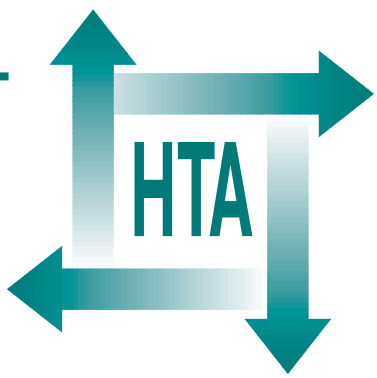
Health Technology Assessment 2001; Vol. 5: No. 34

Review

Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes

AS David
C Adams

Health Technology Assessment
NHS R&D HTA Programme



How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes

AS David[1]*
C Adams[2]

[1] Institute of Psychiatry and GKT School of Medicine, Denmark Hill, London, UK
[2] Cochrane Schizophrenia Group, Oxford, UK

* Corresponding author

Competing interests: Anthony David is carrying out a trial of a new depot antipsychotic preparation, funded by Janssen-Cilag. He has acted as an advisor for Janssen-Cilag in the preparation of educational packages on compliance and cognitive impairment, and received expenses from AstraZeneca to attend a recent schizophrenia research conference.

Clive Adams has led workshops for clinicians sponsored by Janssen, Lilly and Zeneca. The Cochrane Schizophrenia Group editorial base in Oxford has received general support funding from Eli Lilly during the years 1996 to 1999. This, together with funds from other pharmaceutical companies, is used to support any ongoing work of the editorial base and is not linked to any particular review.

Published end of 2001

This report should be referenced as follows:

David AS, Adams C. Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes. *Health Technol Assess* 2001;**5**(34).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

The findings from this HTA review have been published as:
Adams CE, Fenton MKP, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Br J Psychiatry* 2001;**179**:290–9.

Walburn J, Gray R, Gournay K, Quraishi S, David AS. Systematic review of patient and nurse attitudes to depot antipsychotic medication. *Br J Psychiatry* 2001;**179**:300–7.

The information from the efficacy reviews for individual depots is available from the Cochrane Library.

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

The research reported in this monograph was funded as project number 95/38/01.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.

ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

G

Contents

List of abbreviations

BPRS	brief psychiatric rating scale
CGI	clinical global impression (rating scale)
CI	confidence interval
CPN	community psychiatric nurse
CPRS	comprehensive psychopathology rating scale
CSG	Cochrane schizophrenia group
df	degrees of freedom
DSM	*Diagnostic and Statistical Manual (of Mental Disorders)*
ICD	*International Classification of Diseases*
NNH	number needed to harm
NNT	number needed to treat
NOSIE	nurses' observation scale for inpatient evaluation
RCT	randomised controlled trial
RR	risk ratio
UKU SERS	University of Kuopio side-effect rating scale
WMD	weighted mean difference

Executive summary

Background

Antipsychotic ('neuroleptic') medication has an established place in the treatment of schizophrenia. As well as treating the disorder itself, this medication is also used as a long-term maintenance treatment to prevent relapse and may be administered (intramuscularly) in a long-acting depot form every 1–6 weeks. The perceived advantages of this method are that it guarantees consistent delivery of the drug even in those patients who do not take regular tablets – through forgetfulness, disorganisation or ambivalent attitudes towards treatment.

In order to address the efficacy and acceptability of depots, a series of systematic reviews was carried out. The first set were systematic reviews of the efficacy and side-effects of all of the depot neuroleptic preparations available for the treatment of people with psychosis, summarised in this report as a 'meta-review'. These were carried out through collaboration between the GKT School of Medicine and the Cochrane Schizophrenia Group. The individual reviews have been published and disseminated through the Cochrane Library. The second set of reviews examined the published scientific literature on attitudes to (i.e. preferences to and satisfaction with) depot antipsychotic medication as recorded in clinical trials and surveys of patients and health professionals (mostly psychiatric nurses). This included studies examining preferences for depot versus oral medication and reasons given for such preference. Included studies were rated according to study quality and data extracted.

Objectives

Meta-review of depot antipsychotics

To present a synthesis of the findings on the effectiveness of depot neuroleptic medications in the form of a meta-analysis, and to enable evidence-based conclusions to be drawn on the comparative efficacy of depots versus placebo, oral drugs, as well as comparative studies of one depot versus another.

Review of attitudes to depot medication

To review the published literature and explore patient and nurse satisfaction with, and attitudes towards depot antipsychotic medication. Specifically, patient satisfaction with depot antipsychotic medication; the patient-preferred setting for its administration; patient preference for depot or oral antipsychotic medication; nurse (and general practitioner) satisfaction with depot antipsychotic medication.

Cost-effectiveness

To summarise evidence pertaining to the cost-effectiveness and other economic aspects of depot medication.

Methods

Meta-review of depot antipsychotics

Nine systematic reviews on the effects of long-acting antipsychotic medications were included. These comprised: bromperidol decanoate (117 participants from four studies); flupenthixol decanoate (615 from 15); fluphenazine (decanoate or enanthate) (1963 from 48); fluspirilene (290 from seven); haloperidol decanoate (445 from 11); perphenazine decanoate (236 from two); pipothiazine palmitate and undecylenate (771 from 14); and zuclopenthixol decanoate (332 from four). Each was compared with: placebo; any oral antipsychotic drugs; any other depot antipsychotic drugs. All doses were considered. Each review was treated as an individual 'included study' and data were summarised. Each systematic review followed the Cochrane procedures for literature searching, quality assessment, data extraction and analysis. All randomised controlled trials (RCTs) that focused on people with schizophrenia or other similar psychotic disorders were considered and all clinically relevant outcomes sought. The main outcomes for this overview were categorical and those that were reported in more than one single-depot review. Data collection and analysis were performed independently by one reviewer and assessed by two others. For binary outcomes a standard estimation of the risk ratio (RR [random]) and its 95% confidence interval (CI) was calculated. The number needed to

treat statistic (NNT) or the number needed to harm (NNH) was also calculated. Only normally distributed continuous data on clinical and social outcomes were entered. A weighted mean difference (WMD) between groups was estimated using a random effects model.

Review of attitudes to depot medication

A systematic search strategy was implemented of the following electronic databases: MEDLINE, EMBASE, PsycINFO, CINAHL and the Cochrane Library. Each of the included studies was sought as a citation on the SCISEARCH database. Studies were selected if satisfaction/attitude data were described in the title or abstract and original data were included. The reference sections of the selected articles were inspected for other relevant papers. The quality of the studies was assessed using an item checklist constructed specifically for the review.

Results

Meta-review of depot antipsychotics

Studies in the reviews ranged from 2 weeks to 3 years in duration. Most participants were diagnosed according to operationalised definitions of schizophrenia or schizoaffective disorders.

For the depots versus placebo comparisons, the relapse rate was significantly less in the depot group (RR = 0.3; 95% CI, 0.22 to 0.41; NNT = 2; 95% CI, 2 to 3), although this was based on a single agent, fluphenazine. If studies comparing standard with low-dose depots are considered analogous to placebo-controlled studies, they too showed lower relapse rates (RR = 2.5; 95% CI, 1.1 to 5.9). Fewer patients on depots left the studies early. Movement disorders in general were significantly worse in the treated patients, though specific extrapyramidal syndromes did not appear to be so.

The depot versus oral comparison revealed a significant advantage in favour of depots for one outcome, which is equivalent to 'important global change' (RR = 0.68; 95% CI, 0.54 to 0.86; NNT = 4; 95% CI, 2.4 to 9). This was based on only three depots: fluphenazine decanoate and enanthate, and haloperidol decanoate. However, other relevant outcomes such as relapse rates (based on a total of 848 participants) showed little difference (RR = 0.96; 95% CI, 0.80 to 1.14). General and movement-related side-effects, including tardive dyskinesia, were similar for both treatments.

The depot versus depot comparisons failed to show a clear advantage of one depot over another, either in terms of adverse effects or efficacy. Zuclopenthixol decanoate was significantly better than its comparators in terms of relapse rates (RR = 0.64; 95% CI, 0.44 to 0.94; although NNT = 8; 95% CI, 5 to 53).

Finally, high- and low-dose regimes of flupenthixol and fluphenazine depot preparations confer no significant advantages over standard doses.

Review of attitudes to depot medication

The search strategy produced 1374 articles. In all, 22 articles met the inclusion criteria; 82% (n = 18) of the articles were cross-sectional surveys. The checklist showed that the quality of the studies was mixed. A total of 16 studies investigated patient attitudes towards depot antipsychotic medication, four looked at the opinions of nurses and two investigated both. Out of the 12 studies that contained relevant data, ten expressed a positive opinion, one a neutral opinion and one a negative opinion of depot antipsychotic medication. In the five studies that contained data regarding patient preference for treatment location, four studies showed a preference for the depot clinic. Five out of six studies comparing depot antipsychotic medication with oral antipsychotic medication showed patient preference for depot medication.

Conclusions

Meta-review of depot antipsychotics

By combining the results from individual systematic reviews, it has been possible to summarise a great deal of clinical data on the use of depot neuroleptics. Given the number of potential comparisons and outcomes, there are very few significant results, with the exception of placebo comparisons, which demonstrate the superiority of neuroleptic treatment for schizophrenia in preventing relapse. Those significant findings that emerge from the depot versus oral comparisons suggest a marginal benefit of depots over oral drugs but on only one global outcome measure. Side-effects were in general no worse in the depot group. Relapse rates were very similar and this finding was made with good statistical power. The different depots seem to perform very similarly, with zuclopenthixol showing a slight superiority on one outcome. These conclusions must be tempered by

concerns that those patients in whom an advantage from depots may be anticipated, namely those in whom adherence to medication is suboptimal, especially where non-compliance is covert, may not have been represented by the participants in these studies. Furthermore, showing clinically meaningful effects, such as a reduction in relapse rates in community dwelling people with schizophrenia over the long term, can rarely be gleaned from the published literature as it stands.

Review of attitudes to depot medication

There are few data examining patient satisfaction or attitudes regarding depot antipsychotics and even less investigating the attitudes of nurses towards their role in the administration of depots. Higher quality studies are needed. What data there are show a positive attitude to depots from patients, but a broader range of patients needs to be surveyed.

Recommendations

Meta-review of depot antipsychotics

Future studies should concentrate on the depot versus oral comparison. Efforts need to be made to include patients for whom non-compliance may be a problem. These studies will need to be large and of long duration if differences in relapse rates and long-term adverse effects are to be discerned. Outcomes such as user satisfaction, quality of life and economic variables are absent from the data reviewed. This deficit must be remedied in future research.

Review of attitudes to depot medication

More attention needs to be given to user and provider attitudes to and satisfaction with treatment delivery systems. RCTs of depots versus oral drugs that include measures on nurse and patient satisfaction would be valuable, as would data relating satisfaction to clinical outcome.

Chapter 1

Background and objectives

Background

Schizophrenia is widely regarded as the most serious of the so-called 'functional' psychiatric disorders. Its onset is usually in late adolescence or early adult life and it affects men and women approximately equally. It tends to be a relapsing and remitting condition and runs a chronic course. Each year 1:10,000 of the population are diagnosed with the condition, which has a lifetime risk estimated at 1%.[1] Schizophrenia causes severe disruption in personal, social and economic fulfilment and leads to a considerable burden on the individual, family, carers and the NHS.

Antipsychotic (neuroleptic) medication is the mainstay in the effective management of schizophrenia. This medication reduces the symptoms of the disorder and, when used as a maintenance treatment, prevents acute relapse. However, translation of this success into clinical practice is attenuated by patient non-compliance.[2] The reasons for non-compliance are complex, but include such factors as severity and type of side-effects, level of insight, severity of illness, complexity of treatment regime, beliefs about the illness and medication, and the relationship patients have with mental health practitioners.[3,4]

Long-acting depot antipsychotics were developed in the 1960s, and were aimed specifically at promoting compliance in chronic sufferers.[5] They generally consist of an ester of the antipsychotic drug injected (every 1–6 weeks) intramuscularly in an oily solution. The depot is thought to simplify the medication process by requiring the person to attend for injection at a specific clinic, thus guaranteeing the delivery of medication.[6,7] Apart from overcoming missed medication due to disorganisation and forgetfulness, and deliberate covert non-compliance, the pharmacological advantages usually listed for depots include the avoidance of problems associated with absorption and hepatic bio-transformation; disadvantages include concerns over side-effects including tardive dyskinesia, and those associated with parenteral administration *per se*.[8]

Many clinicians have promoted the use of depots[9–11] as being superior to and no more harmful than oral neuroleptics. However, patient and clinician acceptance is highly variable, with the mode of delivery by injection being a major stumbling block. Non-compliance amongst those receiving depot medication persists, with Curson and colleagues,[12] for example, reporting that 40% of depot clinic attendees were non-compliant in some way over a 7-year follow-up period. Patient and clinician choice regarding antipsychotic medication has become even more complicated in recent years with the development of several 'atypical' neuroleptic drugs believed to have, on the whole, fewer extra-pyramidal side-effects and possibly superior efficacy (see Cochrane Library for reviews). To date, however, all of these atypical agents are only available in an oral form.

Although depots are an established part of the clinician's treatment options, their efficacy has seldom been assessed thoroughly and systematically. This includes whether they lead to demonstrable advantages in clinical outcomes in rigorous clinical trials, when compared to oral medication, and whether individual depots offer advantages, one against another. Furthermore, it is not known whether there is a body of data which supports the use of depots on the basis of their impact on quality of life or cost-effectiveness. Similarly, little is known about the acceptability of this form of treatment by either users or healthcare professionals.

In order to address the efficacy and acceptability of depots we carried out a series of systematic reviews. The first set of reviews examined the evidence for the superiority of depots over placebo or other forms of treatment as well their safety and tolerability, and was the primary purpose of a series of systematic reviews carried out in collaboration with the Cochrane Schizophrenia Group, which have since been published in the Cochrane library of systematic reviews,[12–21] and was prompted by a call for proposals under the NHS R&D Health Technology Assessment Programme. This report summarises these constituent reviews in a 'meta-review'. Published individual randomised controlled trials (RCTs) were of course available already, as were data from other designs such as comparison with concurrent controls in cohort studies and

so-called 'mirror image' studies. In the latter, outcomes are measured 'within-subjects' (e.g. relapse rates before and after patients have been switched to depots from oral drugs).[6] Such studies often comprised non-blinded treatment allocations that were not random, so were therefore prone to bias. Nevertheless, on the basis of meta-analysis of these and other studies, Davis and colleagues[6] concluded that depots were superior to oral drugs in many respects. Similarly, Glazer and Kane[9] meta-analysed studies comparing the incidence of tardive dyskinesia in patients on depots and oral agents, and concluded that depots were no more harmful in this respect.

It is ironic that the very reasons why clinicians favour depot medication in certain circumstances are those that make this method of administration unpopular with some users. For example, Anderson and colleagues[22] reported that the depot clinic is perceived as being "out of date, not geared to the needs of the patient, inaccessible and unable to provide personalised care". Pereira and Pinto[23] stated that " 'Consumer advocates' concentrate on the undeniable adverse effects of antipsychotic drugs and upon the accusation that depot treatments involve an element of coercion."

It is against this backdrop that a review of attitudes (i.e. both preferences and satisfaction) was also carried out in a second set of reviews to compliment the review of efficacy. Published scientific literature on attitudes to depot antipsychotic medication, as recorded in clinical trials and surveys of patients and health professionals (mostly psychiatric nurses), was examined. This included studies examining preferences for depot versus oral medication and reasons given for such preference. None of the studies included in the effectiveness reviews reported data that directly assessed patient satisfaction with the medication. Consequently, a wider review incorporating studies of mixed design and not restricted to RCTs was instituted. Included studies were rated according to study quality and data extracted.

Finally, a component of the systematic reviewing of the evidence on depot neuroleptic preparations for treating people with schizophrenia was to examine cost-effectiveness. Apart from the general need to understand the resource consequences of alternative treatments, one of the arguments for depot over oral treatments for schizophrenia is that they improve compliance rates and thus reduce relapse rates. Given the high costs of relapse, particularly because of the need in most cases for in-patient admission,[2] it might be hypothesised that depot treatment would be the more cost-effective than oral treatment (see chapter 5).

Objectives

The objectives of the reviews were to:

- assess the effectiveness and adverse effects of depot medications versus placebo, oral antipsychotics and other depot neuroleptic preparations for individuals with schizophrenia, in terms of clinical, social and economic outcomes on the basis of systematic reviews of individual RCTs
- explore patient and nurse satisfaction with depot antipsychotic medication; specificically, the aims were to investigate: patient satisfaction with depot antipsychotic medication; the patient-preferred setting for the administration of depot antipsychotic medication; patient preference for depot antipsychotic medication or oral antipsychotic medication; nurse (and general practitioner; GP) satisfaction with depot antipsychotic medication
- summarise evidence pertaining to the cost-effectiveness and other economic aspects of depot medication.

Chapter 2
Methods

Search strategy

Meta-review of depot antipsychotics

Selection of reviews

Selection

All systematic reviews of long-acting depot antipsychotics for schizophrenia were undertaken specifically to provide the most recent systematically collected information to inform the overview. The pre-stated comparisons of interest in the reviews were of any long-acting depot antipsychotic medication versus placebo, and versus oral medication, and finally of high-dose depot versus low-dose depot, for people with schizophrenia or schizophrenia-like illnesses. Outcomes of *a priori* interest in the overview 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. A search on PubMed at the time of submission did not find any other systematic reviews of depot medication. Two traditional reviews of depot were found which were not systematic.

Inclusion/exclusion

All systematic reviews of depot medication for those people with schizophrenia were included.

The following depot medications were reviewed: bromperidol decanoate, flupenthixol decanoate, fluspirilene, haloperidol decanoate, perphenazine esters, pipothiazine esters (palmitate and undecylenate), depot versus oral fluphenazine, and zuclopenthixol decanoate. None of the reviews included data that directly assessed patient satisfaction with the medication or economic outcomes.

Electronic searching

The search strategy, methods of selection, quality assessment, data extraction and assimilation within each review is published on the Cochrane Library.[13–21] The reader is referred to these reviews for explicit details and to appendix 1.

Quality assessment

There was no quality assessment of the primary reviews from which these data were extracted. However, empirical evidence shows that Cochrane reviews, in general, have been shown to be of higher quality than others,[24] plus their quality is uniform.

Data extraction

This was performed for this overview independently by one reviewer (MF), and assessed by two others (CA and AD). Where disagreement arose, this was resolved through discussion. Outcomes to be included from each review were based on the outcomes in each review. Data from comparisons of depot medication versus placebo or oral medication and from high dose versus low dose have been combined as no comparison could be entered twice. Data from comparisons against other depots or of high versus low doses of the same depots were not combined as there was a high risk of the same studies contributing to different comparisons and of being entered twice, thus being prone to selection bias and an over-estimate of effect. Each individual review contains more information than is included in this overview; for further information please see each review.

Data analysis

Binary data

For binary outcomes a standard estimation of the risk ratio (RR [random]) and its 95% confidence interval (CI) was calculated. The number needed to treat (NNT) statistic or the number needed to harm (NNH) was also calculated on an intention-to-treat basis. The chi-squared test of heterogeneity was used, as well as visual inspection of graphs, to establish heterogeneity. If heterogeneity was found, the reviewers looked for an explanation to it. If reviews with heterogeneous results were found to be comparable, the statistical synthesis of the results was done using a random effects model.

Continuous data

Skewed data

Only continuous data on clinical and social outcomes that is normally distributed was entered for this overview.

Summary statistics

For continuous outcomes a weighted mean difference (WMD) between groups was estimated using a random effects model.

Valid scales
A wide range of rating scales was employed in the contributing reviews to measure mental health outcomes. These instruments vary in quality and many are not valid, or are *ad hoc*. For outcome instruments some minimum standards had to be set. Continuous data from rating scales were included only if the measuring instrument had been described in a peer-reviewed journal and the instrument was either a self-report or completed by an independent rater or relative (not the therapist).

Endpoint versus change data
Where possible, endpoint data were presented and if both endpoint and change data were available for the same outcomes then only the former were reported in this overview.

Test for heterogeneity
As well as inspecting the graphical presentations, the reviewers checked whether the differences among the results of trials were greater than would be expected by chance alone using chi-squared tests of heterogeneity. A significance level less than 0.10 was interpreted as evidence of heterogeneity.

Display of data
Data displayed in the graphs are labelled 'favours treatment' or 'favours control'. Interpretation of the graphs means that results that fall to the left of the line of unity, the 'favours treatments' side of the graph, indicates a better outcome for depot medication. Consequently, all statistical results that are less than one favour the depot, whilst all results that are greater than one favour the comparator substance.

Review of attitudes to depot medication

Electronic databases
A systematic search strategy was implemented. This involved searching the following electronic databases: MEDLINE, EMBASE, PsycINFO, CINAHL and the Cochrane Library up to the end of May 1999. The review used a subject and text word search strategy with depot, delayed-action preparations, (intramuscular) injections and antipsychotics (agents) and/or neuroleptic (drugs) as the main search terms.

The databases were also searched using specific depot drug names in order to be as comprehensive as possible. These were combined with 'satisfaction', 'attitude' and related terms.

Reference searching
The references of the included studies were inspected for further studies. Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that had cited these studies were inspected in order to identify further studies.

Handsearching
The catalogues at the Institute of Psychiatry (London, UK) and the Royal College of Nursing (London, UK) were searched to obtain secondary sources. The following journals were handsearched for June, July and August 1999 to identify publications that may not have yet been entered on the databases: *Acta Psychiatrica Scandinavica, Journal of Mental Health, British Journal of Psychiatry, Schizophrenia Bulletin* and *Psychiatric Bulletin.*

Inclusion/exclusion criteria
Studies were selected by hand and included if they contained original data describing nurse or patient satisfaction with depot antipsychotic medication according to the title or abstract. The term 'satisfaction' includes data that describes an opinion or attitude towards depot antipsychotic medication. A second independent reviewer selected studies from a random 10% of the references to ensure that selection of studies was reliable. Where differences of opinion occurred, these were resolved by discussion and if necessary the complete study was obtained for further inspection.

Analysis
The quality of the articles was assessed in two stages. The first stage used a 'hierarchy of evidence'. This is a method of categorising studies via the attributes of their design. It is a hierarchy of bias, which increases progressively downwards. We used an amalgamation of two[25,26] – essentially from RCTs, through non-randomised controlled trials, to cohort studies, to case–control studies to case series. The studies were categorised following methods described by Greenhalgh[25] and applied to the hierarchy of evidence. The categorisation for each study was carried out by two of the project group (JW, RG) independently and any disagreements were resolved by discussion.

The second stage comprised the assessment of the studies using a 13-item checklist constructed specifically for the review. The items for this checklist were derived from a number of sources, both refs 25 and 26 and The Cochrane Collaboration for Depression Anxiety & Neuroses, and finalised by discussion between the authors (appendix 2). The checklist focused on justification of sample size, sampling, response/drop-out rates, validity of measures and the generalisability of the results.

Each included study was assessed by two raters independently, and where disagreement occurred a third rater made the decisive judgement.

Description of reviews (meta-review of depot antipsychotics)

Please refer to *Table of included studies* (appendix 3).

There is one systematic review of zuclopenthixol acetate on the Cochrane Library that has not been included. Whilst the authors acknowledge it is a depot preparation, it is only intended to be used in incidents of aggression and is only recommended for short-term use. No other systematic reviews were found. Please consult individual reviews[13–20] for further details of studies that were excluded.

Awaiting assessment

No systematic reviews are awaiting assessment. For further details of studies awaiting assessment in the individual reviews please consult the Cochrane Library.

Included reviews

Refer to references 13–20.

Duration

Studies in the reviews ranged from 2 weeks to 3 years in duration. Studies in the bromperidol review ranged from 6 to 12 months; flupenthixol, 8 weeks to 2 years; fluphenazine decanoate, 2 weeks to 2 years; fluphenazine enanthate, 2 weeks to 1 year; fluspirilene decanoate, 4 weeks to 6 months; haloperidol decanoate, 16–60 weeks; perphenazine depot, 6 weeks to 6 months; pipothiazine, 11 weeks to 3 years; and zuclopenthixol decanoate, 12 weeks to 1 year.

Types of participants

Systematic reviews of depot medication focusing on people with schizophrenia or other similar psychotic disorders, irrespective of mode of diagnosis, age, ethnicity and sex. Where a review described the participant group as suffering from 'serious mental illnesses' and did not give a particular diagnostic grouping, these reviews were included. The exception to this rule was when the majority of those people randomised clearly did not have a functional non-affective psychotic illness.

Most reviews included studies with operationalised definitions of schizophrenia or schizoaffective disorders, which covered several classification systems and revisions of those classification systems. The systems used were the WHO's *International Classification of Diseases* (ICD) 9 and 10, and the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM) II to III-R.[27] Other studies used less well-operationalised diagnoses, such as Bleuler's, Feighner's, Forest and Hay or Schneiderian criteria. A US National Institute of Mental Health (NIMH) classification was used in one study; a French classification was also used in two separate studies in separate reviews. Also used was the present state examination (PSE)[28] or research diagnostic criteria (RDC). The reviews also included people whose diagnosis was made clinically, including a diagnosis of 'psychosis'.

Setting

All reviews included studies that were based either in hospital or the community. Some included participants from both, and one contributing study used treatment-naive participants in a prison hospital.

Types of intervention

The following medications were considered: bromperidol decanoate, flupenthixol decanoate, fluphenazine decanoate or enanthate, fluspirilene, haloperidol decanoate, perphenazine decanoate, pipothiazine palmitate, zuclopenthixol decanoate (*Table 1*).

Outcome measures

The outcomes of interest were:

- death, suicide or natural causes
- leaving the study early
- clinical response
- relapse
- clinically significant response in global state – as defined by each of the reviews
- average score/change in global state
- clinically significant response on psychotic symptoms – as defined by each of the reviews
- average score/change on psychotic symptoms
- clinically significant response on positive symptoms – as defined by each of the reviews
- average score/change in positive symptoms
- clinically significant response on negative symptoms – as defined by each of the reviews
- average score/change in negative symptoms.

Clinical state in the contributing reviews was usually measured using one or more of the following scales:

- global impression: clinical global impression (CGI) rating scale
- mental state: brief psychiatric rating scale (BPRS); comprehensive psychopathology

TABLE 1 *Depot and comparator*

Depot	Compared against
Bromperidol decanoate	Fluphenazine decanoate, haloperidol decanoate, or placebo
Flupenthixol decanoate	Fluphenazine decanoate, haloperidol decanoate, penfluridol, pipothiazine decanoate or zuclopenthixol decanoate
Fluphenazine decanoate	Bromperidol decanoate, chlorpromazine, flupenthixol decanoate, fluphenazine enanthate/ decanoate, fluphenazine hydrochloride (oral), haloperidol decanoate, penfluridol, pimozide, pipothiazine palmitate, placebo, trifluperazine, or zuclopenthixol decanoate
Fluphenazine enanthate	Chlorpromazine, fluphenazine decanoate, fluspirilene decanoate, or pipothiazine palmitate
Fluspirilene	Chlorpromazine, fluphenazine decanoate/enanthate, or pipothiazine undecylenate
Haloperidol decanoate	Fluphenazine decanoate, haloperidol (oral), pipothiazine palmitate, placebo, or zuclopenthixol decanoate
Perphenazine decanoate	Perphenazine enanthate, or zuclopenthixol decanoate
Pipothiazine palmitate*	Fluphenazine decanoate/enanthate, fluspirilene, haloperidol decanoate, or oral antipsychotics (various)
Zuclopenthixol decanoate	Flupenthixol palmitate, haloperidol decanoate, or perphenazine enanthate

* *Data for undecylenate not entered due to the small number of participants (n = 26) in an 11-week trial with limited outcome data*

rating scale (CPRS); Hamilton depression scale; Krawiecka scale[29] (1977); Montgomery–Asberg depression rating scale[30] (MADRS)
- behaviour: nurses' observation scale for inpatient evaluation[31] (NOSIE); Wing Ward scale (see original reviews for details and references[13–20]).

Extrapyramidal side-effects

Measures included: incidence of use of anti-parkinson drugs; clinically significant extra-pyramidal side-effects – as defined by each of the reviews; average score/change in extra-pyramidal side-effects.

Side-effects in the contributing reviews were usually measured using one or more of the following scales: abnormal involuntary movements scale[32] (AIMS); Bordeleau scale; dosage record and treatment emergent symptom scale[32] (DOTES); extra-pyramidal side-effects[33] (EPSE); University of Kuopio side-effect rating scale[34] (UKU SERS); Simpson–Angus rating scale[35] – see original reviews for details and references.[13–20]

Other outcomes included in searches: service utilisation outcomes; hospital admission; days in hospital; economic outcomes; quality of life/satisfaction with care for either recipients of care or carers; significant change in quality of life/satisfaction – as defined by each of the reviews; average score/change in quality of life/satisfaction.

Outcomes were grouped into immediate (0–5 weeks), short term (6 weeks to 5 months), medium term (6 months to 1 year) and longer term (over 12 months).

Methodological quality of included reviews (meta-review of depot antipsychotics)

Although the purpose of this study was to summarise systematic reviews, we present here, under this separate heading, some information on the results of the search for evidence that went into each of these reviews.

In the bromperidol review, only four controlled trials were included. For flupenthixol decanoate, 187 citations were found, resulting in 15 controlled trials being included in the review, with five non-English papers awaiting translation. The search for the fluphenazine review produced 982 citations, although only 69 referred to controlled clinical trials (all published in journals). Eight non-English papers still await assessment due to delays in translation. In the fluspirilene review, seven controlled clinical trials (all published in journals) relating to fluspirilene were found. One non-English paper is still awaiting assessment. The haloperidol search found 307 citations, yielding 11 controlled clinical trials (all published in journals). Four non-English papers are still awaiting assessment. In the perphenazine review two controlled clinical trials, both published in journals, were found; four studies that could have reported useful data had to be excluded because no clinically useful

information was possible to extract. No studies compare depot perphenazine to placebo or oral drugs. The search in the pipothiazine review found 14 controlled clinical trials (all published in journals); five non-English papers are still awaiting assessment. The zuclopenthixol review found 151 citations, with ten studies related to zuclopenthixol decanoate and four being included in the review. Three are awaiting assessment due to no useable data being reported, two were excluded as they did not measure clinical outcomes, and one because people were randomised but neither were their data or original group of allocation reported. The study authors are being contacted for further information. All these trials formed the database for the individual Cochrane reviews and it is the latter that formed the basis of this overview.

Review size

The Cochrane systematic reviews were the basis of the current meta-reviews. However, we summarise here the scope size of the contributing reviews in terms of the number of studies and participants. In the bromperidol review, 58 people were randomised to bromperidol and 59 to comparators, giving a total of 117 in four studies. The flupenthixol review included a total of 615 individuals, with 359 given flupenthixol and 256 comparators in 15 studies. For fluphenazine decanoate it was 1963 to fluphenazine depot and 1199 to comparators, which was 3162 total in 48 studies. In seven studies, 160 people received fluspirilene and 130 comparators, which was 290 in total. For haloperidol depot, 11 studies were included, with 445 participants in total – 238 to haloperidol depot and 207 to comparators. Perphenazine, the smallest review, randomised 111 people to use the experimental compound, whilst 125 received comparators, giving a total of 236 in two studies. The pipothiazine review included 14 studies, with 771 total participants – 365 to pipothiazine and 406 to comparators. Finally, the zuclopenthixol review included 332 in a total of four studies – 171 to zuclopenthixol and 161 to comparators.

Randomisation

All the participants within the individual reviews had been allocated randomly to either the substance under study or its comparator. The quality of reporting of methods used to allocate participants can be found within each review reported in the Cochrane Library.[13–20]

Blinding at outcome

Most of the reviews claimed that the included studies were double blind. Details of quality of reporting blinding can be found in the individual reviews. No review reported that where blinding was mentioned, effort was made to ascertain whether it was successful.

Chapter 3
Results

Meta-review of depot antipsychotics

Comparison 1: depot medication versus placebo

Four reviews compared depot medication against placebo (bromperidol depot, fluphenazine decanoate, fluphenazine enanthate, and haloperidol depot).

Death

One review gave data on the outcome of death (fluphenazine decanoate). This did not reach statistical significance (*N* (number of trials) = 1; *n* (number of participants) = 54; RR = 5; 95% CI, 0.25 to 99.52).

Needing additional antipsychotic medication

Two reviews gave data on the number of participants requiring additional medication. The fluphenazine review found that more people on the active substance required extra medication than those on placebo, but this did not reach statistical significance. In the haloperidol review, a statistically significant number of those receiving the placebo required more additional medication. When the results for these two reviews are pooled, significance is not achieved (*N* = 2; *n* = 97; RR = 1.1; 95% CI, 0.12 to 9.4).

Mental state

Relapse

One review gave data for the outcome of relapse (fluphenazine decanoate). Statistical significance was achieved for those receiving fluphenazine versus placebo (*N* = 1; *n* = 415; RR = 0.3; 95% CI, 0.22 to 0.4; NNT = 2; 95% CI, 2 to 3). See *Figure 1*.

Depression

Again, only one review gave information on the outcome of depression. No significance was achieved (*N* = 1; *n* = 70; RR = 0.8; 95% CI, 0.33 to 1.9).

Behaviour

Leaving the study early

Three reviews gave information on those who left the studies early (bromperidol depot, fluphenazine decanoate, and haloperidol depot). Significantly more people taking depot medication stayed in the studies than those receiving a placebo comparator (*N* = 3; *n* = 152; RR = 0.43; 95% CI, 0.3 to 0.7; NNT = 3; 95% CI, 2 to 7). See *Figure 2*.

Side-effects

Anticholinergic effects

Data from two reviews on the outcomes of blurred vision or dry mouth did not reach statistical significance, but strangely the direction of effect favoured those taking the active substance (blurred vision: *N* = 1; *n* = 32; RR = 0.2; 95% CI, 0.02 to 1.2; dry mouth: *N* = 1; *n* = 20; RR = 0.14; 95% CI, 0.01 to 2.5).

Movement disorders

For the outcomes of akathisia, needing additional anticholinergic drugs, tardive dyskinesia, tremor or stiffness, no outcomes favoured either the active comparator or placebo. When data were reported

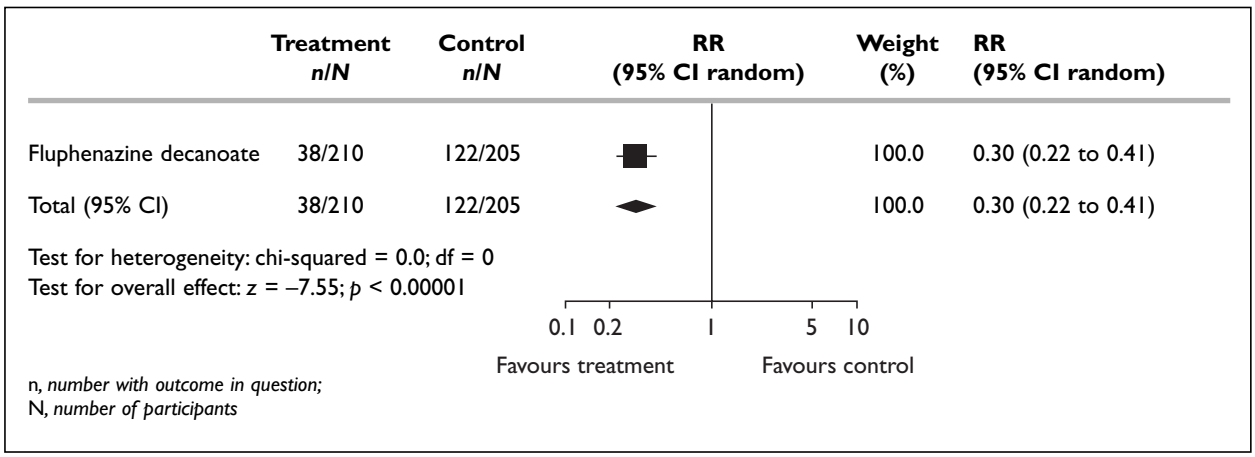


FIGURE 1 *Relapse rates: depot versus placebo*

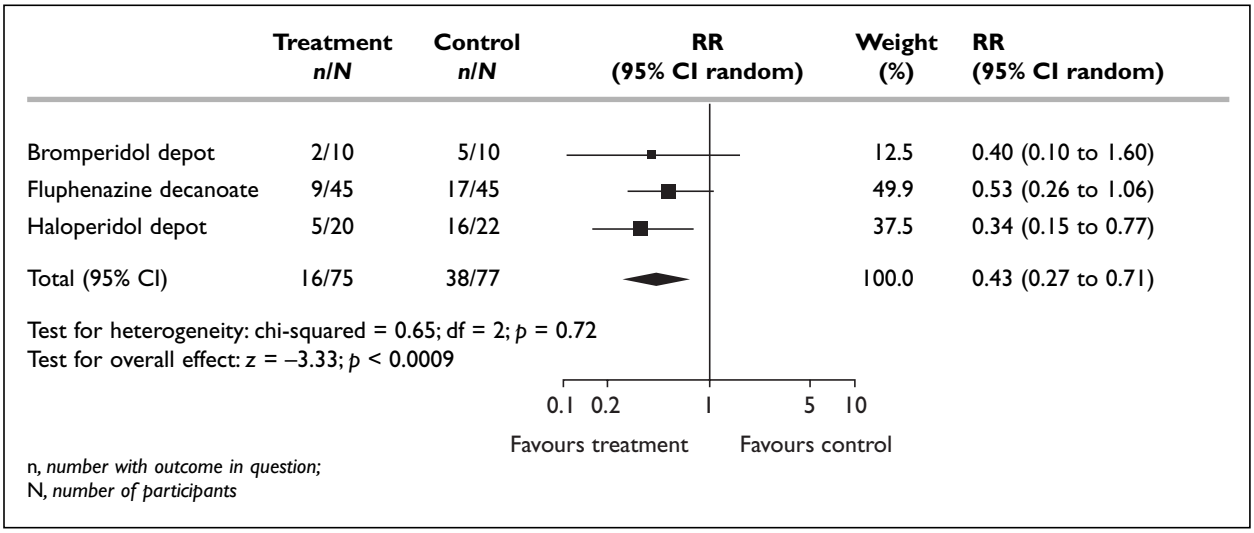


FIGURE 2 *Leaving the study early: depot versus placebo*

in the reviews as 'movement disorders – general', statistical significance was achieved in favour of those taking placebo having less generalised movement disorders ($N = 1$; $n = 51$; RR = 20.5; 95% CI, 1.3 to 338; NNH = 3; 95% CI, 6.5 to 1.9). See *Figure 3*.

Comparison 2: depot medication versus oral antipsychotics

Global functioning: no important global change

Three reviews (fluphenazine decanoate, fluphenazine enanthate and haloperidol depot) gave a result that could be translated into no important global change for this comparison. Results were dichotomised from the CGI rating scale. This result reached conventional levels of statistical significance ($N = 3$; $n = 127$; RR = 0.7; 95% CI, 0.5 to 0.9; NNT = 4; 95% CI, 2.4 to 9), favouring the depot (i.e. fewer patients experienced no change). See *Figure 4*.

Relapse

Three reviews gave usable information on those who relapsed, with no statistical difference noted ($N = 3$; $n = 848$; RR = 0.96; 95% CI, 0.8 to 1.2). See *Figure 5*.

Mental state

BPRS scores – endpoint scores

For the continuous outcome of the endpoint scores of the BPRS, no one review, or when pooled, demonstrated statistical significance ($N = 3$; $n = 266$; WMD = –0.5; 95% CI, –4.0 to 3.0).

Depression

One review gave information on depression, and did not demonstrate significance ($N = 1$; $n = 48$; RR = 1.53; 95% CI, 0.9 to 2.57).

Behaviour

Leaving the study early

Four reviews gave information on those leaving the study early. No statistical significance was found between those on depot medication or oral antipsychotics ($N = 4$; $n = 874$; RR = 1.1; 95% CI, 0.9 to 1.5). See *Figure 6*.

NOSIE-30 endpoint scores

For this continuous outcome, statistical significance was not achieved ($N = 2$; $n = 244$; WMD = 2.2; 95% CI, –2.9 to 7.3).

Side-effects

Needing additional anticholinergic medication

People taking antipsychotic medication orally were equally likely as those who received their medication in the depot preparation to receive additional anticholinergic medication ($N = 5$; $n = 401$; RR = 1.0; 95% CI, 0.9 to 1.3).

Side-effects – general

No outcome had a statistically significant result. For blurred vision, side-effects – general and tremor, all participants were likely to suffer side-effects. For the outcomes of movement disorder and parkinsonism, whilst not having statistical significance, the direction of effect was in favour of those receiving oral antipsychotics ($N = 1$; $n = 138$; RR = 0.94; 95% CI, 0.2 to 4.1; $N = 1$; $n = 31$; RR = 6.6; 95% CI, 0.9 to 47.2). Both these comparisons were of the fluphenazine enanthate depot. All, apart from the outcome of tremor, fell to the right of the line of no effect. See *Figure 7*.

Tardive dyskinesia

This outcome did not reach statistical significance ($N = 2$; $n = 272$; RR = 0.7; 95% CI, 0.3 to 1.3).

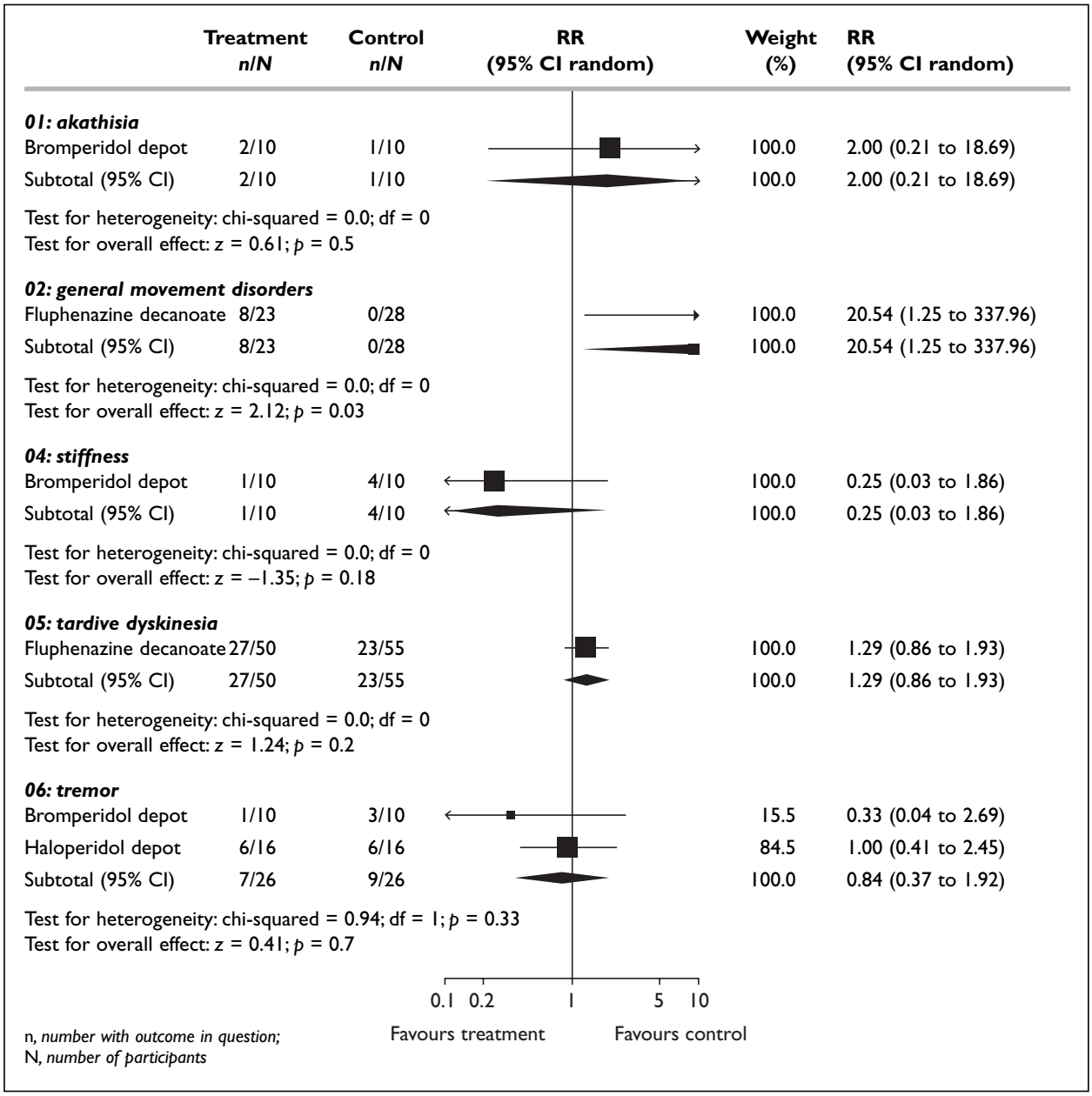


FIGURE 3 *Movement disorders – general: depot versus placebo*

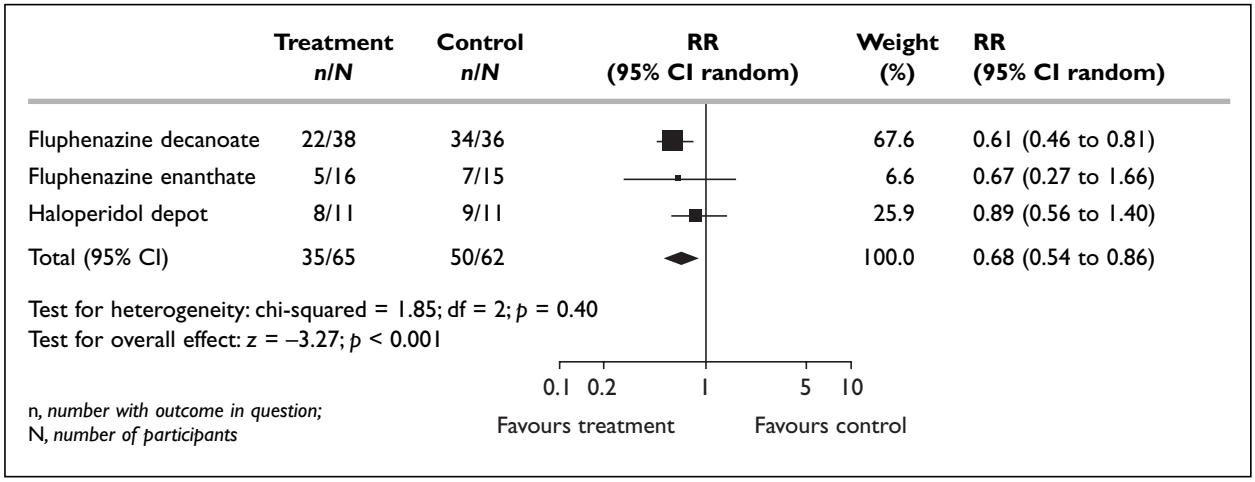


FIGURE 4 *Global functioning – no important change: depot versus oral*

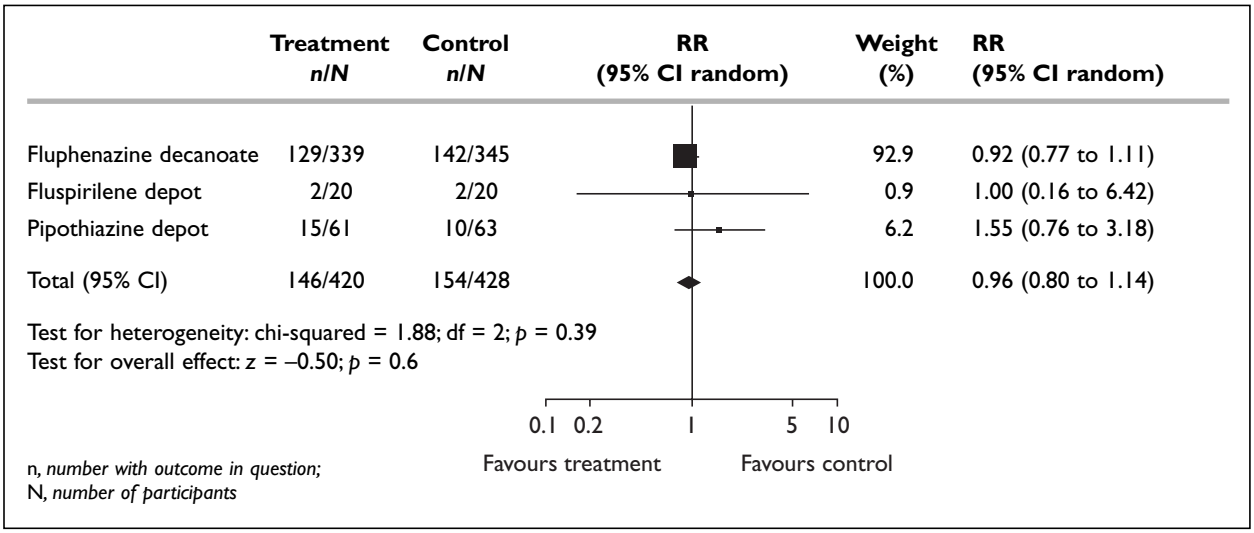


FIGURE 5 *Relapse rates: depot versus oral*

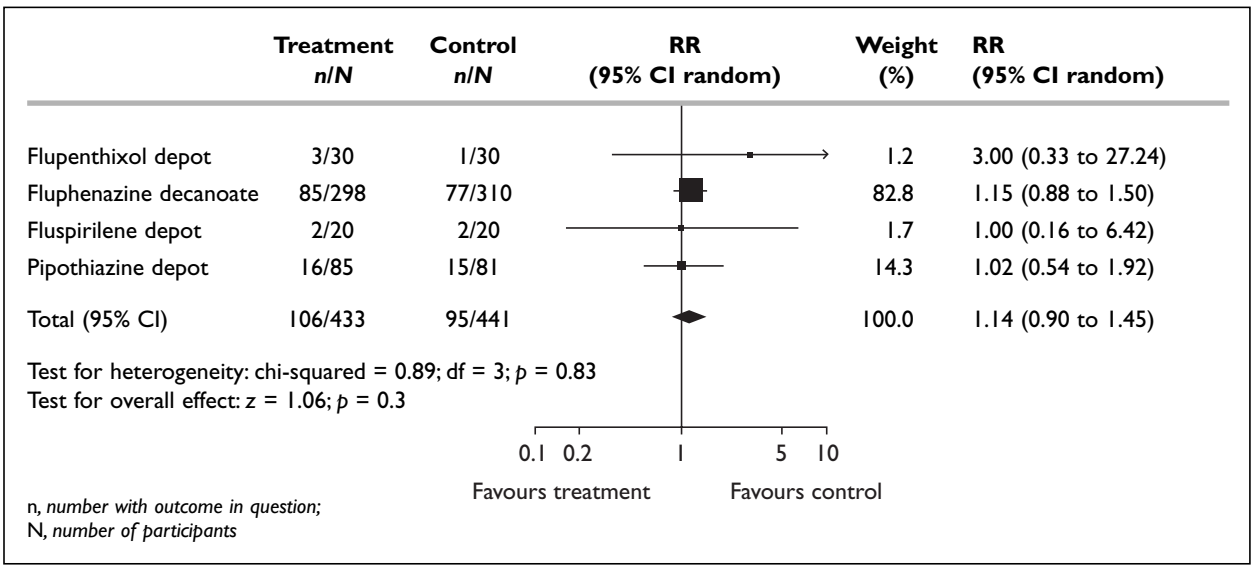


FIGURE 6 *Leaving the study early: depot versus oral*

Comparison 3: depot versus other depots

All nine depot reviews contributed to the outcomes in this comparison, although not each outcome. No data are pooled due to the high risk of including the same study twice in separate outcomes.

Death

Three reviews give data for those who committed suicide and four reviews for those whose cause of death was either unclear or from other causes. Neither of these outcomes reached statistical significance in any review. One person in the fluphenazine review (on the comparator in the haloperidol review) and two people in the zuclopenthixol review committed suicide. The person who died in the haloperidol review is one of the two who committed suicide in the zuclopenthixol review.

Global functioning

No clinically important change

Three reviews reported data that was usable for 'no clinically important change'. No result achieved standard levels of statistical significance. See *Figure 8*.

Severely ill

Two reviews report this outcome, but as the two reviews were fluphenazine decanoate versus pipothiazine and pipothiazine versus fluphenazine decanoate it is one study being reported twice. The result did not reach conventional levels of statistical significance.

CGI – no important improvement

Five reviews report data for this outcome. None reached statistical significance.

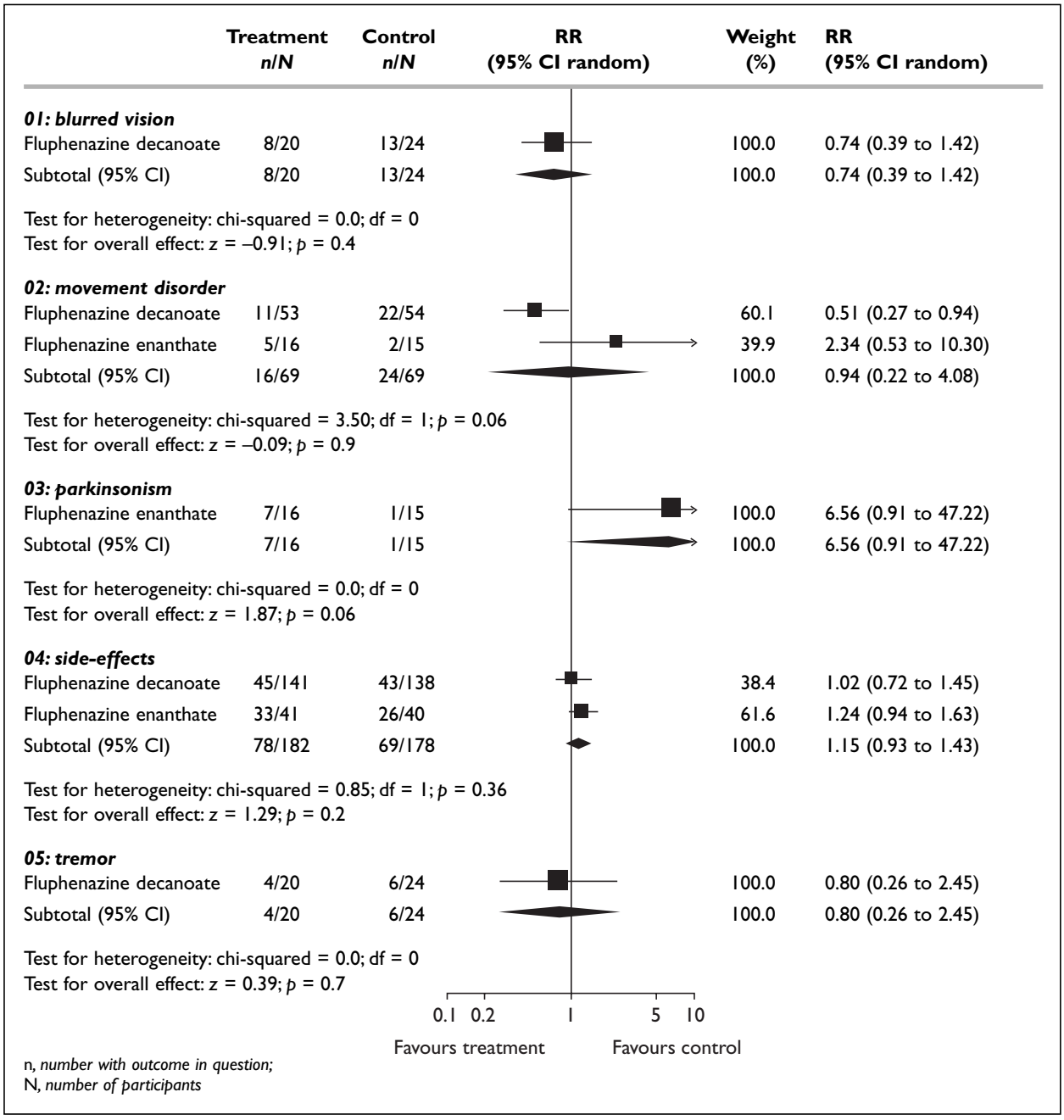


FIGURE 7 *Side-effects – general: depot versus oral*

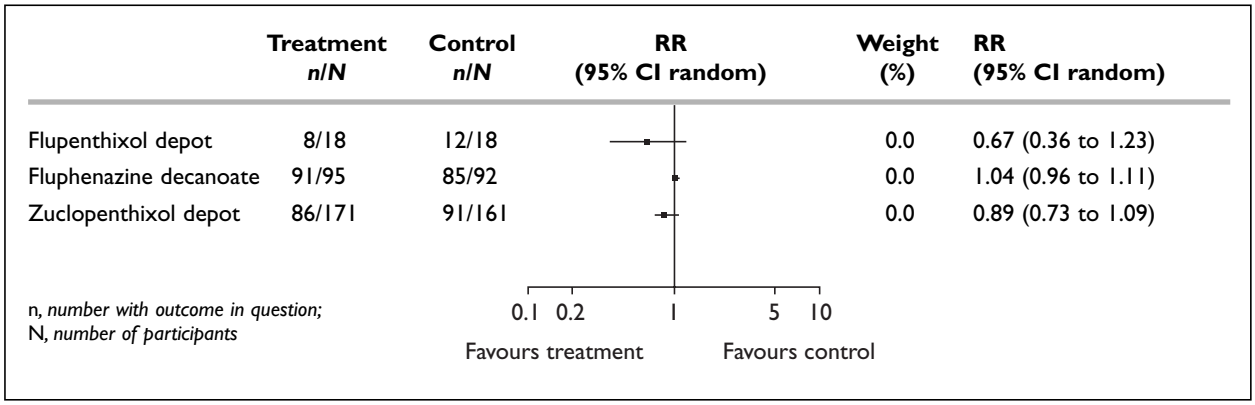


FIGURE 8 *Global functioning – no clinically important change: named depot versus comparator*

Mental state

Relapse

Nine reviews reported data on those who relapsed. Two reviews (bromperidol depot and zuclopenthixol depot) found statistically significant results (n = 67; RR = 4.6; 95% CI, 1.1 to 19.9; NNT = –5; 95% CI, –23.5 to –2.6; n = 296; RR = 0.64; 95% CI, 0.4 to 0.9; NNT = 8; 95% CI, 5 to 53) – a significant difference between two depots. The results do not favour bromperidol (i.e. it was inferior), and do favour zuclopenthixol (i.e. it was superior). No other review reached statistical significance. Three other reviews (fluphenazine decanoate, haloperidol depot and pipothiazine depot) all had higher numbers of participants. See *Figure 9*.

Needing additional medication

Antidepressant medication

Statistical significance was found in the zuclopenthixol depot review, with those taking the experimental substance being given less antidepressant medication (n = 296; RR = 0.7; 95% CI, 0.5 to 0.9; NNT = 7; 95% CI, 4 to 32). No other review reported this information in a usable format.

Antipsychotic medication

Seven reviews gave information that can be used in this overview. Two reviews achieved conventional levels of statistical significance. Those taking fluphenazine enanthate were given less additional antipsychotic medication than those on comparator depot drugs (n = 63; RR = 0.4; 95% CI, 0.2 to 0.9; NNT = 3; 95% CI, 1.9 to 12.6), whilst in the pipothiazine depot review those receiving the comparator drugs received less additional antipsychotic medication (n = 106; RR = 2.3; 95% CI, 1.1 to 4.6; NNH = 5; 95% CI, 20.3 to 2.7). One review just touched the line of no effect (zuclopenthixol depot: n = 172; RR = 0.8; 95% CI, 0.6 to 1.1). No other review reached significance.

Sedative medication – unspecified

Two reviews had data for this outcome. Neither achieved statistical significance, with both close to the line of unity in the forest graph.

Severely ill (BPRS dichotomised data)

One study gave this information, although it is mentioned in two reviews. No significance was found.

Depression

Three reviews gave information on this outcome. None achieved conventional levels of significance.

Behaviour

NOSIE-30 endpoint scores

One review included this outcome from just one study, allowing it to be used in this overview (fluphenazine decanoate). No difference was found (mean difference = –0.33; 95% CI, –0.7 to 0.03).

Leaving the study early

All nine reviews reported data for this outcome. None achieved statistical significance, but two were just touching the line of no effect (pipothiazine depot: n = 455; RR = 1.3; 95% CI, 0.9 to 1.8; zuclopenthixol depot: n = 332; RR = 0.7; 95% CI, 0.5 to 1). See *Figure 10*.

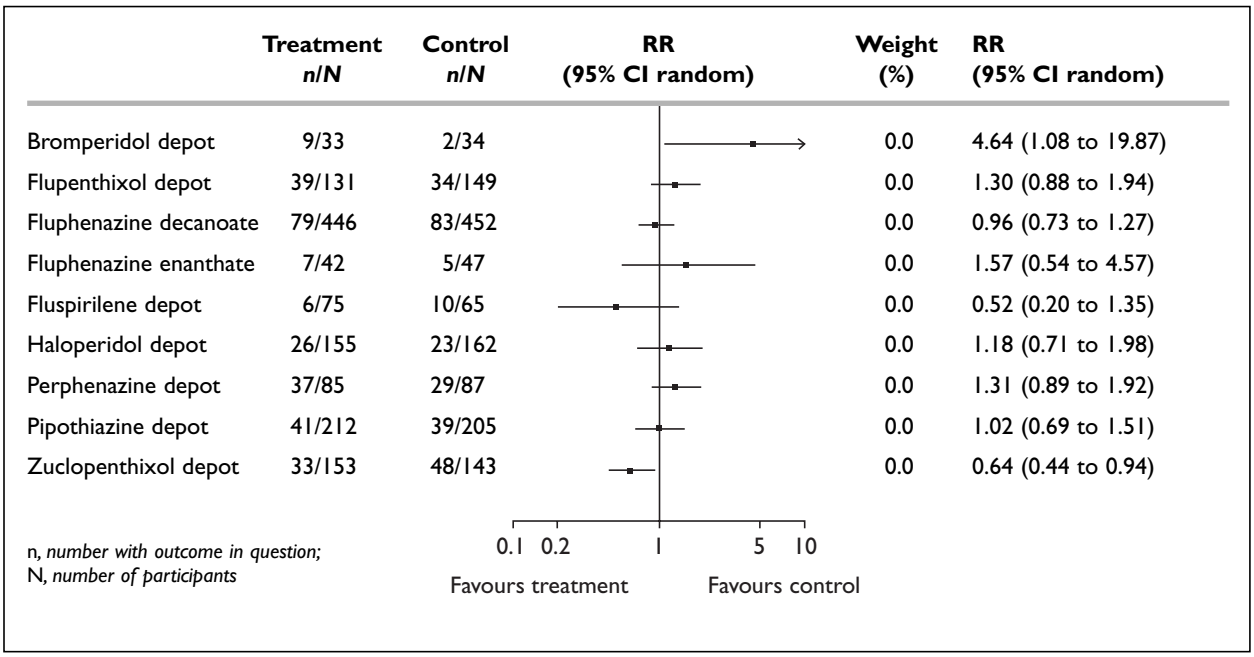


FIGURE 9 *Relapse rates: named depot versus comparator*

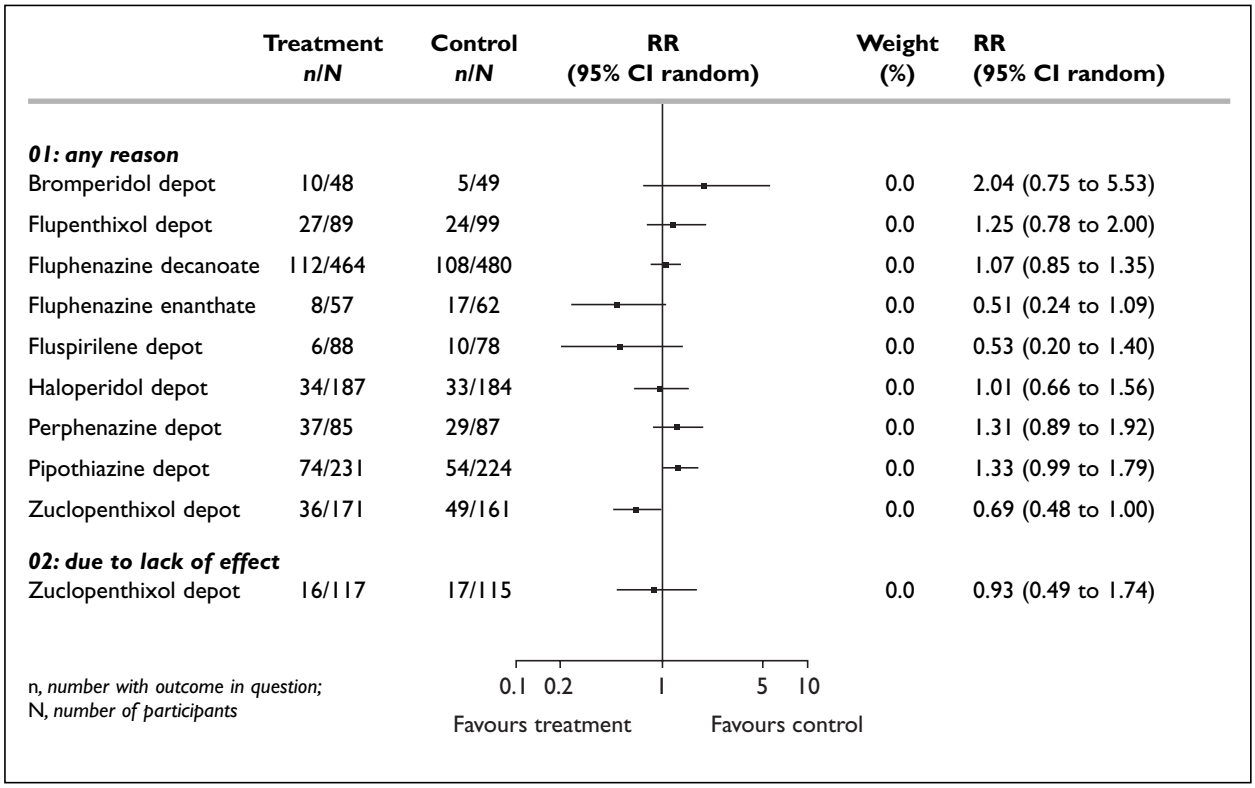


FIGURE 10 *Leaving the study early: named depot versus comparator*

Side-effects

Five reviews give details on the number of participants who experiences side-effects, classified generally. Two reviews report statistical significance, with those receiving flupenthixol and fluspirilene depots having less general side-effects (n = 74; RR = 0.7; 95% CI, 0.5 to 0.9; NNH = 3; 95% CI, 2.1 to 10.3; n = 133; RR = 0.7; 95% CI, 0.5 to 0.9; NNH = 5; 95% CI, 2.6 to 18.7). No other review achieved levels of conventional significance.

Movement disorders: use of adjunctive medication

All nine reviews reported data for this outcome. Three reviews reported statistical significance. In the fluspirilene depot (n = 166; RR = 0.5; 95% CI, 0.4 to 0.9; NNH = 5; 95% CI, 2.8 to 14.5) and the zuclopenthixol depot reviews, those on the experimental depots received less medication for their side-effects than those on comparators (n = 296; RR = 0.8; 95% CI, 0.7 to 0.9; NNH = 7; 95% CI, 4.3 to 35.2), whilst in the fluphenazine decanoate review, those receiving the comparators had less medication for side-effects (n = 727; RR = 1.3; 95% CI, 1.1 to 1.4; NNH = 7; 95% CI, 15.8 to 4.9). See *Figure 11*.

For the outcomes of dyskinesia, parkinsonism, tardive dyskinesia, tremor and unspecified movement disorders, no review reported statistical significance.

Anticholinergic effects

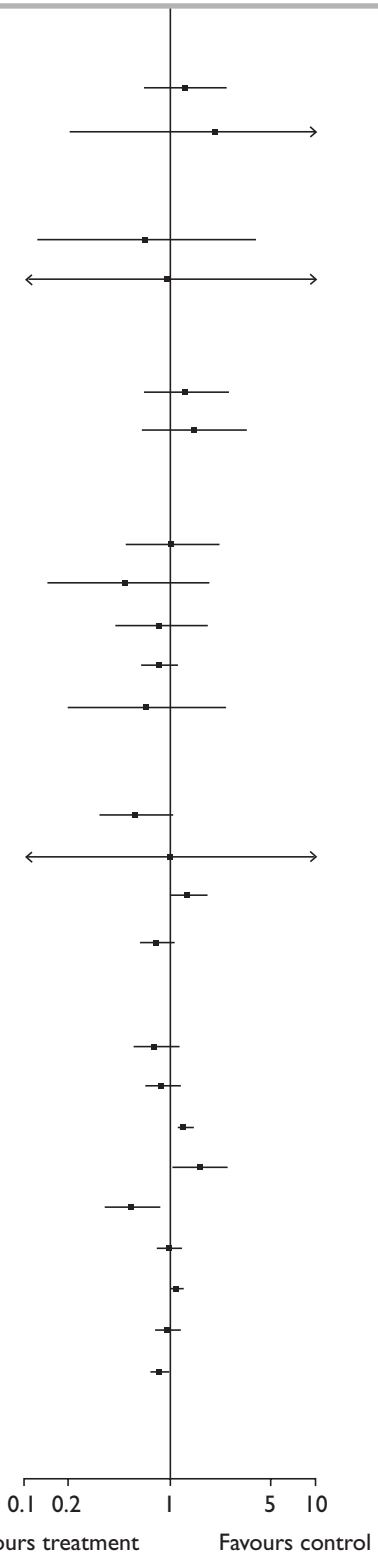
For the outcomes of blurred vision and dry mouth, none of the three reviews (flupenthixol depot, fluspirilene depot and pipothiazine depot) that gave details reported any statistical significance.

Comparisons 4 and 5: high-dose versus standard dose depot and low-dose versus standard/ high-dose depot

These two comparisons have been combined as only one outcome achieved statistical significance once pooled.

When the data for the standard dose versus low-dose comparison is pooled, overall significance is found for the outcome of relapse (n = 638; RR = 2.5; 95% CI, 1.1 to 5.9; NNT = 7; 95% CI, 12.3 to 4.6). In two individual reviews, those receiving the standard dose comparator experienced a lower relapse rate than those receiving the low dose (fluphenazine decanoate: n = 475; RR = 1.5; 95% CI, 1.2 to 2; NNT = 8; 95% CI, 21.7 to 4.8; fluphenazine enanthate: n = 104, RR = 6.7; 95% CI, 1.6 to 28.5; NNT = 5; 95% CI, 11.5 to 2.9), whilst the flupenthixol review did not reach significance. There was no difference found for the outcome of relapse in the high-dose versus standard dose comparison. See *Figures 12* and *13*.

	Treatment *n/N*	Control *n/N*	RR (95% CI random)	Weight (%)	RR (95% CI random)
01: dyskinesia					
Haloperidol depot	14/49	13/56		0.0	1.23 (0.64 to 2.36)
Zuclopenthixol depot	2/18	1/18		0.0	2.00 (0.20 to 20.15)
02: parkinsonism					
Fluspirilene depot	2/38	3/38		0.0	0.67 (0.12 to 3.77)
Pipothiazine depot	1/61	1/57		0.0	0.93 (0.06 to 14.59)
03: tardive dyskinesia					
Flupenthixol depot	10/17	7/15		0.0	1.26 (0.64 to 2.47)
Pipothiazine depot	12/77	8/73		0.0	1.42 (0.62 to 3.28)
04: tremor					
Flupenthixol depot	8/17	7/15		0.0	1.01 (0.48 to 2.11)
Fluspirilene depot	3/25	6/25		0.0	0.50 (0.14 to 1.78)
Haloperidol depot	8/21	9/20		0.0	0.85 (0.41 to 1.76)
Pipothiazine depot	44/103	47/93		0.0	0.85 (0.63 to 1.14)
Zuclopenthixol depot	4/54	5/46		0.0	0.68 (0.19 to 2.39)
05: unspecified movement disorder					
Flupenthixol depot	12/48	21/48		0.0	0.57 (0.32 to 1.03)
Fluspirilene depot	1/13	1/13		0.0	1.00 (0.07 to 14.34)
Perphenazine depot	50/85	39/87		0.0	1.31 (0.98 to 1.76)
Pipothiazine depot	54/149	64/142		0.0	0.80 (0.61 to 1.06)
06: use of adjunctive anticholinergic drugs					
Bromperidol depot	24/48	31/49		0.0	0.79 (0.55 to 1.13)
Flupenthixol depot	45/92	56/101		0.0	0.88 (0.67 to 1.16)
Fluphenazine decanoate	239/362	192/365		0.0	1.26 (1.11 to 1.42)
Fluphenazine enanthate	28/53	23/69		0.0	1.58 (1.04 to 2.41)
Fluspirilene depot	22/88	36/78		0.0	0.54 (0.35 to 0.84)
Haloperidol depot	73/124	80/133		0.0	0.98 (0.80 to 1.20)
Perphenazine depot	82/85	75/87		0.0	1.12 (1.02 to 1.23)
Pipothiazine depot	97/191	95/179		0.0	0.96 (0.79 to 1.16)
Zuclopenthixol depot	100/153	112/143		0.0	0.83 (0.72 to 0.96)



n, *number with outcome in question;*
N, *number of participants*

FIGURE 11 *Side-effects (including movement disorders): named depot versus comparator*

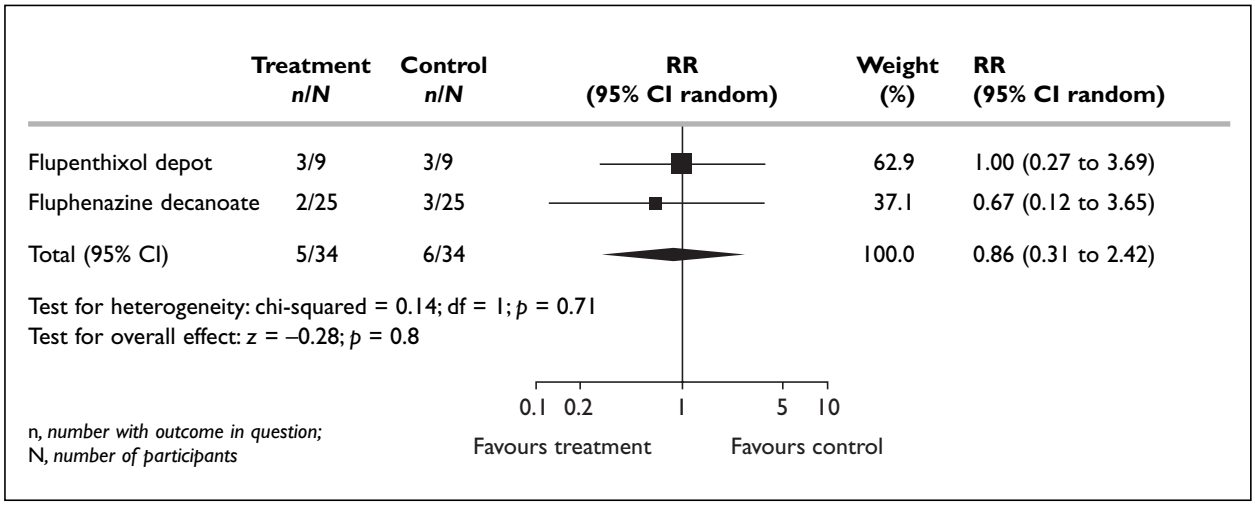


FIGURE 12 *Relapse rates: high versus standard dose depot*

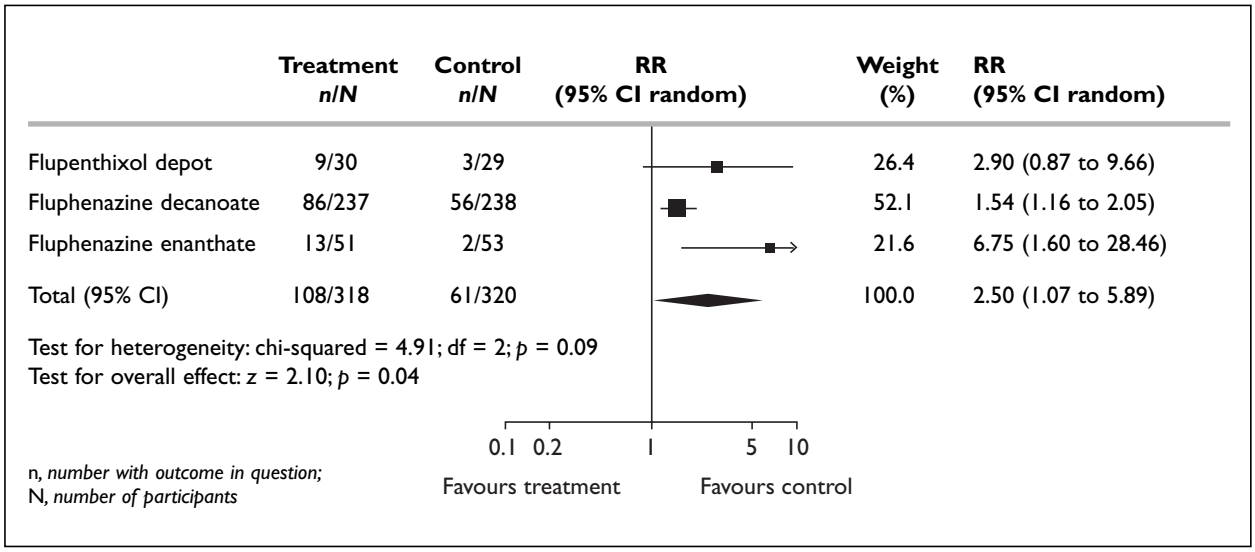


FIGURE 13 *Relapse rates: low versus standard to high-dose depot*

In the comparison of high-dose versus standard dose depot, for the outcomes of needing additional medication, relapse, mental state change from BPRS endpoint scores, leaving the study early, movement disorders subdivided into general, and the use of additional side-effect medication, and in the standard dose versus low-dose comparison, for rehospitalisation, relapse, leaving the study early and movement disorders, no outcome when pooled achieved conventional levels of statistical significance. One review in the high-dose comparison did achieve statistical significance for mental state: BPRS endpoint scores. Fluphenazine decanoate reported a mean difference of –10.4 (95% CI, –18.7 to 2.2; $n = 18$). However, when pooled with a review that had over twice as many participants and did not find a statistical difference ($n = 45$), the WMD came to –3.7 (95% CI, –8.6 to 1.2; $n = 63$). See *Figures 14–17*.

The main results are summarised in appendix 4 (*Figures 18–20*).

Review of attitudes to depot medication

The search strategy produced 1374 articles. Of these, 22 met the inclusion criteria for containing satisfaction data. A total of 16 studies explored patient attitudes towards depot antipsychotic medication, four looked at the opinions of nurses and two investigated both. In all, 18 studies were cross-sectional surveys, three were quasi-case–control studies and there was one randomised controlled trial. The sample size of the studies ranged from 26 to 270 participants. The total number of participants was 2377. Various settings were used for the studies, including hospital-

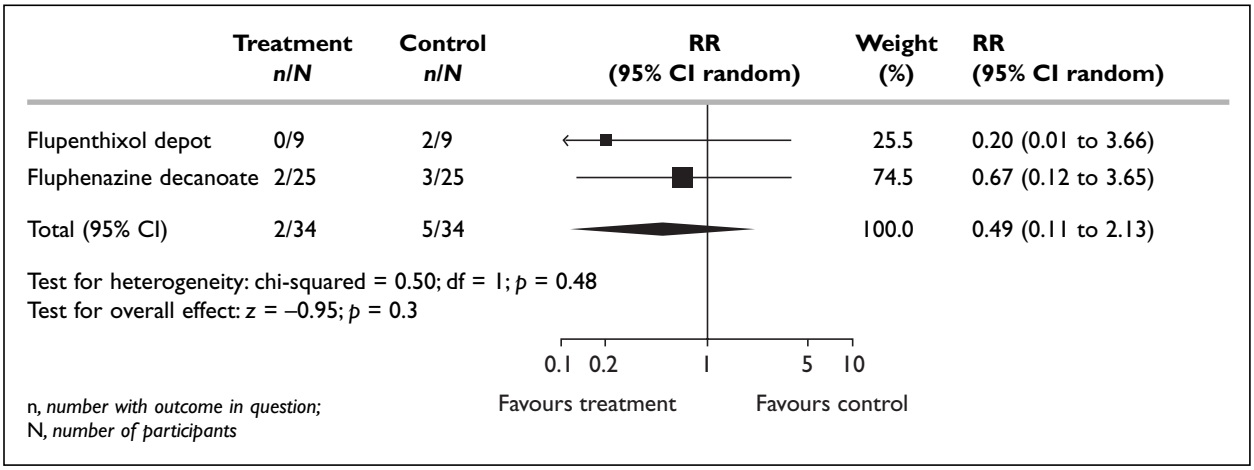


FIGURE 14 *Leaving the study early: high versus standard dose depot*

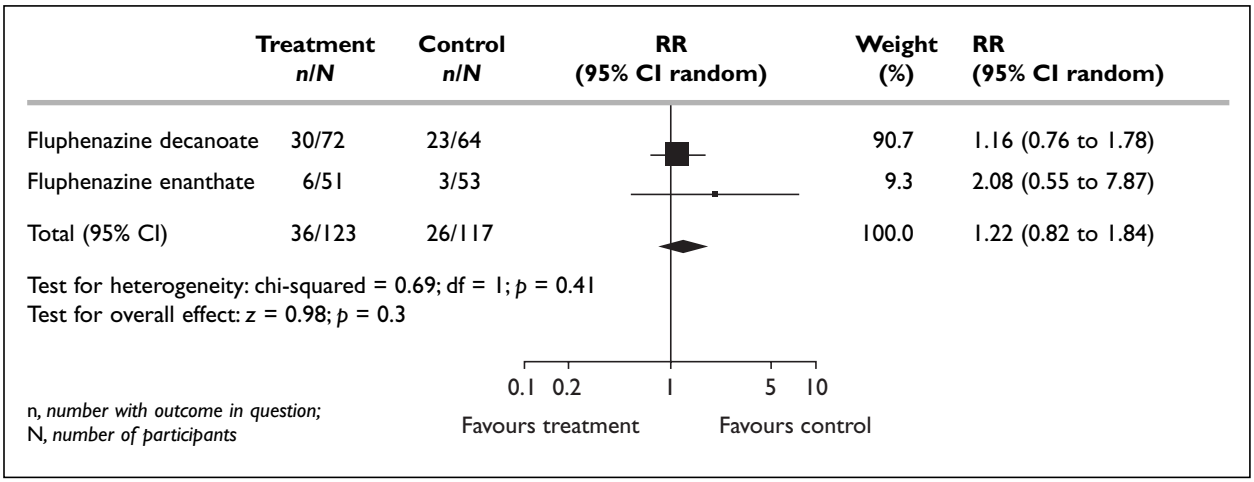


FIGURE 15 *Leaving the study early: low versus standard to high-dose depot*

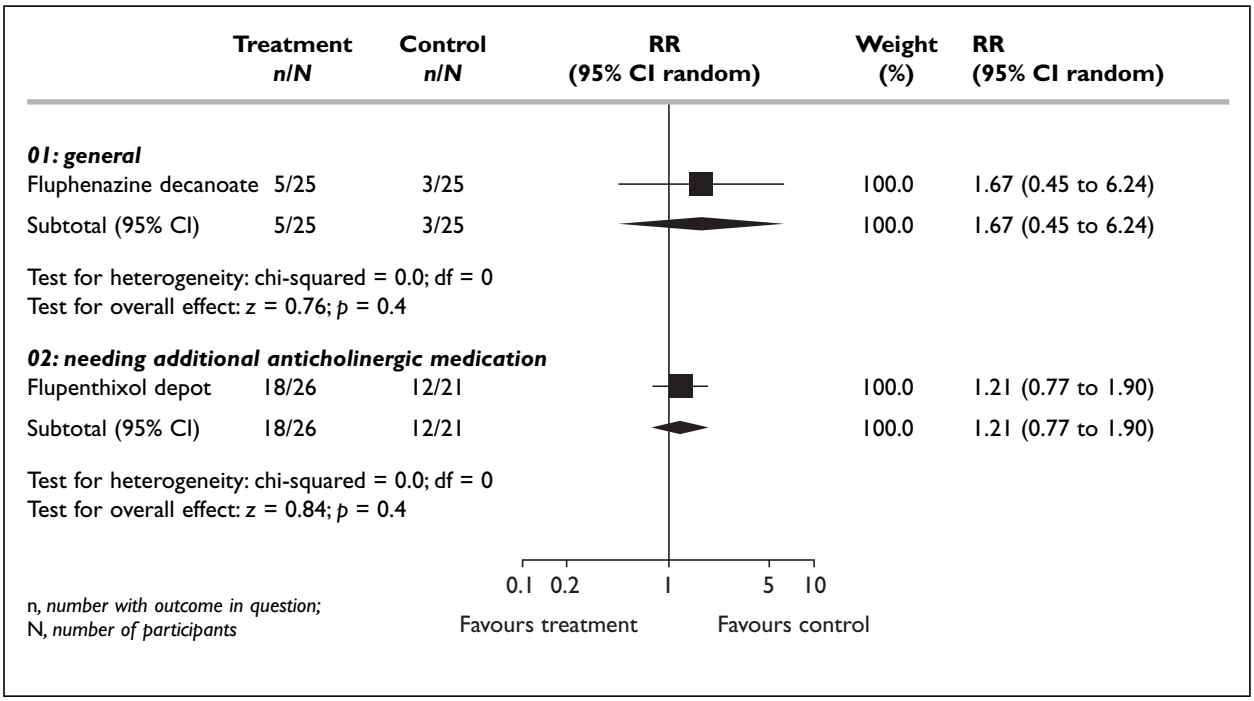


FIGURE 16 *Side-effects: high versus standard dose*

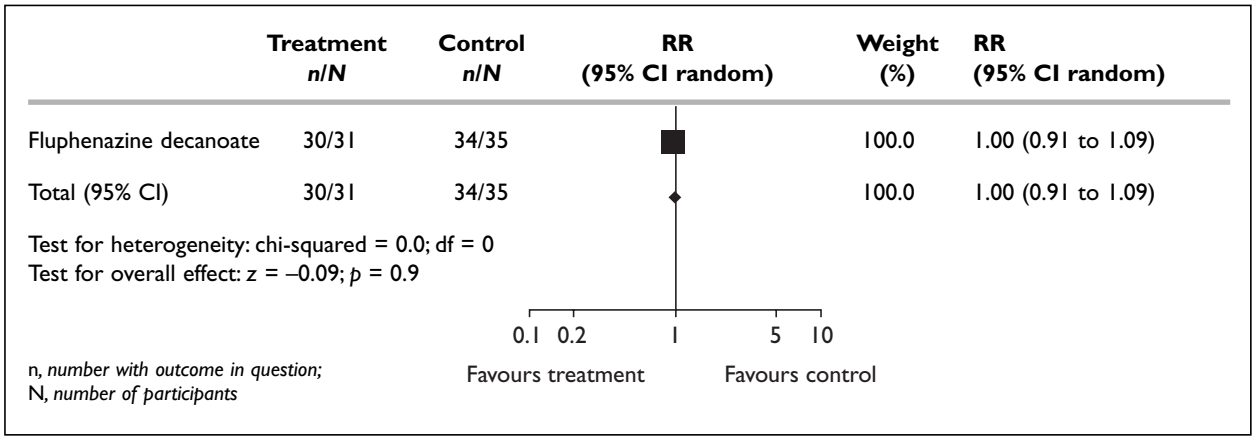


FIGURE 17 *Movement disorders: low versus standard to high-dose depot*

based depot clinics, outpatient clinics and GP surgeries. A total of 20 studies used questionnaires or interviews specifically designed for the study, one adapted an existing measure and one applied an existing measure. The characteristics of the included studies are described in appendix 5.

Quality of studies

The quality of the studies was mixed. Their performance on the checklist (appendix 6) ranged from 1 to 11 out of 13 (mean number of points lost was 6.9). Ten (45%) studies failed to score on eight of the items. The studies performed best for: 'response rate specified' included by 90% of the studies, and 'demographic details' (67%). However, only one study included a sample size calculation, and, although 19 studies stated their response or drop-out rate, only four of these justified or explained these rates. Similarly, 16 studies did not attempt to show that their sample was in any way representative of the population they were aiming to investigate.

Ten of the 12 studies that included specific attitudinal or preferential data found that their patients held some positive views towards depot antipsychotic medication. One reported a neutral view and one a negative attitude (*Table 2*).

Table 2 contains studies that have specific data asking patients how satisfied they are with their depot antipsychotics rather than an overall judgement by the reviewer.

Four of the five studies investigating patient preference regarding treatment setting reported that the majority preferred to receive their medication at the depot clinic, while Poole and Grimes[46] found a large majority preferred the depot to be administered at home (*Table 3*). None of the studies found that a majority of patients were in favour of GP-based treatment. Indeed, this was the third least preferable option for all of the studies.

There were six studies that reported on a direct comparison of oral versus depot from the point of view of patient preference (*Table 4*). Five studies found the majority of participants preferred to receive their medication via depot administration rather than in tablet form. Desai,[38] in an open study comparing patients switched from depot to risperidone, found that 80% of their sample preferred oral medication.

Two studies investigated the importance given to particular side-effects. Buis[49] asked patients to complete an amended version of the UKU SERS[34] where objective criteria had been replaced by subjective criteria. They then formed a hierarchy of the side-effects that were most important or troublesome. The top five were: sleepiness, increased fatigability, weight gain, tension or inner unrest and concentration difficulties. Side-effects associated with movement were amongst the least important. Larsen and Gerlach[37] reported that extra pyramidal symptoms (EPS) (apart from akathisia) were least reported by patients. However, 88% of patients who reported no side-effects had at least one EPS. They also found that non-physical or 'psychic' side-effects (dullness/tiredness) were the most frequently reported.[37] This is contrast with the perception of the patients' physician, who focused mainly on the EPS.

There were minimal data for nurse satisfaction with depot antipsychotics. No one paper focused specifically on the issue of nurse satisfaction with depot antipsychotics, and all data included were embedded within articles looking at other topics.

TABLE 2 *Patient satisfaction data with depot antipsychotics*

Study	Satisfaction data		
	Positive (+)	**Neutral (0)**	**Negative (–)**
Pan & Tantum, 1989[36]		most subjects believed that maintenance treatment was neither beneficial nor harmful for their physical health, family life, marital relationships, finances and social life	
Larsen & Gerlach, 1996[37]	60% of the patients had a positive attitude towards depot medication		
Desai, 1999[38]			patient acceptance of risperidone was significantly higher than that of depot medication 83% versus 23%
Hoencamp *et al.*, 1995[39]	62% of patients taking depots prefer to remain on depots		
Pereira & Pinto, 1997[23]	87% of patients receiving depot medication would prefer to continue with depot either alone or in combination with oral medication		
Wistedt, 1995[40]	a little over 60% seemed satisfied		
Singh *et al.*, 1995[41]	93% enjoyed attending the clinic		
Goldbeck *et al.*, 1999[42]	39% expressed a positive view, 29% neutral, 32% a negative view		
Warren, 1998[43]	86% who responded felt their injections to be useful		
Eastwood & Pugh, 1997[44]	53% preferred depot; 54% considered it helpful		
Anderson *et al.*, 1989[22]	60% positively enjoyed attending the depot clinic		
Jacobsson & Odling, 1980[45*]	77% thought that injection was better than tablet		
Total	**10**	**1**	**1**

The studies are shown in the order of their score on the checklist (see appendix 2)

[*] *Not included in the checklist*

TABLE 3 *Patient preference for treatment setting*

Study	Number	Depot clinic (%)	Home (%)	GP (%)
Brooker *et al.*, 1996[47]	270	74[*]	–	–
Sandford, 1996[48]	58	52	29	19
Singh *et al.*, 1995[41]	218	63/88[†]	37	14
Poole & Grimes, 1998[46]	47	21[*]	64	8.5
Anderson *et al.*, 1989[22]	168	56[*]	39	17
Overall (no. of studies)		**4**	**1**	**0**

Data shown as % of patients

The studies are shown in the order of their score on the checklist

[*] *Patients were given the three options to choose from*

[†] *Patients were given the choice of depot versus home, and depot versus GP*

TABLE 4 *Patient preference for depot versus oral antipsychotics*

Study	Question asked (where stated)	Number*	Depot	Oral	Combination	No preference
Desai, 1999[38†]	Patients asked to compare risperidone with their previous depot medication	143	9	80	–	11
Hoencamp *et al.*, 1995[39‡]	"Rather medication by depot or tablet?"	81	62	33	–	–
Pereira & Pinto, 1997[23]	Patient preference for route of administration	107	59	3	24	–
Eastwood & Pugh, 1997[44]	Patient preference	100	53	23	–	14
Wistedt, 1995[40]	"How do you feel about the medicine you get in the form of injections compared with earlier treatment with tablets?"	73	63	0	–	26
Jacobsson & Odling, 1980[45§]	"The injection is better than the tablets as there is less risk of forgetting to take them"	43	77	23	–	–
Overall (no. of studies)			**5**	**1**	**–**	**–**

Unless otherwise stated, patients are on depot antipsychotics

Data shown as % of patients

The studies are shown in the order of their score on the checklist (however, Jacobsson was not included on the checklist)

* *Total number in the study and does not take account of missing data*

† *Patients thought that oral medication was much better than their previous (depot treatment)*

‡ *Paper does include data for those on oral medication, but not for this question*

§ *Paper asked three questions regarding the difference between medication types: the above is based on the question "the injection is better as there is less risk of forgetting to take them"; all questions show a majority of patients preferring depots*

However, some themes did emerge. There were interesting differences between the attitude of community psychiatric nurses (CPNs) and practice nurses. Bennett and colleagues[50] reported that overall the CPNs' attitude was favourable towards administering and monitoring medication, although 29% felt it did not utilise their skills and that these tasks could be carried out by other trained nurses. However, Burns and colleagues[51] reported that two-thirds of practice nurses administered depots, but most lacked confidence and training. Kendrick and colleagues[52] surveyed practice nurses by post and held a focus group to investigate their attitudes towards depot medication. The study showed that the practice nurses felt unsupervised and that the CPNs should be administering depots. Cantle[53] surveyed 26 delegates (GPs and primary care nurses) at a training day for depot neuroleptics. A total of 88% of the group stated that they would like more training. Warren[43] carried out an audit of depot administration and reported that nurses wanted more training in medication and treating psychoses in general. Finally, only one of the five studies looking at patient preference for treatment setting investigated nurse opinion. Brooker and colleagues[47] asked clinic nurse managers of 135 depot clinics to rate their overall satisfaction (0 = totally unsatisfactory; 8 = excellent) with their clinic arrangements. The mean rating was 4.8, with 40% scoring below this figure. A sizeable minority were not satisfied with the running of their clinic.

Chapter 4
Discussion

Meta-review of depot antipsychotics

Generalisability

The reviews included studies that had used a wide variety of diagnostic tools, some operationalised (DSM-II to DSM-III-R), whilst some used more subjective diagnostic systems (Bleuler's criteria, Feighner's criteria, French criteria). The span of time and variety of diagnostic tools will also have meant that those included in the review were diagnostically heterogeneous. The likelihood that these reviews included those people seen in clinical practice is increased when several different diagnostic criteria are used, rather then just a few, narrow definitions. Whether those people for whom a depot is most likely to be indicated were included, such as those who are reluctant or unable to comply with a prescription for oral antipsychotics, is less likely. The reviews mostly included those who were stable on oral medication, a group in whom it could be expected that medication given in depot form would not be superior to the same drug given orally. Some participants whose course of illness had not previously been helped by a variety of medications were included, but it is unclear whether this meant those who were non-compliant with or unresponsive to treatment.

Much data on global effect and mental state were reported in such a way that it could not be included in this review. Results that have been reported as not being of statistical significance may have wide CIs. Wide 95% CIs make it impossible to draw any firm conclusions about these results, and are a reflection of lack of evidence rather than evidence of no effect.

Some studies which compared people who were stable on oral medication and were then randomised to receive either depot or inactive placebo have not been included in this overview, as we believe they were being treated systematically differently to those who were ill and randomised to an active control. It is our belief that the only data that would have been usable in these studies would have been to answer the question 'what happens to people when you stop treating them'? We have also not entered most of the continuous data from reviews because of the problems combining continuous data in REVMAN. We do not believe that the review suffers because of this since there was very little usable data of this kind in the contributing reviews. Fluspirilene, haloperidol, perphenazine and zuclopenthixol had none, and the remainder had only a few outcomes and these were based on small numbers. Hence, the emphasis in this overview was on binary/categorical data. Where a review did give data for a continuous outcome on one study only, this has been entered. We have also not combined some data, in particular in the depot versus depot comparison, where the danger of entering data more than once was high, leading to a reporting bias and a potential overestimation of effect.

Comparison 1: depot medication versus placebo

We were not surprised that the depot preparations have been compared to inactive placebo infrequently, as the effectiveness of oral antipsychotics is fairly well established,[54] and it may be viewed as unethical not to treat someone if it is known that an effective treatment exists.

Death

No conclusions can be drawn from the data on death in the depot versus placebo comparison as statistical significance was not reached. Fortunately there were very few deaths during the studies.

Needing additional antipsychotic medication

Surprisingly, no significant difference was found between those on active treatment and those receiving the inactive comparison when the results from two reviews were pooled. If needing additional antipsychotic medication can be used as a proxy measure of effectiveness of an experimental drug or its comparator to control the symptoms, then it would be expected that those receiving an inactive placebo would require more additional antipsychotic medication. This pattern was not the case in the fluphenazine decanoate review, but did not reach statistical significance, whilst in the haloperidol review statistical significance was found (NNT = 2) in favour of active treatment.

Mental state

It is hard to know whether relapse should be treated as a measure of mental state or as a proxy measure of global change. The significance in favour of those taking antipsychotic medication underlines the central role that medication has for those with schizophrenia, with fewer people taking antipsychotic medication relapsing than those on inactive placebo (NNT = 2). No comments can be made as to whether those taking depot medication suffer more depression than those on placebo.

Behaviour

Pooled results from the three reviews included showed that significantly more people taking depot medication stayed in the studies than those receiving a placebo comparator (21% versus 49%). As drop-out from these comparisons was so high for the placebo group, results need to be viewed with caution because it is unlikely that those people who left the studies continued to be well.

Side-effects

Those people taking the active depots rather than the inactive comparator suffered more generalised movement disorders, which is not surprising as these are well-recognised side-effects of all of the antipsychotic drugs (NNH = 3). As drop-out from the placebo group was so high and those who left the study early have been added back in as having had the negative outcome, the direction of effect appears to favour those taking the active substance for symptoms of blurred vision and dry mouth (i.e. active depot caused fewer side-effects). This is thought to be a false-negative result.

Comparison 2: depot medication versus oral antipsychotics

An underlying assumption about the use of depot medication is that those with schizophrenia and serious mental illnesses may not take their prescribed medications in a reliable way, resulting in a higher relapse rate for those prescribed oral medication. If this assumption is true, then this comparison should demonstrate the strongest advantage for depots, provided the studies included those people who do not take their medication reliably.

Global functioning: no important global change

In three reviews (fluphenazine decanoate, fluphenazine enanthate and haloperidol depot), those people taking depot medication experienced a better outcome than those taking oral medication (i.e. they did show important global change) when results from the CGI are pooled.

Relapse

It might be expected that this outcome would show the strongest difference between depot and oral medication. Again, three reviews, involving 1403 participants, did not demonstrate statistical significance (RR = 0.9; 95% CI, 0.8 to 1.2). As the RR is 0.9 and the CI so tight around this, it would be fair to say that in those people who entered the studies, receiving medication in the form of a depot did not prevent relapse any more than oral medication. With the relatively high number of people able to be counted for this outcome of research into the care of those with schizophrenia,[54] this must be regarded as a robust finding with good statistical power.

Mental state

BPRS scores, either individually in a review or when pooled, did not demonstrate statistical significance when depot and oral agents were compared, although it could be argued that the numbers reported on (n = 266) were too small to provide adequate statistical power. The same can be said for the outcome of being depressed, which also failed to demonstrate statistical significance (N = 1; n = 48; RR = 1.5; 95% CI, 0.9 to 2.6).

Behaviour

Unlike the depot versus placebo comparison, depot medication did not seem to affect the number of people leaving the studies early (26% versus 21%). Again, the CI around the RR is narrow, and the number of cases reasonably high; hence, it seems unlikely this is a false-negative error (N = 4; n = 874; RR = 1.1; 95% CI, 0.9 to 1.5). Again, statistical significance was not found on the continuous outcome of the NOSIE-30 endpoint scores (N = 2; n = 244; WMD = 2.2; 95% CI, –2.9 to 7.3).

Side-effects

No differences were found on the need for additional anticholinergic medication between those taking depot or oral medication, with both as likely to require additional medication (69% versus 65%). Many of the studies in the fluphenazine and zuclopenthixol reviews also gave regular medication for side-effects, only recording what additional medication was given over that allowed per regular prescription, and although this does not seem to have been reported in the other reviews, it is likely that this happened, suggesting that levels of side-effects with the use of depot medication are high. No side-effects measured reached statistical levels of significance. This may be due in part to the fact that the aim of many of the studies was to show non-inferiority with oral agents and hence the incidence of side-

effects was, regrettably, not of primary interest to the researchers.

Comparison 3: depot versus other depots

The usefulness of depot versus depot comparisons has to be questioned. Depots are primarily seen and used as a method of ensuring that patients who are not compliant with prescriptions for oral antipsychotics receive a regular dose of antipsychotic medication to prevent relapse, however defined. Comparisons with other depot medication can quite reasonably be seen as fulfilling the need to market a new substance rather than answering any relevant clinical questions.

Global functioning

No differences were seen on any of the following global measures of change: no clinically important change; being severely ill at the endpoint; or on the CGI rating scale. As all participants were receiving a depot form of an antipsychotic medication, this is not surprising.

Mental state

All nine reviews reported data on those people who relapsed. As only two reviews (bromperidol and zuclopenthixol depot) found a statistically significant result but in opposite directions, the usefulness of relapse as an outcome is called into question. By chance alone, some reviews are going to find different results from other reviews. The fact that two out of nine found a positive result can reasonably be seen as possible false-positives. It is probably sensible to treat these results with caution. No comments can be usefully made about the changes in mental state as measured by the BPRS or for depression.

It is unclear how to interpret the use of additional antipsychotic medication. It is probably sensible to regard it as a proxy measure for global relapse or worsening, although it is theoretically possible that additional medication may contribute to a poorer outcome in some circumstances. In the fluphenazine enanthate review, it seems that those on the comparator drug had the poorer outcome (n = 63; RR = 0.4; 95% CI, 0.2 to 0.9; NNT = 3; 95% CI, 1.9 to 12.6), whilst in the pipothiazine review, those receiving the comparator received less additional antipsychotic medication (n = 106; RR = 2.3; 95% CI, 1.1 to 4.6; NNH = 5; 95% CI, 20.3 to 2.7). No overall conclusions can be drawn from these data.

The zuclopenthixol review reported an improvement in mental state (fewer relapses) versus comparators, as well as a significant result on the outcome of needing anti depressant medication; namely, those taking the comparator substances are more likely to require antidepressant medication (n = 296; RR = 0.7; 95% CI, 0.5 to 0.9; NNT = 7; 95% CI, 4 to 32). However, data are not available on other depots so we cannot exclude the possibility that there may be something systematically different about the participants in the zuclopenthixol review.

Behaviour

No significance can be found between groups for leaving the study early (14% versus 15%). This could be because most of the participants were already stable on medication before entering the study and it is questionable whether they were representative of those for whom depot preparations are deemed most suitable. The low number leaving the studies early is noteworthy considering research into the newer atypicals that have rates of attrition of between 40% and 60% (see Cochrane Library). Regarding behaviour more generally, one review included information on the use of the NOSIE-30, which did not find a difference.

Side-effects

Two reviews of depots report statistical significance, with those receiving flupenthixol and fluspirilene depots having less general side-effects (n = 74, NNH 3; n = 133, NNH = 5). Three reviews reported statistical significance for the outcome of needing less medication for side-effects. In the fluspirilene depot (NNH = 5), and the zuclopenthixol depot review (NNH = 7), those on the experimental depots received less additional medication for their side-effects than those on comparators, whilst in the fluphenazine decanoate review, those receiving the comparators had less additional medication for side-effects (NNH = 7). For the outcomes of dyskinesia, parkinsonism, tardive dyskinesia, tremor, unspecified movement disorders, blurred vision and dry mouth, no differences were found.

Comparisons 4 and 5: high-dose versus standard dose depot and low-dose versus standard/high-dose depot

The one statistically significant outcome in these comparisons supports the view that so-called low doses are sub-therapeutic (NNT = 7).

No conclusions can be drawn from the data on the outcomes of needing additional medication, relapse, mental state change from BPRS endpoint scores, leaving the study early,

movement disorders – subdived into general and the use of additional side-effect medication – and in the standard dose versus low-dose comparison, rehospitalisation, relapse, leaving the study early and movement disorders.

Review of attitudes to depot medication

There were few data in the literature concerned with patient satisfaction with depot antipsychotic medication and even less investigating the attitudes of nurses. Of the studies that exist the designs used were from the lower levels of the hierarchy of evidence. While the cross-sectional survey is appropriate to investigate satisfaction, more complex longitudinal designs could be used to assess, for example, how attitudes may change over time. The lack of satisfaction data coming from RCTs illustrates the low priority investigators have placed on user perception when testing the clinical efficacy of medication.

We tried to be as inclusive as possible. Any data showing (1) an attitude towards depot medication; (2) a clinic where it was administered; (3) comparison to another medication, were included. The mixed quality of the studies makes generalisations problematic. It would be easy to dismiss many of them due to their flaws, but this would lose valuable data in a subject area that cannot currently afford it. Instead, the checklist enables the data from the studies to be ranked and their position taken into account when assessing the results. The positive finding of the majority of studies is in contrast to the negative popular perception of depot antipsychotic medication and the view put forward in the introduction.[22,23] However, there are a number of limitations to these data. First, no studies asked the same question to gauge overall satisfaction, so amalgamating the responses may be inappropriate. Similarly, comparison between studies was difficult. Secondly, the higher quality studies tended to show less positive results, indicating a possible relationship between study quality and outcome, but since there are only two dissenters this cannot be concluded with confidence. Another more persuasive explanation for the findings is sample selection bias. The patients involved in the studies were by definition 'attendees' and 'compliers'. People who attend depot clinics would be expected to be reasonably positive about depots otherwise they would not attend. Data on non-attendees and the non-compliance are, *ipso facto*, hard to obtain. However, such selection bias may be tempered because the studies may have included individuals who happened to turn up on that particular day but were not regular attendees. The key factor is that the studies did not formally seek a sample that was representative of all those prescribed depot antipsychotic medication but took a convenience sample with all its associated pitfalls. Similarly, a non-selected group of patients on maintenance oral medication would include many who had either been on depots in the past or at least been offered them and declined. The views of such patients on depots (presumably rather negative) would complete the picture as well as perhaps offering insights as to why such patients dislike depots.

Hoencamp and colleagues[39] did compare patients on oral and depot medication but could not obtain data regarding preference from those currently on oral medication. It was reported that 26 of the 93 patients on oral medication had previously been on depot medication, and only two preferred depot medication. Nevertheless, the conclusion that can be drawn from this and similar studies is that the majority of patients on depot antipsychotic medication accept their medication, with approximately a quarter of patients in three of the studies not satisfied. Desai[38] was the only study that reported that patients preferred oral medication to their current depot medication. However, this can be attributed to bias since the sample was composed of patients whose psychiatrists had considered that they would benefit from a switch from depot antipsychotic medication to risperidone, an oral atypical antipsychotic drug. The authors state that this may have been because patients did not want to continue having depot antipsychotics or had experienced severe side-effects.

The results show that the majority of patients in the majority of relevant studies prefer to have their medication administered at a depot clinic. This may be because of the social benefit of attending the clinic. Patients are able to meet others with similar problems and experiences. This may be particularly important in schizophrenia where sufferers are often isolated. Patients may also see the benefit of the clinic, particularly within a community mental health centre, in allowing access to healthcare professionals and general information. These benefits would not follow from attendance at the GP surgery where there would be only a handful of similar patients at most and few other relevant facilities on-site. However, the bias described previously may also explain the preference for treatment setting. All five studies took their sample

from patients receiving their medication at a depot clinic. None of the studies took a representative sample from patients attending clinics, at home or at their GP surgery. This may be because the aim of the individual studies was not to identify patient preference for treatment setting but to find out how satisfied the users of the depot clinic were with their service.

The evidence reviewed showed clear patient preference for depot antipsychotic medication over oral antipsychotic medication. Therefore, while evidence of clinical superiority may be elusive, we have found support for a 'subjective superiority' for depots. One possible explanation is convenience. Wistedt[40] found that 67% of their sample thought that it was easier to have an injection than take tablets once or a couple of times daily. Hoencamp and colleagues[39] also found convenience to be an important factor, as 42% of those who preferred depots cited this as a reason why. In contradiction to the concerns regarding the loss of personal freedom when treated with depot antipsychotic medication, Jacobsson and Odling[45] reported that 67% of their sample taking depot antipsychotics would not prefer to take their medication in tablet form so that they could control how much and when to take them.

The emphasis of patients on the 'psychological' side-effects described in the methodologically weak study by Buis[49] and the stronger study Larsen and Gerlach and its discordance with the emphasis of health professionals,[37] highlights the need for a patient focus. Although the physical side-effects must be addressed for the patient's safety and satisfaction, the psychological aspects also need to be addressed to improve quality of life. The neglect of this dimension may lead to non-compliance if the side-effect, which the patient feels is most detrimental, is ignored.

There are few studies looking at the perception of nurses administering depot antipsychotic medication. We may nevertheless conclude that there is ambiguity regarding the type of nurse who should administer depot antipsychotic medication and that more and better training should be given.[51,52]

Chapter 5

Review of economics evidence

Introduction

One component of the systematic reviewing of the evidence on depot antipsychotic preparations for treating people with schizophrenia was to examine cost-effectiveness. Given the high costs of relapse, particularly because of the need in most cases for inpatient admission,[2] it might be hypothesised that depot treatment would be more cost-effective than oral treatment. Indeed, this assertion has often been made in the literature.[55–57]

This chapter summarises the process and findings of the review of economics evidence, and offers some conclusions.

Methods

Economic evaluation

Health economists have developed a number of techniques for evaluating interventions, grouped around the core definition of an economic evaluation as "the comparative analysis of alternative courses of action in terms of both their costs and consequences".[58] Adopting such a definition leads to a focus on cost-effectiveness, cost–consequences, cost–utility and cost–benefit analyses. However, because there are few such evaluations in many healthcare areas, including in mental health, the review also widened its span to look at studies that (a) examine costs but not outcomes, and (b) report service utilisation patterns without converting them into monetary measures. Such studies alone do not provide sufficient evidence to guide decision-making.

Search strategy

The search strategy used to review the evidence on the effectiveness of depot antipsychotics, after application of the selection criteria and methodological quality check (using the Cochrane Collaboration categories), generated no studies with an economics component. One of the methodological requirements was that studies should be randomised trials. We therefore carried out a second systematic review using the search terms 'antipsychotic', 'neuroleptic' and 'depot' alongside 'cost' and 'economic' in an attempt to find studies that might have some economics evidence.

Five databases were searched, generating the following numbers of papers:

- PsycINFO, 1984 to February 2001: generating eight references
- MEDLINE, 1966 to May 2001: generating 35 references
- EMBASE, 1980 to May 2001: generating 20 references
- NHS EED, May 2001: generating 69 references
- Cochrane Library, May 2001: generating 102 references.

Combining the results from these five searches produced a core set of 207 papers. Papers were excluded if they were case reports or letters to the editor. The great majority of these papers were not relevant to this review. Papers that were potentially relevant were read and their references checked and followed up as necessary. In fact, this did not generate any further studies relevant to this review.

The main dimensions of each study were examined, including country of study, patient group, type of economic evaluation, evaluation design and framework, sample size, method of outcome measurement, method of cost measurement, sensitivity analysis, and potential generalisability. The checklist suggested by Drummond and colleagues[58] assisted this review of the methodological properties of the included studies. The relevance of studies for the UK was also considered.

Results

The review uncovered very few studies of sufficient relevance or quality even to comment upon. As the main meta-review on effectiveness has already found, there are no RCTs that have addressed the cost-effectiveness question.

Most of the papers purporting to examine the economic consequences of depot treatment are methodologically very weak.

- Some studies are mirror image studies of patients treated with and without depot but without any control sample;[59–61] Larach and colleagues[61] is not actually a cost–benefit analysis despite its title.
- Some studies are naturalistic observational studies reporting (narrowly measured) costs but not outcomes, and without any adjustment for differences in patient characteristics;[62,63] the latter, in fact, compared two depots with oral risperidone.
- Some studies are decision models built partly on observational evidence, partly on data from randomised trials and partly on expert views.[64,65] Each of these two decision model studies (the latter for the UK) concludes that switching patients from oral to depot medication could be cost saving under certain assumptions.
- Some studies gave every indication from their titles that they are economic studies but which have no cost or service utilisation data.[66]

The absence of any randomised trial evidence and the methodological weaknesses of the studies based on non-randomised designs make it impossible to draw any firm conclusions.

Discussion

The economic impact of schizophrenia is broad and substantial, with costs borne not only by healthcare agencies but also by social care, housing, criminal justice and other agencies.[67] There are also potentially large costs for the families of people with schizophrenia[68] and some impacts on the wider community given the association between psychosis and violent crime.[69] For people with the illness, there will often be costs associated with not being in employment[70] and with premature mortality.[71]

In contrast to this broad range of cost impacts of schizophrenia, the very few studies of depot neuroleptics that have made some reference to economic issues have focused very narrowly on just a few of the costs, albeit those of most interest (hospitalisation and drug costs) to healthcare decision-makers. Of greater concern is the finding that no randomised studies have been carried out to examine the cost-effectiveness of depot treatment compared to placebo, oral antipsychotics or other depot preparations, nor is the quality of the evidence from the non-randomised studies sufficient to allow conclusions to be drawn.

Chapter 6

Conclusions and recommendations

Conclusions

We have reviewed the published data on both the efficacy of depot antipsychotic drugs and attitudes to depots on the part of patients and health professionals. A large body of information is available, although several important gaps remain.

Meta-review of depot antipsychotics

Generalisations about the use of depot medication for those patients who are non-compliant with prescriptions are difficult to make. This is because of the likelihood that those patients with schizophrenia who participated in the trials included in this review were not representative of those for whom giving a depot medication might be the most obvious clinical option. However, data from the comparison of depots versus inactive placebo underlines the efficacy of antipsychotic medication in the effectiveness of preventing relapse if continued on medication after stability is achieved.

In addition, active treatment compared to no treatment was more effective in keeping people in the trials. However, the use of active treatment is associated with increased side-effects, which is one of the reasons given by people for either altering their dose of oral medication themselves to minimise this, or for not attending for ongoing injections of active treatments.

Depot medication does help achieve a better 'global' outcome than oral medication, though this does not seem to translate into keeping people in contact with trialists or improvement in mental state. How this translates to clinical practice is uncertain. Again, it is uncertain whether a trial based on patients in whom non-adherence with medication has been identified as a problem would show these results to the same extent or even more strongly. The occurrence of side-effects may influence a clinician's choice, though this review suggests that there is little scope to respond to the presence of distressing side-effects by reducing dose levels to below recommended levels. No clear disadvantage emerged with respect to side-effects when depots were compared to oral agents, and this may reassure clinicians.

Differences between different types of depot are fairly inconclusive, with zuclopenthixol decanoate preventing more relapses, and bromperidol preventing fewer relapses than comparators. However, this needs to be seen in the context of seven other inconclusive depot versus depot comparisons. Fewer people on flupenthixol and fluspirilene experienced side-effects. There are no apparent benefits to using low doses of depot medication with more people relapsing than on a standard dose.

The apparent benefits to taking depot medication over oral medication at this point in time are an improvement in global symptoms, which may allow people to concentrate on other activities, such as socialising or work. There are some conflicts with this though, as they do not seem to prevent relapse for people who may be erratic in taking oral medication, the primary reason for giving a medication in depot form. The data on side-effects is unclear and indicates that people receiving depots experience more of some side-effects but not of others. However, this is difficult to interpret since most trial participants in the included studies seemed to be on regular medication for side-effects.

Review of attitudes to depot medication (including economic evidence)

The most conclusive evidence identified by this review is the dearth of studies looking at patient and nurse satisfaction with depot antipsychotic medication. Even scarcer are studies of high quality. This review was unable to have higher methodological criteria for inclusion because of the lack of data to choose from.

The heterogeneous nature of the studies and their quality does make conclusions difficult, but not impossible. The checklist (appendix 2) was devised as a tool in this endeavour, although it in itself suffers from subjectivity.

Drawing together all the strands of this review it may tentatively be concluded that depot antipsychotic medication received a more positive reception from its users than had been expected – given the views quoted in the introduction. Further research is urgently needed to validate this conclusion.

Recommendations

- Much more consideration needs to be given to patient satisfaction and views on drug administration and delivery – including injection *per se* and depot clinics.
- Future studies should clearly adhere to the CONSORT statement[72] for the reporting of all outcomes to make this review more informative. Further research undertaken in the use of depot medication should focus upon those who potentially stand to gain the most benefit (i.e. those patients whose non-compliance is thought to contribute to relapses in their condition). However, research in such people is, by definition, extremely difficult and may even be impossible since non-compliant people are much less likely to be included in standard RCTs. Given that the new atypical antipsychotics are either in various stages of development in depot form or already in trials, it is important that note is made of the current state of knowledge of the effectiveness and limitations of depots.
- Large, simple, pragmatic studies should be organised to establish whether depots do prevent relapse in the group for whom depot is most likely to be of benefit. Such a trial would have to be of longer duration than the majority conducted to date in order to capture a sufficient number of relapses (and to examine longer term outcomes such as tardive dyskinesia). The definition of relapse requires careful consideration and would of course need to be operationalised.
- Useful cost-effectiveness data and that on quality of life, satisfaction, and disability must be a research priority.
- The positive attitudes of patients evident in this review may reflect the nature of the sample (i.e. patients already established on depot treatment). Future surveys should be more comprehensive and include patients who have been offered depots and refused; patients on depot treatment given under a section of the Mental Health Act; patients who have been switched to oral medication from depot for whatever reason; practitioners' views; and finally, comparisons with the newer atypical agents (currently only available in oral form).
- Data from other patient groups for whom parenteral routes of administration of drugs are used routinely (e.g. diabetics and patients on other hormone replacements) may also shed light on general attitudes to 'injections'.
- In future, we recommend more emphasis on the patient's experience of depots and the implications of this kind of treatment versus oral treatment. Qualitative studies may be of value in this regard.
- Very few studies of depot neuroleptics have made reference to economic issues, and these have focused narrowly on just a few of the costs (hospitalisation and drug costs). No randomised studies have been carried out to examine the cost-effectiveness of depot treatment compared to placebo, oral antipsychotics or other depot preparations. The quality of the evidence from the non-randomised studies is insufficient to allow conclusions to be drawn.

Acknowledgements

This study was commissioned by the NHS R&D Health Technology Assessment Programme, project number 95/38/01.

The authors thank Mrs Patsy Mott for her secretarial work.

We are very grateful to the referees for their constructive reviews and the quality of their comments.

The reviews expressed in this report are those of the authors, who are also responsible for any errors.

Project team
Seema Quraishi, Mark Fenton, Jessica Walburn (research workers); Martin Knapp, Professor of Economics of Mental Health (with Dr Sophie Ilson); Richard Gray, Lecturer, Section of Psychiatric Nursing.

Consultant
Kevin Gournay, Professor of Psychiatric Nursing.

References

1. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, *et al.* Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization-ten country study. *Psychol Med (Monograph Supplement)* 1992;**20**:1–97.
2. Weiden PJ, Olfson M. The cost of relapse in schizophrenia. *Schizophr Bull* 1995;**21**:419–29.
3. Kemp R, David A. Insight and compliance. In: Blackwell B, editors. Treatment compliance and the therapeutic alliance. Newark, NJ: Harwood Academic Publishers; 1997. p. 61–84.
4. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull* 1997;**23**:637–51.
5. Simpson GM. A brief history of depot neuroleptics. *J Clin Psychiatry* 1984;**45**(5):3–4.
6. Davis J, Metalon L, Watanabe M, Blake L. Depot antipsychotic drugs: place in therapy. *Drugs* 1994;**47**: 741–73.
7. Barnes TRE, Curson DA. Long term depot antipsychotics. A risk–benefit assessment. *Drug Saf* 1994;**10**:464–79.
8. Johnson DAW. Observations on the use of long-acting depot neuroleptic injections in the maintenance therapy of schizophrenia. *J Clin Psychiatry* 1984;**45**(5):13–21.
9. Glazer WM, Kane JM. Depot neuroleptics therapy: an underutilized treatment option. *J Clin Psychiatry* 1992;**53**:426–33.
10. Gerlach J. Depot neuroleptics in relapse prevention: advantages and disadvantages. *Int Clin Psychopharmacol* 1995;**9** Suppl 5:17–20.
11. Kane JM, Aguglia E, Altamura AC, Gutierrez JLA, Brunello N, Fleischhaker WW, *et al.* Guidelines for depot antipsychotic treatment in schizophrenia. *Eur Neuropsychopharmacol* 1998;**8**:55–66.
12. Curson DA, Barnes TRE, Bamber RW, Platt SD, Hirsch SR, Dutty JC, *et al.* Long-term depot maintenance of chronic schizophrenic outpatients: the seven-year follow-up of the MRC fluphenazine/placebo trial. *Br J Psychiatry* 1985;**146**:464–80.
13. Quraishi S, David A, Adams CE. Depot bromperidol decanoate for schizophrenia (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000.
14. Quraishi S, David A. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000.
15. Adams CE, Eisenbruch M. Depot fluphenazine for schizophrenia (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000. [Includes decanoate and enanthate – this has been counted as two reviews.]
16. Quraishi S, David A. Depot fluspirilene for schizophrenia (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000.
17. Quraishi S, David A. Depot haloperidol decanoate for schizophrenia (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000.
18. Quraishi S, David A. Depot perphenazine decanoate and enanthate for schizophrenia (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000.
19. Quraishi S, David A. Depot pipothiazine palmitate and undecylenate for schizophrenia (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000.
20. Coutinho E, Fenton M, Quraishi S. Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses (Cochrane Review). In: The Cochrane Library. Issue 2. Oxford: Update Software; 2000.
21. Mulrow CD, Oxman AD, editors. Cochrane Collaboration handbook. In: The Cochrane Library [database on disk and CD-ROM]. Oxford: Update Software; updated September 2000 [updated quarterly].
22. Anderson D, Leadbetter A, Williams B. In defence of the depot clinic. The consumers' opinion. *Psychiatr Bull* 1989;**13**:177–9.
23. 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.
24. Jadad AR, Cook DJ, Jones A, Klassen TP, Tugwell P, Moher M, *et al.* Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. *JAMA* 1998;**280**:278–80.

25. Greenhalgh T. How to read a paper. The basics of evidence based medicine. London: BMJ Publishing Group; 1997.

26. University of York NHS Centre for Reviews and Dissemination. Undertaking systemic reviews of research on effectiveness. York: The University of York; 1996. CRD Report 4.

27. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Revised third edition. Washington, DC: American Psychiatric Association; 1987.

28. Wing JK, Cooper JE, Sartorius N. Measurement and classification of psychiatric symptoms. Cambridge: Cambridge University Press; 1974.

29. Krawiecka M, Goldberg D, Vaughan M. A standardised psychiatric assessment scale for rating psychotic patients. *Acta Psychiatrica Scand* 1977;**55**:299–308.

30. Asberg M, Montgomery SA, Perris C, Schalling D, Sedvall GA. A comprehensive psychopathological rating scale. *Acta Psychiatr Scand Suppl* 1978;**271**:5–27.

31. Honigfeld G, Gillis RD, Klett CJ. NOSIE-30: a treatment sensitive ward behavior scale. *Psychol Rep* 1962;**10**:799–812.

32. Guy W, editor. ECDEU assessment manual for psychopharmacology. Revised edition. Rockville, MD: National Institute of Mental Health; 1976.

33. Chouinard G, Ross-Chouinard A, Annable L. Extrapyramidal symptom rating scale. *Can J Neurol Sci* 1980;**7**:233.

34. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987;**334**:1–100.

35. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970;**212**:11–19.

36. Pan PC, Tantum D. Clinical characteristics, health beliefs and compliance with maintenance treatment: a comparison between regular and irregular attenders at a depot clinic. *Acta Psychiat Scand* 1989;**79**:564–70.

37. Larsen EB, Gerlach J. Subjective experience of treatment, side-effects, mental state and quality of life in chronic schizophrenic out-patients treated with depot neuroleptics. *Acta Psychiatr Scand* 1996;**93**:381–8.

38. Desai N. Switching from depot antipsychotics to risperidone: results of a study of chronic schizophrenia. *Adv Ther* 1999;**16**(2):78–88.

39. Hoencamp E, Knegtering H, Kooy JJS, van der Molen AGM. Patient requests and attitude towards neuroleptics. *Nord J Psychiatry* 1995;**49** Suppl 35:47–55.

40. Wistedt B. How does the psychiatric patient feel about depot treatment, compulsion or help? *Nord J Psychiatry* 1995;**49** Suppl 35:41–6.

41. Singh V, Hughes G, Goh E. Depot clinic: consumers' viewpoint. *Psychiatr Bull* 1995;**19**:728–30.

42. Goldbeck R, Tomlinson S, Bouch J. Patients' knowledge and views of their depot neuroleptic medication. *Psychiatr Bull* 1999;**23**:467–70.

43. Warren B. Developing practice through clinical audit. *J Clin Effectiveness* 1998;**3**(4):151–4.

44. Eastwood N, Pugh R. Long-term in depot clinics and patients' rights: an issue for assertive outreach. *Psychiatr Bull* 1997;**21**:273–5.

45. Jacobsson L, Odling H. Psykologiska aspekter på depåbehandling vid schizofrena syndrom. *Lakartidningen* 1980;**77**:3522–6.

46. Poole I, Grimes P. Depot injections at home or clinic? Letting clients choose. *Community Nurse* 1998;**4**(1):15–16.

47. Brooker C, Faugier J, Gray C. An audit of depot clinics in the North West catchment area. University of Sheffield/NHS Executive North West Regional Office; 1996.

48. Sandford T. Involving users in developing phenothiazine services. In: Sandford T, Gournay K, editors. Perspectives in mental health nursing. London: Balliere Tindall; 1996.

49. Buis W. Patients' opinions concerning side effects of depots neuroleptics. *Am J Psychiatry* 1992;**149**:844–5.

50. Bennett J, Done J, Hunt B. Assessing the side-effects of antipsychotic drugs: a survey of CPN practice. *J Psychiatr Ment Health Nurs* 1995;**2**:177–82.

51. Burns T, Millar E, Garland C, Kendrick T, Brock C, Ross F. Randomized controlled trial of teaching practice nurses to carry out structured assessments of patients receiving depot antipsychotic injections. *Br J Gen Pract* 1998;**48**:1845–8.

52. Kendrick T, Millar E, Burns T, Ross F. Practice nurse involvement in giving depot neuroleptic injections: development of a patient assessment and monitoring checklist. *Primary Care Psychiatry* 1998;**4**:149–54.

53. Cantle F. Management of depot neuroleptics. *Practice Nursing* 1997;**8**:14–17.

54. Thornley B, Adams CE. Content and quality of 2000 controlled trials in schizophrenia over 50 years. *BMJ* 1998;**317**:1181–4.

55. Owens D. The use of fluphenazines in a continuing-care programe. *Hosp Community Psychiatry* 1978;**29**: 115–18.

56. Glazer W. Depot neuroleptics: cost-effective and underutilised. *JAMA* 1994;**272**:1722.

57. Osterheider M, Franken-Hiep K, Horn R. Gesamtkrankenkosten der Schizophrenie und monetare Bewertung einer Rezidivprophylaxe am Beispiel eines Standard-Depot-Neuroleptikums (Flupentixoldecanoat). [Total costs involved in the treatment of schizophrenia and cost evaluation of prophylactic treatment with the depot neuroleptic drug flupentixoldecanoate.] *Psychiatr Prax* 1998;**25**:38–43.

58. Drummond MR, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford Medical Publications; 1997.

59. Marriott P, Hiep A. A mirror image outpatient study at a depot phenothiazine clinic. *Aust N Z J Psychiatry* 1976;**10**:163–7.

60. Marriott PF, Grigor JM, Hiep A. Reducing hospital readmission rates among schizophrenics. *Med J Aust* 1976;**2**:897–8.

61. Larach V, Erazo R, Bustos M, Osorio R, Corrales G, Pizarro F, *et al.* Cost–benefit of a depot neuroleptic clinic: 10 years' follow-up of functioning of a clinical–administrative model. *Nord J Psychiatry* 1995;**49** Suppl 35:57–62.

62. Lindholm H, Ljungberg L. Comparison of conventional neuroleptic therapy with depot neuroleptics. An attempt at economic evaluation. *Acta Psychiatr Scand Suppl* 1973;**246**:52–6.

63. Moore DB, Kelly DL, Herr JD, Love RC, Conley RR. Rehospitalisation rates for depot antipsychotics and pharmacoeconomic implications: comparison with risperidone. *Am J Health Sys Pharm* 1998; **55** Suppl 4:S17–19.

64. Glazer WM, Ereshefsky L. A pharmacoeconomic model of outpatient antipsychotic therapy in 'revolving door' schizophrenic patients. *J Clin Psychiatry* 1996;**57**(8):337–45.

65. Hale AS, Wood C. Comparison of direct treatment costs for schizophrenia using oral or depot neuroleptics: a pharmacoeconomic analysis. *Br J Med Econ* 1996;**10**:37–45.

66. Marder SR, van Putten T, Mintz J, McKenzie J, Lebell M, Faltico G, *et al.* Costs and benefits of two doses of fluphenazine. *Arch Gen Psychiatry* 1984;**41**:1025–9.

67. Knapp MRJ. Costs of schizophrenia. *Br J Psychiatry* 1997;**171**:509–15.

68. Magliano L, Fadden G, Madianos M, Calda de Almeida JM, Held T, Guarneri M, *et al.* Burden on the families of patients with schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 1998;**33**:405–12.

69. Taylor P, Gunn J. Homicides by people with mental illness: myth and reality. *Br J Psychiatry* 1999;**174**:9–14.

70. Davies LM, Drummond MF. Economics and schizophrenia: the real cost. *Br J Psychiatry*; **165** Suppl 25:18–21.

71. Harris EC, Barraclough B. Excess mortality of mental disorder. *Br J Psychiatry* 1998;**173**:11–53.

72. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, *et al.* Improving the quality of randomized controlled trials. The CONSORT statement. *JAMA* 1996;**276**:637–9.

73. Garavan J, Browne S, Gervin M. Compliance with neuroleptic medication in outpatients with schizophrenia; relationship to subjective response to neuroleptics: attitudes to medication and insight. *Compr Psychiatry* 1998;**39**:215–19.

74. Smith JA, Hughes I. Non-compliance with anti-psychotic depot medication: users' views on advantages and disadvantages. *J Mental Health* 1999;**8**(3):287–96.

Appendix 1

Search strategies for meta-review of depot antipsychotics

Bromperidol

Biological Abstracts (January 1982 to May 1999)
Searched using the Cochrane schizophrenia group's (CSG's) phrase for both RCTs and schizophrenia combined with the phrase:

and [(BROMPERIDOL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (BROMPERIDOL* or (IMPROMEN* near1 DECAN*) or BROMIDOL*))].

Cochrane Library (Issue 2, 1999)
Searched using the CSG's phrase for schizophrenia combined with the phrase:

and [(BROMPERIDOL* next DECANOATE) or ((DEPOT* or (LONG next ACTING) or (DELAY* next ACTION)) next (BROMPERIDOL* or (IMPROMEN* next DECAN*) or BROMIDOL*)) or (BROMPERIDOL* ME and DELAYED-ACTION-PREPARATIONS* ME))].

CSG's Register (May 1999)
Searched using the phrase:

(BROMPERIDOL* and DECANOATE) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (BROMPERIDOL* or IMPROMEN* DECAN* or BROMIDOL*)) or (#44 = 139).

#44 is the field in which intervention codes are stored; 139 is the code for bromperidol.

EMBASE (January 1980 to May 1999)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(BROMPERIDOL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (BROMPERIDOL* or (IMPROMEN* near1 DECAN*) or BROMIDOL*)) or "BROMPERIDOL-DECANOATE"/all subheadings].

MEDLINE (January 1966 to May 1999)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(BROMPERIDOL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (BROMPERIDOL* or (IMPROMEN* near1 DECAN*) or BROMIDOL*)) or ("BROMPERIDOL-DECANOATE"/all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/all subheadings)].

PsycLIT (January 1974 to May 1999)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(BROMPERIDOL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (BROMPERIDOL* or (IMPROMEN* near1 DECAN*) or BROMIDOL*))].

Flupenthixol

Biological Abstracts (January 1982 to June 1998)
Searched using the CSG's terms for both RCTs and schizophrenia combined with the phrase:

and [(FLUPENT* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (FLUPENT* or FLUANXOL* or DEPIXOL* or LU 7105* or LU 5-110))].

Cochrane Library (Issue 2, 1998)
Searched using the CSG's terms for schizophrenia combined with the phrase:

and [(FLUPENTHIXOL* and DECANOATE) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (FLUPENT* or FLUANXOL* or DEPIXO* or LU 7105* or LU -5-110 or (CLOPENTHIXOL* ME) and DELAYED-ACTION-PREPARATIONS* ME))].

CSG's Register (December 1998)
Searched using the phrase:

(FLUPENTHIXOL* and DECANOATE) or ((DEPOT* or (LONG and ACTING) or (DELAY*

and ACTION)) and (FLUPENT* or FLUANXOL* or DEPIXOL* or LU 7105 or LU 5-110*)).

EMBASE (January 1980 to June 1998)
Searched using the CSG's terms for both RCTs and schizophrenia combined with the phrase:

and [(FLUPENT* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (FLUPENT* or FLUANXOL* or DEPIXOL* or LU 7105* or LU 5-110)) or "FLUPENTHIXOL-DECANOATE"/ all subheadings].

MEDLINE (January 1966 to June 1998)
Searched using the CSG's terms for both RCTs and schizophrenia combined with the phrase:

and [(FLUPENT* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (FLUPENT* or FLUANXOL* or DEPIXOL* or LU 7105* or LU 5-110)] or ("FLUPENTHIXOL"/all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/all subheadings))].

PsycLIT (January 1974 to June 1998)
Searched using the CSG's terms for both RCTs and schizophrenia combined with the phrase:

and [(FLUPENT* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (FLUPENT* or FLUANXOL* or DEPIXOL* or LU 7105* or LU 5-110))].

Fluphenazine

Electronic searching

Relevant studies were identified by searching several electronic databases (Biological Abstracts, the Cochrane Library, the CSG's Register of trials, EMBASE, MEDLINE and PsycLIT).

Biological Abstracts (January 1982 to May 1995)
Searched using the CSG's phrase for RCTs combined with the phrase:

and [(fluphenazine or modec* or moditen*)].

Cochrane Library (May 1995)
Searched using the phrase:

[fluphen* or modec* or moditen*].

CSG's Register (May 1995)
Searched using the phrase:

[fluphen* or modec* or moditen*].

EMBASE (January 1980 to May 1995)
Searched using the CSG's phrase for RCTs combined with the phrase:

and [(fluphenazine or fluphenazine/explode all subheadings or modec* or moditen*)].

MEDLINE (January 1966 to May 1995)
Searched using the CSG's phrase for RCTs combined with the phrase:

and [(fluphenazine or explode fluphenazine/all subheadings or modec* or moditen*)].

PsycLIT (January 1974 to May 1995)
Searched using the CSG's phrase for RCTs combined with the phrase:

and [(fluphenazine or explode fluphenazine or modec* or moditen*)].

SCISEARCH – Science Citation Index
Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that had cited these studies were inspected in order to identify further trials.

Fluspirilene

Biological Abstracts (January 1982 to June 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(FLUSPIR* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (FLUSPIR* or IMAP* or REDEPTIN*))].

Cochrane Library (Issue 2, 1998)
Searched using the CSG's phrase for schizophrenia combined with the phrase:

and [(FLUSPIR* next DECANOATE) or ((DEPOT* or (LONG next ACTING) or (DELAY* next ACTION)) next (FLUSPIR* or IMAP* or REDEPTIN*)) or (FLUSPIRILENE* ME and DELAYED-ACTION-PREPARATIONS* ME)].

CSG's Register (June 1998)
Searched using the phrase:

(FLUSPIR* and DECANOATE) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (FLUSPIR* or IMAP* or REDEPTIN*)) or (#44 = 58 and #44 = 544).

#44 is the field in the register that contains intervention codes; 58 and 544 are codes for fluspirilene.

EMBASE (January 1980 to June 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(FLUSPIR* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (FLUSPIR* or IMAP* or REDEPTIN*)) or "FLUSPIRILENE-DECANOATE"/all subheadings].

MEDLINE (January 1966 to June 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(FLUSPIR* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (FLUSPIR* or IMAP* or REDEPTIN*)) or ("FLUSPIRILENE-DECANOATE"/all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/all subheadings)].

PsycLIT (January 1974 to June 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(FLUSPIR* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (FLUSPIR* or IMAP* or REDEPTIN*))].

Haloperidol

Biological Abstracts (January 1982 to June 1998 – current disc issue)
Searched using the CSG's phrase for RCTs and schizophrenia combined with the phrase:

and [(HAL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES))].

Cochrane Library (Issue 2, 1998)
Searched using the CSG's phrase for schizophrenia combined with the phrase:

and [(HAL* and DECANOATE) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES)) or (HALOPERIDOL* ME and DELAYED-ACTION-PREPARATIONS* ME)].

CSG's Register (June 1998)
Searched using the phrase:

and [(HAL* and DECANOATE) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES)].

EMBASE (January 1980 to June 1998 – current disc issue)
Searched using the CSG's phrase for RCTs and schizophrenia combined with the phrase:

and [(HAL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES)) or "HALOPERIDOL-DECANOATE"/all subheadings].

MEDLINE (January 1966 to June 1998 – current disc issue)
Searched using the CSG's phrase for RCTs and schizophrenia combined with the phrase:

and [(HAL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES)) or ("HALOPERIDOL"/all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/all subheadings)].

PsycLIT (January 1974 to June 1998 – current disc issue)
Searched using the CSG's phrase for RCTs and schizophrenia combined with the phrase:

and [(HAL* near1 DECANOATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (HALO* or HALDOL or SEREN* or SIGAPERIDOL or BROTOPON or EINALON or LINTON or PELUCES))].

Perphenazine

Biological Abstracts (January 1982 to June 1998)
Searched using the CSG's phrase for RCTs and schizophrenia combined with the phrase:

and [(PERPHEN* near1 DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PERPHEN* or TRILAFON* ENANT* or DEKAN* OR DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*))].

Cochrane Library (Issue 2, 1998)
Searched using the CSG's phrase for schizophrenia combined with the phrase:

and [(PERPHEN* next DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG next ACTING) or (DELAY* next ACTION)) next (PERPHEN* or TRILAFON* ENANT* or DEKAN* or DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*)) or (PERPHENAZINE-DECANOATE* ME and DELAYED-ACTION-PREPARATIONS* ME)].

CSG's Register (June 1998)
Searched using the phrase:

(PERPHEN* and DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (PERPHEN* or TRILAFON* ENANT* or DEKAN* OR DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*)).

EMBASE (January 1980 to June 1998)
Searched using the CSG's phrase for RCTs and schizophrenia combined with the phrase:

and [(PERPHEN* near1 DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PERPHEN* or TRILAFON* ENANT* or DEKAN* or DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*)) or "PERPHENAZINE-DECANOATE"/all subheadings or "PERPHENAZINE-ENANTHATE"/all subheadings].

MEDLINE (January 1966 to June 1998)
Searched using the CSG's phrase for RCTs and schizophrenia combined with the phrase:

and [(PERPHEN* near1 DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PERPHEN* or TRILAFON* ENANT* or DEKAN* or DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*) or ("PERPHENAZINE-DECANOATE"/all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/all subheadings)) or ("PERPHENAZINE-ENANTHATE"/all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/all subheadings)].

PsycLIT (January 1974 to June 1998)
Searched using the CSG's phrase for RCTs and schizophrenia combined with the phrase:

and [(PERPHEN* near1 DECANOATE) or (PERPHEN* ENANTHATE*) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PERPHEN* or TRILAFON* ENANT* or DEKAN* or DEKAN* or RETARD* or DECENTAN* ENANT* or PERATSIN* ENANT* or DECAN*))].

Pipothiazine

Biological Abstracts (January 1982 to June 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(PIPOTHIA* near1 PALMITATE) or (PIPOTHIA* near1 UNDECYLENATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PIPOTHIA* or PIPORTIL* DECANOATE* or PIPORTYL* PALMITATE* or LONSEREN*))].

Cochrane Library (Issue 2, 1998)
Searched using the CSG's phrase for schizophrenia combined with the phrase:

and [(PIPOTHIA* next PALMITATE) or (PIPOTHIA* next UNDECYLENATE) or ((DEPOT* or (LONG next ACTING) or (DELAY* next ACTION)) next (PIPOTHIA* or PIPORTIL* DECANOATE* or PIPORTYL* PALMITATE* or LONSEREN*)) or (PIPOTHIAZINE* ME and DELAYED-ACTION-PREPARATIONS* ME)].

CSG's Register (June 1998)
Searched using the phrase:

(PIPOTHIA* and PALMITATE) or (PIPOTHIA* and UNDECYLENATE) or ((DEPOT* or (LONG and ACTING) or (DELAY* and ACTION)) and (PIPOTHIA* or PIPORTIL* DECANOATE* or PIPORTYL* PALMITATE* or LONSEREN*)).

EMBASE (January 1980 to June 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(PIPOTHIA* near1 PALMITATE) or (PIPOTHIA* near1 UNDECYLENATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PIPOTHIA* or PIPORTIL* DECANOATE* or PIPORTYL* PALMITATE* or LONSEREN*)) or "PIPOTHIAZINE PALMITATE"/all subheadings or "PIPOTHIAZINE UNDECYLENATE"/all subheadings].

MEDLINE (January 1966 to June 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(PIPOTHIA* near1 PALMITATE) or (PIPOTHIA* near1 UNDECYLENATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PIPOTHIA* or PIPORTIL* DECANOATE* or PIPORTYL* PALMITATE* or LONSEREN*) or ("PIPOTHIAZINE PALMITATE"/all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/all subheadings)) or ("PIPOTHIAZINE UNDECYLENATE"/all subheadings and explode "DELAYED-ACTION-PREPARATIONS"/all subheadings)].

PsycLIT (January 1974 to June 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

and [(PIPOTHIA* near1 PALMITATE) or (PIPOTHIA* near1 UNDECYLENATE) or ((DEPOT* or (LONG near4 ACTING) or (DELAY* near2 ACTION)) near (PIPOTHIA* or PIPORTIL* DECANOATE* or PIPORTYL* PALMITATE* or LONSEREN*))].

Zuclopenthixol

Biological Abstracts/RRM (January 1982 to April 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

[and zuclopenthixol or ciatyl or cisordinol* or clopenthixol or clopixol* or sordinol].

CINAHL (January 1982 to April 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

[and zuclopenthixol or ciatyl or cisordinol* or clopenthixol or clopixol* or sordinol].

Cochrane Library (Issue 2, 1998)
Searched using the phrase:

[zuclopenthix* or ciatyl or cisordinol* or clopenthix* or clopixol* or sordinol].

CSG's Register (April 1998)
Searched using the phrase:

[zuclopenthix* or (cis and ?-clopenthixol) or 0-108 or cisordinol* or clopenthix* or clopixol*].

EMBASE (January 1980 to May 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

[and zuclopenthixol or zuclopenthixol/explode all subheadings or ciatyl or cisordinol* or clopenthixol or clopixol* or sordinol].

MEDLINE (January 1966 to May 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

[and zuclopenthixol or explode clopenthixol (MeSH)/all subheadings or ciatyl or cisordinol* or clopixol* or sordinol].

PsycLIT (January 1974 to May 1998)
Searched using the CSG's phrase for both RCTs and schizophrenia combined with the phrase:

[and zuclopenthixol or explode zuclopenthixol or ciatyl or cisordinol* or clopixol* or clopenthixol or sordinol].

Appendix 2

Methodological quality checklist for studies looking at patient/nurse attitudes to depot antipsychotic medication

	Criteria
1	Detailed description of *a priori* aims or hypotheses which are clear, unambiguous and explicit
2	Definition and size of the population under investigation
3	Statistical justification of sample size
4	Justification that the sample is representative of the population under investigation
5	Description of criteria for inclusion/exclusion in the sample
6	Description of participant demographic details (e.g. age, gender, ethnicity, DSM/ICD diagnosis)
7	Researcher independent from participant's standard treatment or occupation/role
8	Justification (e.g. validity and reliability data) of questionnaires and other outcome measures used
9	Statement that the original questionnaire is available upon request
10	Response or drop-out rate specified
11	Discussion of the response or drop-out rate
12	Discussion of the generalisability of the results to the population under investigation
13	Declaration of interests (e.g. sources of funding)

Appendix 3

Table of included studies (meta-review of depot antipsychotics)

Review	Methods	Participants	Interventions	Outcomes
Bromperidol decanoate	*Allocation*: all 4 studies randomised *Blinding*: double, no further details *Duration*: 6 months to 1 year	*Diagnosis*: schizophrenia *N* = 4, *n* =117 *Age*: range 20–65 years *Sex*: > 55 M; > 42 F *Setting*: community and inpatients	1. Bromperidol decanoate: dose range 50–242 mg/month; *n* = 58 2. Fluphenazine decanoate: 16.7–300 mg/month; *n* = 39 3. Haloperidol decanoate: mean dose 119 mg/month; *n* = 10 4. Placebo: *n* = 10	• Global effect (CGI) • Leaving the study early • Mental state (use of additional medication) • Side-effects (DOTES, SAFTEE)
Flupenthixol decanoate	*Allocation*: all 15 studies randomised *Blinding*: double, no further details *Duration*: 8 weeks to 2 years Informed consent from participants in 5 studies	*Diagnosis*: schizophrenia *Duration of illness*: 1–29 years *N* = 15, *n* = 615 *Age*: range 17–70 years *Sex*: > 373 M; > 193 F; unknown: 1 trial *Setting*: community and inpatient	1. Flupenthixol decanoate: dose range 9 mg/2–3 weeks; 300 mg/2–3 weeks; *n* = 359 2. Clopenthixol decanoate: dose range 50–600 mg/2 weeks to 1 month; *n* = 48 3. Fluphenazine decanoate: mean dose 25 mg/3-weekly; range 10–50 mg; *n* = 139 4. Haloperidol decanoate: mean dose 151 mg/injection; *n* = 16 5. Penfluridol: mean dose 20 mg/weekly; *n* = 30 6. Pipothiazine: 100 mg/monthly; *n* = 23	• Death • Leaving the study early • Relapse • Use of additional medication • Mental state (BPRS, CPRS, Hamilton depression scale) • Side-effects (Simpson–Angus rating scale)

continued

Review	Methods	Participants	Interventions	Outcomes
Fluphenazine decanoate	*Allocation*: all 48 studies randomised *Blinding*: varying degrees of double blinding *Duration*: 2 weeks to 2 years 2 studies used a crossover method	*Diagnosis*: schizophrenia and schizoaffective *Duration of illness*: range < 2–39 years *N* = 48, *n* = 3348 *Age*: range 24–70 years *Sex*: > 1318 M; > 1054 F *Setting*: community and inpatient	1. Fluphenazine decanoate: mean dose 51.73 mg; range (low 1.25–6.25 mg); standard–high dose 25–1100 mg/2-weekly to monthly; *n* = 1963 2. Bromperidol decanoate: mean dose 242 mg/monthly; range 64–400 mg; *n* = 23 3. Chlorpromazine: dose range 50–100 mg/day; *n* = 36 4. Clopenthixol decanoate: mean dose 220 mg/3–4-weekly; range 200 mg/4 weeks to 600 mg/2 weeks; *n* = 19 5. Flupenthixol: dose range 30–40 mg/ bi-weekly to monthly; *n* = 48 6. Fluphenazine hydrochloride (oral): mean dose 18.9 mg; dose range 2.5–60 mg/day; *n* = 396 7. Fluphenazine enanthate: dose range 2.5–387.5 mg/2–4 weeks; *n* = 96 8. Fluspirilene decanoate: 3–20 mg/weekly; *n* = 93 9. Haloperidol decanoate: mean dose 109.4 mg; range 15–900 mg/2–4-weekly; *n* = 142 10. Penfluridol: dose range 20–160 mg; *n* = 27 11. Pimozide: dose 8 mg/daily to weekly; range 10–60 mg; *n* = 70 12. Pipothiazine palmitate: mean dose 88.3 mg; dose range 6.25–400 mg/2-weekly to 5 weeks; *n* = 184 13. Placebo: *n* = 75 14. Trifluperazine: dose 10 mg/day; *n* = 17	• Global improvement (CGI) • Mental state (BPRS, CPRS) • Behaviour (NOSIE) • Leaving the study early • Use of additional medication • Side-effects (DOTES)

continued

Review	Methods	Participants	Interventions	Outcomes
Fluphenazine enanthate	*Allocation*: all 14 studies randomised *Blinding*: double, no further details *Duration*: 2 weeks to 1 year 1 study used a crossover study	*Diagnosis*: schizophrenia *Duration of illness*: acute to hospitalised > 2 years *N* = 14, *n* = 451 *Age*: range 17–65 years *Setting*: community and inpatient	1. Fluphenazine enanthate: dose range 3.5–387.5 mg/2–4 weeks; *n* = 279 2. Chlorpromazine: mean dose 388 mg/day; *n* = 15 3. Fluphenazine decanoate: dose range 2.5–500 mg/2–4 weeks; *n* = 84 4. Fluspirilene decanoate: dose range 1–14 mg/weekly; *n* = 31 5. Pipothiazine palmitate: range 25–250 mg/2–4 weeks; *n* = 42	• Global effect (CGI) • Mental state (BPRS) • Leaving the study early • Use of additional medication • Side-effects (Bordeleau scale, Hamilton depression scale)
Fluspirilene	*Allocation*: all 7 studies randomised *Blinding*: double, no further details *Duration*: 4 weeks to 6 months	*Diagnosis*: schizophrenia *Duration of illness*: 2–39 years *N* = 7, *n* = 290 *Age*: range 16–80 years *Sex*: > 98 M; > 137 F *Setting*: inpatient and community	1. Fluspirilene decanoate: range 1–23 mg/1–2 weeks; *n* = 160 2. Chlorpromazine: dose range 370–720 mg/day; *n* = 20 3. Fluphenazine decanoate: dose range 25–150 mg/2–3 weeks; *n* = 71 4. Fluphenazine enanthate: dose range 7.550 mg; *n* = 26 5. Pipothiazine undecylenate: mean dose 103.8 mg/bi-weekly; *n* = 13	• Global effect (CGI) • Leaving the study early • Side-effects (rating scale)
Haloperidol decanoate	*Allocation*: all 11 studies randomised *Blinding*: double, no further details *Duration*: 16–60 weeks	*Diagnosis*: schizophrenia or schizoaffective disorder *Duration of illness*: 0–38 years *N* = 11, *n* = 456 *Age*: 18–66 years *Sex*: > 264 M; > 175 F *Setting*: community and inpatient	1. Haloperidol decanoate: dose range 15–900 mg/2–4 weeks; *n* = 238 2. Fluphenazine decanoate: dose range 2.5–300 mg/2–4 weeks; *n* = 125 3. Haloperidol (oral): dose not specified; *n* = 11 4. Pipothiazine palmitate: dose range 50–125 mg/monthly; *n* = 20 5. Placebo: *n* = 39 6. Zuclopenthixol decanoate: mean dose 284 mg/monthly; *n* = 23	• Death • Global impression (CGI) • Mental state (BPRS, CPRS, Hamilton depression scale, Krawiecka scale, MADRS) • Behaviour (Wing Ward scale) • Leaving the study early • Use of additional medication • Side-effects (AIMS, Bordeleau scale, Simpson–Angus rating scale, UKU SERS)
Perphenazine decanoate	*Allocation*: both studies randomised *Blinding*: double, no further details *Duration*: range 6 weeks to 6 months	*Diagnosis*: schizophrenia or acute psychosis *Duration of illness*: < 2–5 years *N* = 2, *n* = 236 *Age*: range 18 to > 60 years *Sex*: > 135 M; > 87 F *Setting*: community and inpatient	1. Perphenazine decanoate: dose range 20–600 mg/bi-weekly; *n* = 111 2. Clopenthixol decanoate: dose range 50–800 mg/2 weeks; *n* = 87 3. Perphenazine enanthate: mean dose 108.5 mg/bi-weekly; *n* = 24	• Death • Global impression (CGI) • Leaving the study early • Use of additional medication • Side-effects

continued

Review	Methods	Participants	Interventions	Outcomes
Pipothiazine palmitate/ undecylenate	*Allocation*: all 14 studies randomised *Blinding*: varying degrees of double blinding *Duration*: range 11 weeks to 3 years Informed consent given in 2 studies	*Diagnosis*: schizophrenia *Duration of illness*: range < 3–34 years *N* = 14, *n* = 771 *Age*: range 18–69 years *Sex*: > 380 M; > 205 F *Setting*: community and inpatient	1. Pipothiazine palmitate and undecylenate: *n* = 365 2. Fluphenazine decanoate: *n* = 198 3. Fluphenazine enanthate: *n* = 87 4. Fluspirilene: *n* = 13 5. Haloperidol decanoate: *n* = 21 6. Oral antipsychotics (various): *n* = 87	• Global impression (CGI) • Mental state (BPRS, Hamilton depression scale) • Leaving the study early • Use of additional medication • Side-effects (AIMS, Bordeleau scale, DOTES)
Zuclopenthixol depot	*Allocation*: all 4 studies randomised *Blinding*: varying degrees of double blinding *Duration*: 12 weeks to 1 year	*Diagnosis*: schizophrenia *Duration of illness*: > 2 years *N* = 4, *n* = 332 *Age*: range 20–65 years *Sex*: > 197 M; > 71 F *Setting*: community and inpatient	1. Zuclopenthixol decanoate: dose range 100–600 mg/2–4 weeks; *n* = 171 2. Flupenthixol palmitate: dose range 25–300 mg/4 weeks; *n* = 48 3. Haloperidol decanoate: dose range 39–200 mg/4 weeks; *n* = 28 4. Perphenazine enanthate: dose range 20–600 mg/2-weekly; *n* = 85	• Death • Global impression (CGI) • Relapse • Leaving the study early • Use of additional medication • Side-effects (UKU SERS) • Discharge

N, *number of trials*; n, *number of participants*; *M, males*; *F, females*

AIMS, abnormal involuntary movement scale (Guy, 1976)[32]*; BPRS (Overall and Gorham, 1962*[*]*); Bordeleau scale (Bordeleau* et al.*, 1967*[†]*); CGI (Guy, 1976)*[32]*; CPRS (Asberg* et al.*, 1978)*[30]*; DOTES, dosage record and treatment emergent symptom scale (Guy, 1976)*[32]*; Hamilton depression scale (Hamilton, 1960*[‡]*); Krawiecka scale (Manchester scale) (Krawiecka, 1977)*[29]*; MADRS, Montgomery–Asberg depression rating scale (Asberg* et al.*, 1978)*[30]*; NOSIE (Honigfeld* et al.*, 1962)*[31]*; Simpson–Angus rating scale (Simpson and Angus, 1970)*[35]*; UKU SERS (Lingjaerde* et al.*, 1987)*[34]*; Wing Ward scale (Wing, 1961*[§]*)*

[*] Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962;**10**:799–812.

[†] Bordeleau JM, Albert JM, Killer J. Médication antiparkinsonienne et bilan extrapyramidal. *Can Psychiatr Assoc J* 1967;**12**:585–95.

[‡] Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;**23**:56–62.

[§] Wing JK. A simple and reliable subclassification of chronic schizophrenia. *J Mental Sci* 1961;**107**:862–76.

Appendix 4

Summary plots of depot comparisons

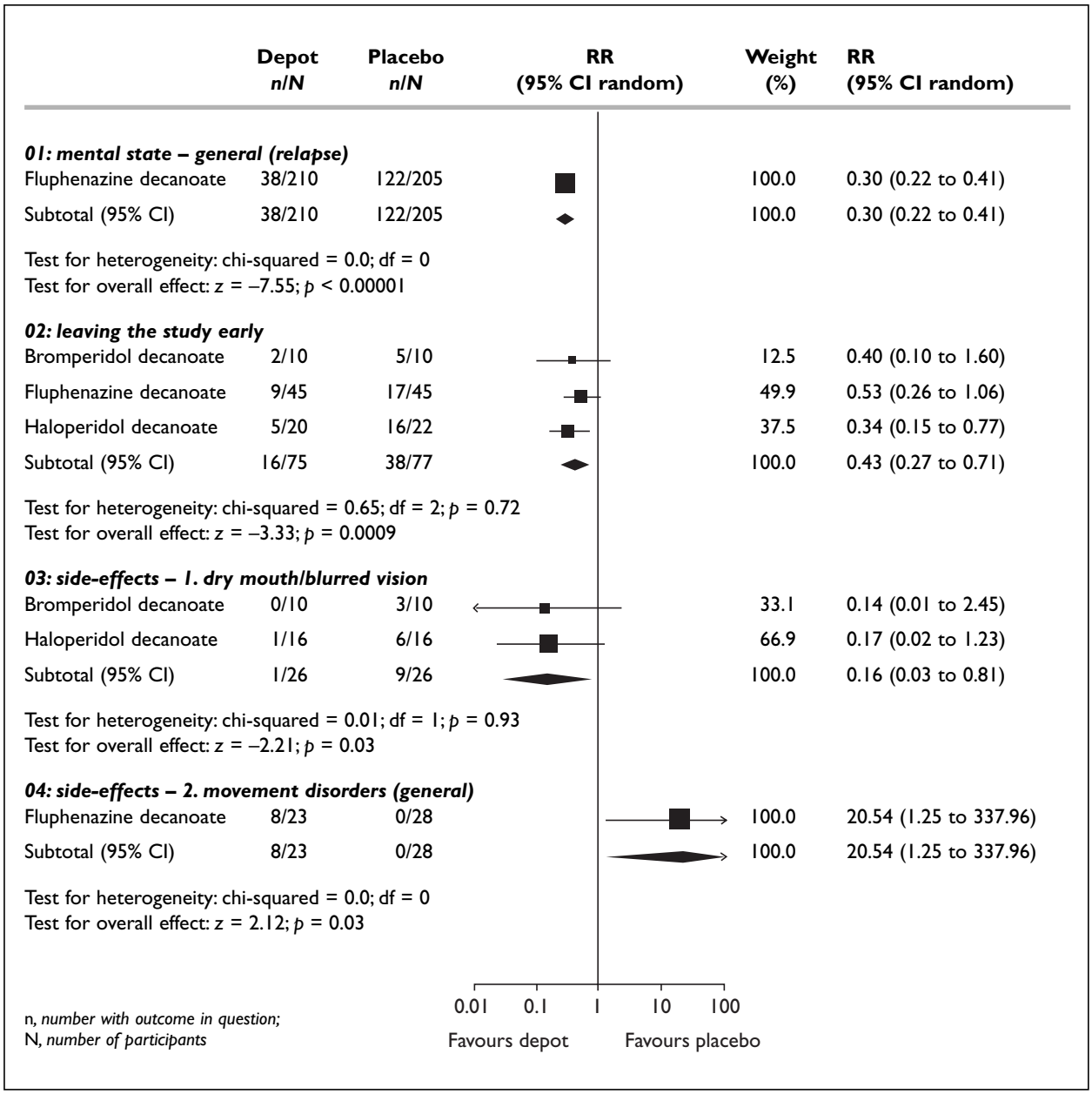


FIGURE 18 *Depot antipsychotic versus placebo depot: all outcomes*

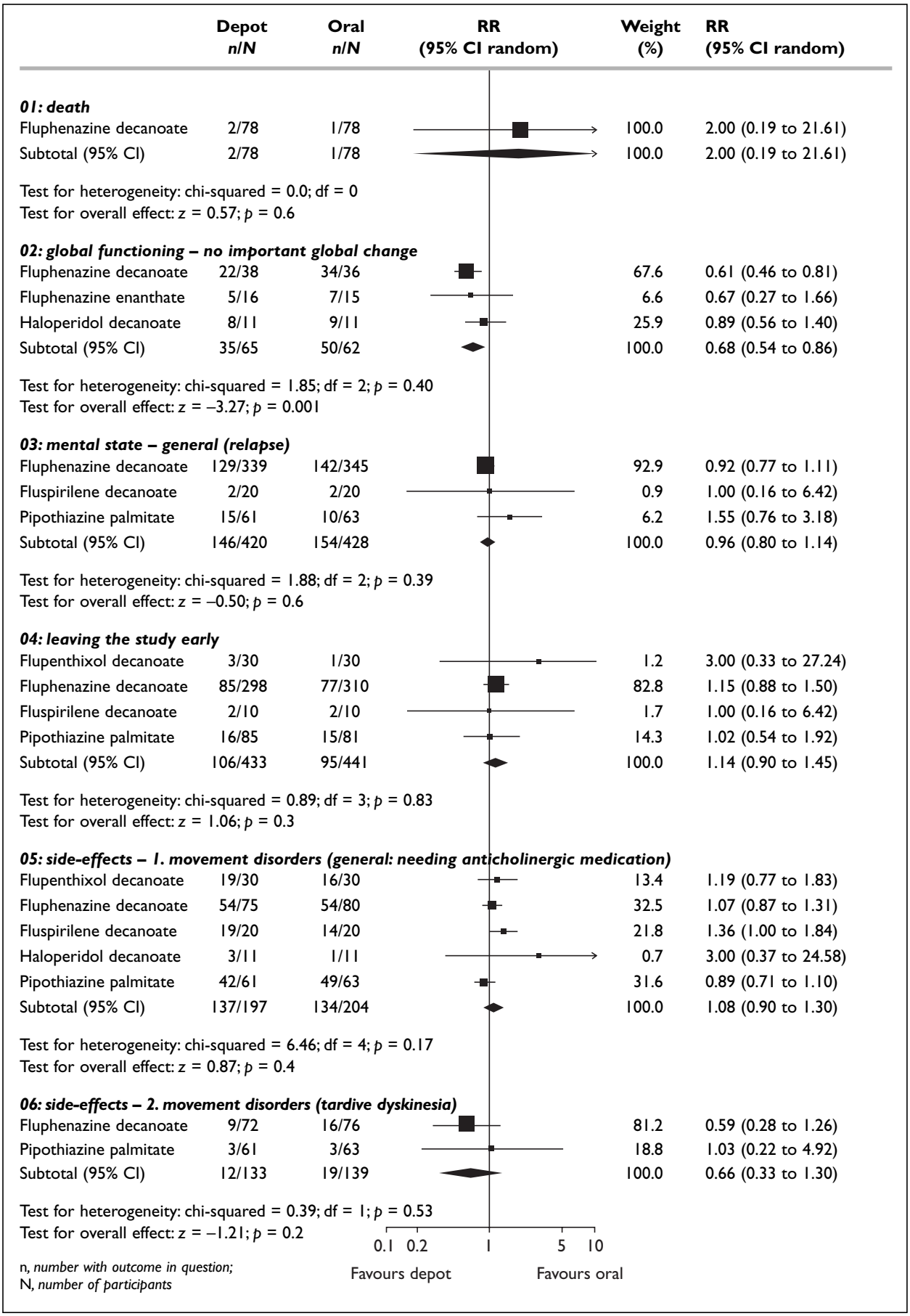


FIGURE 19 *Depot antipsychotics versus oral antipsychotics: all outcomes*

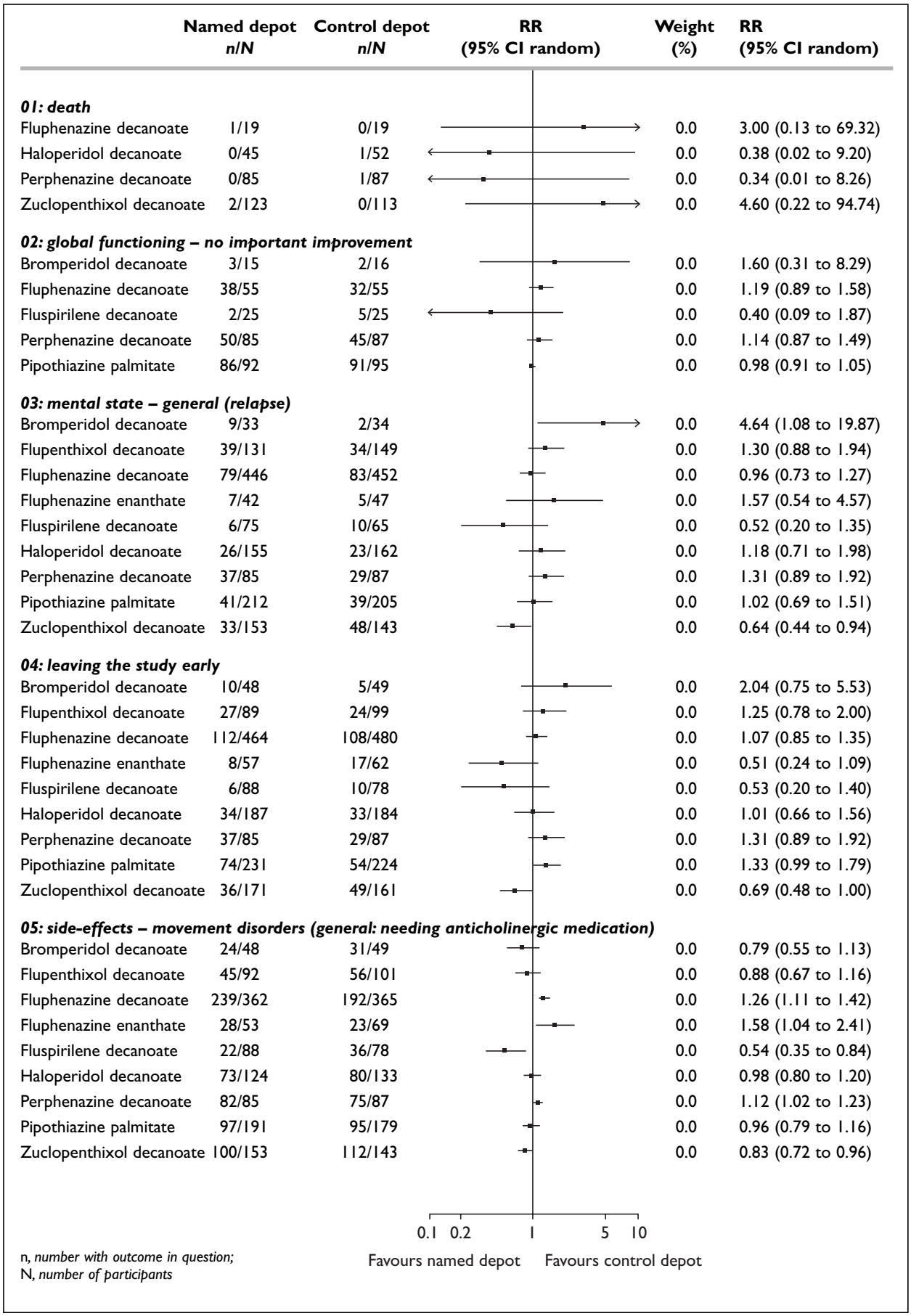


FIGURE 20 *Specific depot antipsychotics versus control depot: all outcomes – no summations*

Appendix 5

Characteristics of included studies (review of attitudes to depot medication)

Study	Design	Participants	*n*	Data collection and outcome measures used
Anderson *et al.*, 1989[22]	Cross-sectional survey	*Diagnosis*: not specified, patients attending 2 depot clinics over a 1-month period *Setting*: hospital-based depot clinics	168	16-item questionnaire investigating general attitudes towards the depot clinic
Bennett *et al.*, 1995[50]	Cross-sectional survey	*Diagnosis*: not specified *Profession*: CPN *Setting*: CPNs in 3 health districts	55	20-item questionnaire investigating CPNs' practice in the administration of depot medication and their attitudes towards it
Brooker *et al.*, 1996[47]	Cross-sectional survey	*Diagnosis*: not specified – attendees of depot clinics in north-west catchment area *Setting*: depot clinics	270	34-item questionnaire investigating clients' views about their depot medication and the arrangements of their depot clinic
Buis, 1992[49]	Cross-sectional survey	*Diagnosis*: not specified – "most had a diagnosis of schizophrenia" *Setting*: outpatient clinic	44	Adapted UKU SERS; objective criteria replaced with subjective
Burns *et al.*, 1998[51]	RCT	*Diagnosis*: schizophrenia *Profession*: practice nurses *Setting*: 140 general practices in south London	149	Exit interviews describing nurse attitudes towards their ability to perform the structured assessments
Cantle, 1997[53]	Cross-sectional survey	*Diagnosis*: not applicable *Profession*: GPs and practice nurses *Setting*: study day	26	10-item questionnaire regarding management of schizophrenic patients in general practice
Desai, 1999[38]	Quasi-case–control	*Diagnosis*: DSM-IV schizophrenia *Setting*: outpatients referred to the study	143	Patient acceptance of medication on 7-point scale Comparison of depot/oral on 7-point scale
Eastwood & Pugh, 1997[44]	Cross-sectional survey	*Diagnosis*: not specified, patients receiving depot medication in a number of settings	100	Semi-structured depot neuroleptic interview investigating patients' knowledge about their medication and their attitudes towards it
Garavan *et al.*, 1998[73]	Cross-sectional survey	*Diagnosis*: DSM-III-R schizophrenia *Setting*: outpatient clinic	70	Drug attitude inventory
Goldbeck *et al.*, 1999[42]	Cross-sectional survey	*Diagnosis*: patients receiving depot medication at a community health centre in Clydebank *Setting*: community health centre	59	Semi-structured interview looking at depot medication issues
Hoencamp *et al.*, 1995[39]	Cross-sectional survey	*Diagnosis*: schizophrenia (DSM-III) *Setting*: outpatient clinic – depot = 81; oral = 93	174	17-item modified patient request scale (Dutch version); 8-item neuroleptic evaluation and attitude list (interview)
Jacobsson & Odling, 1980[45]	Cross-sectional survey	*Diagnosis*: schizophrenia *Setting*: 3 hospital depot clinics	43	Interview; questionnaire
Kendrick *et al.*, 1998[52]	Cross-sectional survey	*Diagnosis*: not applicable *Profession*: practice nurse *Setting*: general practitioner surgery	192	Postal survey; focus group
Larsen & Gerlach, 1996[37]	Cross-sectional survey	*Diagnosis*: schizophrenia (ICD 10) *Setting*: outpatient clinic	53	14-item questionnaire specially designed to evaluate the patients' attitude to treatment Psychological general well-being schedule (PGWS)
Pan & Tantum, 1989[36]	Quasi-case–control	*Diagnosis*: schizophrenia *Setting*: hospital depot clinic Regular/irregular attendees	80	A 4-part health belief questionnaire – specifically designed for the study
Pereira & Pinto, 1997[23]	Cross-sectional survey	*Diagnosis*: Chronic schizophrenia/ paranoid psychotic illness *Setting*: outpatient clinic	173	Semi-structured interview/questionnaire investigating patients' attitudes towards their medication

continued

Study	Design	Participants	*n*	Data collection and outcome measures used
Poole & Grimes, 1998[46]	Cross-sectional survey	*Diagnosis*: not specified *Setting*: patients receiving depots in a number of settings within the locality	47	A questionnaire asking patients to choose where they would prefer to receive their medication
Sandford, 1996[48]	Cross-sectional survey	*Diagnosis*: not specified *Setting*: 5 depot clinics	58	A structured interview investigating patients' knowledge about their medication, attitudes towards it and their compliance
Singh *et al*., 1995[41]	Cross-sectional survey	*Diagnosis*: schizophrenia (188), manic depressive psychosis (15) and schizo-affective disorder (15) *Setting*: hospital-based depot clinic	218	17-item questionnaire investigating patients' views of the care and service they received at the clinic
Smith & Hughes, 1999[74]	Quasi-case–control	*Diagnosis*: schizophrenia DSM-III-R *Setting*: depot clinic and day hospital	40	4-item interview schedule derived from motivational interviewing techniques investigating attitudes towards medication and compliance
Warren, 1998[43]	Cross-sectional survey	*Profession*: nurses and patients receiving depot antipsychotics *Setting*: various	68 nurses; 76 patients	Structured interview schedules investigating the quality of care during the administration of depot medication
Wistedt, 1995[40]	Cross-sectional survey	*Diagnosis*: schizophrenia (68); other diagnoses (5) *Setting*: depot clinic	73	6 set questions investigating patient attitudes towards their depot medication asked by mental health nurse

Appendix 6

Checklist results: quality of studies (review of attitudes to depot medication)

Study*	Explicit *a priori* aims	Definition/ size of population	Sample size calculation	Justification that sample is representative of population	Inclusion/ exclusion criteria stated	Demographic details	Researcher independent of routine care/practice	Justification of validity/ reliability of measures	Original questionnaire available	Response/ drop-out rate specified	Justification of response/ drop-out rate	Discussion of generalisability	Statement of source of funding	Marks lost
Brooker *et al.*, 1996[47]	+	+	–	+	–	+	+	N/A	+	+	+	+	+	2
Pan & Tantum, 1989[36]	+	–	–	–	+	+	+	+	+	+	N/A	+	+	3
Larsen & Gerlach, 1996[37]	+	+	–	–	+	+	+	+	+	+	–	+	+	3
Sandford, 1996[48]	+	+	–	+	+	+	+	+	–	+	+	+	–	3
Burns *et al.*, 1998[51]	+	+	–	–	+	+	+	–	N/A	+	–	+	+	4
Desai, 1999[38]	–	–	+	–	+	+	–	N/A	+	+	+	+	+	4
Garavan *et al.*, 1998[73]	–	–	–	–	+	+	+	+	N/A	+	–	+	+	5
Hoencamp *et al.*, 1995[39]	–	–	–	+	–	+	+	+	+	+	–	+	–	6
Smith & Hughes, 1999[74]	+	–	–	–	+	+	+	N/A	+	+	–	–	–	6
Pereira & Pinto, 1997[23]	+	+	–	–	+	+	–	–	–	+	–	–	+	7
Kendrick *et al.*, 1998[52]	+	+	–	–	–	–	+	–	+	+	–	+	–	7
Cantle, 1997[53]	–	–	–	–	+	–	+	+	–	+	–	+	–	8
Wistedt, 1995[40]	–	–	–	–	+	+	–	N/A	+	+	–	–	–	8

continued

Study*	Explicit *a priori* aims	Definition/ size of population	Sample size calculation	Justification that sample is representative of population	Inclusion/ exclusion criteria stated	Demographic details	Researcher independent of routine care/practice	Justification of validity/ reliability of measures	Original questionnaire available	Response/ drop-out rate specified	Justification of response/ drop-out rate	Discussion of generalisability	Statement of source of funding	Marks lost
Bennett *et al.*, 1995[50]	–	+	–	+	–	–	–	+	–	+	–	+	–	8
Singh *et al.*, 1995[41]	+	–	–	–	+	+	+	–	–	+	–	–	–	8
Goldbeck *et al.*, 1999[42]	–	+	–	–	–	+	–	–	–	+	–	–	–	10
Warren, 1998[43]	–	+	–	+	–	–	–	–	–	+	–	–	–	10
Eastwood & Pugh, 1997[44]	+	–	–	–	–	+	+	–	–	–	–	–	–	10
Poole & Grimes, 1998[46]	–	+	–	–	–	–	–	–	–	+	+	–	–	10
Anderson *et al.*, 1989[22]	–	–	–	–	+	–	–	–	–	–	–	+	–	11
Buis, 1992[49]	–	–	–	–	–	–	–	–	–	+	–	–	–	12
Total	10/21	10/21	1/21	5/21	12/21	14/21	12/21	7/17	8/19	19/21	4/20	12/21	7/21	

+, present; – absent; N/A, not available

* *Jacobsson & Odling[45] is not included in the table because the translation was not literal and the checklist could not be applied*

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair
Professor Kent Woods
Director,
NHS HTA Programme, &
Professor of Therapeutics
University of Leicester

Professor Bruce Campbell
Consultant General Surgeon
Royal Devon & Exeter Hospital

Professor Shah Ebrahim
Professor of Epidemiology
of Ageing
University of Bristol

Dr John Reynolds
Clinical Director
Acute General Medicine SDU
Oxford Radcliffe Hospital

Dr Ron Zimmern
Director, Public Health
Genetics Unit
Strangeways Research
Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director
Professor Kent Woods
Director, NHS HTA
Programme, &
Professor of Therapeutics
University of Leicester

Chair
Professor Shah Ebrahim
Professor of Epidemiology
of Ageing
University of Bristol

Deputy Chair
Professor Jon Nicholl
Director, Medical Care
Research Unit
University of Sheffield

Professor Douglas Altman
Director, ICRF Medical
Statistics Group
University of Oxford

Professor John Bond
Director, Centre for Health
Services Research
University of Newcastle-
upon-Tyne

Ms Christine Clark
Freelance Medical Writer
Bury, Lancs

Professor Martin Eccles
Professor of
Clinical Effectiveness
University of Newcastle-
upon-Tyne

Dr Andrew Farmer
General Practitioner &
NHS R&D
Clinical Scientist
Institute of Health Sciences
University of Oxford

Professor Adrian Grant
Director, Health Services
Research Unit
University of Aberdeen

Dr Alastair Gray
Director, Health Economics
Research Centre
Institute of Health Sciences
University of Oxford

Professor Mark Haggard
Director, MRC Institute
of Hearing Research
University of Nottingham

Professor Jenny Hewison
Senior Lecturer
School of Psychology
University of Leeds

Professor Alison Kitson
Director, Royal College of
Nursing Institute, London

Dr Donna Lamping
Head, Health Services
Research Unit
London School of Hygiene
& Tropical Medicine

Professor David Neal
Professor of Surgery
University of Newcastle-
upon-Tyne

Professor Gillian Parker
Nuffield Professor of
Community Care
University of Leicester

Dr Tim Peters
Reader in Medical Statistics
University of Bristol

Professor Martin Severs
Professor in Elderly
Health Care
University of Portsmouth

Dr Sarah Stewart-Brown
Director, Health Services
Research Unit
University of Oxford

Professor Ala Szczepura
Director, Centre for Health
Services Studies
University of Warwick

Dr Gillian Vivian
Consultant in Nuclear
Medicine & Radiology
Royal Cornwall Hospitals Trust
Truro

Professor Graham Watt
Department of
General Practice
University of Glasgow

Dr Jeremy Wyatt
Senior Fellow
Health Knowledge
Management Centre
University College London

continued

continued

Diagnostic Technologies & Screening Panel

Members

Chair
Dr Ron Zimmern
Director, Public Health Genetics Unit
Strangeways Research Laboratories
Cambridge

Dr Philip J Ayres
Consultant in Epidemiology & Public Health
The Leeds Teaching Hospitals NHS Trust

Mrs Stella Burnside
Chief Executive, Altnagelvin Hospitals Health & Social Services Trust
Londonderry
Northern Ireland

Dr Paul O Collinson
Consultant Chemical Pathologist & Senior Lecturer
St George's Hospital, London

Dr Barry Cookson
Director, Laboratory of Hospital Infection
Public Health Laboratory Service, London

Professor Howard Cuckle
Professor of Reproductive Epidemiology
University of Leeds

Dr Carol Dezateux
Senior Lecturer in Paediatric Epidemiology
Institute of Child Health
London

Professor Adrian K Dixon
Professor of Radiology
Addenbrooke's Hospital
Cambridge

Mr Steve Ebdon-Jackson
Head, Diagnostic Imaging & Radiation Protection Team
Department of Health, London

Dr Tom Fahey
Senior Lecturer in General Practice
University of Bristol

Dr Andrew Farmer
General Practitioner & NHS Clinical Scientist
Institute of Health Sciences
University of Oxford

Mrs Gillian Fletcher
Antenatal Teacher & Tutor
National Childbirth Trust
Reigate

Professor Jane Franklyn
Professor of Medicine
University of Birmingham

Dr JA Muir Gray
Joint Director, National Screening Committee
NHS Executive, Oxford

Dr Peter Howlett
Executive Director – Development
Portsmouth Hospitals NHS Trust

Professor Alistair McGuire
Professor of Health Economics
City University, London

Mrs Kathlyn Slack
Professional Support
Diagnostic Imaging & Radiation Protection Team
Department of Health
London

Mr Tony Tester
Chief Officer, South Bedfordshire Community Health Council
Luton

Pharmaceuticals Panel

Members

Chair
Dr John Reynolds
Clinical Director – Acute General Medicine SDU
Oxford Radcliffe Hospital

Dr Felicity J Gabbay
Managing Director, Transcrip Ltd
Milford-on-Sea, Hants

Mr Peter Golightly
Director, Trent Drug Information Services
Leicester Royal Infirmary

Dr Alastair Gray
Director, Health Economics Research Centre
Institute of Health Sciences
University of Oxford

Mrs Jeannette Howe
Senior Principal Pharmacist
Department of Health, London

Dr Andrew Mortimore
Consultant in Public Health Medicine
Southampton & South West Hants Health Authority

Mr Nigel Offen
Head of Clinical Quality
NHS Executive – Eastern
Milton Keynes

Professor Robert Peveler
Professor of Liaison Psychiatry
Royal South Hants Hospital
Southampton

Mrs Marianne Rigge
Director, College of Health
London

Dr Frances Rotblat
Manager, Biotechnology Group
Medicines Control Agency
London

Mr Bill Sang
Chief Executive
Salford Royal Hospitals NHS Trust

Dr Eamonn Sheridan
Consultant in Clinical Genetics
St James's University Hospital
Leeds

Mrs Katrina Simister
New Products Manager
National Prescribing Centre
Liverpool

Dr Ross Taylor
Senior Lecturer
Department of General Practice & Primary Care
University of Aberdeen

Dr Richard Tiner
Medical Director
Association of the British Pharmaceutical Industry
London

Professor Jenifer Wilson-Barnett
Head, Florence Nightingale Division of Nursing & Midwifery
King's College, London

Mr David J Wright
Chief Executive
International Glaucoma Association, London

Therapeutic Procedures Panel

Members

Chair
Professor Bruce Campbell
Consultant General Surgeon
Royal Devon & Exeter Hospital

Professor John Bond
Professor of
Health Services Research
University of Newcastle-upon-Tyne

Ms Judith Brodie
Head of Cancer
Support Service
Cancer BACUP, London

Ms Tracy Bury
Head of Research
& Development
Chartered Society of
Physiotherapy, London

Mr Michael Clancy
Consultant in A&E Medicine
Southampton General Hospital

Professor Collette Clifford
Professor of Nursing
University of Birmingham

Dr Katherine Darton
Information Unit
MIND – The Mental Health
Charity, London

Mr John Dunning
Consultant Cardiothoracic
Surgeon
Papworth Hospital NHS Trust
Cambridge

Mr Jonothan Earnshaw
Consultant Vascular Surgeon
Gloucestershire Royal Hospital

Professor David Field
Professor of Neonatal Medicine
The Leicester Royal Infirmary
NHS Trust

Professor FD Richard Hobbs
Professor of Primary Care
& General Practice
University of Birmingham

Mr Richard Johanson
Consultant & Senior Lecturer
North Staffordshire Infirmary
NHS Trust, Stoke-on-Trent

Dr Duncan Keeley
General Practitioner
Thame, Oxon

Dr Phillip Leech
Principal Medical Officer
Department of Health, London

Professor James Lindesay
Professor of Psychiatry for
the Elderly
University of Leicester

Professor Rajan Madhok
Director of Health Policy
& Public Health
East Riding & Hull
Health Authority

Dr Mike McGovern
Branch Head
Department of Health
London

Dr John C Pounsford
Consultant Physician
Frenchay Healthcare Trust
Bristol

Dr Mark Sculpher
Senior Research Fellow in
Health Economics
University of York

Dr Ken Stein
Consultant in Public
Health Medicine
North & East Devon
Health Authority, Exeter

Expert Advisory Network

Members

Professor John Brazier
Director of Health Economics
University of Sheffield

Mr Shaun Brogan
Chief Executive, Ridgeway
Primary Care Group
Aylesbury, Bucks

Mr John A Cairns
Director, Health Economics
Research Unit
University of Aberdeen

Dr Nicky Cullum
Reader in Health Studies
University of York

Professor Pam Enderby
Chair of Community
Rehabilitation
University of Sheffield

Mr Leonard R Fenwick
Chief Executive
Freeman Hospital
Newcastle-upon-Tyne

Ms Grace Gibbs
Deputy Chief Executive
West Middlesex
University Hospital

Dr Neville Goodman
Consultant Anaesthetist
Southmead Hospital, Bristol

Professor Robert E Hawkins
CRC Professor & Director of
Medical Oncology
Christie Hospital NHS Trust
Manchester

Professor Allen Hutchinson
Director of Public Health &
Deputy Dean, ScHARR
University of Sheffield

Professor David Mant
Professor of General Practice
Institute of Health Sciences
University of Oxford

Professor Alexander Markham
Director
Molecular Medicine Unit
St James's University Hospital
Leeds

Dr Chris McCall
General Practitioner
Corfe Mullen, Dorset

Dr Peter Moore
Freelance Science Writer
Ashtead, Surrey

Dr Sue Moss
Associate Director, Cancer
Screening Evaluation Unit
Institute of Cancer Research
Sutton, Surrey

Mrs Julietta Patnick
National Coordinator
NHS Cancer Screening
Programmes, Sheffield

Professor Jennie Popay
Professor of Sociology &
Community Health
University of Salford

Professor Chris Price
Professor of
Clinical Biochemistry
St Bartholomew's & The
Royal London School of
Medicine & Dentistry

Mr Simon Robbins
Chief Executive
Camden & Islington
Health Authority, London

Dr William Rosenberg
Senior Lecturer &
Consultant in Medicine
University of Southampton

Dr Sarah Stewart-Brown
Director, Health Services
Research Unit
University of Oxford

Dr Gillian Vivian
Consultant in Nuclear
Medicine & Radiology
Royal Cornwall Hospitals Trust
Truro

Mrs Joan Webster
Former Chair
Southern Derbyshire
Community Health Council
Nottingham

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278