Depot antipsychotic preparations in schizophrenia: the state of the economic evidence

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Depot treatment of schizophrenia – to date restricted to conventional antipsychotic medications – remains widespread. Whilst there have been numerous studies of clinical effectiveness, and systematic reviews of the accumulated evidence, little appears to be known about the cost-effectiveness of depot treatment. A systematic review was conducted of the international literature in an attempt to find, appraise and summarize the economic evaluative evidence. Very few studies of relevance or quality could be found. Most of the papers purporting to examine the economic consequences of depot treatment were methodologically weak. There were no randomized controlled trials of depot vs. oral antipsychotics, the few mirror-image studies were uncontrolled and a single naturalistic observational study measured costs only narrowly. Two modelling studies – which have a number of limitations because of their partial reliance on expert opinion rather than observational data – suggest that depot treatment may lower costs and improve cost-effectiveness. Overall, however, it is not possible to draw conclusions as to the cost-effectiveness of depot conventional antipsychotic treatment for schizophrenia.

Keywords: antipsychotics, depot treatment, cost-effectiveness, systematic review

INTRODUCTION

Although data on the exact numbers of those receiving depot antipsychotic treatment are hard to find, these preparations are widely used for the treatment of schizophrenia in the UK (Desai \textit{et al.}, 1999; Taylor, 1999) and in many other countries. Indeed, there are wide international variations in the extent of their use (Dencker and Axelsson, 1996). For example, one-third of patients on antipsychotics in the South London and Maudsley Health Care Trust are currently on depot medication (Taylor, personal communication), and perhaps as many as 50% in the UK more generally, while only 10–20% receive depot antipsychotic therapy in the USA (Kane, 1993; Glazer, 1994).

Clinical outcomes and side-effects

Depot antipsychotics are thought to improve adherence with medication (Moore \textit{et al.}, 1998) and to reduce the rate of relapse (Davis \textit{et al.}, 1994; Dencker and Axelsson, 1996). For example, five early studies of clinical efficacy reviewed by Davis \textit{et al.} (1993) showed that relapse rates observed on depot preparations were lower than those with orally administered drugs. In theory, by avoiding gut wall and hepatic first pass metabolism, the intramuscular route of depot administration may increase the bioavailability of the drug (Davis \textit{et al.}, 1994; Hirsch and Barnes, 1995). Stable serum concentrations can usually be achieved, although this is not always observed in practice (Tuninger and Levander, 1996; Taylor, 1999). The risk of deliberate or inadvertent overdose with antipsychotic medication is eliminated by depot injections. This is important considering that the risk of suicide in patients with schizophrenia is nine times higher than in the general population (Harris and Barraclough, 1998). Improved patient care and follow-up may
follow from the regular clinical contact necessitated by depot administration.

On the other hand, depot injections may give rise to a higher incidence of extrapyramidal side-effects than oral preparations (Glazer and Kane 1992; Taylor, 1999; British Medical Association, 2001). There are also difficulties with titrating the dosage of depot antipsychotics with the risk of drug accumulation (Dencker and Axelsson, 1996). Local complications at the injection site may also occur (Kane et al., 1998). For example, a mass may be palpable at the site or pain or oedema and pruritis may be experienced. Patients may also be reluctant to accept injections and may have a sense of being overly controlled (Kane et al., 1998).

Meta-review

Despite these adverse properties, depot antipsychotic medications are clearly widely recognized as appropriate treatments by clinicians in the UK and elsewhere. However, surprisingly few studies have assessed their efficacy thoroughly and systematically. A systematic meta-review of depot antipsychotics was previously completed (Adams et al., 2001). Randomized controlled trials of individual depots compared with placebo, oral drugs or other depots were examined. High-dose versus low-dose depot treatments were also reviewed for individuals with schizophrenia or a schizophrenia-like illness. These individual reviews have been published in the Cochrane library of systematic reviews.

Four main conclusions can be drawn from this meta-review. Standard dose depot versus placebo resulted in significantly less relapse but more movement disorders. Compared to patients on oral drugs, depot patients showed more global change on one outcome measure, while relapse and adverse effects showed no difference. Comparisons showed no convincing advantage for one depot over another. High doses showed no advantages over standard doses, but low doses were significantly less effective than standard doses. It was not possible to extract any meaningful data on quality of life outcomes.

The meta-review concluded that depot antipsychotics are safe and effective. They may confer a small benefit over oral drugs in terms of global outcome. Adams et al. (2001) recommended the need for larger studies in order to test more thoroughly for differences in relapse rates and long-term adverse effects.

Cost-effectiveness

Clinical and other decision makers appropriately emphasize not only clinical effectiveness and the avoidance of side-effects when considering treatment options, but also cost-effectiveness. Given the high costs of relapse for schizophrenia patients, particularly because relapse leads in most cases to inpatient admission (Weiden and Olfson, 1995), it might be assumed that depot treatment would be more cost-effective than oral treatment. Indeed, this assertion has often been made in the literature (Owens, 1978; Glazer, 1994; Osterheider et al., 1998). We aimed to examine the cost-effectiveness implications of depot treatment by carrying out a systematic review of the published literature as a supplement to the meta-review by Adams et al. (2001).

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’ (Drummond et al., 1997). The most common techniques of evaluation today are cost-effectiveness, cost-consequences, cost-utility and cost-benefit analyses. The systematic review of economic evaluations of depot treatment of schizophrenia examined any such analyses. However, because there are few such evaluations in some health care areas, including in the mental health field, the review also widened its span to look at studies that (i) examine costs but not outcomes, or (ii) that report service utilization patterns without converting them into monetary measures. Such studies alone do not provide sufficient evidence to guide decision making, but may contribute to an understanding of the (comparative) resource consequences of depot treatment.

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), had generated no studies with an economics component. (Adams et al., 2001). One of the methodological requirements of that review was that studies should be randomized 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 which might have some economic evidence.

Five data bases were searched, generating the following numbers of references: (i) PsychINFO,
1984 to February 2001, 8 references; (ii) Medline, 1966 to May 2001, 35 references; (iii) EMBASE, 1980 to May 2001, 20 references; (iv) NHS Economic Evaluation Database at May 2001, 69 references; and (v) Cochrane Library at May 2001, 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 because, although they included discussion of depot treatment and some mention of costs, they were not evaluative. Papers that were potentially relevant were read and their references checked and followed up as necessary. However, 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, nature of any sensitivity analysis and potential generalizability. The checklists suggested by Drummond et al. (1997) and Gold et al. (1996) assisted this review of the methodological properties of the included studies. The relevance of studies for the UK was also considered, but was not used as an exclusion criterion.

RESULTS

The review uncovered very few studies of sufficient relevance or quality to be included. As already noted, the main meta-review found no randomized controlled trials that addressed the cost-effectiveness question, which was a finding confirmed by our supplementary electronic search.

Most of the papers purporting to examine the economic consequences of depot treatment are methodologically weak. Indeed, one study suggested by its title that it was an economic evaluation (‘Costs and benefits of two doses of fluphenazine’) but, on closer examination, was found to report no cost or service utilization data (Marder et al., 1984).

Some of the studies identified were mirror-image studies of the same patients treated with and without depot (Marriott and Hiep, 1976; Marriott et al., 1976; Larach et al., 1995). The last of these is not actually a cost–benefit analysis, despite its title. Although they have the advantages of being naturalistic and quick to conduct, mirror-image studies have a number of well-known drawbacks. They run the risks of patient or location selection bias, limited outcome and cost measurement (particularly when relying on retrospec-

tive data collection), high drop-out rates (with discontinued patients not always followed up, which is somewhat perverse given the importance of compliance in schizophrenia treatment) and missing sensitivity analysis.

Moreover, all three of these studies were uncontrolled (there was no parallel collection of data for patients whose treatment remained unchanged) and so each is susceptible to two potentially terminal problems. First, care arrangements (such as the propensity to admit or keep people in in-patient facilities) and extraneous factors may have altered over the course of the study period. Second, patients are usually started off on a new medication when they are quite ill, so that symptom improvement and reduced service use over time could simply occur through natural remission (the statistical regression problem). Thus, while Marriott and Hiep (1976) found that inpatient costs were more than twice as high before depot phenothiazine treatment than after, it is not possible to identify the exclusive effect of the depot. Similarly, Larach et al. (1995) found a 77% drop in hospitalization costs in their 10-year evaluation of a depot clinic in Santiago, Chile, but it seems highly unlikely that the mental health system remained unchanged over such a long period.

One of the studies found in the systematic search was based on naturalistic (observational) studies from Sweden (Lindholm and Ljungberg, 1973). Although an interesting, early attempt to compare the costs of depot and oral drugs, the study was flawed in at least three respects: (i) the authors measured costs very narrowly; (ii) they did not measure or report clinical or other patient outcomes; and (iii) they failed to make adjustments for differences in patient characteristics.

Two of the studies found by our search were decision models, one for ‘revolving door’ patients in the US and the other community-living UK patients (Glazer and Ereshefsky, 1996; Hale and Wood, 1996). The purpose of a decision model is to simulate the clinical management of a disorder and the service use patterns that follow, and thereby to estimate the costs and outcomes of two or more treatment regimes. The structure and parameters of a model are built up from evidence taken from clinical, epidemiological and health economic literatures, from expert opinion, from data collected in naturalistic settings and from completed clinical trials. Decision models are generally most helpful in the early period after introduction of a new treatment, or when seeking to make long-term projections from only short-term data, or when the information necessary for decision-making is scant, as is clearly the case in this field.
Each of the two decision model studies concluded that switching patients from oral to depot medication could be cost saving under certain assumptions. Each model used expert opinion to fill gaps in the (observational) evidence base. As Glazer and Ereshefsky explain: ‘In the absence of consistent data, the probabilities can be derived from the clinician’s experience or consensus panels. For our analysis, we arrived at “reasonable” assumptions based on published data and personal clinical experience and “typical” costs based on those at the authors’ institutions’ (Glazer and Ereshefsky, 1996). In the past, excessive reliance on expert opinion has led to concerns about model bias, unrealistic assumptions of care arrangements and idealistic outcomes. An almost inevitable feature of many decision models is imprecision in the estimates (good modelling studies test for the sensitivity of the results, but are often hampered by a simple lack of robust evidence) and opacity of methods or assumptions. Another limitation is that modelling tractability usually demands that the analysis focuses on a single outcome dimension; for example, in the case studied by Hale and Wood (1996), they examine costs but not outcomes.

Two studies have made cost comparisons between depot drugs but have not compared them with oral drug treatment. Laurier et al. (1997) constructed a decision model to compare depot haloperidol and zuclopenthixol acetate in the Quebec health care system. Observational data on patterns of schizophrenia treatment in general, and haloperidol treatment in particular, were supplemented by expert panels’ views on likely patterns of service use with zuclopenthixol (not available in the Canadian market at that time). Under certain assumptions, the newer depot generated (health system) cost savings, but the results could only be speculative given the way the model was constructed.

Another recent comparison between two depot drugs (haloperidol and fluphenazine) was based on observational data on a small sample (n = 43) of patients discharged from a large state hospital in Baltimore, MD, USA (Moore et al., 1998). The main purpose of this study was actually to compare these depot patients with 75 patients discharged from any state psychiatric facility in Maryland with prescriptions for risperidone (n = 75). Only inpatient and drug costs were calculated and no adjustments were made for illness severity or duration; however, fluphenazine appeared to have lower acquisition and rehospitalization costs, although the sample was too small to allow a robust test of significance.

In summary, the absence of any randomized controlled trial evidence, and the methodological weaknesses of the studies based on non-randomized designs, both make it impossible to draw any firm conclusions. The two decision models (Glazer and Ereshefsky, 1996; Hale and Wood, 1996) suggest that depot treatment may lower costs and improve cost-effectiveness, but both models were necessarily built on a number of expert assumptions in the absence of trial or direct observational data.

**DISCUSSION**

The economic impact of schizophrenia is broad and substantial, with costs borne not only by the health care system, but also by social care, housing, criminal justice and other agencies (Knapp, 1997). There are also potential sizeable costs for the families of people with schizophrenia (Magliano et al., 1998) and potential impacts on the wider community given that there is an association between psychosis and violent crime (Taylor and Gunn, 1999). For people with the illness, there will often be costs associated with not being in employment (Davies and Drummond, 1994) and premature mortality (Harris and Barraclough, 1998).

In contrast to this broad range of cost impacts of schizophrenia, the few studies of depot antipsychotics that sought to examine economic issues have all focused very narrowly on just a few of the costs, albeit those of most interest to health care decision makers (hospitalization and drug costs). It must be of concern that no randomized 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-randomized studies sufficient to allow robust conclusions to be drawn. Given the slow take-up of atypical antipsychotics in many countries, the continuing widespread use of depot treatment for people with schizophrenia and the increasing emphasis on cost-effectiveness in the use of scarce health service resources, such a state of affairs is clearly unsatisfactory.

However, it should not be a surprise that there is little economic evidence relating to depot treatment. All of the depot preparations of ‘conventional’ antipsychotic drugs were introduced some years ago and, at that time, there was little expressed imperative to examine cost-effectiveness. In recent years, the attentions of strategic decision makers, research funding bodies and the ‘evaluation community’ have concentrated on the newer emerging treatments, not just for schizophrenia but for other psychiatric disorders. Consequently, very few studies of depot effectiveness or cost-effectiveness have been conducted.
in the period in which decision makers in health systems have been demanding efficacy as well as effectiveness data.

The arrival of (some) atypical antipsychotics in depot form will highlight the unacceptability of this absence of economic data. While it is reasonable to expect pharmaceutical companies, as well as health service funding bodies, to sponsor the completion of economic evaluations of depot atypicals, just as they have for the oral preparations of atypical antipsychotics, there may be one or two additional difficulties. Some of the effects of atypical antipsychotics take some time to reveal themselves, notably some of the cost impacts, quality of life improvements and effects on socialization and employment patterns for patients. In order to evaluate whether depot atypical antipsychotics have effects in these domains may therefore require studies of a duration that would present challenges to the research community. Depot antipsychotics are often prescribed for patients who do not take their oral medications, and it may be these same patients who are less likely to be willing to continue to participate in medium or long-term research studies. Of course, what we do not know from the evidence on depot versus oral preparations of conventional antipsychotics is what might be expected of the depot atypicals. Only time and the accumulation of good quality research evidence will tell.

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