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Antipsychotic Medication for People with First Episode Schizophrenia: An Exploratory Economic Analysis of Alternative Treatment Algorithms

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ANTIPSYCHOTIC MEDICATION FOR PEOPLE WITH FIRST EPISODE SCHIZOPHRENIA: AN EXPLORATORY ECONOMIC ANALYSIS OF ALTERNATIVE TREATMENT ALGORITHMS

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1. INTRODUCTION

Available clinical evidence suggests that the newer antipsychotics are similar to conventional antipsychotics for positive symptom control. It has been suggested that they may also be superior for negative symptoms and side effects, but the evidence for this is unclear (Duggan et al, 1999, Kennedy et al, 1999, Srisurapanont et al, 1999, Thornley et al, 1999, Tuunainen and Gilbody, 1999, Wahlbeck et al, 1999). These differences if they exist, may lead to improvements in quality of life and patient satisfaction and subsequent rates of compliance with therapy. If the latter occurs, there may also be improvements in the overall level of symptom control and rate of relapse. Economic evaluations of risperidone suggest that these differences could lead to savings in the use of hospital inpatient care compared to conventional antipsychotics (Guest et al, 1996, Glennie, 1997).

The available economic evidence suggests that the use of clozapine has the potential to improve the efficient use of health and social service resources in some patients (Revicki et al, 1990, Davies & Drummond, 1993, Meltzer et al, 1993, Aitchison & Kerwin, 1997, Glennie, 1997, Rosenheck et al, 1997). All of these studies indicate that overall, clozapine is associated with lower rates of hospital inpatient admissions and lower duration of inpatient stay. These are due to earlier discharge from the index inpatient admission and lower rates of relapse. These differences in the use of inpatient care are sufficient to offset the additional costs of purchasing clozapine.

However, the designs of all the economic studies raise several issues of concern, such as control for biases, sources of data and methods of data collection, measurement of outcomes, the type and dose regimes of comparator drugs. In addition, the clinical and economic data for these evaluations were collected for a patient population with a long duration of illness and/or who are treatment resistant or intolerant of typical antipsychotic therapy. It is not clear that these are applicable to people with early schizophrenia or those who have not had problems with previous antipsychotics.

Patients currently categorised as treatment resistant or treatment intolerant are likely to have a long history of schizophrenia. This is partly due to historical factors, such as the limited number of antipsychotics available, concerns about the safety of clozapine and the restricted use of expensive atypical antipsychotics. These factors may be associated with a relatively poor quality of life and more intensive use of health care services in patients with a longer duration of illness. Any improvements in clinical outcome as a result of a change in antipsychotic may also result in relatively important changes in health status and intensity of health service utilisation, compared to those with a recent diagnosis of schizophrenia. In

addition, there is some limited evidence that the use of services following entry to a clinical trial is related to the level of resource use prior to entry (Rosenheck et al, 1999).

Furthermore, there is a trend to reduce reliance on inpatient or institutional care for people with acute or chronic mental illness. The total number of commissioned hospital bed days for people with mental illness decreased from 14 million to 11.5 million between 1992-3 and 1997-8 and the number of ward attendees fell from 124000 to 93000 (Department of Health, 1998a). Over the same period the number of daily available hospital beds for people with mental illness declined from 47000 to 37000, while the number of outpatient attendances rose from 1.8 million to 2.1 million (HPSS, 1998). Creed et al (1997) suggest that approximately 40% of people with acute episodes of mental illness (including schizophrenia) can be treated by attending psychiatric day hospitals rather then with hospital inpatient admissions.

These factors may over estimate the likely value for money of the atypical antipsychotics, in cohorts of people with first episode schizophrenia in the current UK mental health service (Rosenheck et al, 1999).

Given the constraints on health and social care budgets, purchasers and providers need to ensure that resources are used efficiently. A variety of guidelines and treatment protocols have been published, or developed for use at a local level to support decisions about the choice of antipsychotic for people with a first episode of schizophrenia. In addition, there are wide variations in the availability and use of the atypical antipsychotics in the UK. Current published literature is not sufficient to address all the economic issues of concern and there is a need for evaluation of the relative efficiency of clozapine and the new antipsychotics. The NHS R&D HTA has funded primary research to assess the relative costs and utility of typical and atypical antipsychotics for people who are resistant to or intolerant of at least two antipsychotics. However, the results of the research will not be available for at least 3 years. In addition, it is also important to assess the value of the new drugs in the context of alternative prescribing guidelines, and for people with a first episode of schizophrenia. This paper presents the results of secondary research to explore the potential economic impact of atypical antipsychotics for people in the context of current clinical guidelines.

2. METHODS

2.1 Objectives

The primary objective was to compare the potential economic impact of typical and atypical antipsychotics, for people with a first episode of schizophrenia for a number of different scenarios. The first of these made no assumptions about the antipsychotic therapy given to

patients who were intolerant to or did not respond to the initial antipsychotic. The second scenario explored the impact of specifying the sequence of antipsychotic therapies following withdrawal from the first.

2.2 Comparators

The antipsychotics included in the analysis were constrained to two typical antipsychotics: chlorpromazine and haloperidol and three atypical antipsychotics: risperidone, clozapine and olanzapine. Other antipsychotics were excluded due to concerns about safety and lack of efficacy (eg Sertindole) when compared to typical antipsychotics, or relatively small market share in the UK (eg quetiapine, amisulpiride).

2.3 Approach

The study used the framework of economic evaluation to estimate the potential efficiency or value for money of the typical and newer atypical antipsychotics. This included an assessment of the likely clinical and patient outcomes and associated health and social service resource use. A decision analytic model was developed from existing clinical guidelines to compare the expected costs and outcomes associated with each of the therapies and estimate the range of uncertainty surrounding these results.

2.4 Perspective

The perspective of the analysis was constrained to that of the providers/funders of health and social care services and patients. Whilst this did not extend to a full societal perspective, it did include those perspectives where the use of atypical antipsychotics is likely to have a major impact.

2.5 Patient population

To be consistent with the population targeted by current clinical guidelines (Conley and Buchanan, 1997, McEvoy et al, 1997, Lehman et al, 1998, Kerwin et al, 1999, Stubbs and Haw, 2000), the analysis was restricted to a consideration of the likely costs and outcomes for patients with a first episode of schizophrenia. This allowed exploration of the future potential of the atypical antipsychotics in a mental health service that is itself subject to change.

2.6 Time frame

The analysis used a three year time frame to assess alternative prescribing strategies. The time frame of the model allows up to 3 switches of therapy within the first year, plus a 4^{th}, undefined, therapy for those patients who are intolerant of or resistant to three medication. For those patients who move to maintenance therapy, there is a small but significant annual risk of tardive dyskinesia. The three year time frame of the model allows a patient to try

three antipsychotics at annual intervals (the maximum number of antipsychotics with differential rates of estimated tardive dyskinesia). It also allows the patient to complete one year of the final antipsychotic.

2.7 Outcome measures

The analysis uses one intermediate and two final outcomes. First, the proportion of people who require one or more changes in therapy. Secondly, the expected total direct costs of the resources used to provide health and social care services. Thirdly, the benefits to patients in terms of expected quality adjusted life years (QALY's). For the latter measure, the analysis assumes no difference in survival over the time frame of the evaluation. However it is assumed that differences in symptom control and side effect profiles will affect the utility associated with each of the comparators (Glennie, 1997, Rosenheck et al, 1998).

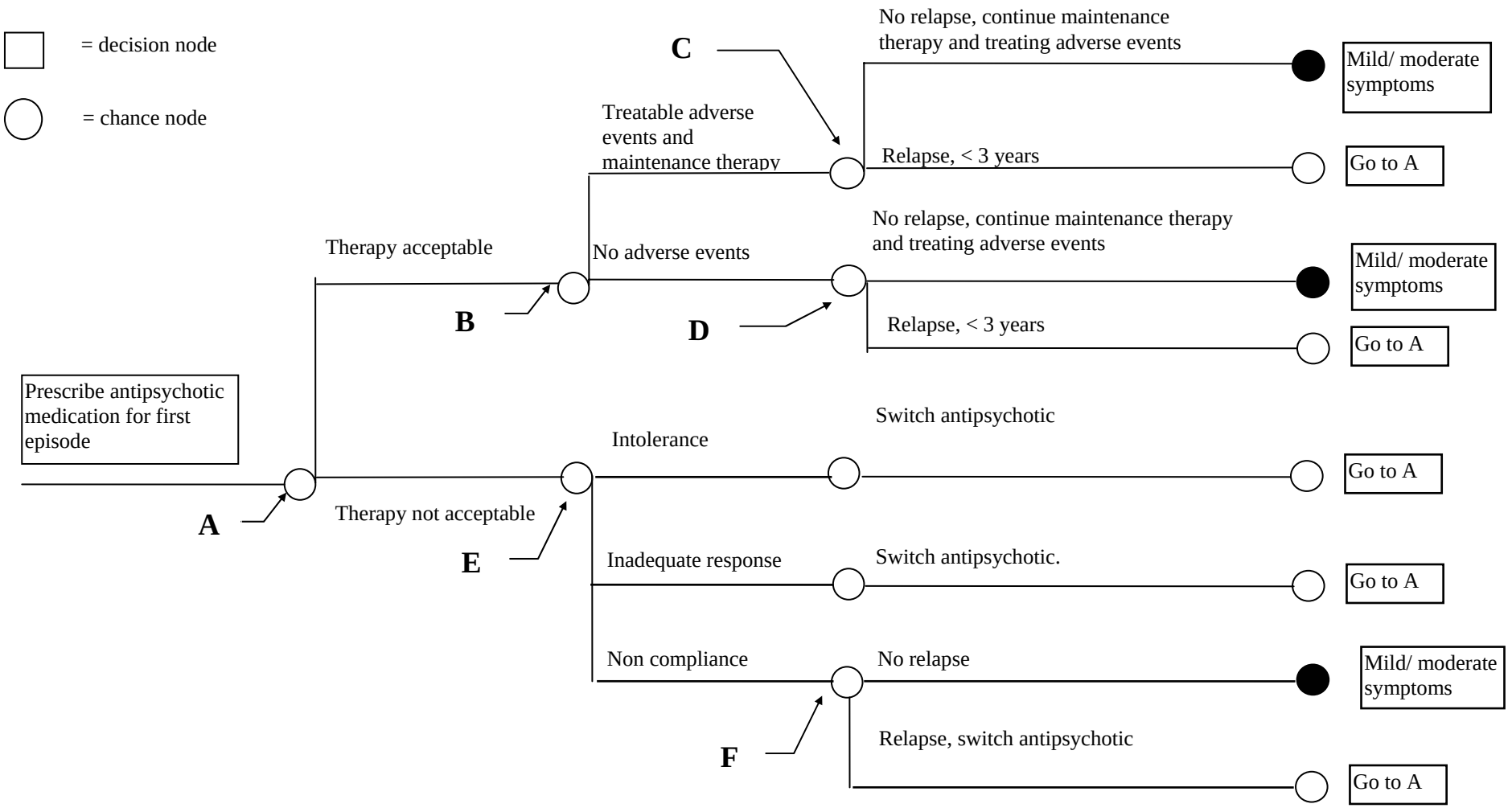
2.8 Decision analytic model

Figure 1 presents a decision path to illustrate the potential consequences associated with the initial decision to prescribe an antipsychotic medication for people with a first episode of schizophrenia. The model starts at the point at which a person presents with a first episode of schizophrenia. The clinician and patient then have a choice of antipsychotic drug therapies for the treatment of the acute episode. It is assumed that the option of no drug therapy is not applicable in this case (Thornley et al, 1999). Whichever therapy is chosen, the range of possible events is assumed to be the same. However, the probability of those events occurring may vary between the alternative antipsychotics.

Following initiation of antipsychotic therapy for first episode schizophrenia, there is a chance that the treatment will be acceptable to both patient and clinician or not acceptable (chance node A). For those patients who find treatment acceptable, there may be associated adverse events, which are treatable and/or acceptable (chance node B). If the patient has no adverse events or treatable adverse events, they are transferred to maintenance therapy. Whilst on maintenance therapy the patient may relapse within the three year time frame (chance nodes C and D). If the patient relapses, following acceptable treatment it is assumed that they will be treated for an acute episode, with the same antipsychotic. Following each relapse there will be a chance that therapy is acceptable or not acceptable (chance node A). For those patients continuing on maintenance therapy, there is a chance that they will have an adequate response to therapy or not. Those with an adequate response are assumed to have mild symptoms, and those with an inadequate response to have moderate symptoms.

If the initial therapy is not acceptable, this may be due to intolerance (adverse events which are not treatable or not acceptable), inadequate response or non compliance (chance node E).

Figure 1 Simplified decision path for the treatment of people with schizophrenia



If the patient is intolerant to therapy, there will be a switch to an alternative antipsychotic. Following each switch in therapy there is a chance that the new treatment will be acceptable or not (chance node A).

If the patient has an inadequate response to therapy which is unacceptable, there will be a switch to an alternative antipsychotic. Following each switch in therapy there is a chance that the new treatment will be acceptable or not (chance node A).

If the patient does not comply with therapy, for whatever reason, there is a chance that they will have a relapse. If they relapse, there will be a switch in antipsychotic. Following each switch in therapy there is a chance that the new treatment will be acceptable or not (chance node A). If the patient does not relapse, it is assumed that there will be no change in treatment strategy.

2.9 Analyses of data

Probabilistic simulations were used to estimate the expected costs and outcomes associated with each of the antipsychotics, and alternative guidelines or treatment protocols (Doubillet et al, 1985). To conduct the simulations, key variables were each assigned a central value (e.g. mean, best guess) and a distribution or spread around that measure (e.g. standard deviation, minimum or maximum). The key variables, methods of estimation and sources of data are described in section 3. The simulation recalculated the results over a number of iterations. For each iteration the value of the key variables was sampled at random from the distributions specified. By repeating the calculations of expected costs and outcomes in this way a spread of estimates is obtained, which allow estimation of the mean expected costs and QALY's and associated 95% confidence intervals.

Two analyses were conducted using alternative distributional forms for the data. For the first, the normal distribution was specified for the majority of the variables for the base case analyses. A truncated form of the distribution was specified for the probability parameters, which were constrained to values between 0 and 1. Resource use and unit cost variables were also constrained to values between the minimum and maximum possible for each item. For example, inpatient stay per year must be constrained to be equal to or greater than 0 days, but less than 366 days. Where national statistics gave minimum and maximum values for variables these were used in preference to hypothetical constraints.

The main advantage of the normal distribution is that it incorporates all the estimates of event rates or resource use identified. However, it does require that the data are approximately

normally distributed around the measure of central tendency. There was some evidence that the input data were skewed, which could in principle, result in a type 1 error.

To assess whether the distribution used would affect the results in terms of mean expected values, variance and statistical significance of differences in expected values, the second analysis used the triangular distribution. The main advantage of the triangular distribution is that it makes no assumptions about the distribution or spread of values around the most likely estimate of a parameter. However, it may be inefficient in that it only uses three pieces of information. For each variable these were the minimum and maximum values found, plus an estimate of the most likely value. The most likely value was calculated as the mean of all estimates identified.

The sampling method used was Monte Carlo, true expected value. The simulation software used was @RISK, as an add on to MSOFFICE Excel v.7.0. Every simulation requires sufficient iterations to ensure that each variable is sampled over the full distribution of values specified and the statistics generated are reliable. As the number of iterations increases, the distribution for the outcomes is described in more detail and becomes more stable. The amount of change in the percentile values, mean and standard deviation decreases with each subsequent iteration. The number of iterations for each simulation were determined by the software, which halted the simulation when convergence at less than 1.5% in percentile values, mean and standard deviation was achieved.

2.9.1 Simulated three year expected costs and QALY's

The analysis of expected costs and QALY's associated with each of the antipsychotics was conducted in three stages. It was assumed for this analysis that the choice of 2nd, 3rd and 4th line therapies was not governed by pre-determined decision rules. The expected costs and QALY's of follow on therapy were estimated using a triangular distribution. This requires three values, minimum, best guess and maximum. The minimum and maximum were determined by the range of expected costs and QALY's estimated by the model. The best guess estimate was set as the median value of these variables.

The first stage was to determine the costs of failure of 3rd line therapy. This was imputed by estimating the expected costs and quality adjusted life years associated with each of the antipsychotics when used as 3rd line therapy, excluding follow on medication for those who found 3rd line therapy unacceptable. The median expected costs and QALY's were used to proxy the expected costs and QALY's of 4th line therapy. A triangular distribution was used, based on the minimum and maximum values found, with the median values used as the measure of central tendency.

In the second stage, the imputed total expected costs and QALY's for follow on medication for patients who failed 2nd line therapy were estimated. These were calculated as the expected costs and QALY's of 3rd line therapy (including the expected costs and QALY's of 4th line follow on medication and care). The imputed costs and benefits of 3rd line medication for those patients who found the 2nd line antipsychotic unacceptable, were estimated from the median values using a triangular distribution.

The third stage was to calculate the expected costs and quality adjusted life years of follow on therapy for those patients who found the 1st line antipsychotic unacceptable, which were calculated as for 2nd line therapy.

2.9.2 Simulated three year expected costs and QALY's of alternative treatment protocols

The simulation analysis was repeated to assess the relative impact on expected costs and QALY's of 8 protocols specifying the sequence of antipsychotics from the first episode of schizophrenia. The term typical antipsychotic refers to chlorpromazine or haloperidol, atypical antipsychotic refers to risperidone or olanzapine, and excludes clozapine. The protocols are summarised as:

1. Typical antipsychotic 1st and 2nd line, atypical antipsychotic 3rd line, clozapine 4th line;
2. Typical antipsychotic 1st and 2nd line, clozapine 3rd line, atypical antipsychotic 4th line;
3. Typical antipsychotic 1st line, atypical antipsychotic 2nd line, atypical antipsychotic 3rd line, clozapine 4th line;
4. Typical antipsychotic 1st line, atypical antipsychotic 2nd line, clozapine 3rd line, typical antipsychotic 4th line;
5. Typical antipsychotic 1st line, atypical antipsychotic 2nd line, clozapine 3rd line, atypical antipsychotic 4th line;
6. Atypical antipsychotic 1st and 2nd line, clozapine 3rd line, typical antipsychotic 4th line;
7. Lower dose typical antipsychotic 1st line, atypical antipsychotic 2nd line, atypical antipsychotic 3rd line, clozapine 4th line;
8. Lower dose typical antipsychotic 1st line, atypical antipsychotic 2nd line, clozapine 3rd line, typical antipsychotic 4th line;

The expected costs and QALY's for these protocols were estimated in three stages as above. In addition, each antipsychotic could not be used for more than one stage of therapy within the protocol. For example, in protocol 1, if the first typical antipsychotic used was chlorpromazine, then the 2nd line therapy was restricted to haloperidol.

3. DATA AND VARIABLE ESTIMATION

3.1 Sources of data

The principle source of data was a review of published clinical and economic literature. Relevant literature was identified from a search of Medline, Econlit, Cinahl and the Cochrane library. If a systematic review from the Cochrane Library was available, this was used as the principal source of clinical data. The other clinical papers included in the review were used to supplement the data from the systematic reviews. Where a Cochrane review was used, the data for this analysis was derived from all the studies included in the Cochrane review, which used an active comparator. Placebo controlled trials were excluded for this economic evaluation. The general inclusion criteria for the Cochrane reviews are that the studies are randomised controlled trials (RCTs) with low (category A) to moderate bias (category B) (Cochrane Schizophrenia Group, 1999).

Specific exclusion criteria for individual clinical papers to supplement the Cochrane systematic reviews were: trials with no active comparator, non RCTs, pharmacologic or pharmacokinetic studies, dosing/titration studies or studies which did not include final clinical outcomes in terms of symptom control or patient acceptability. Some papers which did not meet these criteria were included only if they contained information relevant to the estimation of economic endpoints in terms of resource use or costs. There were relatively few economic publications, so all economic evaluations which included a comparison of the costs and outcomes of alternative treatments were included in the review.

3.2 Variable estimation: probabilities of events

The probability data for the model were drawn from a variety of sources, for heterogeneous populations. In addition, many of the data for the probability of events were drawn from a number of clinical trials. The variability in antipsychotic trial design, comparators, outcome measure and length of follow up is well documented (Thornley et al, 1999, Wahlbeck, 1999, Kennedy et al, 1999, Tuunainen et al, 1999). This meant that the available data on event rates were not consistent or directly comparable across studies. Composite variables were defined to reduce variation in the outcome measures reported.

Where more than one source of data was available the mean (standard deviation) probability values for the model were estimated as the average probability of an event weighted by the size of the trial. This gave more weight to larger trials: $\sum(p_{ti}*n_{ti})$/ no. of trials.

3.2.1 Probabilities of events: composite variables

To reduce inconsistency due to differences in the measures of outcome and adverse events used in different trials and differences in the methods of reporting these data a number of composite variables were defined. These also simplified the construction of the model and

analysis of the data. These were clinical improvement, acceptability of treatment, intolerance, compliance and inadequate response.

The definition of inadequate response was taken as that used by the systematic review or trial investigators. Adequate response or clinical improvement was estimated as 1- the probability of inadequate response.

Acceptability of treatment was defined as the proportion of people able and willing to continue with the prescribed antipsychotic as maintenance therapy. These people may have no adverse events associated with therapy, or adverse events which are tolerable or treatable. They may also have an inadequate response, but prefer to remain on allocated treatment. Acceptability of treatment was estimated from systematic review or clinical trial data on the number of people who remained in allocated therapy. Unacceptable treatment was estimated as 1- the probability that treatment was acceptable.

Intolerance, inadequate response and non compliance were then defined as unacceptable levels of these events which led to discontinuation of allocated therapy. Intolerance was defined as events which mandated a switch in therapy because of:

- irreversible or life threatening consequences which could not be adequately treated (for instance neuroleptic malignant syndrome (NMS), tardive dyskinesia, agranulocytosis and hepatic dysfunction);

- a level of severity of adverse events which could not be adequately resolved with additional treatment.

The conditional probability of intolerance, given unacceptable treatment was estimated as:

$$\frac{[P_{ae} - (P_{ae} * P_{at}) + P_{td} + P_{nms} + P_{ag} + P_{hd}]}{P_{at}}$$

P_{ae} = the probability of adverse events which are not irreversible or life threatening;
P_{at} = the probability that treatment is acceptable;
P_{td} = the probability of tardive dyskinesia;
P_{nms} = the probability of neuroleptic malignant syndrome;
P_{ag} = the probability of agranulocytosis;
P_{hd} = the probability of hepatic dysfunction

This calculation ensures that adverse events which are not irreversible or life threatening are weighted by the acceptability of treatment and that there is no double counting. It also ensures that events which are irreversible or life threatening are only represented in the intolerance branch of the model, and are not under estimated.

Non compliance was defined as refusal to adhere to a treatment regime which had adequate symptom control. In addition, depot therapy had either failed or was not an appropriate option. The probability of non compliance was estimated from the literature. The conditional probability of non compliance given unacceptable treatment was estimated as the probability of non compliance divided by the probability of unacceptable treatment.

The definition of adequate and inadequate response to therapy used in clinical trials varied considerably. Therefore inadequate response requiring a change in therapy was defined as a default variable. The conditional probability of an inadequate response, given unacceptability of treatment was defined as 1 minus the conditional probability of intolerance minus the conditional probability of non compliance.

3.2.2 Probabilities of events: Lower dose typical antipsychotics

Descriptions of the maximum allowable dose of the typical antipsychotics were used to determine trials which used lower dose therapy only. Lower dose typical antipsychotic medication was defined as equal to or less than 12mg haloperidol per day or chlorpromazine equivalent.

3.3 Variable estimation: costs of events

The costs of events were estimated from measures of the health and social care service use associated with the events, multiplied by the unit costs or prices of those events. Wherever possible, resource use was estimated from clinical guidelines or best practice. In addition, it was assumed that the use of long stay residential or institutional care for first episode patients would be determined by the socio deomographic characteristics of the patients and severity of disease, rather than the choice of antipsychotic drug. This implied the further assumption that the choice of antipsychotic would only affect the need for acute inpatient services for initiation of therapy, switch of antipsychotic and acute management of relapses. In particular, the costs of long term maintenance therapy excluded the costs of long stay nursing home or residential care, since it was assumed that these would not be affected by the choice of drug in the patient population considered.

These assumptions **do not** reflect the relative impact of the antipsychotics on the current cohort of patients with long standing schizophrenia and who may be treatment resistant or intolerant of therapy. However, the assumptions are consistent with the objectives and patient group for this analysis.

3.4 Variable estimation: quality adjusted life years

Quality adjusted life years (QALY's) were estimated as life years weighted by the utility of the health status experienced within the period of analysis. It was assumed that all patients would survive for the full period of analysis (3 years). This may overestimate the total survival and therefore QALY's for each of the comparisons. There is no evidence of differences in survival for the antipsychotics included in this analysis, so is unlikely to affect relative differences in the estimates of expected QALY's. However health status and health related quality of life would vary according to symptoms and adverse events. It was assumed that all patients would have either mild symptoms or moderate to severe symptoms. It was also assumed that adverse events and admission to hospital would incur a disutility (or negative utility). Utility values between 0 and 1 were attached to mild symptoms and moderate to severe symptoms.

4 RESULTS

4.1 Probabilities of events

The majority of the clinical trial data were for people with chronic schizophrenia. It was not possible to estimate probabilities of events using data which were specific to a first episode population only. There was considerable inconsistency in the measurement and reporting of events. In particular, many of the reports did not include events which occurred in less than a pre-defined proportion of patients, or for which there was no statistically significant difference between comparators.

This meant that the adverse events included in the analysis were restricted to those where data was available for all comparators, or were irreversible or life threatening. These were EPS (excluding tardive dyskinesia), tardive dyskinesia, neuroleptic malignant syndrome, hepatic dysfunction and agranulocytosis. It is likely that other events were indirectly included if they were severe enough to lead to discontinuation of therapy. In addition, these were the main events with clearly defined management strategies.

Table 1 presents the average or best guess estimates of the probabilities of events, (with standard deviations where appropriate), which were estimated from the raw data from the clinical trials and systematic reviews included in the analysis. The majority of data were drawn from existing systematic reviews (Table 1). There were insufficient trials which

reported the rates of specific events to estimate standard deviations or minimum and maximum values for tardive dyskinesia, neuroleptic malignant syndrome, hepatic dysfunction and agranulocytosis. These events were not assigned a distribution in the model.

Tables 2 and 3 present the derived probabilities of the events included in the model, for two alternative distributions of data. The data in Table 2 were derived from the mean value and standard deviation, assuming a truncated normal distribution, which was restricted to a minimum value of zero and a maximum value of 1. It was assumed that the total number of patients within the included trials represented a sufficiently large sample to approximate a normal distribution. However, the use of the normal distribution may bias the results and/or be inefficient if the data take an alternative distributional form.

Table 3 presents the derived probabilities when a triangular distributional form was imposed. This was estimated from data on the weighted average or best guess, minimum and maximum values for events which were assigned a distribution. The weighted average or best guess was assigned as the most likely value. The direction of the skew of the data was determined by the most likely value in relation to the minimum and maximum values specified. There were differences in most of the values assigned to different events between the two distributional forms. However, there was no consistent trend which affected the relative differences between the event rates assigned to each of the antipsychotics.

4.2 Use of health and social care services

Table 4 presents the estimated use of inpatient care from available economic evaluations of antipsychotic therapy. All of the studies were based on data for patients with a relatively long duration of schizophrenia, many of whom also had a history of long durations of inpatient care. The average number of inpatient admissions ranges from less than 1 per year to 2 per year. The average length of stay per year ranges from 25 to 365 days. Many of these studies included patients with a long duration of illness and/or previous inpatient or residential and were not considered appropriate for the patient population included in this analysis.

Table 5 presents the data for the model on use of health and social care services associated with initial therapy, maintenance therapy, management of relapses, switch in antipsychotic medications and treatment of adverse events. The probability of inpatient admission for initiation of therapy was estimated from a recent trial of day and inpatient therapy for people with acute psychiatric illness (Creed et al, 1997). Nearly half of the patients in the trial had schizophrenia.

The mean length of stay (and standard deviation) for people who had an inpatient admission was estimated from national data on the average length of stay for mental illness (CIPFA, 1998). A truncated normal distribution was applied. This included the mean and standard deviation, with a minimum stay of 1 day and a maximum of 130 days stay. The estimates of the probability of inpatient admission and average length of stay per admission were similar to those reported by a number of the studies reviewed in Table 4.

The number of days per year for which community based services were required was calculated as 365 minus the length of inpatient stay for initiation/change of therapy and relapse.

4.3 Unit costs of resources

Table 6 presents the unit costs of resources. The mean (standard deviation) costs of inpatient stay, day patient and outpatient visits were estimated from national hospital costs data (CIPFA, 1998). They were assigned a normal truncated distribution. The costs of community services were taken from published data on the national average costs of health and social care services. (Netten et al, 1998). The costs of drug therapy were estimated from the British National Formulary, 1998.

4.4 Utility and quality adjusted life years

A number of studies have included quality of life measures such as the Quality of Life inventory, Heinrichs-Carpenter Quality of Life Scale or the Short Form - 36 for people with schizophrenia (Essock et al, 1996, Rosenheck et al, 1997, Mahmoud et al, 1998, Rosenheck et al, 1999). Three studies indicated that there may be small improvements in the quality of life associated with clozapine and risperidone. These were significant in favour of risperidone in one study (Mahmoud et al, 1998).

Only three economic evaluations of antipsychotic therapy have used methods such as linear analogue, standard gamble and time-trade off techniques to estimate the preferences or utility associated with alternative health state scenarios for people with schizophrenia. Rosenheck et al (1998) converted a Composite Health Index for Schizophrenia. This was used to estimate improvements in health state over a 12 month period. Converting these gains in health state to a 0-1 worst health-good health scale, gave a preference weighted improvement of 0.049 for clozapine and 0.027 for haloperidol. In a double blind randomised clinical trial, this measure indicated a QALY gain of 2 for clozapine compared to haloperidol (Rosenheck, 1999).

Chouinard et al, (1997) generated health state descriptions from data for 135 patients. These included the domains of thought quality, emotional quality, social functioning, physical

functioning and extra pyramidal side effects. The descriptions were clustered into mild, moderate and severe cases. Psychiatric nurses were asked to imagine they had the health states described and rate them on a linear analogue scale. The standard gamble technique was also used with the nurses to generate utility values for each of the health states. The utility values for each health state were: mild 0.58-0.61, moderate 0.35-0.36 and severe 0.25-0.29. These values were applied to patients in a trial comparing haloperidol and risperidone. Overall, patients taking risperidone were found to have a gain in utility of 0.08 over patients taking haloperidol. This translated into a lifetime gain of 2.72-2.97 QALY's (assuming equal life expectancy between treatment groups).

The second evaluation (Glennie, 1997) estimated utility values for 7 patients with schizophrenia, using the standard gamble and rating scale techniques. The patients were selected by health care professionals in one clinic and were judged as able to understand the scenarios presented and the process. These data were used to generate utility values for chlorpromazine, haloperidol, clozapine and risperidone, for mild and moderate-severe symptoms, and the disutility associated with EPS and hospitalisation.

The values generated suggested a higher quality of life for each health state than those estimated by Chouinard et al (1997). The differences between typical and atypical antipsychotics are also smaller (Table 7). Overall, the utility estimates of Glennie (1997) appeared to be more conservative in favour of typical antipsychotics, and were the values used for this analysis. However, the slightly higher utility value estimated for clozapine, compared to the alternative antipsychotics may favour any comparisons between clozapine and other atypical drugs. The limited evidence from clinical trials suggest that clozapine and risperidone may be associated with higher quality of life and patient satisfaction than typical antipsychotics (Mahmoud et al, 1998, Rosenheck et al, 1998, Rosenheck et al, 1999). However, there is no trial based evidence of significant differences between the atypical antipsychotics in quality of life or patient satisfaction.

4.5 Expected costs and outcomes: three years therapy

Tables 8-9 present the simulated data for the expected three year costs and QALY's of first treatment, by distributional form, for all patients, and patients who complete or fail initial therapy. The costs and QALY's for patients who fail initial therapy are estimated as the median values from data for all the antipsychotics. Clozapine is not indicated for first or second line therapy and has been excluded from these analyses. The mean values and 95% confidence intervals are shown. The confidence intervals would suggest that haloperidol and olanzapine are less effective (in terms of the likelihood of failing initial therapy and QALY's) and more costly than chlorpromazine for both the normal and triangular distribution (i.e. the

confidence intervals for haloperidol and olanzapine do not overlap with those for chlorpromazine).

These results imply that haloperidol and olanzapine are not efficient compared to chlorpromazine or risperidone. This appears to be related to differences in the relative costs and QALY's of patients who continue on initial therapy, and the proportion of patients who switch from the initial antipsychotic. In particular, both haloperidol and olanzapine were associated with a high probability of relapse compared to the other antipsychotics, which increased the cost of patients who completed therapy. The higher rate of relapse would also reduce the expected utility and QALY's associated with these two treatments.

Risperidone was associated with both higher expected costs and QALY's than chlorpromazine. The additional cost/QALY gained by risperidone compared to chlorpromazine ranged from £34241 (triangular distribution) to £109935 (truncated normal distribution).

The expected costs of patients who completed the three year time frame on the initial allocated therapy were lower than those who had to switch to at least one other therapy (Table 9). The expected QALY's for patients remaining on the initial allocated therapy were higher than those who switched. For those patients who switched allocated therapy, the expected costs and QALY's were similar for each of the initial therapies. However, for those patients who remained on allocated therapy, chlorpromazine dominated both haloperidol and olanzapine. Risperidone was associated with higher expected costs and QALY's than haloperidol, and dominated olanzapine.

Table 10 presents the expected costs and QALY's for 2nd, 3rd and 4th line therapy, by distributional form. Clozapine was excluded from the analysis of 2nd line treatment. The percentage of patients completing or failing each line of therapy was assumed to be the same as for first line treatment. The results of these analyses again suggest that haloperidol and olanzapine may not be efficient compared to risperidone, clozapine and chlorpromazine.

They also suggest that risperidone and clozapine may be more effective than chlorpromazine but at an additional cost. The expected cost/QALY gained by risperidone ranged from £59050 to £153600 using the truncated normal distribution and £15289 to £29437 using the triangular distribution. The expected cost/QALY gained by clozapine compared to chlorpromazine ranged from £35689 to £47980 using the truncated normal distribution and £14054 to £15546 using the triangular distribution. When clozapine is compared to risperidone, it is equivalent in expected costs and QALY's using the truncated normal

distribution. If the triangular distribution is used then clozapine is associated with higher expected costs and QALY's compared to risperidone. The expected cost/QALY gained ranges from £5314 to £22500.

4.6 Expected costs and outcomes: treatment guidelines

Tables 11 & 14 present the expected costs and QALY's for alternative treatment guidelines, using the truncated normal distribution and triangular distributions. The results for each distribution are summarised in Tables 12 & 15. Tables 13 & 16 compare the guidelines in terms of incremental cost/QALY gained for each of the distributions.

4.6.1 Choice of first line therapy

For each of the guidelines which specify a typical antipsychotic as first line therapy, chlorpromazine as 1st line treatment was consistently associated with lower expected costs and higher expected QALY's than haloperidol used 1st line (i.e. the 95% confidence intervals do not overlap). In addition, lower dose typical antipsychotics were of lower cost or higher QALY's than the average dose estimations. Risperidone was associated with lower expected costs and higher expected QALY's than olanzapine when used as first line therapy.

Overall, the results suggest that lower dose chlorpromazine is associated with lower expected costs than risperidone or olanzapine. In addition, lower dose chlorpromazine is associated with equivalent or higher expected QALY's than olanzapine. The expected QALY's associated with lower dose chlorpromazine are lower than those associated with risperidone. The expected cost/QALY gained by risperidone ranges from £54755 (triangular distribution) to £663170 (triangular distribution). The results suggest that risperidone is more efficient in terms of expected costs and QALY's than haloperidol (low or average dose) as first line therapy. Olanzapine may be a better choice than haloperidol (low or average dose) as first line therapy in some cases.

The expected costs and QALY's for average dose typical antipsychotics suggest that risperidone may be more efficient in terms of expected costs and QALY's than haloperidol in all cases, and chlorpromazine in some cases. Olanzapine may be preferred to haloperidol in some cases, but not chlorpromazine.

4.6.2 Choice of second line therapy

The results suggest that chlorpromazine is associated with lower expected costs and higher expected QALY's than haloperidol and olanzapine as second line therapy (Table 17). Risperidone used as second line therapy dominates both haloperidol and olanzapine, in that it is associated with higher expected QALY's at lower or equivalent expected cost. If a

truncated normal distribution is used then chlorpromazine may be the preferred option compared to risperidone, in that the expected costs are lower, with only small differences in QALY's. However the results using a triangular distribution would suggest that risperidone may be preferred to chlorpromazine, with higher expected costs and QALY's. The expected cost/QALY gained by risperidone is between £25000 and £26000.

4.6.3 Choice of third and fourth line therapy

As with the previous analyses, haloperidol and olanzapine are associated with higher expected costs and QALY's than the alternative antipsychotics. Chlorpromazine is associated with lower expected costs and QALY's than risperidone or clozapine. Using the truncated normal distribution, the expected cost/QALY gained by risperidone compared to chlorpromazine ranges from £57800 to £66200 for third line therapy. Clozapine dominates risperidone for fourth line therapy. The expected cost/QALY gained by clozapine compared to chlorpromazine ranges from £31100 to £38000 for third line therapy and is £48000 for fourth line therapy. Clozapine may be preferred to risperidone in terms of expected costs and QALY's or expected costs/QALY gained compared to chlorpromazine.

Using the triangular distribution the expected costs and QALY's of chlorpromazine, risperidone and clozapine dominate those associated with haloperidol and olanzapine. The expected costs and QALY's of risperidone and clozapine are equivalent for most comparisons of third line therapy. However, risperidone may be preferred to clozapine as fourth line therapy. Both risperidone and clozapine are associated with relatively low expected costs/QALY gained when compared with chlorpromazine.

5. CONCLUSIONS

Overall, the data from the simulation analysis of three year expected costs and outcomes suggest that chlorpromazine, risperidone and clozapine (third and fourth line therapy only) were more efficient in terms of expected costs and QALY's than haloperidol and olanzapine.

The results also suggest that the expected costs and QALY's associated with clozapine were always higher than for chlorpromazine. The expected cost/QALY gained for clozapine ranged from £14000 to £48000, depending upon the distributional form and method of estimating probabilities of events used. The data for risperidone was less clear.

The results of the simulation to evaluate 6 alternative treatment protocols also suggested that haloperidol and olanzapine were less efficient options for 1^{st}, 2^{nd}, 3^{rd} or 4^{th} line therapy. The results also suggested that risperidone was more efficient than chlorpromazine and haloperidol as 1^{st} and 2^{nd} line therapy for most analyses. Clozapine was more efficient than

haloperidol or chlorpromazine for 3rd or 4th line therapy and equivalent to or more efficient than risperidone.

The analysis used a probabalistic simulation analysis to incorporate uncertainty in the estimates of event rates, resource use and unit costs. Additional sensitivity analysis indicated that the results of the simulation were sensitive to the distributional form used to derive estimates of probabilities, costs and utility values.

However, there are a number of issues with the data and analyses which mean that the results are uncertain. First, the analyses were exploratory in nature. There were no hypotheses stated a priori. This meant that there is a chance that some comparisons would yield apparently statistically significant results due to the large number of analyses conducted. Despite this, there were substantial similarities between the analyses in the results generated.

Secondly, the differences in expected costs and QALY's were small. Analysis of the 95% confidence intervals suggests that many of the differences were statistically important. However, it is not clear that they would be clinically or economically relevant. In particular it is not obvious that patients or clinicians would judge the very small differences in expected QALY's to be important. In addition, the exploratory nature of the analysis means that multiple comparisons of expected costs and QALY's (with associated confidence intervals) have been made. This means that although no formal tests of significance were used, some apparently statistically important differences may have occurred by chance rather than reflect true differences. Both of these factors mean that there may be fewer relevant or statistically important differences than the analyses suggest.

Thirdly, the data for olanzapine comes primarily from one main trial with limited follow up, a high rate of reported relapse, high rate of patient drop out and relatively less severe patients. It is possible that as new data become available, the estimates of effectiveness and cost effectiveness will be altered. This trial may also have dominated the estimation of the probabilities of events for haloperidol, biasing the evaluation against haloperidol. In addition, the probabilities of events for chlorpromazine (average and lower dose) and lower dose haloperidol were based on a relatively small number of trials and patients. The data from these showed marked variation in results. Again, this may mean that the evaluation of expected costs and outcomes for these drugs is not based on robust evidence.

Fourthly, the analyses did not explicitly include the impact of a range of adverse events associated with antipsychotic medication. It was assumed that these were included indirectly through two mechanisms. First, side effects which were important to the patient or clinician

may be reflected in the rate of withdrawal from the trial. Secondly, patients with mild symptoms were assigned utility values which varied by the type of antipsychotic. Again it was assumed that these would reflect differences in the side effect profiles of the medications.

Fifthly, the probabilities of events for average dose haloperidol and chlorpromazine were estimated from trials to compare these drugs to clozapine or other atypical antipsychotics. It has been suggested that some of the trials may have used dose regimes for haloperidol or chlorpromazine which were higher than would be used in routine practice. There is some evidence that higher doses may lead to worsening of symptoms (Bollini et al, 1994). In addition, if the occurrence of adverse events are positively related to dose (Zimbroff et al, 1997), the rates of some or all the adverse events for haloperidol in this analysis may be higher than those found in routine practice. These two factors may have resulted in an under estimation of the expected QALY's for chlorpromazine and haloperidol and an over estimation of expected costs.

The main conclusions that can be drawn are first, that clozapine and risperidone, for the patient population assessed, may be more effective than typical antipsychotics and olanzapine, but at higher cost. Not all of the additional cost of the drugs is offset by reductions in the use of services to manage people with schizophrenia. Uncertainty about the validity of the clinical data for typical antipsychotics, the appropriate distributional form to be used and what is an acceptable cost/QALY mean that the analysis is unclear about whether these additional costs and benefits represent value for money.

Secondly, despite the higher acquisition cost, the data and analyses suggest that clozapine is equivalent to or, in some cases more efficient than risperidone when used as 3rd or 4th line treatment, in terms of expected costs and QALY's.

Finally, a key determinant of the three year expected costs and QALY's of treating first episode patients is likely to be the 1st line therapy used.

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Table 1 Probability of Events

	Chlorpromazine mean (range) [2-5]		Haloperidol mean (range) [2-5]		Risperidone mean (range)[2,4,5,8]	Clozapine mean (range) [3,4,5]	Olanzapine mean (range) [4,5,13]
	All	Lower dose	All	Lower dose			
Inadequate response	0.73 (0.2-1)	0.48 (0.4-0.64)	0.64 (0.2-0.9)	0.63 (0.2-0.9)	0.48 (0.19-0.9)	0.54 (0.08-0.75)	0.59 (0.41-0.96)
Adverse events movement disorders	0.36 (0-0.68)	0.41 (0-0.68)	0.46 (0.14-1)	0.45 (0.27-1)	0.21 (0.07-0.59)	0.29 (0-0.75)	0.16 (0.03-0.29)
tardive dyskinesia	0.05[6]	0.05[6]	0.05	0.05	0.003[9]	0.00	0.01[9,13]
NMS[7]	0.005	0.005	0.005	0.005	0.00	0.00	0.00
hepatic dysfunction	0.06	0.06	0.06	0.06	0.00	0.02[12]	nr
agranulocytosis	0.00	0.00	0.00	0.00	0.00	0.02	nr
Therapy not acceptable/ withdrawal	0.23 (0.07-0.73)	0.16 (0.07-0.55)	0.49 (0-0.86)	0.46 (0-0.76)	0.27 (0-0.49)	0.25 (0-0.57)	0.60 (0.22-0.86)
Relapse -with therapy	0.13 (0.05-0.52)	0.14 (0.05-0.52)	0.42 (0-0.97)	0.48 (0.38-0.63)	0.27[10] (0.08-0.45)[11]	0.08 (00-0.29)	0.91 (0.08-0.91)
- without therapy[7]	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Non compliance, adequate therapy[7]	0.09	0.09	0.09	0.09	0.09	0.09	0.09

Notes to Table 1

1. Estimated as weighted average of probability over trials included in analysis
2. Kennedy et al, 1999
3. Wahlbeck et al, 1999,
4. Tuunainen and Gilbody, 1999
5. Duggan et al, 1999
6. Assumed equal to haloperidol
7. Estimated value
8. Song et al, 1997
9. Esteinou and Grebb,
10. No data reported, estimated from average rates for chlorpromazine (0.45) and clozapine (0.08), using assumption of uniform distribution
11. Minimum and maximum values assumed
12. Kane et al, 1988
13. Tollefson et al, 1997

Table 2 Derived probability of events, truncated normal distribution

	Chlorpromazine		Haloperidol		Risperidone	Clozapine	Olanzapine
	All	Lower dose	All	Lower dose			
Inadequate response	0.66	0.48	0.63	0.63	0.48	0.54	0.59
Adverse events							
- movement disorders	0.37	0.42	0.46	0.45	0.22	0.34	0.16
- tardive dyskinesia	0.05	0.05	0.05	0.05	0.003	0.00	0.01
- NMS	0.005	0.005	0.005	0.005	0.00	0.00	0.00
- hepatic dysfunction	0.06	0.06	0.06	0.06	0.00	0.02	0.00
- agranulocytosis	0.00	0.00	0.00	0.00	0.00	0.02	0.00
Therapy not acceptable/ withdrawal	0.28	0.23	0.49	0.47	0.28	0.27	0.60
Relapse							
-with therapy	0.17	0.21	0.44	0.48	0.27	0.10	0.63
- without therapy	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Non compliance, adequate therapy	0.09	0.09	0.09	0.09	0.09	0.09	0.09
Therapy not acceptable[*]							
-non compliance	0.08	0.09	0.07	0.07	0.11	0.09	0.11
- intolerance	0.37	0.46	0.42	0.42	0.28	0.37	0.19
- inadequate response	0.56	0.46	0.51	0.51	0.61	0.54	0.70

* Probabilities may not sum to 1 due to rounding error

Table 3 Derived probability of events, triangular distribution

	Chlorpromazine		Haloperidol		Risperidone	Clozapine	Olanzapine
	All	Lower dose	All	Lower dose			
Inadequate response	0.64	0.51	0.58	0.58	0.52	0.46	0.65
Adverse events							
- movement disorders	0.35	0.36	0.53	0.57	0.29	0.35	0.16
- tardive dyskinesia	0.05	0.05	0.05	0.05	0.003	0.00	0.01
- NMS	0.005	0.005	0.005	0.005	0.00	0.00	0.00
- hepatic dysfunction	0.06	0.06	0.06	0.06	0.00	0.02	0.00
- agranulocytosis	0.00	0.00	0.00	0.00	0.00	0.02	0.00
Therapy not acceptable/ withdrawal	0.34	0.26	0.45	0.41	0.25	0.27	0.56
Relapse							
-with therapy	0.23	0.24	0.46	0.50	0.27	0.12	0.63
- without therapy	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Non compliance, adequate therapy	0.09	0.09	0.09	0.09	0.09	0.09	0.09
Therapy not acceptable[*]							
-non compliance	0.08	0.09	0.07	0.07	0.10	0.10	0.10
- intolerance	0.36	0.42	0.47	0.49	0.32	0.41	0.18
- inadequate response	0.56	0.49	0.46	0.44	0.58	0.49	0.72

* Probabilities may not sum to 1 due to rounding error

Table 4 Inpatient care associated with schizophrenia

Study	Hospital admissions	Average length of stay (days per year)
Addington et al, 1993		
(a) prior to risperidone therapy	na	106
(b) with risperidone therapy	na	85
Aitchison and Kerwin, 1997		
(a) prior to clozapine therapy	2 per patient/year	130
(b) with clozapine therapy	0.13 per patient/year	87.5
Almond and O'Donnel, 1998		
(a) acute stay		
initial therapy	60% patients admitted	27 days per admission
relapse	90% patients admitted	27 days per admission
relapse	10% patients admitted	81 days per admission
(b) long stay	1.25% patients admitted	91 days per admission
Davies and Drummond, 1993		
(a) re-admission	100% patients admitted	42 days per admission
(b) long stay/residential care		
clozapine	82% patients admitted	365 days per admission
standard neuroleptics	94% patients admitted	365 per admission
Guest et al, 1996		
(a) prior to risperidone	na	172
(b) 1st year with risperidone	na	119
(c) 2nd year with risperidone	na	51
Mahmoud et al, 1998		
(a) risperidone	1.25 per patient/year	43
(b) conventional therapy	1.32 per patient/year	43
Meltzer et al, 1993		
(a) prior to clozapine therapy	1-1.5 per patient per year	64-133
(b) with clozapine therapy	0.15-1 per patient per year	4-143
Rosenheck et al, 1997 (inpatient psychiatric admissions)		
(a) clozapine	1.7	144
(b) haloperidol	1.5	168
Viale et al, 1997		
(a) prior to risperidone therapy	0.47	25
(b) with risperidone therapy	0.37	28
UK national statistics		
CIPFA, 1998 (mental illness)	na	45
Department of health 1998b		
(a) Schizophrenia, (F20-F29)	na	101
(b) Mental illness (ICD-9, 710)	na	54

Table 5 Resource use of events: model

EVENT	Probability	Days	Total
Initiation of 1st therapy and treatment of acute episode or relapse			
Inpatient admission	0.60	45.00 (sd:20)	27.00
Daypatient admission	0.40	24.00	10.00
Antipsychotic therapy	1.00	49.00	9.00
Change antipsychotic			
Clozapine			
Daypatient admission	1.00	14.00	14.00
Antipsychotic therapy	1.00	56.00	56.00
Other antipsychotics			
Outpatient visits	1.00	6.00	6.00
Antipsychotic therapy	1.00	56.00	56.00
Additional treatment for adverse events/year			
EPS			
Anticholinergic	1.00	365.00	365.00
Akathisia			
Beta blocker	1.00	365.00	365.00
Seizures			
Valproate	1.00	365.00	365.00

Table 6 Unit costs of resources (1997 £)

	mean (sd)	minimum	maximum
Hospital based services			
inpatient stay (per day)	137.00 (42)	12.00	388.00
outpatient visits (per visit)	81.00 (56)		
day patient (per day)	56.61	37.00	57.00
Community services (per day)	7.86	6.43	12.00
Drugs (per patient day)			
Chlorpromazine	0.10	0.06	0.20
Haloperidol	0.43	0.26	0.52
Risperidone	3.90	2.57	5.15
Clozapine	5.36	3.57	7.15
Olanzapine	3.77	2.82	5.64
anticholinergics	0.06		
beta adrenergic blocker (propranolol, 40mg bid)	0.01		
anticonvulsant, valproate, 1g/day	0.28		

TABLE 7 UTILITY AND QUALITY ADJUSTED DAYS OF EVENTS

Event	Chlorpromazine mean (95%CI)	Haloperidol mean (95%CI)	Risperidone mean (95%CI)	Clozapine mean (95%CI)	Olanzapine mean (95%CI)
Utility values[1]					
Mild symptoms	0.86 (0.77-0.95)	0.86(0.77-0.95)	0.89 (0.84-0.94)	0.91 (0.86-0.96)	0.89 (0.84-0.94)
Moderate-severe symptoms	0.82 (0.76-0.88)	0.82 (0.76-0.88)	0.82 (0.76-0.88)	0.82 (0.76-0.88)	0.82 (0.76-0.88)
Disutility of EPS or unacceptable treatment	-0.07	-0.07	-0.07	-0.07	-0.07
Disutility of inpatient care	-0.07	-0.07	-0.07	-0.07	-0.07

1. Glennie, 1997

TABLE 8 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S OF FIRST THERAPY: PER COHORT OF 1000 PATIENTS

Antipsychotic	Therapy change % patients	Expected Cost mean (95%CI)	Expected QALY mean (95%CI)	Comparison	Cost/QALY
Triangular distribution					
chlorpromazine					
- all doses	34.32 (33.66-34.99)	17982170 (17844285-18120055)	2336 (2334-2339)		
- lower dose	25.62 (25.12-26.13)	19921520 (19739726-20103314)	2300 (2295-2304)	Dominated CPZ	not relevant
haloperidol					
- all doses	44.45 (43.64-45.27)	20160470 (19994590-20326350)	2298 (2295-2301)	Dominated CPZ	not relevant
- lower dose	40.64 (39.89-41.40)	23944640 (23727756-24161524)	2199 (2193-2206)	Dominated CPZ	not relevant
risperidone	24.64 (24.17-25.12)	20653000 (20507377-20798623)	2414 (2411-2416)	CPZ	34241
olanzapine	54.65 (54.03-55.26)	22312200 (22146241-22478159)	2326 (2324-2329)	Dominated CPZ	not relevant

TABLE 9 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S: PER PATIENT COMPLETING OR SWITCHING THERAPY

Antipsychotic	Expected Cost (mean, 95%CI)		Expected QALY (mean, 95%CI)	
	Complete therapy	Switch 1st therapy	Complete therapy	Switch 1st therapy
Truncated normal distribution				
Chlorpromazine				
- all doses	15627 (15369-15884)	21271 (20657-21886)	2.44 (2.41-2.47)	2.20 (2.13-2.26)
- lower dose	16009 (15766-16253)	21337 (20705-21969)	2.46 (2.43-2.48)	2.19 (2.13-2.26)
Haloperidol				
- all doses	18631 (18109-19153)	21093 (20572-21615)	2.39 (2.33-2.44)	2.21 (2.16-2.26)
- lower dose	19031 (18528-19534)	21038 (20506-21570)	2.39 (2.33-2.44)	2.21 (2.16-2.27)
Risperidone	20150 (19894-20405)	21229 (20718-21740)	2.50 (2.48-2.52)	2.23 (2.17-2.28)
Olanzapine	22896 (22307-23484)	21229 (20890-21568)	2.47 (2.42-2.52)	2.22 (2.16-2.27)
Triangular distribution				
Chlorpromazine				
- all doses	15998 (15771-16225)	21779 (21345-22212)	2.41 (2.38-2.43)	2.20 (2.16-2.24)
- lower dose	15966 (15770-16162)	31403 (30718-32088)	2.42 (2.41-2.44)	1.94 (1.90-1.98)
Haloperidol				
- all doses	18909 (18537-19280)	21725 (21311-22138)	2.37 (2.34-2.41)	2.20 (2.16-2.25)
- lower dose	19155 (18809-19501)	30939 (30294-31585)	2.36 (2.33-2.39)	1.96 (1.93-2.00)
Risperidone	20307 (20099-20516)	21710 (21279-22140)	2.48 (2.46-2.49)	2.22 (2.18-2.26)
Olanzapine	22989 (22570-23408)	21750 (21481-22019)	2.46 (2.42-2.49)	2.22 (2.19-2.24)

TABLE 10 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S OF ADDITIONAL THERAPY: PER PATIENT FAILING PREVIOUS THERAPY

Antipsychotic	Expected Cost (mean, 95%CI)	Expected QALY (mean, 95%CI)	Incremental cost/QALY
Truncated normal distribution			
Second line therapy			
Chlorpromazine	13646 (13432-13859)	2.26 (2.23-2.29)	
Haloperidol	16056 (15724-16388)	2.08 (2.04-2.13)	Dominated
Risperidone	16718 (16516-16920)	2.28 (2.26-2.30)	£153600 vs CPZ
Olanzapine	18703 (18408-18997)	2.13 (2.10-2.16)	Dominated
Third line therapy			
Chlorpromazine	13031 (12828-13235)	1.99 (1.97-2.02)	
Haloperidol	15951 (15609-16292)	1.78 (1.75-1.82)	Dominated
Risperidone	16574 (16361-16788)	2.05 (2.03-2.07)	£59050 vs CPZ
Clozapine	16243 (16039-16446)	2.08 (2.06-2.10)	£35689 vs CPZ
Olanzapine	18992 (18697-19286)	1.78 (1.75-1.81)	Dominated
Fourth line therapy			
Chlorpromazine	10776 (10691-10861)	1.60 (1.58-1.62)	
Haloperidol	14249 (14086-14412)	1.12 (1.09-1.15)	Dominated
Risperidone	15912 (15801-16023)	1.68 (1.66-1.70)	£64200 vs CPZ
Clozapine	15574 (15506-15642)	1.70 (1.68-1.72)	£47980 vs CPZ
Olanzapine	19599 (19377-19821)	0.95 (0.93-0.96)	Dominated

TABLE 10 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S OF ADDITIONAL THERAPY: PER PATIENT FAILING PREVIOUS THERAPY

Antipsychotic	Expected Cost (mean, 95%CI)	Expected QALY (mean, 95%CI)	Incremental cost/QALY
Triangular distribution			
Second line therapy			
Chlorpromazine	14477 (14277-14676)	2.20 (2.18-2.23)	
Haloperidol	16651 (16382-16920)	2.12 (2.10-2.15)	Dominated
Risperidone	16832 (16654-17011)	2.28 (2.26-2.30)	£29437 vs CPZ
Olanzapine	19113 (18868-19359)	2.13 (2.10-2.15)	Dominated
Third line therapy			
Chlorpromazine	17570 (17314-17826)	2.09 (2.07-2.12)	
Haloperidol	20967 (20615-21319)	2.00 (1.97-2.03)	Dominated
Risperidone	19025 (18809-19241)	2.15 (2.13-2.17)	£24250 vs CPZ
Clozapine	19397 (19166-19630)	2.22 (2.20-2.40)	£14054 vs CPZ £5314 vs risperidone
Olanzapine	25085 (24725-25445)	2.05 (2.03-2.07)	Dominated
Fourth line therapy			
Chlorpromazine	11574 (11472-11676)	1.44 (1.42-1.46)	
Haloperidol	14804 (14633-14975)	1.20 (1.18-1.22)	Dominated
Risperidone	15702 (15592-15812)	1.71 (1.70-1.72)	£15289 vs CPZ
Clozapine	15928 (15851-16004)	1.72 (1.70-1.74)	£15550 vs CPZ £22500 vs risperidone
Olanzapine	19702 (19486-19918)	1.03 (1.01-1.05)	Dominated

TABLE 11 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S PER COHORT OF 1000 PATIENTS: BY TREATMENT GUIDELINE, TRUNCATED NORMAL DISTRIBUTION

Guideline	Expected Cost mean (95%CI)	Expected QALY mean (95%CI)
1. Typical, typical, atypical, clozapine		
(a) Chlor'zine, hal., risp., cloz.	17312380 (17146606-17478154)	2298 (2290-2306)
(b) Chlor'zine, hal., olanz., cloz.	17520510 (17372242-17668778)	2277 (2269-2285)
(c) Hal., chlor'zine, risp., cloz.	18591970 (18386521-18797419)	2247 (2239-2255)
(d) Hal., chlor'zine, olanz., cloz.	18802200 (18632165-18972235)	2232 (2224-2240)
2. Typical, typical, clozapine, atypical		
(a) Chlor'zine, hal., cloz., risp.	17347900 (17173853-17521947)	2289 (2280-2298)
(b) Chlor'zine, hal., cloz., olanz.	17573540 (17400548-17746532)	2272 (2262-2281)
(c) Hal., chlor'zine, cloz., risp.	18484450 (18285586-18683314)	2265 (2257-2273)
(d) Hal., chlor'zine, cloz., olanz.	18459120 (18258174-18660066)	2238 (2228-2247)
3. Typical, atypical, atypical, clozapine		
(a) Chlor'zine, risp., olanz., cloz.	17475160 (17312058-17638262)	2365 (2358-2371)
(b) Chlor'zine, olanz., risp., cloz.	17871550 (17711665-18031435)	2329 (2323-2336)
(c) Hal., risp., olanz., cloz.	20381310 (20174928-20587692)	2289 (2281-2296)
(d) Hal., olanz., risp., cloz.	21174570 (20976831-21372309)	2229 (2221-2238)

TABLE 11 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S PER COHORT OF 1000 PATIENTS: BY TREATMENT GUIDELINE, TRUNCATED NORMAL DISTRIBUTION

Guideline	Expected Cost mean (95%CI)	Expected QALY mean (95%CI)
4. Typical, atypical, clozapine, typical		
(a) Chlor'zine, risp., cloz., hal.	17590420 (17399038-17781802)	2369 (2362-2376)
(b) Chlor'zine, olanz., cloz., hal.	17704610 (17497650-17911570)	2326 (2317-2334)
(c) Hal., risp., cloz., chlor'zine.	20097030 (19874636-20319424)	2307 (2300-2315)
(d) Hal., olanz., cloz., chlor'zine	20569910 (20330631-20809189)	2211 (2200-2222)
5. Typical, atypical, clozapine, atypical		
(a) Chlor'zine, risp., cloz., olanz.	17409010 (17249765-17568255)	2360 (2354-2366)
(b) Chlor'zine, olanz., cloz., risp.	18024500 (17867894-18181106)	2329 (2322-2336)
(c) Hal., risp., cloz., olanz.	20324950 (20128612-20521288)	2284 (2277-2291)
(d) Hal., olanz., cloz., risp.	21083060 (20882353-21283767)	2230 (2221-2238)
6. Atypical, atypical, clozapine, typical		
(a) Risp., olanz., cloz., chlor'zine	20893250 (20720656-21065844)	2375 (2368-2381)
(b) Olanz., risp., cloz., chlor'zine	21997490 (21799135-22195845)	2315 (2306-2324)
(c) Risp., olanz., cloz., hal.	21024620 (20871119-21178121)	2375 (2369-2381)
(d) Olanz., risp., cloz., hal.	22106220 (21934678-22277762)	2326 (2318-2334)

TABLE 11 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S PER COHORT OF 1000 PATIENTS: BY TREATMENT GUIDELINE, TRUNCATED NORMAL DISTRIBUTION

Guideline	Expected Cost mean (95%CI)	Expected QALY mean (95%CI)
7. Lower dose typical, atypical, atypical, clozapine		
(a) Chlor'zine, risp., olanz., cloz.	17643240 (17470744-17815736)	2391 (2384-2397)
(b) Chlor'zine, olanz., risp., cloz.	18112900 (17934687-18291113)	2365 (2358-2372)
(c) Hal., risp., olanz., cloz.	20582760 (20392089-20773431)	2291 (2284-2298)
(d) Hal., olanz., risp., cloz.	21575460 (21365952-21784968)	2239 (2230-2248)
8. Lower dose typical, atypical, clozapine, atypical		
(a) Chlor'zine, risp., cloz., olanz.	17496610 (17317783-17675437)	2381 (2374-2389)
(b) Chlor'zine, olanz., cloz., risp.	18041710 (17860908-18222512)	2351 (2344-2359)
(c) Hal., risp., cloz., olanz.	20333050 (20122891-20543209)	2287 (2279-2295)
(d) Hal., olanz., cloz., risp.	21362870 (21147150-21578590)	2235 (2226-2245)

TABLE 12 SUMMARY OF SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S PER COHORT OF 1000 PATIENTS: BY TREATMENT GUIDELINE, TRUNCATED NORMAL DISTRIBUTION

Guideline	Expected Cost mean	Expected QALY mean	95% CI overlap* Costs	QALY's
Guidelines 1-5, 7, 8				
• chlorpromazine 1st line	17252360-18112900	2272-2391	NO	NO
• haloperidol 1st line	18459120-21575460	2211-2307	NO	NO
• chlorpromazine vs haloperidol 1st line			NO	NO
Guidelines 1 & 2				
• chlorpromazine 1st line	17312380-17573540	2272-2298	YES	YES
• haloperidol,1st line	18459120-18802200	2232-2265	YES	NO
Guidelines 3 & 5				
• chlorpromazine 1st line	17409010-18024500	2329-2365	YES	YES
• haloperidol, 1st line	20324950-21174570	2229-2289	YES	YES
Guideline 4				
• chlorpromazine 1st line	17590420-17704610	2326-2369	YES	NO
• haloperidol, 1st line	20097030-20569910	2211-2307	NO	NO
Guideline 6				
• risperidone 1st line	20893250-21024520	2375	YES	YES
• olanzapine 1st line	21997490-22106220	2315-2326	YES	YES
• risperidone vs olanzapine 1st line			NO	NO
Guidelines 7 & 8				
• chlorpromazine 1st line	17496610-18112900	2351-2391	YES	YES
• haloperidol, 1st line	20333050-21575460	2235-2291	YES	YES

TABLE 13 EXPECTED COST/QALY GAINED OF ALTERNATIVE GUIDELINES, TRUNCATED NORMAL DISTRIBUTION

Comparison	Incremental expected cost/QALY	Preferred guideline
Guidelines 1 & 2 versus guidelines 3 & 5		
• chlorpromazine 1st line	861-18038	guidelines 3 & 5
• haloperidol, 1st line	27704-96868	guidelines 1 & 2
Guidelines 1 & 2 versus guideline 4		
• chlorpromazine 1st line	174-14008	guideline 4
• haloperidol, 1st line, 1c, 2c, 1d, 2d versus 4c	17264-38395	guideline 4 c
• haloperidol, 1st line, 1c, 2c, 1d, 2d versus 4d	not relevant	guideline 1c, 2c, 1d, 2d
Guidelines 1 & 2 versus guideline 6		
• risperidone 1st line versus chlorpromazine 1st line	32230-48211	guideline 6a, 6c
• olanzapine 1st line versus chlorpromazine 1st line	83938-275594	guideline 1a, 3a, 1b, 3b
• risperidone 1st line versus haloperidol 1st line	14623-23092	guideline 6a, 6c
• olanzapine 1st line versus haloperidol 1st line, 1c, 2c	44484-70261	unclear
• olanzapine 1st line versus haloperidol 1st line, 1d, 2d	35149-45953	guideline 6b, 6d
Guidelines 1 & 2 versus guidelines 7 & 8		
• chlorpromazine 1st line	1616-13761	guidelines 7a, 8a, 7b, 8b
• haloperidol 1st line, 1c	43527-45245	guidelines 7c, 8c
• haloperidol 1st line, 7d, 8d	not relevant	guidelines 1c, 1d

TABLE 13 EXPECTED COST/QALY GAINED OF ALTERNATIVE GUIDELINES, TRUNCATED NORMAL DISTRIBUTION

Comparison	Incremental expected cost/QALY	Preferred guideline
Guideline 4 versus guidelines 3 & 5		
• chlorpromazine 1st line	not relevant	equivalent

• haloperidol 1st line	not relevant	guideline 4 c & 4d

Guideline 4 versus guideline 6

• risperidone 1st line versus chlorpromazine 1st line	65074-572367	guideline 4a, 4b
• olanzapine 1st line versus chlorpromazine 1st line	not relevant	guideline 4a, 4b
• risperidone 1st line versus haloperidol 1st line	1972-13641	guideline 6a, 6c
• olanzapine 1st line versus haloperidol 1st line, 4c	105747-237558	guideline 4c
• olanzapine 1st line versus haloperidol 1st line, 4d	13359-13728	guideline 6b, 6d

Guideline 4 versus guidelines 7 & 8

• chlorpromazine 1st line	2401-13484	guideline 7a, 8a, 7b, 8b
• haloperidol 1st line, 4c versus 7c, 8c	not relevant	guideline 4 c
• haloperidol 1st line, 4d versus 7d, 8d	33040-35912	guideline 7d, 8d

TABLE 13 EXPECTED COST/QALY GAINED OF ALTERNATIVE GUIDELINES, TRUNCATED NORMAL DISTRIBUTION

Comparison	Incremental expected cost/QALY	Preferred guideline
Guideline 6 versus guideline 3 & 5		
• risperidone1st line versus chlorpromazine 1st line	62364-354946	guideline 3a, 5a, 3b, 5b
• olanzapine 1st line versus chlorpromazine 1st line	not relevant	guideline 3a, 5a, 3b, 5b
• risperidone 1st line versus haloperidol 1st line, 3c, 5c	5953-7689	guideline 6a, 6c
• risperidone 1st line versus haloperidol 1st line, 3d, 5d	not relevant	guideline 6a, 6c
• olanzapine 1st line versus haloperidol 1st line, 3c, 5c	42411-62161	unclear
• olanzapine 1st line versus haloperidol 1st line, 1d, 2d	9569-10658	guideline 6b, 6d
Guideline 6 versus guideline 7 & 8		
• risperidone 1st line versus chlorpromazine 1st line, 7a, 8a, 7b	not relevant	guideline 7a, 8a, 7b
• risperidone 1st line versus chlorpromazine 1st line, 8b	118814-124288	guideline 8b
• olanzpine 1st line versus chlorpromazine 1st line	not relevant	guideline 7a, 8a, 7b, 8b
• risperidone 1st line versus haloperidol 1st line, 7c, 8c	3696-7859	guideline 6a, 6c
• risperidone 1st line versus haloperidol 1st line, 7d, 8d	not relevant	guideline 6a, 6c
• olanzapine 1st line versus haloperidol 1st line,	5553-59444	guideline 6b, 6d

TABLE 14 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S PER COHORT OF 1000 PATIENTS: BY TREATMENT GUIDELINE, TRIANGULAR DISTRIBUTION

Guideline	Expected Cost mean (95%CI)	Expected QALY mean (95%CI)
1. Typical, typical, atypical, clozapine		
(a) Chlor'zine, hal., risp., cloz.	20488210 (20277470-20698950)	2210 (2202-2217)
(b) Chlor'zine, hal., olanz., cloz.	20450810 (20235049-20666571)	2217 (2209-2224)
(c) Hal., chlor'zine, risp., cloz.	23062060 (22802328-23321792)	2184 (2177-2191)
(d) Hal., chlor'zine, olanz., cloz.	23107690 (22850041-23365339)	2177 (2169-2185)
2. Typical, typical, clozapine, atypical		
(a) Chlor'zine, hal., cloz., risp.	20252300 (20034825-20469775)	2204 (2196-2212)
(b) Chlor'zine, hal., cloz., olanz.	20231020 (20035084-20426956)	2212 (2205-2218)
(c) Hal., chlor'zine, cloz., risp.	23021850 (22758217-23285483)	2193 (2186-2201)
(d) Hal., chlor'zine, cloz., olanz.	22822150 (22585733-23058567)	2181 (2174-2188)
3. Typical, atypical, atypical, clozapine		
(a) Chlor'zine, risp., olanz., cloz.	20887550 (20669050-21106050)	2307 (2301-2312)
(b) Chlor'zine, olanz., risp., cloz.	21024140 (20802433-21245847)	2252 (2246-2258)
(c) Hal., risp., olanz., cloz.	23756410 (23500903-24011917)	2249 (2242-2255)
(d) Hal., olanz., risp., cloz.	24279740 (24016550-24542930)	2179 (2170-2187)

TABLE 14 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S PER COHORT OF 1000 PATIENTS: BY TREATMENT GUIDELINE, TRIANGULAR DISTRIBUTION

Guideline	Expected Cost mean (95%CI)	Expected QALY mean (95%CI)
4. Typical, atypical, clozapine, typical		
(a) Chlor'zine, risp., cloz., hal.	20748010 (20522917-20973103)	2314 (2308-2319)
(b) Chlor'zine, olanz., cloz., hal.	21038060 (20803675-21272445)	2257 (2251-2264)
(c) Hal., risp., cloz., chlor'zine.	23887890 (23621629-24154151)	2269 (2263-2275)
(d) Hal., olanz., cloz., chlor'zine	24160070 (23877586-24442554)	2193 (2184-2201)
5. Typical, atypical, clozapine, atypical		
(a) Chlor'zine, risp., cloz., olanz.	20441890 (20218382-20665398)	2318 (2313-2323)
(b) Chlor'zine, olanz., cloz., risp.	21096480 (20870549-21322411)	2253 (2247-2259)
(c) Hal., risp., cloz., olanz.	23611710 (23341015-23882405)	2269 (2263-2275)
(d) Hal., olanz., cloz., risp.	24306150 (24044908-24567392)	2179 (2171-2186)
6. Atypical, atypical, clozapine, typical		
(a) Risp., olanz., cloz., chlor'zine	22911030 (22679844-23142216)	2350 (2344-2356)
(b) Olanz., risp., cloz., chlor'zine	26994180 (26662205-27326155)	2296 (2288-2305)
(c) Risp., olanz., cloz., hal.	22961460 (22757089-23165831)	2351 (2345-2357)
(d) Olanz., risp., cloz., hal.	26839930 (26544676-27135184)	2284 (2276-2292)

TABLE 14 SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S PER COHORT OF 1000 PATIENTS: BY TREATMENT GUIDELINE, TRIANGULAR DISTRIBUTION

Guideline	Expected Cost mean (95%CI)	Expected QALY mean (95%CI)
7. Lower dose typical, atypical, atypical, clozapine		
(a) Chlor'zine, risp., olanz., cloz.	19902400 (19697110-20107690)	2339 (2334-2343)
(b) Chlor'zine, olanz., risp., cloz.	19895190 (19702302-20088078)	2295 (2289-2300)
(c) Hal., risp., olanz., cloz.	23773980 (23517663-24030297)	2257 (2251-2263)
(d) Hal., olanz., risp., cloz.	23967000 (23725732-24208268)	2187 (2180-2194)
8. Lower dose typical, atypical, clozapine, atypical		
(a) Chlor'zine, risp., cloz., olanz.	19595180 (19392337-19798023)	2345 (2340-2350)
(b) Chlor'zine, olanz., cloz., risp.	19927810 (19724477-20131143)	2304 (2299-2310)
(c) Hal., risp., cloz., olanz.	23489940 (23231551-23748329)	2267 (2261-2273)
(d) Hal., olanz., cloz., risp.	23913110 (23663915-24162305)	2195 (2188-2202)

TABLE 15 SUMMARY OF SIMULATED THREE YEAR EXPECTED COSTS (£) AND QALY'S PER 1000 PATIENTS: BY TREATMENT GUIDELINE, TRIANGULAR DISTRIBUTION

Guideline	Expected Cost mean	Expected QALY mean	95% CI overlap* Costs	QALY's
Guidelines 1-5, 7, 8				
• chlorpromazine 1st line	19595180-21096480	2204-2345	NO	NO
• haloperidol 1st line	22822150-24306159	2177-2269	NO	NO
• chlorpromazine vs haloperidol 1st line			NO	NO
Guidelines 1 & 2				
• chlorpromazine 1st line	20231020-20488210	2204-2217	YES	YES
• haloperidol1st line	22822150-23107690	2177-2193	YES	YES
Guidelines 3 & 5				
• chlorpromazine 1st line	20441890-21096480	2252-2318	NO	NO
• haloperidol 1st line	23611710-24306159	2179-2269	NO	NO
Guideline 4				
• chlorpromazine 1st line	20748010-21038060	2257-2314	YES	NO
• haloperidol 1st line	23887890-24160070	2193-2269	NO	NO
Guideline 6				
• risperidone 1st line	22911030-22961460	2350-2351	YES	YES
• olanzapine 1st line	26839930-26994180	2284-2296	YES	YES
• risperidone vs olanzapine 1st line			NO	NO
Guidelines 7 & 8				
• chlorpromazine 1st line	19595180-19927810	2295-2345	YES	NO
• haloperidol 1st line	23489940-23967000	2187-2267	YES	NO

TABLE 16 EXPECTED COST/QALY GAINED OF ALTERNATIVE GUIDELINES: TRIANGULAR DISTRIBUTION

Comparison	Incremental expected cost/QALY	Preferred guideline
Guidelines 1 & 2 versus guidelines 3 & 5		
• chlorpromazine 1st line	1663-21109	guidelines 3 & 5
• haloperidol1st line, 1c, 2c	7761-10682	guidelines 3 & 5
• haloperidol 1st line, 1d, 2d versus 3d, 5d	not relevant	guidelines 1 & 2
• haloperidol 1st line, 1d, 2d versus 3c, 5c	8972-9010	guidelines 3 & 5
Guidelines 1 & 2 versus guideline 4		
• chlorpromazine 1st line	2498-17934	guideline 4
• haloperidol 1st line, 1c, 2c, 1d, 2d versus 4c	8480-12111	guideline 4 c
• haloperidol 1st line, 1c, 2c, 1d, 2d versus 4d	not relevant	guideline 1c, 2c, 1d, 2d
Guidelines 1 & 2 versus guideline 6		
• risperidone1st line versus chlorpromazine 1st line	17306-19643	guideline 6a, 6c
• olanzapine 1st line versus chlorpromazine 1st line	73281-95360	guideline 1a, 3a, 1b, 3b
• risperidone1st line versus haloperidol 1st line	not relevant	guideline 6a, 6c
• olanzapine 1st line versus haloperidol 1st line	32660-41957	guideline 6b, 6d
Guidelines 1 & 2 versus guidelines 7 & 8		
• chlorpromazine 1st line	not relevant	guidelines 7a, 8a, 7b, 8b
• haloperidol1st line, 1, 2 versus 7c, 8c	6325-9752	guidelines 7c, 8c
• haloperidol 1st line, 1, 2 versus 7d, 8d	not relevant	guidelines 1d, 2d

TABLE 16 EXPECTED COST/QALY GAINED OF ALTERNATIVE GUIDELINES: TRIANGULAR DISTRIBUTION

Comparison	Incremental expected cost/QALY	Preferred guideline
Guideline 4 versus guidelines 3 & 5		
• chlorpromazine 1st line	not relevant	equivalent
• haloperidol 1st line	not relevant	equivalent
Guideline 4 versus guideline 6		
• risperidone 1st line versus chlorpromazine 1st line, 4a	59823-60084	guideline 4a
• risperidone1st line versus chlorpromazine 1st line, 4b	20139-20462	guideline 6a, 6c
• olanzapine 1st line versus chlorpromazine 1st line	152721-214884	guideline 4a, 4b
• risperidone 1st line versus haloperidol 1st line	not relevant	guideline 6a, 6c
• olanzapine 1st line versus haloperidol 1st line, 4c	115048-196803	guideline 4c
• olanzapine 1st line versus haloperidol 1st line, 4d	27516-29449	guideline 6b, 6d
Guideline 4 versus guidelines 7 & 8		
• chlorpromazine 1st line	not relevant	guideline 7a, 8a, 7b, 8b
• haloperidol 1st line, 4c versus 7c, 8c	not relevant	equivalent
• haloperidol 1st line, 4d versus 7d, 8d	not relevant	equivalent

TABLE 16 EXPECTED COST/QALY GAINED OF ALTERNATIVE GUIDELINES: TRIANGULAR DISTRIBUTION

Comparison	Incremental expected cost/QALY	Preferred guideline
Guideline 6 versus guideline 3 & 5		
• risperidone1st line versus chlorpromazine 1st line, 3a, 3b, 5b	18707-47134	guideline 6a, 6c
• risperidone 1st line versus chlorpromazine 1st line, 5b	76351-77161	guideline 5a
• olanzapine 1st line versus chlorpromazine 1st line	not relevant	guideline 3a, 5a, 3b, 5b
• risperidone 1st line versus haloperidol 1st line	not relevant	guideline 6a, 6c
• olanzapine 1st line versus haloperidol 1st line, 3c, 5c	68889-215215	guideline 3c, 5c
• olanzapine 1st line versus haloperidol 1st line, 3d, 5d	22975-24383	guideline 6b, 6d
Guideline 6 versus guideline 7 & 8		
• risperidone1st line versus chlorpromazine 1st line	54755-663170	guideline 7a, 8a
• olanzpine 1st line versus chlorpromazine 1st line	not relevant	guideline 7a, 8a, 7b, 8b
• risperidone1st line versus haloperidol 1st line	not relevant	guideline 6a, 6c
• olanzapine 1st line versus haloperidol 1st line, 7c, 8c	82569-197058	guideline 7c, 8c
• olanzapine 1st line versus haloperidol 1st line, 7d, 8d	27772-32886	guideline 6b, 6d

TABLE 17 EXPECTED COSTS (£) AND QALY'S PER PATIENT FAILING THERAPY OF 2ND, 3RD, AND 4TH LINE DRUGS: BY TREATMENT GUIDELINE

Therapy	Expected costs	Expected QALY's	Net expected cost/QALY
Truncated normal distribution			
2nd line therapy			
1. Chlorpromazine followed by			
a) risperidone, clozapine	13461 (13218-13704)	2.26 (2.22-2.30)	Equivalent to 1c, 1d
b) olanzapine, clozapine	14238 (13988-14488)	2.22 (2.19-2.25)	Dominated by 1a, 1c, 1d
c) clozapine, risperidone	13607 (13402-13812)	2.32 (2.29-2.35)	Equivalent to 1a, 1d
d) clozapine, olanzapine	13725 (13497-13953)	2.23 (2.20-2.26)	Equivalent to 1a, 1c
2. Haloperidol followed by			
a) risperidone, clozapine	16599 (16178-17020)	2.25 (2.20-2.30)	}
b) olanzapine, clozapine	17528 (17138-17918)	2.13 (2.09-2.17)	}
c) clozapine, risperidone	16854 (16520-17188)	2.21 (2.17-2.25)	}Dominated by 1, chlorpromazine
d) clozapine, olanzapine	17299 (16923-17675)	2.13 (2.08-2.17)	}
3. Risperidone followed by			
a) olanzapine, clozapine	17468 (17235-17701)	2.28 (2.26-2.30)	versus 1b, = £53833
b) clozapine, haloperidol	16793 (16554-17032)	2.32 (2.30-2.35)	}Dominates 4, olanzapine
c) clozapine, chlorpromazine	16328 (16128-16528)	2.32 (2.30-2.34)	}
d) clozapine, olanzapine	17159 (16926-17392)	2.27 (2.24-2.29)	Dominated by 1, chlorpromazine

TABLE 17 EXPECTED COSTS (£) AND QALY'S PER PATIENT FAILING THERAPY OF 2ND, 3RD, AND 4TH LINE DRUGS: BY TREATMENT GUIDELINE

Therapy	Expected costs	Expected QALY's	Net expected cost/QALY
Truncated normal distribution			
2nd line therapy			
4. Olanzapine followed by			
a) risperidone, clozapine	19104 (18733-19475)	2.27 (2.23-2.31)	} Dominated by 1, chlorpromazine
b) clozapine haloperidol	18450 (18077-18822)	2.16 (2.12-2.20)	} Dominated by 3b, risperidone
c) clozapine, chlorpromazine	17890 (17598-18182)	2.21 (2.18-2.24)	} Dominated by 3b, risperidone
d) clozapine, risperidone	18860 (18553-19167)	2.26 (2.23-2.29)	} Dominated by 1, chlorpromazine
3rd line therapy			
1. Chlorpromazine followed by			
a) haloperidol	12784 (12571-12997)	1.92 (1.90-1.95)	Dominated by 1b, 1c
b) risperidone	13031 (12826-13236)	2.07 (2.04-2.09)	Equivalent 1c
c) clozapine	13077 (12872-13281)	2.09 (2.06-2.11)	Equivalent 1b
d) olanzapine	14339 (14128-14549)	1.86 (1.84-1.88)	Dominated by 1a, 1b, 1c
2. Haloperidol followed by			
a) chlorpromazine	14134 (13856-14412)	1.91 (1.88-1.94)	}
b) risperidone	16434 (16110-16758)	1.90 (1.86-1.94)	}
c) clozapine	16307 (15979-16635)	1.94 (1.90-1.98)	} Dominated by 1, chlorpromazine
d) olanzapine	18323 (17985-18661)	1.58 (1.55-1.61)	}

TABLE 17 EXPECTED COSTS (£) AND QALY'S PER PATIENT FAILING THERAPY OF 2ND, 3RD, AND 4TH LINE DRUGS: BY TREATMENT GUIDELINE

Therapy	Expected costs	Expected QALY's	Net expected cost/QALY
Truncated normal distribution			
3rd line therapy			
3. Risperidone followed by			
a) chlorpromazine	15298 (15117-15479)	2.07 (2.05-2.09)	Dominated by 4a, clozapine
b) haloperidol	16422 (16203-16641)	1.96 (1.94-1.98)	Dominated by 1, chlorpromazine, 4 clozapine
c) clozapine	16388 (16189-16587)	2.14 (2.12-2.16)	versus 1c = £66220
d) olanzapine	17805 (17593-18017)	1.92 (1.90-1.94)	versus 1d = £57767, dominated by 4 clozapine
4. Clozapine followed by			
a) chlorpromazine	15218 (15049-15387)	2.12 (2.10-2.14)	Dominates 3a, risperidone
b) haloperidol	16067 (15862-16272)	2.01 (1.99-2.03)	versus 1a = £36478
c) risperidone	16447 (16244-16650)	2.16 (2.14-2.18)	versus 1b = £37956
d) olanzapine	17134 (16935-17333)	1.95 (1.93-1.97)	versus 1d = £31056
5. Olanzapine followed by			
a) chlorpromazine	16127 (15879-16375)	1.90 (1.87-1.93)	}
b) haloperidol	18445 (18129-18761)	1.60 (1.57-1.63)	}Dominated by 1, chlorpromazine
c) risperidone	19138 (18836-19440)	1.94 (1.92-1.97)	}
d) clozapine	19144 (18848-19440)	1.91 (1.88-1.94)	}

TABLE 17 EXPECTED COSTS (£) AND QALY'S PER PATIENT FAILING THERAPY OF 2ND, 3RD, AND 4TH LINE DRUGS: BY TREATMENT GUIDELINE

Therapy	Expected costs	Expected QALY's	Net expected cost/QALY
Truncated normal distribution			
4th line therapy			
1. Chlorpromazine	10776 (10691-10861)	1.60 (1.58-1.62)	
2. Haloperidol	14249 (14086-14412)	1.12 (1.09-1.15)	Dominated by 1, chlorpromazine
3. Risperidone	15912 (15801-16023)	1.68 (1.66-1.70)	Dominated by 4, clozapine
4. Clozapine	15574 (15506-15642)	1.70 (1.68-1.72)	versus 1 = £47980
5. Olanzapine	19599 (19377-19821)	0.95 (0.93-0.96)	Dominated by 1, chlorpromazine
Triangular distribution			
2nd line therapy			
1. Chlorpromazine followed by			
a) risperidone, clozapine	14355 (14172-14538)	2.18 (2.16-2.20)	}
b) olanzapine, clozapine	14393 (14207-14579)	2.19 (2.17-2.21)	}Equivalent
c) clozapine, risperidone	14322 (14137-14507)	2.18 (2.16-2.20)	}
d) clozapine, olanzapine	14385 (14196-14574)	2.18 (2.16-2.20)	}
2. Haloperidol followed by			
a) risperidone, clozapine	16555 (16291-16819)	2.12 (2.09-2.15)	}
b) olanzapine, clozapine	16829 (16576-17082)	2.15 (2.12-2.18)	} Dominated by 1, chlorpromazine
c) clozapine, risperidone	16617 (16359-16875)	2.13 (2.10-2.16)	}
d) clozapine, olanzapine	16651 (16393-16909)	2.13 (2.10-2.16)	}

TABLE 17 EXPECTED COSTS (£) AND QALY'S PER PATIENT FAILING THERAPY OF 2ND, 3RD, AND 4TH LINE DRUGS: BY TREATMENT GUIDELINE

Therapy	Expected costs	Expected QALY's	Net expected cost/QALY
Triangular distribution **2nd line therapy**			
3. Risperidone followed by			
a) olanzapine, clozapine	16964 (16780-17112)	2.29 (2.27-2.31)	versus 1b = £25710
b) clozapine, haloperidol	17062 (16900-17224)	2.31 (2.29-2.33)	}Dominates 4, olanzapine
c) clozapine, chlorpromazine	16946 (16777-17115)	2.28 (2.26-2.30)	}
d) clozapine, olanzapine	16902 (16737-17067)	2.28 (2.26-2.30)	versus 1d = £25170
4. Olanzapine followed by			
a) risperidone, clozapine	19099 (18873-19325)	2.14 (2.11-2.16)	}
b) clozapine haloperidol	19128 (18898-19358)	2.13 (2.11-2.15)	} Dominated by 1, chlorpromazine
c) clozapine, chlorpromazine	19085 (18851-19318)	2.13 (2.11-2.15)	}
d) clozapine, risperidone	18900 (18673-19127)	2.11 (2.09-2.13)	}

TABLE 17 EXPECTED COSTS (£) AND QALY'S PER PATIENT FAILING THERAPY OF 2ND, 3RD, AND 4TH LINE DRUGS: BY TREATMENT GUIDELINE

Therapy	Expected costs	Expected QALY's	Net expected cost/QALY
Triangular distribution **3rd line therapy**			
1. Chlorpromazine followed by			
a) haloperidol	16776 (16527-17024)	1.93 (1.91-1.95)	Dominated by 1b
b) risperidone	17256 (17003-17509)	2.09 (2.07-2.11)	Equivalent 1c
c) clozapine	17570 (17314-17826)	2.08 (2.06-2.10)	versus 1a = £5293
d) olanzapine	17436 (17182-17690)	2.00 (1.98-2.02)	Dominated 1b, 1c
2. Haloperidol followed by			
a) chlorpromazine	19426 (19105-19747)	2.00 (1.97-2.03)	}
b) risperidone	20683 (20346-21020)	2.01 (1.98-2.04)	} Dominated by 1, chlorpromazine
c) clozapine	20967 (20614-21318)	2.00 (1.97-2.03)	}
d) olanzapine	21081 (20723-21439)	1.92 (1.89-1.95)	}
3. Risperidone followed by			
a) chlorpromazine	18254 (18039-18469)	2.15 (2.13-2.17)	Dominates 5a, olanzapine
b) haloperidol	18486 (18272-18700)	2.05 (2.03-2.07)	versus 1a= £14250
c) clozapine	19025 (18809-19241)	2.15 (2.13-2.17)	versus 1c= £20786
d) olanzapine	19332 (19104-19560)	2.12 (2.10-2.14)	versus 1d= £15800

TABLE 17 EXPECTED COSTS (£) AND QALY'S PER PATIENT FAILING THERAPY OF 2ND, 3RD, AND 4TH LINE DRUGS: BY TREATMENT GUIDELINE

Therapy	Expected costs	Expected QALY's	Net expected cost/QALY
Triangular distribution			
3rd line therapy			
4. Clozapine followed by			
a) chlorpromazine	18864 (18637-19091)	2.22 (2.20-2.24)	versus 3a = £8714
b) haloperidol	18825 (18601-19049)	2.08 (2.06-2.10)	versus 1a= £13660
c) risperidone	19408 (19171-19645)	2.21 (2.19-2.23)	versus 1b= £17933
d) olanzapine	19874 (19633-20114)	2.15 (2.14-2.17)	versus 1d= £16253
5. Olanzapine followed by			
a) chlorpromazine	23418 (23063-23773)	2.05 (2.03-2.07)	}
b) haloperidol	23603 (23260-23945)	1.80 (1.78-1.82)	} Dominated by 1, chlorpromazine
c) risperidone	24390 (24037-24742)	2.01 (1.99-2.03)	}
d) clozapine	25085 (24725-25445)	2.02 (2.00-2.04)	}
4th line therapy			
1. Chlorpromazine	11574 (11473-11676)	1.44 (1.42-1.46)	
2. Haloperidol	14804 (14633-14975)	1.20 (1.18-1.22)	Dominated by 1, chlorpromazine
3. Risperidone	15702 (15592-15812)	1.71 (1.70-1.72)	versus1 = £15289
4. Clozapine	15928 (15851-16003)	1.72 (1.70-1.74)	Dominated by 3, risperidone
5. Olanzapine	19702 (19486-19918)	1.03 (1.02-1.05)	Dominated by 1, chlorpromazine