formulations of conventional antipsychotics, despite the unfavourable risk/benefit ratio, are still often preferred in the treatment of acute exacerbations in psychotic patients with poor compliance.

In summary, parenteral formulations of antipsychotics are a valuable tool in noncompliant psychotic patients for both the acute and the long-term management of the illness. Furthermore, it has been reported that some patients may prefer the long-acting intramuscular formulations of their antipsychotic treatment, thus suggesting that physicians should more often recommend and prescribe depot medication when antipsychotic maintenance therapy is indicated.^[11]

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References

- Madhusoodanan S, Brenner R, Cohen CI. Role of atypical antipsychotics in the treatment of psychosis and agitation associated with dementia. *CNS Drugs* 1999; 12 (2): 135-50
- Thomas CS, Lewis S. Which atypical antipsychotic? *Br J Psychiatry* 1998; 172: 106-9
- Carman J, Peuskens J, Vangeneugden A. Risperidone in the treatment of negative symptoms of schizophrenia: a meta-analysis. *Int J Psychopharmacol* 1995; 10: 207-13
- Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ* 2000 Dec 2; 321 (7273): 1371-6
- Adams CE, Fenton MK, Quraishi S, et al. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Br J Psychiatry* 2001; 179: 290-9
- Barnes TRE, Curson DA. Long-term depot antipsychotics a risk-benefit assessment. *Drug Saf* 1994; 10 (6): 464-79
- Ayd FJ. The depot fluphenazines: a reappraisal after 10 years clinical experience. *Am J Psychiatry* 1975; 132: 491-500
- Johnson DAW. Practical considerations in the use of depot neuroleptics for the treatment of schizophrenia. *Br J Hosp Med* 1977; 17: 546-58
- Altamura AC, Tacchini GL, Maes M. Haloperidol plasma 'Threshold' levels for relapse prevention in schizophrenia: a study with haloperidol decanoate. *Eur Neuropsychopharmacol* 1995; 5 (S): 55-8
- Walburn J, Gray R, Gournay K, et al. Systematic review of patient and nurse attitudes to depot antipsychotic medication. *Br J Psychiatry* 2001; 179: 300-7
- Pereira S, Pinto R. A survey of the attitudes of chronic psychiatric patients living in the community toward their medication. *Acta Psychiatr Scand* 1997; 95: 464-8
- Davis JM, Leor M, Watanabe MD, et al. Depot antipsychotic drugs, place in therapy. *Drugs* 1994; 47 (5): 741-73
- Altamura AC, Whelpton R, Curry SH. Animal model for investigation of fluphenazine kinetics after administration of long-acting esters. *Biopharm Drug Dispos* 1979; 1: 65-72
- Curry SH, Altamura AC, Montgomery S. Unwanted effects of fluphenazine enanthate and decanoate. *Lancet* 1979; I: 331-3
- Milton GV, Jann MW. Emergency treatment of psychotic symptoms: pharmacokinetic considerations for antipsychotic drugs. *Clin Pharmacokinet* 1995; 28 (6): 494-504
- Tune L. The role of antipsychotics in treating delirium. *Curr Psychiatry Rep* 2002; 4 (3): 209-12
- Altamura AC. Novel antipsychotics and the problem of clinical stabilization in schizophrenia: are they 'stabilizer' rather than typical compounds? *Int Clin Psychopharmacol* 1996; 11: 1-3
- Jones B, Taylor CC, Meehan K. The efficacy of a rapid-acting intramuscular formulation of olanzapine for positive symptoms. *J Clin Psychiatry* 2001; 62 Suppl. 2: 22-4
- Clinton JE, Serner S, Stelmachers Z, et al. Haloperidol for sedation of disruptive emergency patients. *Ann Emerg Med* 1987; 16 (3): 319-22
- Schaffer CB, Shahid A, Javadi JJ, et al. Bioavailability of intramuscular versus oral haloperidol in schizophrenic patients. *J Clin Psychopharmacol* 1982; 2: 274-7
- Dubin WR, Wasman HM, Weiss KJ, et al. Rapid tranquilization: the efficacy of oral concentrate. *J Clin Psychiatry* 1985; 46: 475-8
- Hughes DH. Acute polypharmacological management of the aggressive psychotic patient. *Psychiatr Serv* 1999; 50: 1135-7
- Garza-Trevino ES, Hollister LE, Overall JE, et al. Efficacy of combinations of intramuscular antipsychotics and sedative-hypnotics for control of psychotic agitation. *Am J Psychiatry* 1989; 146: 1598-601
- Hyman SE. Acute psychoses and catatonia. In: Hyman SE, Tesar GE, editors. *Manual of psychiatric emergencies*. 3rd ed. Boston (MA): Little, Brown, 1994: 143-57

25. Osser DN, Sigadel R. Short-term inpatient pharmacotherapy of schizophrenia. *Harv Rev Psychiatry* 2001; 9 (3): 89-104
26. Lazarus A, Dubin WR, Jaffe R. Rapid tranquilization with neuroleptic drugs. *Clin Neuropharmacol* 1989; 12: 303-11
27. Ericksen SE, Hurt SW, Chang S, et al. Haloperidol dose, plasma levels, and clinical response: a double blind study. *Psychopharmacol Bull* 1978; 14: 15-6
28. Donlon PT, Meadow A, Tupin JP, et al. High versus standard dose of fluphenazine HCL in acute schizophrenia. *J Clin Psychiatry* 1978; 39: 800-4
29. Escobar JJ, Barron A, Kiriakos R. A controlled study of neuroleptisation with fluphenazine hydrochloride injections. *J Clin Psychopharmacol* 1983; 3: 359-62
30. Kane JM, Aguglia E, Altamura AC, et al. Guidelines for depot antipsychotic treatment in schizophrenia. *Eur Neuro-psychopharmacol* 1998; 8: 55-66
31. Gerlach J. Depot neuroleptics in relapse prevention: advantages and disadvantages. *Int Clin Psychopharmacol* 1995; 9: 17-20
32. Currier GW, Simpson GM. Risperidone liquid concentrate and oral lorazepam versus intramuscular haloperidol and intramuscular lorazepam for treatment of psychotic agitation. *J Clin Psychiatry* 2001; 62 (3): 153-7
33. Dencker SJ, Axelsson R. Optimising the use of depot antipsychotics. *CNS Drugs* 1996; 6 (5): 367-81
34. Falloon I, Watt DC, Shepherd M. A comparative control trial of pimozide and fluphenazine decanoate in the continuation therapy of schizophrenia. *Psychol Med* 1978; 8: 59-70
35. Quitkin F, Rifkin A, Kane JM, et al. Long-acting oral vs injectable antipsychotic drugs in schizophrenics. *Arch Gen Psychiatry* 1978; 35: 889-92
36. Weiden P, Rapkin B, Zygmunt A, et al. Postdischarge medication compliance of inpatients converted from an oral to a depot neuroleptic regimen. *Psychiatr Serv* 1995; 46 (10): 1049-54
37. Curry SH. Metabolism and kinetics of chlorpromazine in relation to effect. In: Sedvall G, Uvnas B, Zolterman R, editors. *Antipsychotic drugs: pharmacokinetics and pharmacodynamics*. Oxford: Pergamon Press, 1976: 343-52
38. Altamura AC. A multidimensional (pharmacokinetic and clinical-biological) approach to the neuroleptic response in schizophrenia. *Schizophr Res* 1992; 8: 187-98
39. Roy A. Suicide in chronic schizophrenia. *Br J Psychiatry* 1982; 141: 171-7
40. Wilkinson D. The suicide rate in schizophrenia. *Br J Psychiatry* 1982; 140: 138-41
41. Altamura AC, Bassetti R, Bignotti S, et al. Clinical variables related to suicide attempts in schizophrenic patients: a retrospective study. *Schizophr Res* 2003; 60 (1): 47-55
42. Schooler NR. Treatment of schizophrenia: maintenance strategies and pharmacologic tactics. In: Albert M, editor. *Controversies in schizophrenia*. New York: Guilford Press, 1985: 380
43. Soni SD, Sampath G, Shah A, et al. Rationalizing neuroleptic polypharmacy in chronic schizophrenics: effects of changing to a single depot preparation. *Acta Psychiatr Scand* 1992; 85 (5): 354-9
44. Babiker IE. Comparative efficacy of long-acting depot and oral neuroleptic medication in preventing schizophrenic recidivism. *J Clin Psychiatry* 1987; 48 (3): 94-7
45. Johnson DA. Oral versus depot medication in schizophrenia. *Acta Psychiatr Scand Suppl* 1981; 291: 56-64
46. Kane JM. Dosing issues and depot medication in the maintenance treatment of schizophrenia. *Int Clin Psychopharmacol* 1995; 10 Suppl. 3: 65-71
47. Altamura AC, Mauri M, Mantero M, et al. Clonazepam/haloperidol combination therapy in schizophrenia: a double blind study. *Acta Psychiatr Scand* 1987; 76: 702-6
48. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med* 1997; 15: 335-40
49. Neborsky R, Janowsky D, Munson E, et al. Rapid treatment of acute psychotic symptoms with high- and low-dose haloperidol: behavioral considerations. *Arch Gen Psychiatry* 1981; 38: 195-9
50. Salzman C, Solomon D, Miyawaki E, et al. Parenteral lorazepam versus parenteral haloperidol for the control of psychotic disruptive behavior. *J Clin Psychiatry* 1991; 52: 177-80
51. Chien CP, Cole JO. Depot phenothiazine treatment in acute psychosis: a sequential comparative clinical study. *Am J Psychiatry* 1973; 130: 13-8
52. Del Giudice J, Clark WG, Gocka EF. Prevention of recidivism of schizophrenics treated with fluphenazine enanthate. *Psychosomatics* 1975; 16: 32-6
53. Kessler KA, Waletzky JP. Clinical use of the antipsychotics. *Am J Psychiatry* 1981; 138: 202-9
54. Gelenberg AJ, Doller JC, Schooler NR, et al. Acute extrapyramidal reactions with fluphenazine hydrochloride and fluphenazine decanoate. *Am J Psychiatry* 1979; 136: 217-9
55. Vasavan NP, Suranyi-Cadotte B, Schwartz G, et al. A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: efficacy, safety, and dosage equivalence. *J Clin Psychopharmacol* 1986; 6 (1): 30S-7S
56. Burch EA, Ayd FJ. Depot pipotiazine 1970-1982: a review. *J Clin Psychiatry* 1983; 44: 242-7
57. Pakes GE. Haloperidol: profile of side-effects. In: Johnson P, editor. *Haloperidol decanoate and the treatment of chronic schizophrenia*. New York: Adis Press, 1982: 58-63
58. Youssef HA. Haloperidol decanoate in place of multiple drug therapy in chronic schizophrenic patients. *Acta Therapeutica* 1983; 9: 215-25
59. Knudsen P, Hansen LB, Auken G, et al. Perphenazine decanoate vs perphenazine enanthate: efficacy and side effects in a 6 week double-blind, comparative study of 50 drug monitored psychotic patients. *Acta Psychiatr Scand Suppl* 1985; 322: 15-28
60. Bransgrove LL, Kelly MW. Movement disorders in patients treated with long-acting injectable antipsychotic drugs. *Am J Hosp Pharm* 1994 Apr 1; 51 (7): 895-9
61. Altamura AC, Curry SH, Montgomery S, et al. Early unwanted effects of fluphenazine esters related to plasma fluphenazine concentration in schizophrenic patients. *Psychopharmacology (Berl)* 1985; 87 (1): 30-3
62. Glazer WM, Kane JM. Depot neuroleptic therapy: an underutilized treatment option. *J Clin Psychiatry* 1992 Dec; 53: 426-33
63. Kaneko S, Edwards JG, Goldie A, et al. Effect of haloperidol decanoate on the cardiovascular system. *Jpn J Psychiatry Neurol* 1991; 45 (1): 73-7
64. Starmark JE, Forsman A, Wahlstrom J. Abscesses following prolonged intramuscular administration of perphenazine enanthate. *Acta Psychiatr Scand* 1980; 62: 154-7

65. British National Formulary. British Medical Association and Royal Pharmaceutical Society of Great Britain: London, 1993
66. Beresford R, Ward A. Haloperidol decanoate: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in psychoses. *Drugs* 1987; 33: 31-49
67. Wei FC, Jann MW, Lin HN, et al. A practical loading dose method for converting schizophrenic patients from oral to depot haloperidol therapy. *J Clin Psychiatry* 1996; 57 (7): 298-302
68. Ereshefsky L, Toney G, Saklad SR, et al. A loading-dose strategy for converting from oral to depot haloperidol. *Hosp Community Psychiatry* 1993; 44 (12): 1155-61
69. Altamura AC, Colacurcio F, Mauri MC, et al. Haloperidol decanoate in chronic schizophrenia: a follow-up study of 12 months with plasma levels. *Prog Neuropsychopharmacol Biol Psychiatry* 1990; 14: 163-70
70. Altamura AC, Vita A, Giobbio GM, et al. Prediction of response to haloperidol in schizophrenia: neuroendocrine, neuromorphological and clinical variables. *Int Clin Psychopharmacol* 1994; 9 (1): 3-7
71. Kane JM, Davis JM, Schooler NR, et al. A one-year comparison of four dosages of haloperidol decanoate. *Psychopharmacol Bull* 1994; 30: 107, 1994
72. Zonda T, Kovari E. Use of haloperidol decanoate in psychiatric diseases. *Ther Hung* 1992; 40 (2): 64-8
73. Froemming JS, Lam YW, Jann MW, et al. Pharmacokinetics of haloperidol. *Clin Pharmacokinet* 1989; 17 (6): 396-423
74. Deberdt R, Elens P, Berghmans W, et al. Intramuscular haloperidol decanoate for neuroleptic maintenance therapy: efficacy, dosage schedule and plasma levels. An open multicenter study. *Acta Psychiatr Scand* 1980; 62 (4): 356-63
75. Kane JM, Davis JM, Schooler N, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. *Am J Psychiatry* 2002; 159 (4): 554-60
76. Gelders YG, Reyntjens AJ, Ash CW, et al. 12-month study of haloperidol decanoate in chronic schizophrenic patients. *Int Pharmacopsychiatry* 1982; 17 (4): 247-54
77. Eberhard G, Hellbom E. Haloperidol decanoate and flupenthixol decanoate in schizophrenia: a long-term double-blind cross-over comparison. *Acta Psychiatr Scand* 1986; 74 (3): 255-62
78. McKane JP, Robinson AD, Wiles DH, et al. Haloperidol decanoate vs fluphenazine decanoate as maintenance therapy in chronic schizophrenic in-patients. *Br J Psychiatry* 1987; 151: 333-6
79. Youssef HA. Duration of neuroleptic treatment and relapse rate: a 5-year follow-up study with haloperidol decanoate. *Clin Neuropharmacol* 1991; 14 Suppl. 2: S16-21
80. Quraishi S, David A. Depot haloperidol decanoate for schizophrenia. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 2. Oxford: Update software, 2000. CD001717
81. Brook S, Lucey JV, Gunn K. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 2000; 61: 933-41
82. Wright P, Birkhof MA, David S, et al. Double-blind, placebo controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatry* 2001; 158: 1149-51
83. Ulrich S, Neuhof S, Braun V, et al. Reduced haloperidol does not interfere with antipsychotic activity of haloperidol in the treatment of acute schizophrenia. *Int Clin Psychopharmacol* 1999; 14: 219-28
84. Altamura AC, Bareggi SR. Comment on 'Reduced haloperidol does not interfere with antipsychotic activity of haloperidol in the treatment of acute schizophrenia'. *Int Clin Psychopharmacol* 2000; 15: 303-4
85. Bucci L, Fuchs M, Simeon J, et al. Depot fluphenazine in the treatment of psychosis in a community mental health clinic. *Dis Nerv Syst* 1970; 31: 28-31
86. Caffey EM, Diamond LS, Frank TV, et al. Discontinuation or reduction of chemotherapy in chronic schizophrenics. *J Chronic Dis* 1964; 17: 347-58
87. Carpenter Jr WT, Buchanan RW, Kirkpatrick B, et al. Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. *Am J Psychiatry* 1999 Mar; 156 (3): 412-8
88. Marder SR, Van Putten T, Mintz J, et al. Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two year outcome. *Arch Gen Psychiatry* 1987; 44: 518-21
89. Chouinard G, Annable L, Campbell W. A randomized clinical trial of haloperidol decanoate and fluphenazine decanoate in the outpatient treatment of schizophrenia. *J Clin Psychopharmacol* 1989 Aug; 9 (4): 247-53
90. Woerner MG, Mannuzza S, Kane JM. Anchoring the BPRS: an aid to improved reliability. *Psychopharmacol Bull* 1988; 24: 112-7
91. Ahlfors UG, Dencker SJ, Gravem A, et al. Clopenthixol decanoate and perphenazine enantate in schizophrenic patients: a double-blind Nordic multicentre trial. *Acta Psychiatr Scand Suppl* 1980; 279: 77-91
92. Martyns-Yellow IS. The decanoate of flupenthixol and clopenthixol in the treatment of chronic schizophrenia in-patients: implications for community psychiatry. *West Afr J Med* 1993; 12 (2): 110-3
93. Borsetti G, Rocco P, Spilimbergo PG, et al. Long-term treatment of chronic schizophrenics with clopenthixol decanoate. *Pharmatherapeutica* 1984; 4 (1): 53-6
94. Carney MW. A 5-year follow-up study of chronic schizophrenics treated with clopenthixol decanoate. *Pharmatherapeutica* 1984; 4 (1): 57-63
95. Aaes-Jorgensen T. Pharmacokinetics of three different injectable zuclopenthixol preparations. *Prog Neuropsychopharmacol Biol Psychiatry* 1989; 13: 77-85
96. Sieberns S, Spechtmeier H. cis (Z)-Clopenthixol decanoate: a new depot neuroleptic. *Int Pharmacopsychiatry* 1982; 17 (3): 170-84
97. Lambert PA, Chabannes JP. A new injectable delayed-action neuroleptic with sedative and antipsychotic action: cis- (Z)-clopenthixol decanoate: clinical trials. *Encephale* 1984; 10 (2): 83-91
98. Solgaard T, Kistrup K, Aaes-Jorgensen T, et al. Zuclopenthixol decanoate in maintenance treatment of schizophrenic outpatients: minimum effective dose and corresponding serum levels. *Pharmacopsychiatry* 1994 May; 27 (3): 119-23
99. Kasi HA. An open clinical trial with the long-acting neuroleptic zuclopenthixol decanoate in the maintenance of schizophrenia. *Pharmatherapeutica* 1986; 4 (9): 555-60
100. Bttig D. Use of clopixol acutard 50 and 100mg (zuclopenthixol acetate) as a therapeutic drug in crisis at the Cery psychiatric hospital. *Schweiz Arch Neurol Psychiatr* 1988; 139 (5): 35-47
101. Lowert AC, Rasmussen EM, Holm R, et al. Acute psychotic disorders treated with 5% zuclopenthixol acetate in

- 'Viscoleo' (Cisordinol-Acutard), a global assessment of the clinical effect: an open multi-centre study. *Pharmatherapeutica* 1989; 5 (6): 380-6
102. Reynolds JEF. Anxiolytic sedatives, hypnotics and neuroleptics. In: Reynolds JEF, editor. *Martindale: the extra pharmacopoeia*. 30th ed. London: Pharmaceutical Press, 1993: 364-623
103. Budde G. Efficacy and tolerability of flupenthixol decanoate in the treatment of depression and psychosomatic disorders: a multicenter trial in general practice. *Prog Neuropsychopharmacol Biol Psychiatry* 1992; 16 (5): 677-89
104. Maragakis BP. A double-blind comparison of oral amitriptyline and low-dose intramuscular flupenthixol decanoate in depressive illness. *Curr Med Res Opin* 1990; 12 (1): 51-7
105. Poldinger W, Siebens S. Depression-inducing and antidepressive effects of neuroleptics: experiences with flupenthixol and flupenthixol decanoate. *Neuropsychobiol* 1983; 10 (2-3): 131-6
106. Quraishi S, David A. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 2. Oxford: Update software, 2000. CD001470
107. Pach J, Finkbeiner T, Glaser T, et al. Positive and negative symptoms in chronic schizophrenic patients under maintenance therapy with flupenthixol decanoate for a twelve month period. *Fortschr Neurol Psychiatr* 1998; 66 (10): 442-9
108. Kong DS, Yeo SH. An open clinical trial with the long-acting neuroleptics flupenthixol decanoate and fluphenazine decanoate in the maintenance treatment of schizophrenia. *Pharmatherapeutica* 1989; 5 (6): 371-9
109. Singh AN. Therapeutic efficacy of flupenthixol decanoate in schizoaffective disorder: a clinical evaluation. *J Int Med Res* 1984; 12 (1): 17-22
110. Knudsen P, Hansen LB, Larsen NE. Perphenazine decanoate in sesame oil vs perphenazine enanthate in sesame oil: a comparative study of pharmacokinetic properties and some clinical implications. *Acta Psychiatr Scand Suppl* 1985; 322: 11-4
111. Quraishi S, David A. Depot perphenazine decanoate and enanthate for schizophrenia. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 2. Oxford: Update software, 2000. CD001717
112. Tuninger E, Levander S. Large variations of plasma levels during maintenance treatment with depot neuroleptics. *Br J Psychiatry* 1996; 169 (5): 618-21
113. Tegeler J, Floru L. A comparative study of the longacting neuroleptics perphenazine-enanthate and fluspirilene. *Pharmakopsychiatr Neuropsychopharmacol* 1979 Sep; 12 (5): 357-65
114. Dencker SJ, Gios I, Martensson E, et al. A long-term cross-over pharmacokinetic study comparing perphenazine decanoate and haloperidol decanoate in schizophrenic patients. *Psychopharmacology (Berl)* 1994 Feb; 114 (1): 24-30
115. Imlah NW, Murphy KP. Ten-year follow-up of schizophrenic patients on pipothiazine palmitate. *Curr Med Res Opin* 1985; 9 (7): 449-53
116. Woggon B, Dick P, Fleischhauer HJ, et al. Comparison of the effects of pipothiazine palmitate and fluphenazine decanoate: results of a multicenter double-blind trial. *Int Pharmacopsychiatry* 1977; 12 (4): 193-209
117. Chouinard G, Annable L, Kropsky M. A double-blind controlled study of pipothiazine palmitate in the maintenance treatment of schizophrenic outpatients. *J Clin Pharmacol* 1978 Feb-Mar; 18 (2-3): 148-54
118. Leong OK, Wong KE, Tay WK, et al. A comparative study of pipothiazine palmitate and fluphenazine decanoate in the maintenance of remission of schizophrenia. *Singapore Med J* 1989; 30 (5): 436-40
119. Bechelli LP, Navas-Filho F. Short-term double-blind trial of pipothiazine palmitate and haloperidol in the acute phase of schizophrenia. *Encephale* 1986; 12 (3): 121-5
120. Steinert J, Neder A, Erba E, et al. A comparative trial of depot pipothiazine. *J Int Med Res* 1986; 14 (2): 72-7
121. Quraishi S, David A. Depot pipothiazine palmitate and undecylate for schizophrenia. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 2. Oxford: Update software, 2000. CD001720
122. Chouinard G, Annable L, Steinberg S. A controlled clinical trial of fluspirilene, a long acting injectable neuroleptic, in schizophrenic patients with acute exacerbation. *J Clin Psychopharmacol* 1986; 6: 21-6
123. Kanowski S, Paur R. Experience with fluspirilene in gerontopsychiatry. *Pharmakopsychiatr Neuropsychopharmacol* 1980 May; 13 (3): 137-43
124. Tanghe A. A retrospective evaluation of long-term fluspirilene (IMAP) treatment. *Acta Psychiatr Belg* 1976 May; 76 (3): 480-90
125. Soni SD. Fluspirilene in the treatment of non-hospitalized schizophrenic patients. *Curr Med Res Opin* 1977; 4 (9): 645-9
126. Russel N, Landmark J, Merskey H, et al. A double blind comparison of fluspirilene and fluphenazine decanoate in schizophrenia. *Can J Psychiatry* 1982; 27 (7): 593-6
127. Quraishi S, David A. Depot fluspirilene for schizophrenia. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 2. Oxford: Update software, 2000. CD001718
128. Carpenter Jr WT, Zito JM, Vitrai J, et al. Hypothesis testing: is clozapine's superior efficacy dependent on moderate D2 receptor occupancy? *Biol Psychiatry* 1998 Jan 15; 43 (2): 79-83
129. Meehan K, Zhang F, David S, et al. A Double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol* 2001; 21 (4): 389-97
130. Wright P, Jewell H, Mitchell M, et al. A preliminary study of the safety, efficacy and pharmacokinetics of intramuscular olanzapine in patients with acute nonorganic psychosis [abstract]. *Schizophr Res* 1999; 36: 318
131. Wright P, Kiesler G, Mitchell M, et al. Safety and efficacy of intramuscular olanzapine in patients with acute non organic psychosis [abstract]. *Schizophr Res* 1999; 36: 318
132. Eerdekens M, Rasmussen M, Vermeulen A, et al. Kinetics and safety of a novel risperidone depot formulation [abstract]. *Int J Neuropsychopharmacol* 2000; 3 Suppl. 1: S135
133. Gefvert O, Nyberg S, Persson P, et al. Pharmacokinetics, D2 receptor occupancy, and clinical effects of a long-acting injectable formulation of risperidone in patients with schizophrenia [abstract]. *Biol Psychiatry* 2001; 49 Suppl. 8: 117S
134. Kay SR, Opler LA, Lindenmayer JP. The positive and negative syndrome scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl* 1989; (7): 59-67

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135. Eerdekens M, Fleischhacker WW, Xie Y, et al. Long-term safety of long-acting risperidone microspheres [abstract]. *Schizophr Res* 2002; 53 Suppl. 3: 174
 136. Chue P, Eerdekens M, Augustyns I, et al. Efficacy and safety of long-acting risperidone microspheres and risperidone oral tablets. *Schizophr Res* 2002; 53 Suppl. 3: 174-5
 137. Miceli J, Wilner K, Folger C, et al. Pharmacokinetics of intramuscular ziprasidone in schizophrenic patients: population pharmacokinetic modelling [abstract]. *Eur Neuropsychopharmacol* 1998; 8: S215
 138. Brook S, Swift R, Harrigan EP. The tolerability and efficacy of intramuscular ziprasidone [abstract]. *Eur Neuropsychopharmacol* 1997; 7 Suppl. 2: 215
 139. Daniel DG, Potkin SG, Reeves KR, et al. Intramuscular ziprasidone 20mg is effective in reducing agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacol* 2001; 155: 128-34
 140. Lesem MD, Zajecka JM, Swift RH, et al. Intramuscular ziprasidone 2mg versus 10mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry* 2001; 62: 12-8
 141. Dernovsek MZ, Prevornik Rupel V, Rebolj M, et al. Quality of life and treatment costs in schizophrenic outpatients, treated with depot neuroleptics. *Eur Psychiatry* 2001; 16 (8): 474-82
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