

## RETURNING TO THE ISSUE OF THE COST-EFFECTIVENESS OF ANTIPSYCHOTICS IN THE TREATMENT OF SCHIZOPHRENIA

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### Abstract

**Object:** To give an overview of the current literature on the cost-effectiveness of antipsychotics used in the treatment of schizophrenia.

**Method:** We conducted a relevant literature search and contacted authors who had published literature in the field of pharmacoeconomics.

**Results:** Much of the evidence in pharmacoeconomic studies is contradictory, and results may be determined by study methodology and the scope of outcome evaluations. More studies are needed to draw firm conclusions about the cost-effectiveness of various individual antipsychotics. However, with respect to clozapine, there is evidence that it is cost-effective in treatment-resistant patients after at least one year, especially if high users of inpatient facilities.

**Conclusions:** Calculating the cost-effectiveness of a treatment is complex, and should incorporate real world parameters such as the value of good clinical outcome, tolerability and quality of life against the direct and indirect costs of schizophrenia to the individual and society as a whole. The variety of methodological issues employed in pharmacoeconomic studies is a limiting factor in seeking to synthesise the evidence, and comparisons between different agents in this field will undoubtedly continue to be a matter of debate, with further studies being required.

**Key Words:** Cost-Effectiveness – Tolerability – Antipsychotics – Schizophrenia

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### Introduction

The pharmacological treatment of schizophrenia has evolved dramatically since the 1950s, with the introduction of many new drugs, and new formulations of existing products. Prescribing practice has also evolved to encompass tolerability as well as efficacy; the concept of clinical effectiveness is now regarded as a “gold standard” for treatment.

The wide usage of second generation antipsychotics (SGAs), some with more selective dopamine blockade and a lower propensity for extrapyramidal side effects has been regarded as a significant progression towards both effective and tolerable pharmacotherapy. However, some SGAs have limited tolerability, as well

as being more expensive than their predecessors. In a chronic illness often requiring lifelong treatment, the issue of cost is a key consideration for prescribers.

Antipsychotic medication remains the mainstay of treatment for schizophrenia, and accounts for only a small proportion of the overall cost of treatment. However, among the antipsychotics (APs) currently available, there is a wide variation in their cost both to the manufacturers and to health care providers ([www.healthcarerepublic.com](http://www.healthcarerepublic.com)). Typical antipsychotic drugs, or “first generation antipsychotics” (FGAs) have been available since the 1950s, and are in general cheaper to prescribe than second generation antipsychotics (SGAs), which have only been widely available since the 1990s. It has been argued that SGAs

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may confer benefits that offset both the indirect and direct cost of schizophrenia in that they may offer both improved quality of life and a more tolerable adverse effect profile as perceived by patients (De Millas et al. 2006), leading to improved compliance with a reduction in relapse and hospitalisation, and a lessening of the burden to carers, both in the short and long term. SGAs are also known to be more effective in treating the negative symptoms of schizophrenia, potentially enhancing response to psychosocial intervention, and improving functional outcome (Marder 2000). Additionally, drugs that enhance cognition may also have a beneficial effect on insight, which is known to have a positive effect on compliance (Rocca et al. 2008).

However, more recent evidence has suggested that the differences between FGAs and SGAs in terms of clinical effectiveness and relapse prevention may not be as significant as previously believed (Stargardt et al. 2008, Lewis and Lieberman 2008). Adverse drug reactions (ADRs) associated with some SGAs, especially of a metabolic nature such as diabetes mellitus (DM), obesity, hypercholesterolaemia and hyperlipidaemia, also incur significant costs, both financially and in terms of poorer quality of life, and secondary increased morbidity and mortality (Fontaine et al. 2001).

We here present an assessment of the cost-effectiveness of APs in schizophrenia based on a review of the current pharmacoeconomic literature. Comparative analyses of pharmacoeconomic cost-effectiveness may only be relevant for a limited time period, as patents for SGAs expire (and therefore a generic, cheaper product becomes available) and new products and new formulations of existing products become more widely used. There are various methodologies employed for the calculation of cost-effectiveness, hence findings may be influenced by the specific method. There are also a wide range of variables which may or may not be incorporated into such analyses, including the cost of a drug (**Table 1**), and the cost of delivery including potential drug-specific factors, such as the haematological monitoring required for clozapine. Other variables include relevant measures of clinical outcome; in the case of clozapine, the monitoring costs may be offset by the greater propensity for efficacy; and in the case of injectable APs, potential enhancement of compliance, reducing relapse rates and hence also hospitalisation (Davis et al. 1994). Different ways of measuring such outcomes are available, and appropriate for different methods of economic evaluation. Drugs that are associated with a high frequency of ADRs may incur additional costs in terms of requiring adjunctive medication and additional medical care, *e.g.*, costs to primary care and to endocrinologists in the case of DM. These and any other additional costs also need to be included, and may be affected by the relative efficacy of the antipsychotic in question.

### The cost of pharmacotherapy for schizophrenia

The point prevalence of schizophrenia has been estimated at 4.0 per 1,000 (McGrath et al. 2008). However, in the UK the care of patients with schizophrenia consumes over 5% of the NHS budget

(Hargreaves 2003). This is due to the chronic nature of the disorder in most cases and the high cost of hospitalisation. In fact, schizophrenia is the most expensive mental illness to treat (McGuire et al. 1991, Rice 1999). The total cost of schizophrenia in England alone was estimated to be around £6.7 billion in 2004/5, with approximately £2 billion being spent on direct costs of treatment, which include hospitalisation, community and day care and medication (Mangalore and Knapp 2007). The remaining £4.7 billion comprised indirect costs, including benefit (social security) payments, and loss of productivity for both patients and carers (*e.g.*, lost employment and earnings by patients and family members caring for them). Many studies look only at the direct costs of the illness, which ignores the substantial burden placed on the patient and their family. Indirect costs at a “conservative estimate” make 75% of the total lifetime costs (Davies and Drummond 1994). The significant degree of disability caused by schizophrenia accounted for 2.8% of Disability-Adjusted Life Years (DALYs) according to the Global Burden of Disease Study (Rössler et al. 2005). People with schizophrenia also have a shorter life expectancy and increased incidence of physical co-morbidity (Rössler et al. 2005, Brown et al. 2000). The various indirect costs may not be so easily expressed in monetary terms but may in fact be more important, such as the psychological impact of symptoms on the patients, and their psychological and social sequelae for carers.

Although the cost of pharmacotherapy as a proportion of the total direct costs of schizophrenia was only approximately 4% (Knapp 1997) ten years ago, drug costs have risen and Freedman et al. (2006) in the USA estimated that approximately one-third of a patient's treatment costs were spent on medication if the patient was receiving an SGA during its patent life.

There is increasing concern about the cost of health care, with service providers considering not only efficacy and safety of a therapy, but also the cost-effectiveness of the various alternatives. Drug prescription budget holders may be reluctant to pay for the higher costs of SGAs, which may be perceived as prohibitively expensive in the short term, and thus underused. Moreover, budgets within the NHS are separate (*e.g.*, pharmacy and hospital bed days). Local budgetary restraints in the UK give rise to the phenomenon of “postcode prescribing,” whereby the geographical area in which a patient lives may limit choice of AP treatment to the cheaper options, even if an alternative medication would be more appropriate (Hayhurst et al. 2003). In areas of the United States of America, the managed health care system often does not provide for continuing cover; the result is that the patient may need to cover the cost of the drug after only a few months of treatment. Even on subsidised care (*e.g.*, Medicare), patients may have to contribute to the cost of their medication. This means that patients switch to cheaper FGAs. However, the “out of pocket” saving does not necessarily translate into good long-term economic sense, as switching to a less suitable, albeit cheaper medication may adversely impact on compliance and clinical outcome (Wang et al. 2008). Thus, the development and availability of potentially more effective and tolerable, but more expensive, SGAs

Table 1. *Cost of medications at manufacturer's recommended doses (from healthcarerepublic.com, accessed September 26th 2008)*

Drug	Recommended daily dose (mg) (schizophrenia)*	Cost (£ Sterling) per day
Amisulpride (patent brand)	400-800 mg initially	2.05 (400 mg) - 4.10 (800 mg)
	Up to 1200 mg maintenance	5.12 (1000 mg)
		6.14 (1200 mg)
Amisulpride (generic)	400-800 mg initially	1.88 (400 mg) – 3.77 (800 mg)
	Up to 1200 mg maintenance	4.72 (1000 mg)
		5.65 (1200 mg)
Aripiprazole	10-15 initially	3.63. (10 mg)
	15mg maintenance	3.63 (15 mg)
		7.26 (30mg)
Clozapine (patent brand)	Initial titration up to 2 -3 weeks	Variable
	Maintenance: 300 - 900 mg	2.64 (300mg)
		3.96 (450 mg)
		5.28 (600 mg)
		7.92 (900mg)
Clozapine (generic brand)	Initial titration up to 2 -3 weeks	Variable
	Maintenance: 300 - 900 mg	Available generic UK brand has the same pricing as patented brand
Olanzapine	Initial: 10 mg	2.84 (10 mg)
	Maintenance 10-20 mg	4.26 (15 mg)
		5.68 (20 mg)
Quetiapine**	Initial titration 25mg-300mg (4 days)	1.93 (first 4 days)
	Maintenance 300 mg-800 mg	2.83 (300 mg)
		4.72 (450 mg)
		5.66 (600 mg)
		7.54 (750mg)
Risperidone (patent)	Initial 2 mg	1.44 (2 mg)
	Maintenance 4-6 mg	2.22 (4 mg)
		3.37 (6 mg)
Risperidone (generic)	Initial 2 mg	0.79 (2 mg)
	Maintenance 4-6 mg	1.53 (4 mg)
		2.32 (6 mg)

has raised economic as well as clinical questions.

The question of cost-effectiveness became a matter of debate following a meta-analysis by Geddes et al. (2000), which showed low dose FGAs to have apparently comparable efficacy and acceptability in terms of ADR profile versus SGAs. Further meta-analyses (Davis et al. 2003, Leucht et al. 2003) and more recent data from both the Cost Utility of the Latest Antipsychotics in Schizophrenia Study (CULASS) and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trials, support, it would appear, the hypothesis that in terms of real-world outcomes, FGAs may in fact be as effective and tolerable as SGAs, with the exception of clozapine (Davies et al. 2007, Lewis and Lieberman 2008). The latter has been amply demonstrated to be clinically more effective than other currently available APs for treatment-resistant schizophrenia.

The following section will give examples of pharmacoeconomic studies of antipsychotics. For earlier reviews of the pharmacoeconomics of atypical antipsychotics, see Taylor and Aitchison (1999), and Tandon and Aitchison (2002).

## Design issues of pharmacoeconomic trials

Ideally, a study should reflect the treatment choices that clinicians face. Few trials, particularly double-blind, randomised, controlled studies, include a comparator that clearly represents standard therapy. Patients in these trials may have their medication switched, or become “drop-outs” if efficacy or tolerability does not match the strict parameters of the trial protocol. In trials comparing SGAs with FGAs, the dose of drugs, particularly of the FGA, has been repeatedly highlighted as an important issue; standard doses of SGAs have been compared with high doses of FGAs (10–20 mg of haloperidol a day), where lower doses might have sufficed (McEvoy et al. 1991, Aitchison et al. 1999). Moreover, in some trials, lower potency FGAs might have improved tolerability (Leucht et al. 2003). Higher doses result in a more unfavourable ADR profile and may result in reduced efficacy (Geddes et al. 2000). The latter study also demonstrates the importance of assessing outcomes on an intention to treat basis and the need to continue to collect data on costs once a patient has switched therapy.

Studies should be conducted over a sufficiently long time frame to capture the longer-term consequences of an outcome. For example, olanzapine, which has been shown to be cost-effective in studies spanning up to 18 months, may be found to decrease in cost-effectiveness as metabolic ADRs become apparent and incur secondary costs. By contrast, some studies have shown that the costs associated with clozapine are high, especially in the first year of treatment, but owing to increasing efficacy, decrease in the second year and continue to decrease (Essock et al. 2000, Drew et al. 2002).

There is an inherent bias in favour of the SGA in FGA vs. SGA studies focused on treatment-refractory patients, many of whom have failed to respond to FGAs. An analysis of the impact of clozapine in patients in the top tertile of length of hospital stay (mean 215 days),

compared with those in the lowest two tertiles (mean 58 days) showed that the cost savings reported for high hospital users did not generalise to low hospital use patients (Rosenheck et al. 1999).

‘Mirror-image’ pharmacoeconomic studies look at changes in cost prior to and post commencement of a drug. Taylor et al. (2007a), in a controlled, mirror-image study spanning six years found significant increased hospital days (though not admissions) for 18 patients who were switched from an FGA to either olanzapine or risperidone, compared to the 18 patients in the “control” group who were switched from one FGA to another. Switching to clozapine resulted in increased hospital days, though not to a significant degree. Little difference in cost was found in patients who had been switched from depot medication or oral, which might have otherwise accounted for increased time in hospital due to non-compliance related relapse. The authors mention that the patients in this study may not be characteristic in that they had been switched because of clinical indications, therefore they may have been on a “deteriorating path”. However, that should hold true for the control group as well as the group that switched to an SGA. Aitchison and Kerwin (1997) used a mirror-image design to compare costs and effectiveness (quality of life) in the three-year pre- and post-initiation period of clozapine treatment in 26 outpatients in the UK. The costs after treatment with clozapine were significantly less, with a mean cost saving of £3,768 per patient per year, compared with the prior treatment. Mirror image studies are, however vulnerable to cohort effects unless a control group is included, which could control for longitudinal changes in, for example, a local policy providing for fewer admissions or a change in provision of community services. In this particular study, the mean duration of hospitalisation per admission *increased* in the post clozapine period, thereby showing that the decreased costs could not be attributed merely to a change in admission policy.

## Cost-effectiveness of individual APs

### *A. Clozapine*

Several studies measuring the cost-effectiveness of clozapine have been mentioned in the previous section, the general conclusion being that clozapine becomes more cost-effective over time. Recent data support this, as well as the principle that clozapine, though an expensive drug with ongoing monitoring costs, has advantages in monetary terms because of reduced hospitalisation rates, a particularly significant consideration for treatment-refractory patients.

Davies et al. (2008) conducted a randomised, controlled trial comparing the cost effectiveness of a generic clozapine (just over half the price of the previously patented brand) with other SGAs. The trial ran over a year: the primary outcome measure was quality adjusted life years (QALYs); the secondary outcome measure was clinical improvement. Clozapine was clinically more effective than other SGAs, and would have been cost-effective, if the value of one QALY were estimated at more than £33,000. A trend



towards a decrease in cost was noted over the second half of the year.

This appeared to be because of a decrease in hospitalisation costs. Furthermore, a prior study with a longer follow-up period (Drew et al. 2002) had shown that over time, the cost-effectiveness increased further, with continued improvement, less time spent in hospital and subsequent decrease in costs over 5 years in a cohort of clozapine treated community patients. Costs before the initiation of clozapine treatment were compared through a retrospective analysis of records, and at five year follow-up, the authors concluded that clozapine was a clinically beneficial and cost-effective treatment for appropriate patients in the community.

A two year open-label, double-blind, randomised controlled trial (Essock et al. 2000) compared the cost-effectiveness of clozapine with standard care; *i.e.* a variety of different FGAs. Costs for clozapine treated patients overall were similar, but changed significantly over the two year period, the clozapine group costing \$1,112 more than standard care in the first year, but \$7,149 less in the second year, mainly owing to a large number of patient being discharged to the community.

In summary, continued clinical improvement and decreased hospitalisation has been observed in the long term in clozapine treated patients. In addition, there may be further cost savings with generic clozapine and as the practice of initiating on an outpatient rather than an inpatient basis may become increasingly common (O'Brien, 2004). Attrition rates for clozapine treated patients are, however, high. Atkinson et al. (2007) found that a common cause of discontinuation was death. Otherwise, discontinuation of clozapine seemed to result in markedly worsened outcome, and increased hospitalisation in the year after discontinuation, particularly if clozapine is stopped because of ADRs rather than non compliance.

### B. Aripiprazole

Aripiprazole has been licensed for a shorter time than the other available antipsychotic drugs discussed in this review, so data on cost-effectiveness are scarce. Nevertheless, the available data suggest that its cost-effectiveness profile is promising. A recent study showed improved quality of life with reduced overall costs by one year in an aripiprazole add-on or switching study in treatment-refractory and/or -intolerant outpatients in the community (Aitchison et al. submitted).

The ongoing Schizophrenia Trial of Aripiprazole (STAR) Study (Kerwin et al. 2007) (a multicentre, randomised, naturalistic open-label trial) has used comprehensive clinical and biological ratings to assess the efficacy, tolerability and impact on quality of life of aripiprazole *vs.* treatment with "standard of care" (SOC) *i.e.*, other SGAs (olanzapine, quetiapine, risperidone) over a 26-week period in 555 patients in the community requiring a change in their medication. The results show that patients receiving aripiprazole reported better quality of life, and felt better on their medication. Tolerability ratings were similar between aripiprazole and SOC. However, different ADRs were reported with the aripiprazole group experiencing more

extrapyramidal symptoms (EPS) than the SOC group, who experienced substantially more weight gain, and a higher incidence of elevated lipids, cholesterol and prolactin. Cost-effectiveness analysis is awaited.

Taylor et al. (2007b) conducted an observational study on the effectiveness of aripiprazole in 211 patients over six months, reporting broadly similar efficacy and tolerability to other APs, though 51% of subjects discontinued treatment, mostly because of minor ADRs. The authors point out that this cohort of patients was possibly not representative in that some may have been treatment refractory. At baseline, 107 patients had been inpatients and there was a significant association between being an inpatient at baseline and discontinuation of aripiprazole within six months. Furthermore, the study was conducted at a time when most clinicians had little experience of prescribing and managing treatment with aripiprazole. Attending to and managing ADRs soon after initiation could have somewhat lowered the discontinuation rate; the majority of patients who discontinued aripiprazole because of ADRs did so in the early stages of treatment. No formal cost-effectiveness analysis was done, but there was no significant difference in the number of hospital days in the six months post- initiation between patients who discontinued treatment and those who did not.

### C. Risperidone

Oral risperidone was taken off patent in 2007, and thus any cost-effectiveness trials conducted afterwards using generic formulations are likely to demonstrate a more favourable profile. No cost-effectiveness data are available as yet, but already, suggestions have been made about rethinking prescribing policy in the light of the availability of generic risperidone (Rosenheck et al. 2008). In the same publication, the authors suggest an alternative algorithm to current prescribing practice, taking into account not only efficacy and tolerability, but also cost (Table 2).

A cost-utility analysis that was part of the pan-European Schizophrenia Outpatients Health Outcomes (SOHO) study found branded risperidone to be less cost-effective than olanzapine, but more cost-effective than quetiapine and amisulpride (Knapp et al. 2008). These data confirmed earlier European research (Obradovic et al. 2007), where decision analyses were used to estimate costs, based on a review of the data on relapse and hospitalisation rates from 34 studies of a variety of APs. There are studies concerning risperidone prior to the introduction of generics. A comparison of the effectiveness and cost of risperidone to olanzapine in 501 inpatients (Taylor et al. 2003) showed significantly lower costs for risperidone, and although clinical outcome at endpoint was found to be "broadly similar", time to clinical efficacy (as documented in casenotes) was found to be significantly shorter for risperidone treated patients than for those on olanzapine. Nightengale et al. (1998) performed a controlled retrospective mirror-image study on patients who were treated with an FGA for at least one year prior being started on risperidone ( $n = 88$ ) or another FGA ( $n = 62$ ). There was only a trend for lower cost in the risperidone group in the post period between the two

Table 2. *Proposed prescribing algorithm based on cost-effectiveness (adapted from Rosenheck et al. 2008)*

	Drug	Reasons (as stated by Rosenheck et al.)	Comments
First line	Risperidone, intermediate potency FGAs such as perphenazine, loxapine (loxapine), thiothixine	Cost, efficacy and tolerability (equivalent to other SGAs) relatively low risk of EPS and metabolic side effects. Perphenazine equally effective as aripiprazole in patients previously unresponsive to olanzapine or risperidone.	Chakrabati et al. 2008 (Cochrane Database Review) found loxapine (loxapine) to be as effective as other antipsychotics but with a greater propensity for EPS than SGAs. However, loxapine and thiothixine are not licensed in the UK, and perphenazine rarely used, owing to ADRs including systemic lupus erythematosus.
Second line	Clozapine	Generic clozapine available more cheaply. Should be used early, after a trial of 2 or 3 other APs	Caveats including the risk of weight gain, metabolic disorders, blood dyscrasias, and relapse on cessation.
Third line	Aripiprazole, quetiapine, ziprasidone	Third line because they are patented, and thus more expensive than generic SGAs or FGAs. Use before olanzapine because less risk of weight gain.	Ziprasidone is unavailable in the UK. The ADRs of these drugs differ from each other, and may be used in selection of drug for a given patient.
Fourth line	Olanzapine	Fourth line because more expensive than other drugs. In addition, high risk of weight gain and no robust evidence of greater effectiveness.	Rosenheck et al's comments are interesting in the light of the prevalence of prescribing of olanzapine in the UK.
Other drugs	RLAI (should be classed as 3 <sup>rd</sup> or 4 <sup>th</sup> line)	No comparative efficacy data with oral risperidone available, expensive	Data comparing RLAI with oral risperidone are now available.
	FGA depot drugs (should be classed as 3 <sup>rd</sup> or 4 <sup>th</sup> line)	Lack of comparative efficacy data vs. oral FGAs or RLAI, high risk of neurological side effects	FGA depots vary in ADR profile, and may be found to be acceptable by patients (Patel et al. 2008). Once steady state has been reached, on discontinuation it may take up to 3 months for the drug to clear out of the body. However, this should be balanced against advantages such as treatment adherence, etc. Unfortunately, funding of studies of these is now difficult to obtain.

groups. Dickson and colleagues (1999) performed a retrospective, uncontrolled, mirror-image study on patients with schizophrenia or schizoaffective disorder started on risperidone. Data on total hospital days three years pre- and three years post-risperidone were collected for 120 patients. On an intention to treat basis, there was no significant reduction in the number of days spent in hospital pre- and post-risperidone.

When cost-effectiveness is measured in terms of relapse, it would be expected that an injectable, long-acting medication, associated with improved compliance and lower rates of relapse (Davis et al. 1994), should compare favourably with oral medications. Obradovic et al. (2007) did not find this to be the case. Risperidone long-acting injection (RLAI)

incurred higher costs than the other medications and was found to be not as cost-effective as olanzapine, oral risperidone or aripiprazole. Recent data from Taylor and colleagues (in press) showed a significant increase in costs after initiation of RLAI in a six-year (three year pre-, three year post- initiation) mirror-image comparison study of 211 patients prescribed RLAI. Number of hospital days was the main outcome measure, secondary outcomes being number of admissions and direct healthcare utilisation costs. Hospital bed days remained similar for those patients who had continued on RLAI for three years. Attrition rates were high, with only 16% remaining on RLAI.

These results extend findings from an earlier study on the same cohort (Young and Taylor 2006) who had reported a 67.6% discontinuation rate after one year,

with an increase in hospital days after initiation. However, days spent in hospital for the three years preceding initiation of RLAI were increasing steadily year by year; it would appear that these patients may have been deteriorating clinically for some time before initiation of treatment. It is possible that because of the cost of RLAI, it is used most often in patients who may be treatment refractory, or intolerant to other medication, and so a poorer outcome and attrition rate may be expected. Results from modelling studies, in which recommended doses have been used, and projected outcomes analysed may not be generalisable to clinical practice (where response to this agent appears to be somewhat difficult to predict); in the latter, patients may require higher doses for efficacy and a longer duration of adjunctive oral treatment at initiation. Additionally, as RLAI is an expensive drug to prescribe, it may be reserved for patients who have already been unresponsive to or intolerant of other APs.

However, these results have not been borne out by other studies. Data from the electronic Schizophrenia Treatment Adherence Register (eSTAR) in Spain was used for a mirror-image cost effectiveness analysis of RLAI by Olivares and colleagues (2008). Three different outcome parameters (relapse with hospitalisation, relapse without hospitalisation, and neither relapse nor hospitalisation) were compared pre- and post-initiation of RLAI at 12 months ( $n=788$ ) and 24 months ( $n=757$ ). The cost was found to be lower after treatment with RLAI. As the measure of clinical effectiveness was “not relapsing or requiring treatment,” RLAI emerged as “dominant” in pharmacoeconomic terms (i.e. lower costs and better outcomes). The authors, however, urged caution in interpreting the results because of the methodological limitations and recommended a prospective study.

Edwards et al. (2005) found risperidone long-acting injection (RLAI) to be more cost-effective than its oral counterpart, as well as aripiprazole, oral haloperidol, olanzapine, quetiapine, ziprasidone or even haloperidol depot. These findings were based on costs incurred by relapse and hospitalisation rates over a year; patients taking RLAI experiencing fewer and shorter relapses.

Laux and colleagues (2005) used a discrete event simulation (DES) model to determine the cost-effectiveness of RLAI *vs.* depot haloperidol *vs.* oral olanzapine and RLAI over five years. Outcome measures in this study were hospitalisations, number and length of psychotic episodes, QALYs and cumulative symptom scores. Direct costs were calculated, but indirect costs and tolerability were not taken into account. The authors found RLAI to be “dominant” over both IM haloperidol and oral olanzapine. These findings are of interest in that although tolerability was not factored into the analysis, RLAI was still favourable over olanzapine on efficacy and cost alone.

Llorca et al. (2005) found RLAI to be “dominant” against olanzapine and haloperidol depot in a two-year, cost-effectiveness analysis of recently (one year or less) diagnosed patients. This modelling study employed effectiveness and ADR data from the published literature to estimate treatment response, and measured direct costs only, based on the French healthcare system. Doses were based on the recommended daily dose for

each drug as specified in the Marketing Application Authorisation (MAA). The costs incurred for successfully treating (defined by good clinical response and tolerability) a patient over 2 years were €16,995 (RLAI), €19,186 (olanzapine) and €30,023 (haloperidol). A higher percentage of patients were successfully treated with RLAI (82.7) than olanzapine (74.8) or haloperidol depot (57.3). These results are interesting in that RLAI, though an appreciably more expensive drug to purchase than olanzapine and haloperidol, was “dominant” over both the other comparator drugs. Injectable long-acting medication does enhance compliance; however, this cannot be the only relevant factor in this study, as the much cheaper haloperidol depot medication was found to be almost 50% less cost-effective than RLAI.

The above data seem to be at odds with findings from other trials in which olanzapine was found to be more cost-effective than oral risperidone. Knapp et al. 2008 (in data from the SOHO study) reported that olanzapine was more cost-effective than risperidone, even when tolerability, which would be expected to overall not be in favour of olanzapine, was included in the analysis. This may be an illustration of the extent to which study design (DES modelling *vs.* naturalistic trial) and methodology (different parameters for measuring cost-effectiveness) affect study outcome and interpretation.

There are several possible factors pertinent to the above. The patients in the studies in which RLAI appears to have a favourable pharmacoeconomic profile had a shorter duration of illness compared to those in CATIE and CUtLASS (mean duration of illness 13-14 years) (Lieberman et al. 2005, Jones et al. 2006). Therefore, they might be expected to have a better response to treatment with SGAs, which may have a slight advantage over haloperidol in the treatment of negative symptoms, especially for patients relatively early on in their illness trajectory. Moreover, in such patients, if social structures are still relatively intact, any treatment impacting on negative symptoms may have a larger effect.

#### D. Olanzapine

Recent data on the cost-effectiveness of olanzapine appear favourable (Knapp et al. 2008 - SOHO Study; Rosenheck et al. 2006 - CATIE Study). Both of these studies were large, multicentre, naturalistic trials, in which cost-effectiveness was measured by time to discontinuation of treatment and relapse rates. Obradovic et al. (2007) also found olanzapine to be the most cost-effective of the SGAs (omitting clozapine) in a review of published studies. Taylor et al. (2003), as mentioned earlier, found olanzapine to be a similarly effective but more expensive option when compared to oral risperidone, mainly because of direct drug costs.

Hamilton and colleagues (1999) collected direct costs alongside a randomised, double-blind trial of olanzapine and haloperidol in non-treatment resistant patients (Tollefson et al. 1997). No follow-up data were collected on patients after the acute phase if they were deemed to have failed to respond, or if they dropped out of the trial. Since no data were collected on drop-

outs, the investigators attempted to control for different periods of follow-up by deriving the mean total costs per day. This was then multiplied by the number of days in the phase in which costs were being compared (43 and 323 days for the acute and maintenance phases respectively). There was no statistical difference in the patient groups in terms of rates of completion or clinical response. There was, however, a significant reduction in the cost of hospitalisation in the olanzapine group, offsetting the higher medication costs in this group, and resulting in a trend for an overall lower cost in the olanzapine treated group.

A cost-utility analysis of drugs used in the three-year, prospective, open label SOHO study (Knapp et al. 2008) found olanzapine to be slightly more cost-effective than clozapine, and more effective than all the other SGAs used (amisulpride, quetiapine and risperidone) as well as oral and depot FGAs, when measured in QALYs.

Rabinowitz and colleagues (2000) had previously found olanzapine to be less cost-effective than risperidone in a head-to-head comparison study, in which clinical outcomes, costs and prescriber preference were measured. In the cost-effectiveness analysis (which was limited to a comparison of the cost of the drugs themselves), risperidone was found to be more than twice as cheap as olanzapine, and in terms of clinical outcome, of six trials reviewed, three found better outcome with risperidone, and three found equivalent clinical outcome between the two drugs.

Cost-effectiveness data on olanzapine seems to suggest that it is a cost-effective, though expensive treatment, and that costs may be offset by good adherence, good clinical outcome and quality of life. However, in view of the high risk of weight gain and metabolic problems associated with olanzapine, studies assessing longer-term outcomes (*i.e.*, more than 18 month's duration) and addressing the ongoing costs of ADRS sustained would be enlightening.

### *E. Quetiapine*

There are not yet many available data regarding the cost-effectiveness of quetiapine except in large head to head studies. Swartz et al (2008) in their analysis of the CATIE trial results found quetiapine to be less effective than olanzapine (measured by time to discontinuation of the drug), but more effective than other APs in the second phase of the trial, in which patients intolerant of perphenazine were randomised to either quetiapine, olanzapine, risperidone or ziprasidone.

The pan-European SOHO study found quetiapine to be less cost-effective than olanzapine (which achieved "dominance" over quetiapine) and risperidone (Knapp et al. 2008). Likewise, Rosenheck et al. (2008) in their cost-effective analysis of the CATIE data found it to be less cost-effective than olanzapine and risperidone. However, in the second phase of the study, in which patients who had been intolerant of perphenazine were switched to an alternative drug, quetiapine was found to be the most effective, and best tolerated. The large cost-effectiveness review conducted by Obradovic et al. (2007), using remission days to calculate clinical effectiveness against the cost of

treatment reported that quetiapine was less cost-effective than olanzapine and risperidone. However, Edwards et al. (2005), using a decision analytical model found it to be equivalent to aripiprazole, olanzapine, oral risperidone, and ziprasidone, when outcome was measured in relapse and hospitalisation days. An earlier mirror-image study comparing costs for a year pre- and post-initiation of quetiapine (Lynch et al. 2001) found it to be a clinically effective treatment, but that there was no significant difference in pre- and post-costs.

A new extended release formulation of quetiapine (Seroquel XL) became available in the UK in September 2008. Greater ease of administration (once daily and slow titration not required) may improve the cost-effectiveness profile, as the pill burden is reduced and the regime more simple, potentially enhancing patient and prescriber acceptability.

### *FGAs vs. SGAs*

The two major studies in favour of FGAs in pharmaco-economic terms are the CuTLASS and CATIE trials. Both were large, multicentre, government funded RCTs that tested the hypothesis that low doses of FGAs may be as effective and tolerable, and cheaper than SGAs; the previous data reporting the superior efficacy, tolerability and cost-effectiveness of SGAs were derived from studies in which disproportionately high doses of a high potency FGA (usually haloperidol) had been given and had compared unfavourably to SGAs given at average doses.

The CuTLASS study protocol permitted the treating clinician to choose the individual drug within the "class" (FGA or SGA) assigned. The findings were that FGAs were as effective and as well-tolerated as SGAs, as well as being cheaper; hence, more cost-effective. Both trials allowed the introduction of clozapine for patients unresponsive to treatment where it was clinically indicated, and both trials found clozapine to be a more effective treatment than any other drug. Controlled, six-year mirror-image analysis of hospital bed use in patients switched from FGAs to SGAs vs. switching between FGAs in the CuTLASS Study (Taylor et al. 2007) found that patients switched to an SGA spent significantly more days in hospital after the switch than those who remained on an FGA; a switch to clozapine was associated with a non-significant increase.

However, there were important limitations in the CATIE trial, which should be taken into account when interpreting the data. Rosenheck et al. (2006) (for the CATIE trial study group) stated that the results found were not generalisable to many groups of psychiatric patients (such as first episode), nor beyond 18 months of treatment, as no follow-up data on the incidence of tardive dyskinesia (TD) or metabolic disorders in the participants was available during the cost-effectiveness analysis. Patients with existing TD were not permitted to receive perphenazine, and were thus allocated to SGAs, which introduces a systematic bias into the study. Specifically, this may have been to the advantage of the FGAs, in that patients with TD might have had a longer duration of illness, been exposed to more pharmacotherapy, and so may have been relatively more



treatment-refractory. Such patients might have been more appropriately treated with clozapine. Moreover, importantly, TD is associated with poorer clinical outcome across a number of domains (Ascher-Svanum et al. 2008); hence those allocated to the SGA arm owing to pre-existing TD would not be expected to do as well. Indeed, patients who met the Schooler and Kane criteria for TD on baseline entry to CATIE were characterised by being “older,” having “higher ratings of psychopathology,” a longer duration of receiving AP medication (more likely to be FGA and in addition an anticholinergic), and were more likely to have a history of substance misuse (Miller et al. 2005). Although the TD group allocated to SGAs were not involved in any head-to-head analysis *vs.* perphenazine (Swartz et al. 2008), the finding of cost-effectiveness of perphenazine can therefore be generalised only to a limited extent. Additionally, the analysis was limited to 18 months; after which only 25.9% of patients had completed treatment with the drug assigned at the beginning of the study (Rosenheck et al. 2006), further limiting interpretation of this study. Other studies, both “real world” and using modelling, have been able to demonstrate that SGAs may be more cost-effective or show “dominance” over FGAs.

Heeg et al. (2008) used a discrete event simulation (DES) model to mimic patient care in the UK based on NICE Guidelines to compare cost-effectiveness of SGAs *vs.* FGAs. The study used fairly comprehensive outcome criteria, encompassing QALYs, symptoms, ADRs, and compliance against direct costs. The model covered a five-year period, longer than most cost-effectiveness studies, but as demonstrated by Drew et al. (2002) in their five year clozapine study, SGAs tend to prove more and more cost-effective over time. The findings of Heeg and colleagues were that SGAs are cost-effective, when superior efficacy was taken into account as well as tolerability – the latter would not alone have been enough to offset the higher cost of the drugs. The authors stated that naturalistic studies are needed in order to validate these results.

Gau et al. (2008) in a naturalistic open-label study, compared the overall costs of treatment with haloperidol to treatment with an SGA (clozapine, olanzapine, quetiapine, risperidone, zotepine) in 3,047 first-episode patients over a year. When total costs were calculated, haloperidol was more expensive than all the other drugs except clozapine, which incurred higher hospitalisation costs. Treatment with all other SGAs resulted in fewer and shorter hospital stays, incurring lower costs. Patients on SGAs had more outpatient visits, and incurred much higher drug costs but this was offset by the lower rate of hospitalisation. As this sample were first episode patients the authors concluded that SGA treatment was appropriate and cost-effective in this group.

## Comparisons within SGAs

As already mentioned, the two largest comparisons *within* atypical studies are the SOHO and the CATIE Studies, as already outlined (Knapp et al. 2008 - SOHO study; Rosenheck et al. 2008 - CATIE). A cost-effectiveness review comparing a wide range of

antipsychotics over a year using decision tree analysis found olanzapine and risperidone to be the most cost-effective when outcomes were based on published data for remission and rehospitalisation rates (Obradovic et al. 2007). Quetiapine was found to be the least effective (32.7% only remained in remission).

Gau et al. (2008) calculated the cost-effectiveness of individual SGAs, using the number of hospital days, outpatient visits and prescription days as economic outcomes. Clozapine was found to be the most expensive, owing to longer hospital stays, and olanzapine the most cost-effective, followed by quetiapine. Risperidone was less cost-effective than the other SGAs.

## Discussion

Schizophrenia is a lifetime illness, and a large proportion of patients will require different treatment strategies throughout its course. Response to treatment remains an individual and idiosyncratic phenomenon, without the degree of predictability that would allow the results of most cost-effectiveness studies to be broadly generalisable. There are an abundance of data regarding the cost-effectiveness and cost utility of individual drugs, as well as classes of drugs, much of it contradictory, with results that may be somewhat dependent on study design.

Thus, there are clearly various methodological issues in pharmacoeconomic studies that may limit the conclusions that can be drawn. There are problems with attaching economic evaluations to double-blind controlled trials designed to assess efficacy and safety. Economic studies in general require larger sample sizes to be adequately powered. This is due to the greater variance in cost outcomes (Drummond & Davies 1991). In modelling studies, assumptions based on relative drug efficacy may lead to conclusions that do not translate to clinical practice. Pharmacoeconomic studies that do not use tolerability in their assessment of clinical outcome may likewise result in having limited generalisability. With respect to clozapine, there is evidence that it is cost-effective in patients who are resistant to treatment, particularly high users of inpatient facilities. For patients able to continue on clozapine, the cost savings are realised after clozapine treatment has continued for at least one year, and economic value continues to increase over time. There is at present insufficient evidence to draw *firm* conclusions about the cost-effectiveness of aripiprazole, risperidone, olanzapine, quetiapine, or other SGAs. Comparisons between FGAs and SGAs continue to be a matter of debate, and undoubtedly, further studies will add to the body of knowledge on the cost-effectiveness of drugs for schizophrenia.

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