# Systematic meta-review of depot antipsychotic drugs for people with schizophrenia†

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**Background** Long-acting depot antipsychotic medication is a widely used treatment for schizophrenia.

**Aims** To synthesise relevant systematic Cochrane reviews.

**Method** The Cochrane Database was searched and summary data were extracted from randomised controlled clinical trials of depots.

**Results** Standard dose depot *v.* placebo resulted in significantly less relapse but more movement disorders. Those on depots (*v.* oral drugs) showed more global change on one outcome measure; relapse and adverse effects showed no difference. Comparisons showed no convincing advantages for one depot over another.

**Conclusions** Depot antipsychotics are safe and effective. They may confer a small benefit over oral drugs on global outcome. Those for whom depots are most indicated may not be represented. Large studies are required to discern differences in relapse rates and long-term adverse effects, and data on satisfaction, quality of life and economics.

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Antipsychotic medication is the mainstay in the effective management of schizophrenia. These drugs reduce symptoms and, when used as a maintenance treatment, prevent relapse (Davis & Andriukaitis, 1986). Translation of this success into clinical practice is attenuated by poor compliance (Weiden & Olfson, 1995), reasons for which include adverse effects, level of insight, severity of illness, complexity of treatment regimen and the relationship that patients have with mental health practitioners (Fenton *et al*, 1997; Kemp & David, 1997). Long-acting depot antipsychotics were developed in the 1960s, to promote compliance in people with chronic psychotic illnesses (Simpson, 1984). They generally consist of an ester of the antipsychotic drug in an oily solution injected intramuscularly every 1–6 weeks. Depots simplify the treatment process by requiring, for example, the person to attend for injection at a specific clinic, thus guaranteeing the delivery of a known quantity of medication (Barnes & Curson, 1994; Davis *et al*, 1994). Apart from overcoming covert non-compliance, the pharmacological advantages for depots include the avoidance of problems associated with absorption and hepatic biotransformation. Disadvantages include concerns over adverse effects, including tardive dyskinesia and those associated with parenteral administration *per se* (Johnson, 1984). Many clinicians have promoted the use of depots (Glazer & Kane, 1992; Gerlach, 1995; Kane *et al*, 1998), yet patient and clinician acceptance is variable, with the mode of delivery being a major stumbling block (reviewed in companion paper – Walburn *et al*, 2001, this issue). Figures on the use of depots are sparse but a UK national household survey found that approximately 29% of 390 non-hospitalised patients with psychotic disorders were prescribed depots (Foster *et al*, 1996).

Davis undertook meta-analyses, incorporating several methodologies (Davis *et al*, 1994) including 'mirror image' and influential discontinuation trials (e.g. Hirsch *et al*, 1973), and concluded that depots were superior to oral drugs in many respects. Similarly, Glazer & Kane (1992) combined several studies comparing the incidence of tardive dyskinesia for people on depots with those on oral agents. They concluded that depots were no more harmful than oral drugs in this respect. Because non-randomised evaluative studies, including before and after ('mirror image') trials, repeatedly have been shown to overestimate the effect of experimental interventions (Chalmers *et al*, 1983; Schulz *et al*, 1995), these have not been included in Cochrane schizophrenia reviews (see Adams & Eisenbruch, 2000; Coutinho *et al*, 2000; Quraishi & David, 2000*a–e*; Quraishi *et al*, 2000).

### Objective

The aim of this paper is to provide a synthesis and quantitative summary of the findings of Cochrane depot reviews.

## METHOD

### Search

The search strategy, methods of selection, quality assessment, data extraction and assimilation within each review are published in *The Cochrane Library*. The reader is referred to these reviews for explicit details.

### Selection

All reviews of long-acting depot antipsychotics for schizophrenia were obtained from *The Cochrane Library* (Issue 1, 2000) by searching using the term SCHIZOPHRENIA and scanning the titles of completed reviews. The pre-stated comparisons of interest were of any long-acting depot antipsychotic medication *v.* placebo or *v.* oral medication and, finally, high-dose depot *v.* low-dose depot, for people with schizophrenia or schizophrenia-like illnesses. Outcomes of *a priori* interest were intention-to-treat data on death, improvement in global functioning, mental state, behaviour, social functioning, quality of life, carer burden and incidence of attrition and adverse effects.

### Quality assessment

There was no quality assessment of the primary reviews from which these data



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were extracted but the empirical-evidence-based Cochrane reviews have, in general, been shown to be of higher quality than others (Jadad *et al*, 1998).

### Data extraction

Data were extracted from reviews by M.K.P.F. and re-extracted by either C.E.A. or A.S.D. Where disagreement arose, this was resolved through discussion.

### Data analysis

All intention-to-treat data were binary outcomes. Risk ratios (RRs, random) and their 95% confidence intervals (CI) were extracted from the original review and entered into RevMan 4.1 (http://www.update-software.com/ccweb/cochrane/revman.htm). These were calculated in preference to odds ratios because they are robust to heterogeneity and more intuitive to clinicians (Boissel *et al*, 1999). In turn, where appropriate, summary data from each review were summated and an overall RR and the summary 95% CI were calculated. Where possible, we calculated the numbers needed to treat (NNT) or harm (NNH). For a test of heterogeneity we visually inspected graphs as well as employing the $\chi^2$ test.

There are some dangers in this overall approach. Because it was not possible to avoid spurious results by counting participants twice in the 'specific depot *v*. other depots' comparison, totals are not produced. Totalling across different pharmacological classes of antipsychotics is statistically attractive. Power to demonstrate outcomes of interest afforded by summation is increased so that any important effects that the small source trials and reviews would have missed may be highlighted. Clinically and pharmacologically, however, such totalling may not make sense. Clinicians who choose to prescribe a specific depot may not be interested in a summary statistic across all depots. In some circumstances effects could cancel out in an overall summary statistic and causative and protective effects could be masked or cancelled out. Data using summated totals must therefore be interpreted with caution.

## RESULTS

### The original reviews

Details of the studies included and excluded in specific reviews can be found in the individual Cochrane publications. Overall, composite data for some compounds were sparse (see Table 1). Only 111 people have been randomised within trials of perphenazine and 117 in bromperidol decanoate studies. On the other hand, 3348 people have been randomised in trials of fluphenazine decanoate. The duration of studies in the reviews ranged from 2 weeks to 3 years. Most of the included studies employed operationalised definitions of schizophrenia, which covered several classification systems and their revisions. Doses of depots varied from the very low (1.25 mg of fluphenazine every 2 weeks) to the very high (250–1100 mg of fluphenazine weekly–monthly), although analysis was undertaken only between comparable dose ranges where appropriate, with most falling within *British National Formulary* ranges (British Medical Association & Royal Pharmaceutical Society of Great Britain, 1999). Reviewers sought clinically relevant outcomes but only a limited range were recorded consistently or presented in a usable form. Overall, study attrition was remarkably low. For example, only about 14% of those randomised to the comparisons of one depot with another left the trials early. Trials of oral atypical antipsychotic agents have rates of attrition of 40–60% (Thornley & Adams, 1998).

### Depot antipsychotics *v.* placebo depots

Understandably, few people have been randomised within this comparison. Three reviews compared depot medication against placebo (bromperidol, fluphenazine and haloperidol decanoate). Only one small trial within the fluphenazine review reported mortality, with no clear differences between groups ($n$=54, RR=5, CI=0.25–99). One review reported on relapse (fluphenazine decanoate *v.* placebo), with the results favouring the active drug ($n$=415, RR=0.3, CI=0.22–0.4; NNT=2, CI=1.8–2.6; see Fig. 1). Three reviews presented data for the numbers leaving the studies early. Significantly more people taking depot medication stayed in the studies than those receiving placebo ($n$=152, RR=0.43, CI=0.27–0.71). Two reviews reported on the adverse effects of blurred vision or dry mouth. Curiously, these symptoms were more frequent in the placebo group ($n$=52, RR=0.16, CI=0.03–0.8; NNT=3, CI=2–9). When data were reported in the review as 'movement disorders – general', statistical significance was achieved in favour of those taking placebo ($n$=51, RR=20.5, CI=1.3–338; NNH=3, CI=6.5–1.9).

### Depot antipsychotics *v.* oral antipsychotics

Death is a rare, inconsistently reported outcome. One review presented limited data and there is no clear effect of either depot or oral antipsychotic ($n$=156, RR=2, CI=0.19–21). Three reviews present data on global change. Significantly fewer numbers of people allocated to depot preparations had no clinically meaningful change ($n$=127, RR=0.7, CI=0.5–0.9; NNT=4, CI=2.4–9; see Fig. 2). For outcomes such as relapse, study attrition, needing adjunctive anticholinergic medication and incidence of tardive dyskinesia, no clear differences were demonstrated between those taking depot and people allocated to oral antipsychotics (relapse, $n$=844, RR=0.96, CI=0.8–1.1).

### Specific depot antipsychotic *v.* another depot

All nine depot reviews contributed to at least one of the outcomes in this comparison. No data were pooled because it was impossible to avoid counting data twice: one review's experimental group was another's control. For all outcomes (see Fig. 3) there were few convincing data that any real differences exist between depots. All data from reviews that compared the depot antipsychotic of interest with another, for the outcome of 'no important improvement in global functioning' as indexed by Clinical Global Impression (CGI) scores (Guy, 1976), included the possibility that there were no differences between depots. This also applies to the outcome of leaving the study early (25% attrition in the experimental groups). The outcome of 'mental state – relapse' showed that zuclopenthixol decanoate was statistically superior to the control depots (largely fluphenazine decanoate) ($n$=296, RR=0.64, CI=0.4–0.9, NNT=8, CI=5–53), but this could be a function of publication bias (see Discussion).

### High-dose depot *v.* standard dose, and standard dose *v.* low dose

There are limited data, but reviews found no differences between high-dose (250 mg of fluphenazine weekly; 200 mg of flupentixol every 2 weeks) *v.* standard-dose



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**Table 1** Summary of included reviews

| Review | Methods | Participants | Intervention | Outcomes |
|---|---|---|---|---|
| Bromperidol decanoate | Allocation: all 4 studies randomised<br>Blinding: double, no further details<br>Duration: 6 months–1 year | Diagnosis: schizophrenia<br>Age: range 20–65 years<br>Gender: >55 M; >42 F<br>*N*=4, *n*=117<br>Setting: community and in-patients | 1. Bromperidol decanoate: dose range 50–242 mg/month (*n*=58)<br>2. Fluphenazine decanoate: dose range 16.7–300 mg/month (*n*=39)<br>3. Haloperidol decanoate: mean dose 119 mg/month (*n*=10)<br>4. Placebo (*n*=10) | Global effect (CGI)<br>Leaving the study early<br>Mental state (use of additional medication)<br>Side-effects (DOTES) |
| Flupentixol depot | Allocation: all 15 studies randomised<br>Blinding: double, no further details<br>Duration: 8 weeks–2 years<br>Informed consent from participants in 5 studies | Diagnosis: schizophrenia<br>Duration of illness: 1–29 years<br>*N*=15, *n*=615<br>Gender: >373 M; >193 F, unknown in 1 trial<br>Age: range 17–79 years<br>Setting: community and in-patient | 1. Flupentixol decanoate: dose range 9 mg/2–3 weeks to 300 mg/2–3 weeks (*n*=359)<br>2. Clopenthixol decanoate: dose range 50–600 mg/2–4 weeks (*n*=48)<br>3. Flupenthixol decanoate: mean dose 25 mg/3 weeks, range 10–50 mg (*n*=139)<br>4. Haloperidol decanoate: mean dose 151 mg/injection (*n*=16)<br>5. Penfluridol: mean dose 20 mg/week (*n*=30)<br>6. Pipothiazine: mean dose 100 mg/month (*n*=23) | Death<br>Leaving the study early<br>Relapse<br>Use of additional medication<br>Mental state (BPRS, CPRS, HRSD)<br>Side-effects (SAS) |
| Fluphenazine decanoate | Allocation: all 48 studies randomised<br>Blinding: varying degrees of double blinding<br>Duration: 2 weeks–2 years<br>Two studies used a crossover method | Diagnosis: schizophrenia and schizoaffective disorder<br>Duration of illness: range <2–39 years<br>*N*=48, *n*=3348<br>Gender: >1318 M; >1054 F<br>Age: range 24–70 years<br>Setting: community and in-patient | 1. Fluphenazine decanoate: mean dose 51.73 mg, range (low 1.25–6.25 mg) standard–high dose 25–1100 mg/2–4 weeks (*n*=1963)<br>2. Bromperidol decanoate: mean dose 242 mg/month, range 64–400 mg (*n*=23)<br>3. Chlorpromazine: dose range 50–100 mg/day (*n*=36)<br>4. Clopenthixol decanoate: mean dose 220 mg/3–4 weeks, range 200 mg/4 weeks to 600 mg/2 weeks (*n*=19)<br>5. Flupentixol: dose range 30–40 mg/2–4 weeks (*n*=48)<br>6. Fluphenazine hydrochloride (oral): mean dose 18.9 mg, dose range 2.5–60 mg/day (*n*=396)<br>7. Fluphenazine enanthate: dose range 2.5–387.5 mg/2–4 weeks (*n*=96)<br>8. Fluspirilene decanoate: 3–20 mg/week (*n*=93)<br>9. Haloperidol decanoate: mean dose 109.4 mg, range 15–900 mg/2–4 weeks (*n*=142)<br>10. Penfluridol: dose range 20–160 mg (*n*=27)<br>11. Pimozide: dose 8 mg/day–week, range 10–60 mg (*n*=70)<br>12. Pipotiazine palmitate: mean dose 88.3 mg, dose range 6.25–400 mg/2–5 weeks (*n*=184)<br>13. Placebo (*n*=75)<br>14. Trifluoperazine: dose 10 mg/day (*n*=17) | Global improvement (CGI)<br>Mental state (BPRS, CPRS)<br>Behaviour (NOSIE)<br>Leaving the study early<br>Use of additional medication<br>Side-effects |

| | | | | |
|---|---|---|---|---|
| Fluphenazine enanthate | Allocation: all 14 studies randomised<br>Blinding: double, no further details<br>Duration: 2 weeks–1 year<br>One study used a crossover design | Diagnosis: schizophrenia<br>Duration of illness: acute to hospitalised > 2 years<br>*N*=14, *n*=451<br>Age: range 17–65 years<br>Setting: community and in-patient | 1. Fluphenazine enanthate: dose range 3.5–387.5 mg/2–4 weeks (*n*=279)<br>2. Chlorpromazine: mean dose 388 mg/day (*n*=15)<br>3. Fluphenazine decanoate: dose range 2.5–500 mg/2–4 weeks (*n*=284)<br>4. Fluspirilene decanoate: dose range 1–14 mg/week (*n*=31)<br>5. Pipotiazine palmitate: dose range 25–250 mg/2–4 weeks (*n*=42) | Global effect (CGI)<br>Mental state (BPRS)<br>Leaving the study early<br>Use of additional medication<br>Side-effects (Bordeleau Scale, HRSD) |
| Fluspirilene | Allocation: all 7 studies randomised<br>Blinding: double, no further details<br>Duration: 4 weeks–6 months | Diagnosis: schizophrenia<br>Duration of illness: 2–39 years<br>*N*=7, *n*=290<br>Age: range 16–80 years<br>Gender: > 98 M; > 137 F<br>Setting: in-patient and community | 1. Fluspirilene decanoate: dose range 1–23 mg/1–2 weeks (*n*=160)<br>2. Chlorpromazine: dose range 370–720 mg/day (*n*=20)<br>3. Fluphenazine decanoate: dose range 25–150 mg/2–3 weeks (*n*=71)<br>4. Fluphenazine enanthate: mean dose 7.55 mg/week (*n*=26)<br>5. Pipotiazine undecylenate: mean dose 103.8 mg/2 weeks (*n*=13) | Global effect (CGI)<br>Leaving the study early<br>Side-effects (UKU) |
| Haloperidol decanoate | Allocation: all 11 studies randomised<br>Blinding: double, no further details<br>Duration: 16–60 weeks | Diagnosis: schizophrenia or schizoaffective disorder<br>Duration of illness: 0–38 years<br>*N*=11, *n*=455<br>Age: range 18–66 years<br>Gender: > 264 M; > 175 F<br>Setting: community and in-patient | 1. Haloperidol decanoate: dose range 15–900 mg/2–4 weeks (*n*=238)<br>2. Fluphenazine decanoate: dose range 2.5–300 mg/2–4 weeks (*n*=125)<br>3. Haloperidol (oral): dose not specified (*n*=11)<br>4. Pipotiazine palmitate: dose range 50–125 mg/month (*n*=20)<br>5. Placebo (*n*=39)<br>6. Zuclopenthixol decanoate: mean dose 284 mg/month (*n*=23) | Death<br>Global impression (CGI)<br>Mental state (BPRS, CPRS, depression, Krawiecka Scale, MADRS)<br>Behaviour (Wing Ward Scale)<br>Leaving the study early<br>Use of additional medication<br>Side-effects (AIMS, Bordeleau Scale, SAS, UKU) |
| Perphenazine depot | Allocation: both studies randomised<br>Blinding: double, no further details<br>Duration: range 6 weeks–6 months | Diagnosis: schizophrenia or acute psychosis<br>Duration of illness: <2–25 years<br>*N*=2, *n*=236<br>Age: range 18 to > 60 years<br>Gender: > 135 M; > 87 F<br>Setting: community and in-patient | 1. Perphenazine decanoate: dose range 20–600 mg/2 weeks (*n*=111)<br>2. Clopenthixol decanoate: dose range 50–800 mg/2 weeks (*n*=87)<br>3. Perphenazine enanthate: mean dose 108.5 mg/2 weeks (*n*=24) | Death<br>Global impression (CGI)<br>Leaving the study early<br>Use of additional medication<br>Side-effects |

*Continued*

**Table 1** *Continued*

| Review | Methods | Participants | Intervention | Outcomes |
|---|---|---|---|---|
| Pipotiazine depot | Allocation: all 14 studies randomised<br>Blinding: varying degrees of double blinding<br>Duration: range 11 weeks–3 years | Diagnosis: schizophrenia<br>Duration of illness: range <3–34 years<br>*N*=14, *n*=771<br>Age: range 18–69 years<br>Gender: >380 M; >205 F<br>Informed consent given in 2 studies<br>Setting: community and in-patient | 1. Pipotiazine palmitate and undecylenate (*n*=365)<br>2. Fluphenazine decanoate (*n*=198)<br>3. Fluphenazine enanthate (*n*=87)<br>4. Fluspirilene (*n*=13)<br>5. Haloperidol decanoate (*n*=21)<br>6. Oral antipsychotics (various) (*n*=87) | Global impression (CGI)<br>Mental state (BPRS, HRSD)<br>Leaving the study early<br>Use of additional medication<br>Side-effects (AIMS, Bordeleau Scale, DOTES) |
| Zuclopenthixol depot | Allocation: all 4 studies randomised<br>Blinding: varying degrees of double blinding<br>Duration: 12 weeks–1 year | Diagnosis: schizophrenia<br>Duration of illness: >2 years<br>*N*=4, *n*=332<br>Age: range 20–65 years<br>Gender: >197 M; >71 F<br>Setting: community and in-patient | 1. Zuclopenthixol decanoate: dose range 100–600 mg/2–4 weeks (*n*=17)<br>2. Flupentixol palmitate: dose range 25–300 mg/4 weeks (*n*=48)<br>3.Haloperidol decanoate: dose range 39–200 mg/4 weeks (*n*=28)<br>4. Perphenazine enanthate: dose range 20–600 mg/2 weeks (*n*=85) | Death<br>Global impression (CGI)<br>Relapse<br>Leaving the study early<br>Use of additional medication<br>Side-effects (UKU)<br>Discharge |

*N*, number of trials; *n*, number of participants; M, males; F, females; AIMS, Abnormal Involuntary Movement Scale (Guy, 1976); BPRS, Brief Psychiatric Rating Scale (Overall & Gorham, 1962); Bordeleau Scale (Bordeleau *et al*, 1967); CGI, Clinical Global Impression (Guy, 1976); CPRS, Comprehensive Psychopathological Rating Scale (Åsberg *et al*, 1978); DOTES, Dosage Record and Treatment Emergent Symptom Scale (Guy, 1976); HRSD, Hamilton Rating Scale for Depression (Hamilton, 1960); Krawiecka Scale (Manchester Scale) (Krawiecka *et al*, 1977); MADRS, Montgomery–Åsberg Depression Rating Scale (Montgomery *et al*, 1978); NOSIE, Nurses' Observation Scale for In-patient Evaluation (Honigfeld *et al*, 1962); SAS, Simpson–Angus Scale (Simpson & Angus, 1970); UKU, UKU Side Effects Rating Scale (Lingjaerde *et al*, 1987); Wing Ward Scale (Wing, 1961).

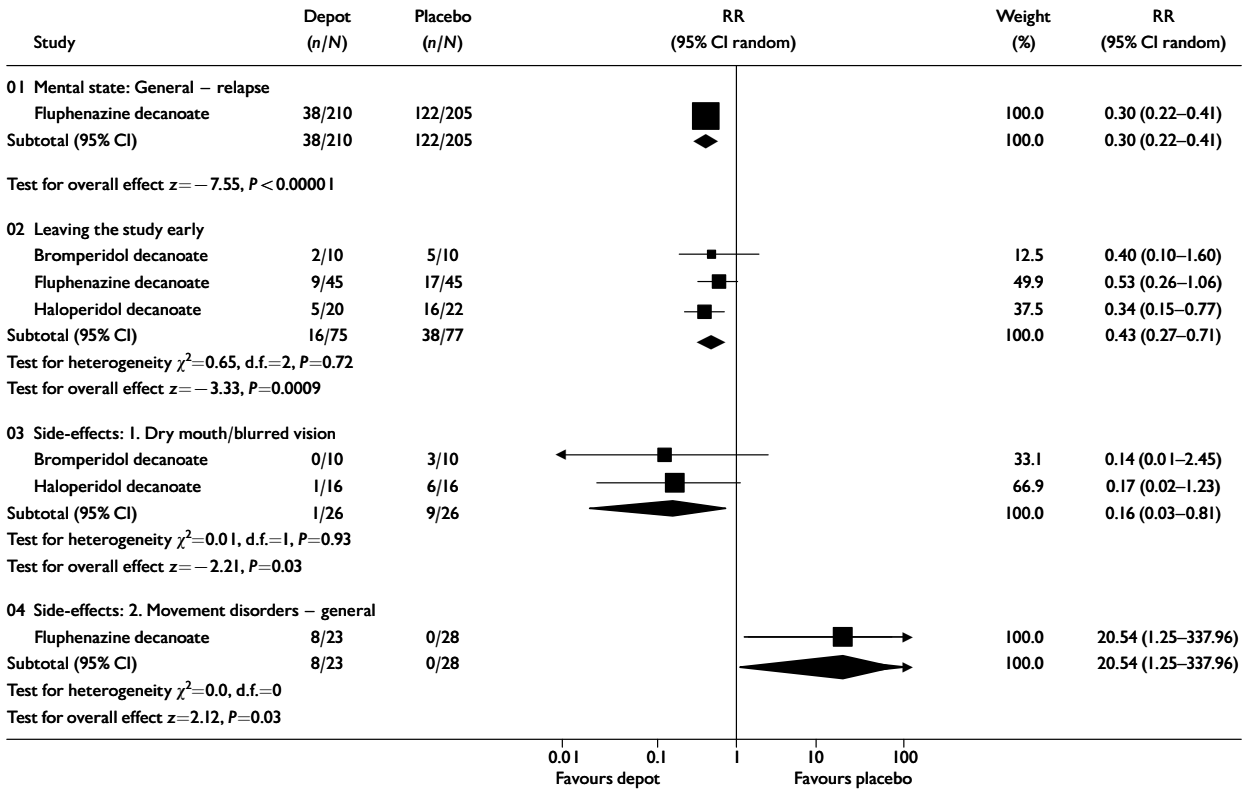


**Fig. 1** Depot antipsychotic *v.* placebo depot: all outcomes.

(12.5–50 mg of fluphenazine every 2 weeks; 40 mg of flupentixol biweekly) depot antipsychotics for global outcome, mental state, adverse effects or attrition. The estimates of effect all had wide confidence intervals. Within the standard dose *v.* low dose comparison, most data were available for the outcome of relapse ($n$=638). Pooled data across three phenothiazine preparations (flupentixol, fluphenazine decanoate and enanthate) suggest that the standard dose (12.5–50 mg every 2 weeks) is more effective than the low doses (1.25–25 mg every 2 weeks) (RR=2.5, CI=1.1–5.9; NNT=7, CI=5–12). Although no clear differences were demonstrated between the standard dose and low dose on global functioning, attrition and adverse effects (movement disorders), data are limited.

## DISCUSSION

### Generalisability

This overview collates a great deal of trial data. All trial populations were slightly different and this clinical heterogeneity may mean that at least some participants, treatment regimens and circumstances should resemble those seen in everyday practice. Whether those patients for whom a depot is most indicated were included, however, is less certain. It would be problematic to recruit those who are reluctant with a prescription for oral antipsychotics into any clinical trial. The reviews mostly comprised those who were stable on oral medication. Some participants whose course of illness had not been helped previously by a variety of medications were included, but it is unclear whether these people were non-compliant or unresponsive to treatment. Studies that compared people who were stable on oral medication and then were randomised to receive either depot or inactive placebo, such that the comparison group are undergoing discontinuation of treatment, were not included in this overview.

### Depot antipsychotics *v.* placebo depots

Currently, it would be difficult to undertake a trial comparing placebo to neuroleptic depot in the treatment of schizophrenia, given the availability of effective treatments. Even with the limited data ($n$=415), fluphenazine decanoate clearly reduces relapse between 12 weeks and 2 years (NNT=2). That significantly more people stayed in the study if allocated to depot (21% *v.* 49% over the same time period) can be interpreted as a positive outcome, assuming that those who left early were unlikely to be well. Data from within this comparison suggest that the adverse effects of blurred vision or dry mouth are not good indicators of antipsychotic activity because they are more frequent in the placebo group. Unsurprisingly, drugs such as fluphenazine decanoate are associated with movement disorders. We have calculated that, on average, between two and seven people have to be given depot for one person to suffer significant general movement disorders (NNH=3, CI=2–6.5), which is admittedly a crude index.

### Depot antipsychotics *v.* oral antipsychotics

An underlying assumption in psychiatric therapeutics is that people with serious mental illnesses may not take oral medication reliably, resulting in relapse. If this assumption is correct, then the comparison of relapse rates should demonstrate an advantage for those on depots *v.* oral drugs. Although the advantage on one outcome measure in favour of depots was statistically significant (global improvement:



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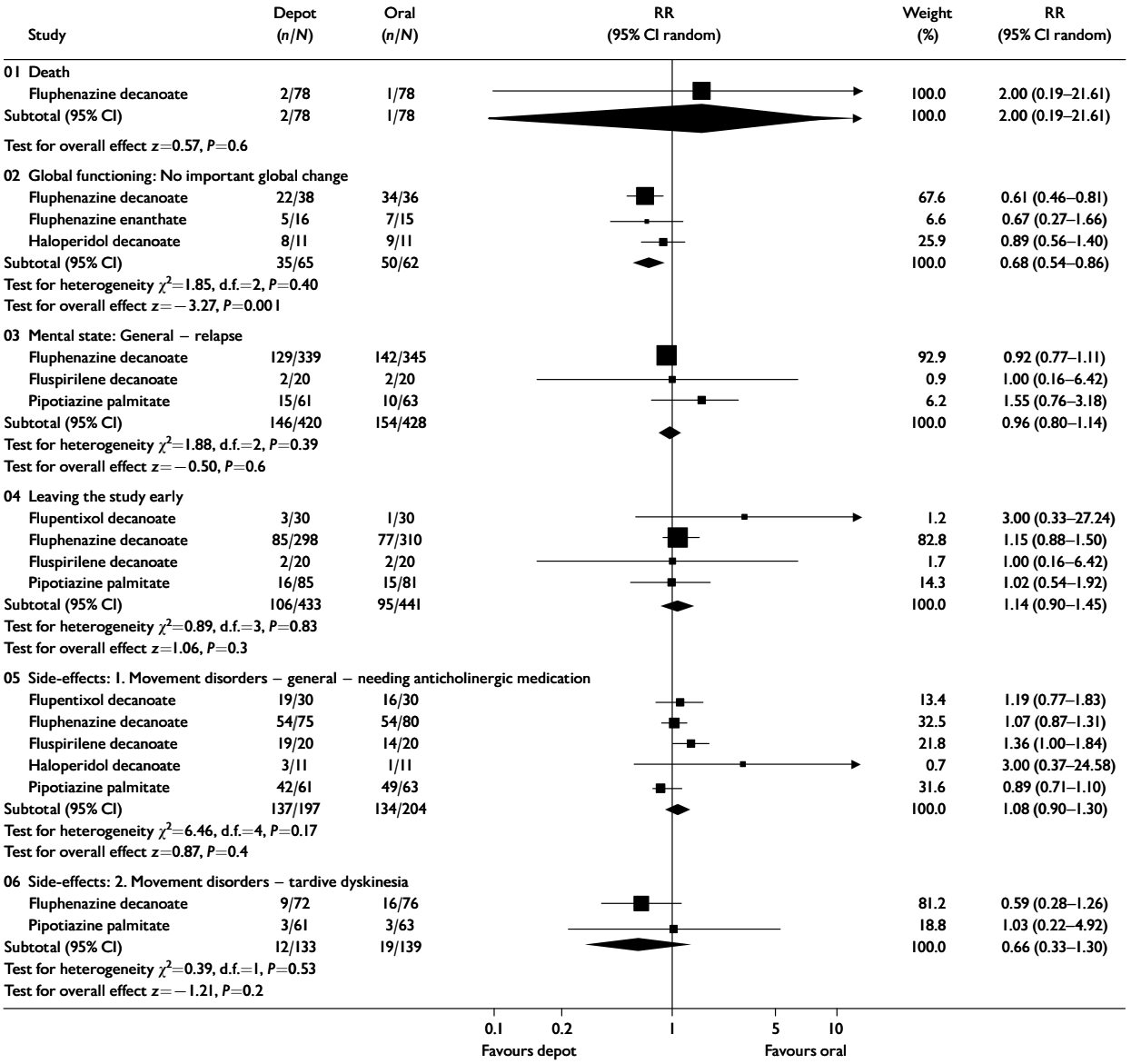


**Fig. 2** Depot antipsychotic *v.* oral antipsychotic: all outcomes.

NNT=4, CI=2–9), other important outcomes such as relapse, attrition and adverse effects were not. Reviews involving over 800 participants did not demonstrate a statistically significant difference between depots and oral medications (RR=0.9, CI=0.8–1.2) in terms of relapse, despite good statistical power. It could be argued that those participating in trials were reasonably compliant with oral medications so that the demonstration of *any* advantages to depot (and absence of disadvantages) is noteworthy. Trials suggest that adverse effects, reported as the proxy outcome of 'needing additional anticholinergic medication', occur in about two-thirds of people on antipsychotics, whether administered by depot or given orally.

## Specific depot antipsychotic *v.* another depot

Many of these comparisons can be seen as fulfilling the need to market a new substance rather than answering any relevant clinical question. No differences were seen on any global measures of change. All nine reviews reported data on relapse. One found a statistically significant result in favour of zuclopenthixol decanoate (NNT=8, CI=5–53). Unlike the other depots, this finding in favour of zuclopenthixol was consistent across the outcomes of leaving the study early and needing additional anticholinergic drugs. It is feasible that zuclopenthixol decanoate is indeed a better depot in terms of the outcomes measured, although relapse rates in the comparator drugs were high and, pharmacologically, there are no grounds to suspect any superiority. On the other hand, being one of the newest preparations, it has not been used as the comparator depot in any other trial (Gilbody & Song, 2000). By the same token, this may explain, to some extent, the poor results for fluphenazine compounds, at least when it comes to adverse effects. These compounds have been used more than any other as the control drugs and these data may be the summation of a publication/reporting bias.

## High-dose depot *v.* standard dose, and standard dose *v.* low dose

Data from trials support the clinical impression that there is no clear advantage



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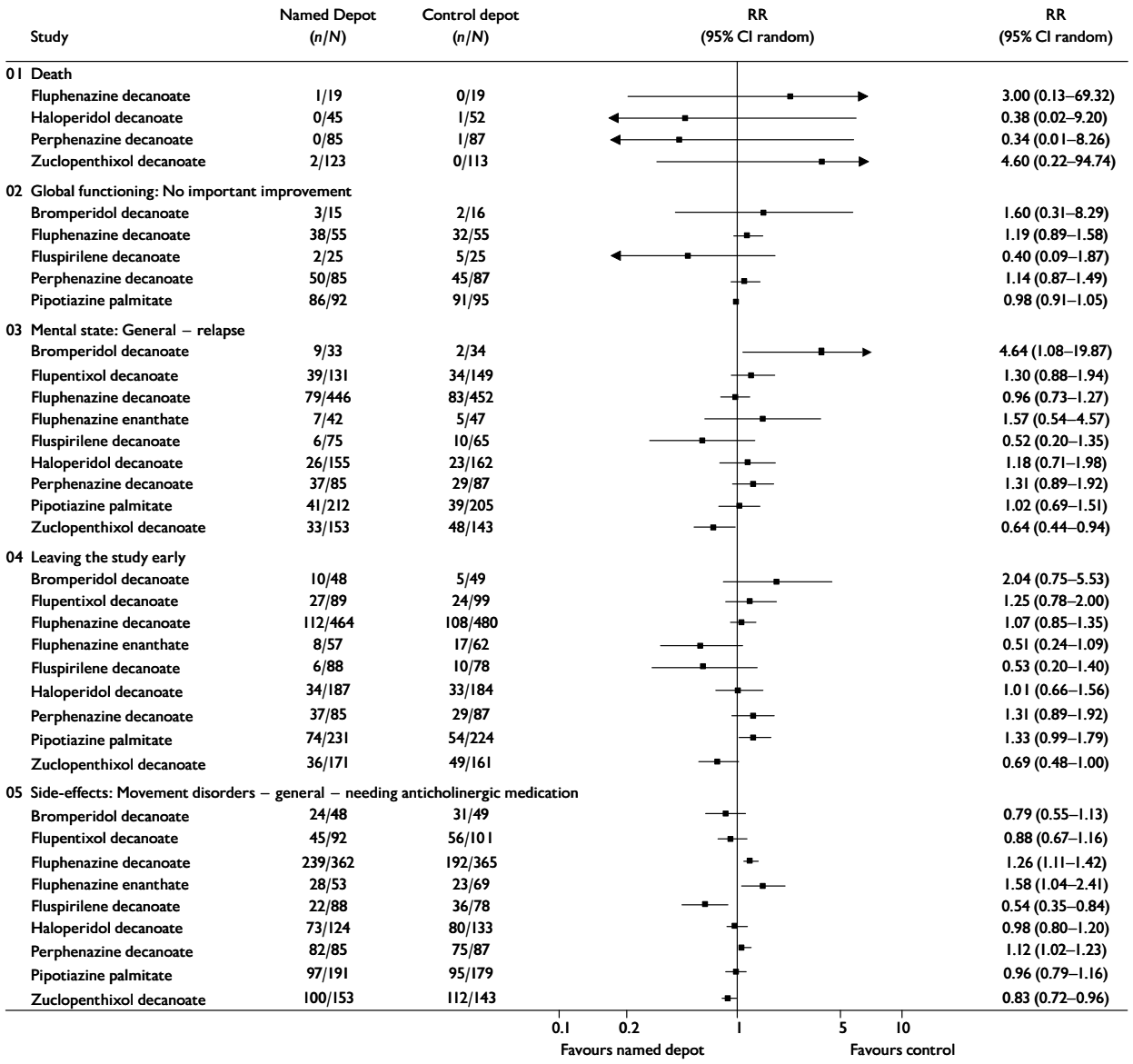


**Fig. 3** Specific depot antipsychotic *v.* control depot: all outcomes, no summations.

in the use of high-dose depot preparations introduced for treatment-resistant cases, and that ultralow doses are little more than placebo.

## Limitations

Many outcomes, stated by trialists to have been recorded, were lost owing to poor reporting. Modern trialists recommend that all outcome measures should be reported (Begg *et al*, 1996). Data from often poorly reported, small trials of limited generalisability, when taken together with larger trials, support the value of depot antipsychotic preparations. This complements information from less methodologically rigorous studies (Davis *et al*, 1994). There is little convincing evidence that one depot is clearly better than another, and none that high or ultralow doses have advantages.

Direct data on economic outcomes, quality of life and satisfaction were not found. Such outcomes were scarcely considered in randomised trials from the 1960s to early 1980s. A review of what limited evidence there is relating to satisfaction with depot antipsychotics suggests that patients on depots are, on average, reasonably satisfied (see companion paper – Walburn *et al*, 2001, this issue).

## Future studies

Clinicians and recipients of care could still benefit from thorough evaluation of any one of these widely used compounds within a large, long, simple and clinically relevant randomised trial (Hotopf *et al*, 1999). Further research should, ideally, focus on those living outside of hospital in community settings, whose non-adherence to treatment and follow-up is thought to contribute to relapses in their condition. Such studies are, by their very nature, difficult to perform. Those designing evaluative studies of depots in the future, including 'atypical' compounds, should learn from the limitations and strengths seen in depot trial design over the past three decades. Such studies would have to be of longer duration than the majority conducted to date, in order to capture a sufficient number of relapses. Long-term



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trials specifically designed to examine outcomes such as tardive dyskinesia also are required. The definition of relapse requires careful consideration and would need to be operationalised. Obtaining useful cost-effectiveness data and data on quality of life, satisfaction, disability, etc. is a research priority.

**CLINICAL IMPLICATIONS**

- Depot neuroleptic medication is an effective maintenance therapy for schizophrenia.
- There may be a slight therapeutic advantage (and no obvious disadvantage) of depot over oral medication, but the evidence is weak.
- There are few advantages of one depot over another.

**LIMITATIONS**

- Data on patients for whom depots are most indicated are lacking.
- Patient satisfaction, cost-effectiveness and other outcomes have not been studied in controlled trials.
- There may be unforeseen methodological problems in meta-analyses of several systematic reviews.

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