

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

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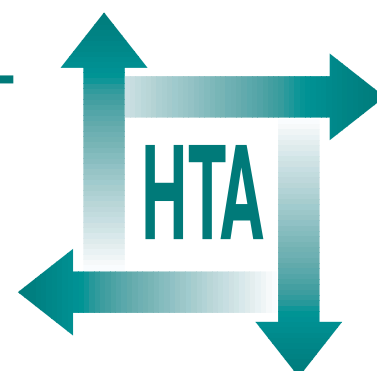
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## *Executive summary*

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## 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 anti-psychotic 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.

## **Publication**

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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.

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