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Pharmacoeconomic modelling in schizophrenia

Trap or support for decision makers?

Introduction

Schizophrenia is, arguably, the most costly of mental illnesses. The economic burden it places upon society, health care systems, caregivers, and families in particular is staggering. The present research presents a structure for analysing models used to study schizophrenia treatments, seeking to provide cost and outcome estimates when data are limited and/or based on varying assumptions.

Treatment options for schizophrenia have expanded greatly with the introduction of atypical antipsychotics, often referred to as second-generation antipsychotics. These new drugs include clozapine, risperidone, olanzapine, sertindole, ziprasidone, quetiapine, and aripiprazole and have demonstrated marked improvements in negative symptoms and lower levels of extrapyramidal symptoms (EPS) [1, 2, 3]. While presenting several medical advantages, their acquisition costs are markedly higher than first-generation antipsychotics. Yet the latest published data available reveal that drug acquisition costs account for only 2–6% of the total cost of care for all psychotic illnesses [4, 5, 6, 7].

Despite their higher acquisition costs, several studies have demonstrated that atypical antipsychotics are more cost-effective than less expensive typical antipsychotics. Because most health economic studies collect data retrospectively, they are limited in resource use measurement methodology and design. Decision analysis models are frequently used to identify cost-effective solutions when extensive prospective health economic data are unavailable. Such models strive to represent the clinical and temporal sequence of possible decisions and options open to clinicians when treating a particular condition or disease.

Pharmacoeconomic evaluations of new drugs are becoming increasingly more important and, in some cases, obligatory. These studies directly affect the decision-making process, beginning with physician prescription and continuing with regulatory authorities (pricing and reimbursement approval) through to formulary inscription. The ever-increasing cost of innovative drugs requires an answer to the all-important question, "Does a drug's benefit to the patient justify its cost?" Recent polls have indicated that the market for antipsychotics clearly opposed a second generation of atypical antipsychotics; first-generation compounds were still favoured.

Clinical impact of atypical antipsychotics

The comparative effectiveness between the two generations of antipsychotics is similar. The tolerability profile of atypicals, however, has been shown to be significantly better than that of typical antipsychotics. Notably, atypicals are essentially free of EPS compared with typicals. Conversely, atypicals are associated with a number of side effects, predominantly sedation and weight gain [8, 9, 10], but these are not as pronounced as side effects associated with typical antipsychotics. The importance of side effects must be considered when taking into account compliance, quality of life, and rehabilitation. None of these factors has been assessed as thoroughly as EPS. Yet data from a study of amisulpride [11] suggest better efficacy of atypicals as opposed to typicals in controlling negative symptoms.

Economic impact of atypical antipsychotics

All factors considered, atypicals are generally perceived as presenting an economic advantage over typical antipsychotics because they are expected to generate savings that will effectively outweigh their comparatively high cost. As is common with all drugs, no actual data are available at the time of market launch, and published material is not always persuasive. Data can therefore be obtained solely from four sources: clinical trials, mirror studies, naturalistic studies, and modelling exercises. The first two sources are biased be-

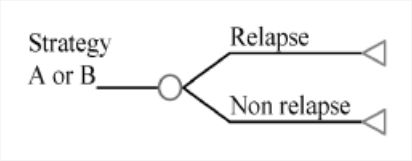

Fig. 1 ▲ **Relapse model**

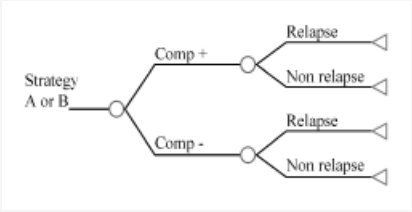

Fig. 2 ▲ **Compliance model**

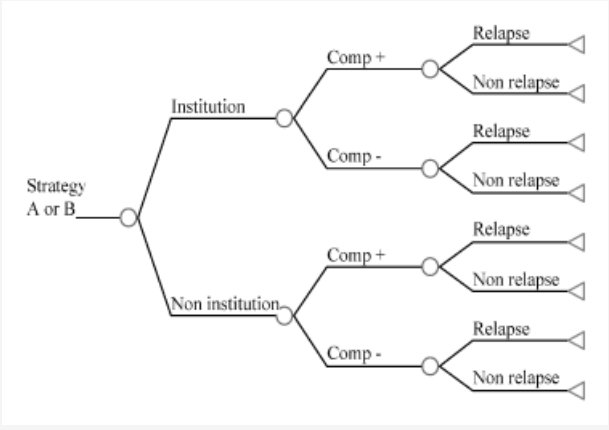

Fig. 3 ◀ **Institution model**

cause they are based on a restricted group of patients and conducted under strict controls. The third source has limited external validity; there is uncertainty regarding the relevant target group in the population to be studied. This leaves modelling exercises as the best available method [12].

The modelling exercise presents the most relevant approach because it enables nonpharmacologic treatment and confounding factors that modulate a drug's potential impact to be incorporated into the analysis. Modelling involves simplifying reality to a level that describes the essential complications and consequences of different options in decision making, but it provides only "best estimates" derived from currently available information. It is often said, however, that modelled results, when compared with results from randomised clinical trials (RCTs), are more relevant because they reflect daily practice more accurately. RCTs are protocol driven and have low external validity. They use a selected population that is not necessarily representative of the target population; resource utilisation is mandated by the study protocol; and, above all, the choice of comparator is arbitrary and does not necessarily reflect real-life practice.

Models may take the form of simple decision analysis trees, which are appropriate for acute episodes. However, this approach may be too simplistic for describing situations in which there are several alternative actions, situations in which probabilities may change over time, or chronic diseases (such as schizophrenia) in which the same decisions are frequently repeated. Therefore, other models or modelling approaches have been created. Markov models, for example, are particularly suited to modelling repeated events or the progression of chronic diseases. Markov models require strict assumptions concerning "zero memory," referred to as the Markovian assumption [13], which specifies that the behaviour of the process subsequent to any cycle depends only on its description in that cycle [14, 15]. In other words, the process has no "memory" of earlier cycles.

By definition, a model is a distilled picture of reality. Its validity rests on whether its assumptions are both reasonable and based on the needs and purposes of the decision maker and, more importantly, whether the implications make sense. Hence, the quality of a model's prediction is only as good as the quality of the empirical data put into the model.

Various schizophrenia models

The present theoretic model development used in conjunction with the following modelling review is a method for evaluating the economic and effectiveness strengths of modelling in schizophrenia. Base case costs and probabilities that will be implemented in the models along with the theoretic development will be considered. The first model, illustrated in ◘ **Fig. 1**, is a simple two-branch model that will be made more complex as additional variables are added to it. In other words, the additional variables create subsequent branches (options) in the model. The models are kept relatively simple in order to facilitate their outlines. One is able to recalculate the obtained results with the information given in the base case and the additional information given before each model.

Two treatment strategies, A (atypical) and B (typical), with the following hypothetical half-yearly base-case costs and relative probabilities, are illustrated in ◘ **Table 1**.

Relapse model

The relapse model is based on a well-accepted assumption that strategy A versus strategy B decreases the relapse rate in a clinical trial. Assuming that a reliable cost of relapse is available, we can easily calculate the incremental cost-effectiveness of treatments A versus B using a decision tree. Effectiveness can then be measured as time without relapse or as success without relapse. In the base-case scenario, the incremental cost (ΔC = cost of strategy A minus cost of strategy B) is USD 4,300, and the incremental effectiveness (ΔE = effectiveness of strategy A minus effectiveness of strategy B) is −0.20, which represents a difference of 5.2 weeks without relapse. Treatment strategy B is more costly and less effective than strategy A; thus, strategy A "dominates" strategy B.

Compliance model

In real practice, a certain percentage of patients are always noncompliant. This is a major cause of relapse. Some patients re-

lapse even though they are compliant with their treatment regimen, but relapse resulting from noncompliance presents more serious consequences. Weiden et al. found that relapse in noncompliant patients was more common, disruptive, and severe [16]. Hence, a 10% reduction in relapse rates was shown for patients compliant with their treatment regimen. An illustration of a compliance model can be found in **Fig. 2**.

In this case the incremental cost is USD 4,000, and the incremental effectiveness is −0.188, which represents a difference of 4.8 weeks without relapse. The difference between effectiveness and cost is reduced when the compliance rate is introduced in the model.

Institution model

A number of patients with schizophrenia are unable to live with their families or in the community and require institutionalisation. These patients are expected to have a 50% increase in compliance because of closer surveillance by treatment staff, and several published articles suggest that compliance is higher among inpatients than outpatients [17, 18].

In this model, the incremental cost is USD 3,900 and the incremental effectiveness is −0.187, which amounts to a difference of 4.8 weeks without relapse. The Δ effectiveness of −0.187 in the model equals a difference of 4.8 weeks without relapse, which does not differ from the previous compliance model. The introduction of the institutional variable in the model does not modify the difference in effectiveness nor does it significantly alter the difference in costs. An example of an institution model can be seen in **Fig. 3**.

Dropout model

It is common in schizophrenia pathology that patients who drop out of health care systems often reappear at hospitals later, experiencing relapse. An estimated cost of dropout has been entered in the model illustrated in **Fig. 4**.

In this scenario, the incremental cost is USD 3,700, and the incremental effectiveness is −0.180, which represents a difference of 4.6 weeks without relapse. The difference in effectiveness and cost is reduced when the dropout variable is introduced in the model.

Switch model

Patients who do not respond to or cannot tolerate a particular treatment require a change to different medication. Some patients switch from typical to atypical antipsychotics, and for others the reverse is true. One explanation for switching from atypicals to typicals is that atypicals, with the exception of risperidone, are not available in depot form. Cost considerations may be another factor [7]. Regardless of the reason for switching, nonresponders to strategy A switch to B or *vice versa*, and a cost of switching (additional consultations, etc.) is introduced in the model, as illustrated in **Fig. 5**. In this scenario, the incremental cost estimated from this hypothetical model is USD 4,000 and the incremental effectiveness is −0.180, which amounts to a difference of 4.6 weeks without relapse. The introduction of the switch variable in the model increases the difference in cost but does not modify the difference in effectiveness.

Mixed case model

Risks and costs of relapse are quite different among subgroups of patients with schizophrenia, as demonstrated by a 6-month prospective cohort [19]. In this model, three groups of patients were identified: institutionalised patients, intensive care patients, and moderate care patients, and rates of relapse were 2%, 8%, and 10%, respectively. The 6-month cost of resource utilisation when relapse occurred was USD 42,300 for institutionalised patients, USD 18,900 for intensive care patients, and USD 2,900 for the moderate population. When relapse did not occur, costs decreased to USD 36,900 for the institutionalised patients, USD 18,500 for the intensive care patients, and USD 1,500 for the moderate care patients. Considering that costs decrease 24-fold when patients are transferred from an institution to a less-managed care setting, it is important to identify each individual setting and not consider them as one group. Introducing this information to the model will, in

Abstract

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Abstract
Pharmacoeconomic evaluations are important elements in the decision making process, and decision tree analyses are statistical models that analyse both clinical and economic consequences of medical actions. Using one theoretic model, key confounding variables were identified that constituted a standardised framework for economic evaluation of schizophrenia management. The extent to which they were included in several previously published schizophrenia models was appraised. Five different models were developed, and a systematic review of schizophrenia modelling studies was conducted. Results indicate that atypical antipsychotics may be more or less cost-effective depending upon whether key confounding variables were taken into account, but vigilance is warranted when assessing data because serious discrepancies can occur between different methods of analysis. A need for standardised schizophrenia pharmacoeconomic models exists. Additionally, social rehabilitation should be considered because this may also influence outcomes. Standardising modelling techniques will facilitate adherence to guidelines issued by decision makers.

Keywords
Atypical antipsychotic · Economic modelling · Schizophrenia · Cost-effectiveness analysis

Table 1

Base case costs (USD as of 1997) and probabilities used in the five models

Factor	Unit
Cost of drug A	$1,500
Cost of drug B	$750
Cost of relapse	$67,000
Cost of non-relapse	$42,000
Cost of dropout	$10,000
Cost of switch	$1,000
Rate	**%**
Relapse rate of strategy A	30%
Relapse rate of strategy B	50%
Non-compliance rate	40%
Institutional rate	10%
Dropout rate	4%
Switch rate drug A	30%
Switch rate drug B	40%

Source: database of schizophrenia patients in the catchment area of Pau, France [19]

effect, balance cost and effectiveness between atypical and typical antipsychotics.

Summary of the theoretic model development

To better understand the impact of including an extra confounding factor in a schizophrenia model, we have gathered all the results (Δ cost, Δ effectiveness) from the different models and summarised them in **Table 2**. As confounding factors are added to the model, the marginal cost-effectiveness decreases or increases along with the marginal cost-effectiveness ratio.

Literature review of modelling studies in schizophrenia

A review of all published models in schizophrenia was conducted to analyse the extent to which examples of existing models consider key confounding factors. Inclusion criteria for our analyses were the use of a modelling technique to assess the costs and outcomes of different pharmacologic treatment strategies and all levels of care, notably inpatient, outpatient, and day care treatments. Our comments will centre on the treatment comparators, therapeutic regimens, efficacy/effectiveness parameters, exclusion of key variables and assumptions, and other factors. Because all of the models are based on assumptions, their appropriateness was determined, unless specifically stated, by the individual authors themselves. Other considerations such as the data inputs and results were examined. When reviewing the different papers, the following aspects were considered: the time frame for the adopted perspective, the possibility of titration, the use of the most appropriate model (i.e. decision analysis, Markov, or a combination thereof) for the time frames considered, and reasonable probabilities derived from appropriate trials. Also considered were the functions of expert panels, metaanalyses of the literature, appropriate costs (i.e. direct and/or indirect costs), and appropriate outcomes (i.e. cost-effectiveness, cost-efficacy, and cost-utility). We believe the present selected reviews represent the overall status of published modelling studies in the treatment of schizophrenia. A Boolean search of Medline using the terms "decision support technique," "cost-effectiveness," "pharmacoeconomic," "antipsychotic," "neuroleptic," and "schizophrenia," for the years 1990–2004 revealed 20 different articles. We eliminated two studies that only modelled the cost of treating schizophrenia [20, 21]; two studies [22, 23] based on previously published models by Almond and O'Donnell in 1998 [24] and Glennie in 1997 [25]; one study in Spanish [26]; one cost-of-illness model [27];

Table 2

Summary of the theoretic model development (rounded sums; K=thousand)

Model	Δ Cost (USD as of 1997)	Δ Effectiveness time without relapse
Relapse	4.3 K	–0.200
Compliance	4.0 K	–0.188
Institution	3.9 K	–0.187
Dropout	3.7 K	–0.180
Switch	4.0 K	–0.180

Table 3

Overview of articles included in the review (DB double-blind)

Reference	Study design: length, model type	Analysis
Davies LM, Drummond MF (1993)	1 year + lifetime, decision analytic model	Cost-effectiveness analysis
Glazer WM, Ereshefsky L (1996)	1 year, decision analytic model	Cost-effectiveness analysis
Glennie JL (1997)	1 year + lifetime, decision analytic model	Cost-utility analysis
Laurier C et al. (1997)	9 days, decision analytic model	Cost-effectiveness analysis
Byrom B et al. (1998)	8 weeks + 1 year, decision analytic model	Cost-effectiveness analysis
Palmer CS et al. (1998)	3 months + 5 years, Markov model	Cost-effectiveness analysis
Davies A et al. (1998)	2 years, decision analytic model	Cost-effectiveness analysis
Almond S, O'Donnell O (1998)	5 years, Markov process model	Cost-effectiveness analysis
Launois R et al. (1998)	10 years, Markov process model	Cost-effectiveness analysis
Almond S, O'Donnell O (2000)	5 years, Markov process model	Cost-effectiveness analysis
Lecomte P et al. (2000)	1 year, semi-Markov model	Cost-effectiveness analysis
Tilden D et al. (2002)	5 years, Markov model	Cost-effectiveness analysis
Ganguly R et al. (2003)	1 year, decision analytic model	Cost-effectiveness analysis

and one study that was not based on a real cost-effectiveness model [28]. In the end, 13 articles were chosen to be included in this review. **Table 3** depicts the types of modelling for each of the 13 studies selected.

Discussing and appraising published models helps assimilate new information and evaluate the models' economic and effectiveness strengths and weaknesses. It is important to evaluate various types of study designs by length, model type, and style of analysis. The following section presents a short description and assessment of 13 different studies.

Davies LM, Drummond MF (1993) Assessment of costs and benefits of drug therapy for treatment-resistant schizophrenia in the United Kingdom. Br J Psychiatry 162:38–42 [29]

This study was a clinical decision tree model based on a United States (US) cost-effectiveness analysis (CEA) of clozapine for inpatients with longstanding, treatment-resistant schizophrenia. The two timeframes chosen to illustrate expected net savings and outcomes per person were 1 year and an entire lifetime. A Delphi panel of five British psychiatrists assessed how use of resources would have differed in the United Kingdom (UK). Patient outcomes were defined as the number of years with mild or no disability.

Assessment. Even though the authors admitted that they adapted the US model to a UK setting, it cannot be assumed that US management of treatment-resistant schizophrenia would be the same as in the UK. The authors listed different path probabilities, but the probabilities for discharge to a group home were not given. Subsequent and nonsubsequent hospital admissions were not broken down into two separate probabilities, whereas two path possibilities appear in the decision tree. Additionally, different probability names appear in the tables and the model, thus rendering them confusing. Assessing how use of resources would have differed in the UK was a positive element in the study, but the unknown process by which the Delphi panel was composed is questionable.

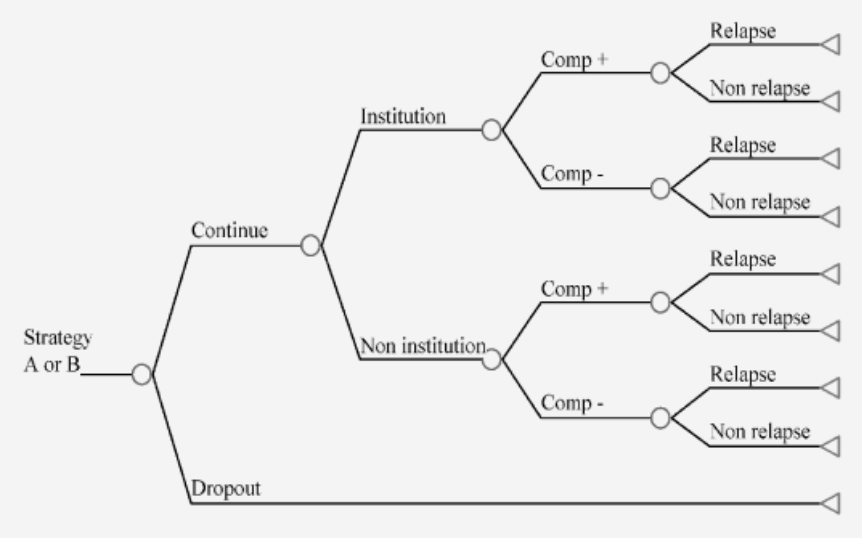

Fig. 4 ▲ **Dropout model**

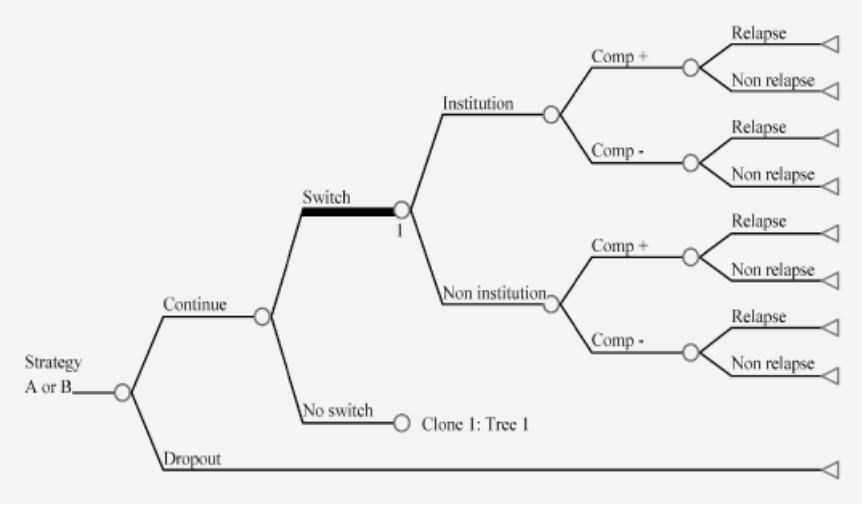

Fig. 5 ▲ **Switch model**

Glazer WM, Ereshefsky L (1996) A pharmacoeconomic model of outpatient antipsychotic therapy in "revolving door" schizophrenic patients. J Clin Psychiatry 57(8):337–345 [30]

This clinical decision analysis indicates that under a variety of assumptions, switching a "revolving door" patient with schizophrenia to a depot medication for outpatient maintenance therapy could result in lower total direct treatment costs. Covering a timeframe of 1 year, this cost-effectiveness analysis employed a model designed to take into account compliance and associated rehospitalisation rates and to compare the direct treatment costs associated with alternate outpatient antipsychotic strategies for "revolving door" patients.

Assessment. The model is a simple decision analytic model that considers compliance and then adherence to drug therapy (stable, exacerbation) and associated rehospitalisation. The study lacked systematically collected data, and the probabilities were based on the authors' clinical experiences. The chosen time horizon of 1 year can be justified when considering compliance as the only variable. However, because schizophrenia is a long-term and often chronic disease, a lifetime impact of the different drug strategies might also have been considered. Somewhat alarming, due to the fact that they were not discussed in the paper, were the representa-

tion and use of costs derived from the authors' own institutions.

Glennie JL (1997) Pharmacoeconomic evaluations of clozapine in treatment-resistant schizophrenia and risperidone in chronic schizophrenia. Technology overview: pharmaceuticals. Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Ottawa, issue 7.0 [25]

This cost-effective analysis sought to evaluate treatment sequences for clozapine and risperidone. The authors constructed decision analysis models based on the literature and expert panel input. The basic design for each tree highlighted a specific drug and then delineated possible downstream events that included tolerability, "success" versus "failure," discharge from hospital, and relapse. The risperidone tree also incorporated the development of EPS into its design.

Assessment. The decision analytic model was not illustrated in the paper, thus rendering it difficult for the reader to visualise its structure. The composition of the expert panel, their involvement in the construction of the model, and their method of agreement was unclear. The studies used in the two models were of moderately short duration (6–8 weeks), and the authors themselves recognise that their work did not explicitly report on economically relevant parameters. The model used short-term data to estimate events over a 1-year period, the results of which were then extrapolated over 37 years. This probably biased the results. Key variables such as compliance or a switch to an alternative antipsychotic were not included in the model.

Laurier C, Kennedy W, Lachaine J, Gariepy L, Tessier G (1997) Economic evaluation of zuclopenthixol acetate compared with injectable haloperidol in schizophrenic patients with acute psychosis. Clin Ther 19(2):316–329 [31]

A cost-effectiveness analysis of intramuscular zuclopenthixol acetate and intramuscular haloperidol was performed using the Quebec Health Care System perspective. Total costs associated with both drugs were modelled using a decision tree built around the number of injections necessary to achieve stabilisation. Patients were assessed for a total of 9 days after starting treatment. Costs were established from expert panel input as well as from reviewing patient files. Only direct medical costs were considered, and published literature was the principal source of comparative data for clinical outcomes.

Assessment. Of all registered published models concerning schizophrenia, this may be one of the simplest. It is an uncomplicated clinical decision analytic model and by no means an acute episode management model. Its short time horizon of only 9 days does not fall within any recognised recommendations. However, if this model were considered a "submodel," it might be able to be used as part of a global model or as an intervening factor in the control of an acute episode of schizophrenia. Finally, the composition of the expert panel was according to standard, but the report did not state how agreement was reached (i.e. Delphi rounds).

Byrom B, Garratt C, Kilpatrick AT (1998) Influence of antipsychotic profile on cost of treatment of schizophrenia: a decision analysis approach. Int J Psychiatry 2:129–138 [32]

The authors present a health economic model for the treatment of an acute episode of schizophrenia and its subsequent control through maintenance treatment. Its predictions indicate that reported clinical profiles of atypical antipsychotics could lead to significant savings and large improvements in effectiveness over conventional therapy. A decision analytic model was used to make a cost-effective analysis and was divided into two modules, each represented in decision tree form. The first relates to the management of an acute episode of schizophrenia, and the second to the subsequent stabilisation/maintenance period of treatment. Default values for each parameter were obtained from the literature. A meta-analysis was used to report average compliance rates for compliant and noncompliant patients receiving typical antipsychotic treatment.

Assessment. Given the repetitive nature of schizophrenia, combining the author's two-part decision analytic model with a Markov model may have been a better idea. The chosen time horizons of 8 weeks and 1 year corresponded to the length of the clinical trial, but it would have been interesting to consider lifetime predictions as well. Assuming that patients will relapse only once in a year seems quite conservative, as does the assumption that the timing of relapse could be uniformly distributed across the same period. The model is limited by the experimental data available and does not contain a dropout or a switch arm. However, there is transparency about the probabilities implemented, and the different experiments (sensitivity analyses on variables) make it possible to detect the influence of the antipsychotic profile.

Palmer CS, Revicki DA, Genduso LA, Hamilton SH, Brown RE (1998) A cost-effectiveness clinical decision analysis model for schizophrenia. Am J Manag Care 4(3):345–355 [33]

The authors employed a decision analytic model to determine the cost-effectiveness of treatments and outcomes that patients treated for schizophrenia may experience during a 3-month cycle over a 5-year period. In cases where clinical trial results were unavailable, parameter estimates were based on published medical literature and the advice of experts from an 11-member international advisory panel composed of psychiatrists and health economists.

Assessment. Because the authors chose to use a Markov model, it would have been interesting to make lifetime calculations. Measures of health utility were based on the calculation of quality-adjusted life years. These were estimated from standard gamble utilities assigned to hypothetical schizophrenia-related health states by 12 psychiatrists in the UK. The appropriateness of this method and the exclusive use of psychiatrists may be a topic for

further discussion. When looking closely at the "treatment tree" and in particular at the "switch 2" arm, it is not stated to where or to what the patient was switched. Furthermore, suicide seems to be the only cause of death in the model, whereas other causes of mortality (notably cardiovascular events) are far from being negligible for this population. In the tables, no probabilities are given for the first four arms of the "symptoms tree." It is also interesting to note that the "no therapy" strategy exhibits lower relapse rates than the three other pharmacotherapies from cycle 3 and beyond. Moreover, the process by which agreement was reached within the expert panel was not stated, nor was it clear whether they had participated in the construction of the global decision tree. Finally, one of the effectiveness outcomes used in the model was the Brief Psychiatric Rating Scale (BPRS) score. The extent to which this score is suited for long-term modelling should be examined in further detail.

Davies A, Langley PC, Keks NA, Catts SV, Lambert T, Schweitzer I (1998) Risperidone versus haloperidol: II. Cost-effectiveness. Clin Ther 20(1):196–213 [34]

The authors developed a decision analytic model to estimate the comparative effectiveness of risperidone and haloperidol in patients with schizophrenia. The model consisted of a decision tree that simulated the treatment of patients with chronic schizophrenia and tracked distribution along different pathways over a 2-year period. The model was built using the results of a metaanalysis of efficacy, tolerability, dropout rates, and information from the literature as well as advice from a panel of psychiatric experts.

Assessment. The reasons for selecting a 2-year time horizon were not sufficiently set forth and led us to question why cost-effectiveness calculations were not calculated for those patients with chronic schizophrenia. The transparency of the construction of the model was quite good; however, the composition of the group constructing the model remains unclear. The probabilities not found in the metaanalysis were assigned based on an open discussion with the panel. Again, not only was the composition of the panel unknown but the process of agreement was not identified. All the probabilities were not listed in the tables and, as such, did not enable a reanalysis of the model. Finally, key variables such as dropout and switch were not included in the model.

Almond S, O'Donnell O (1998) Cost analysis of the treatment of schizophrenia in the UK: a comparison of olanzapine and haloperidol. Pharmacoeconomics 13(5 Pt 2):575–588 [24]

A decision tree simulation model was used to examine the costs associated with the treatment of patients with schizophrenia. The authors employed a Markov process to iterate patients through a series of 20 three-month cycles. During each cycle, patients received treatment and faced the probabilities of experiencing events such as relapse or dropout. Parameter values were taken from either an international randomised clinical trial or from the relevant literature and were the same as those used in the application of the model in US.

Assessment. The values and outcomes used in the analysis were derived from international clinical trial data. While the trial included some UK participants, the number was relatively low (too low, in fact, for UK-specific trial data to be used). To establish the cost-effectiveness of olanzapine in a UK context, it would have been preferable to rely on UK data to estimate parameter values and outcomes. The management of schizophrenia differs from country to country; the model should have been adapted to the UK and not simply copied from the US. In the UK, a substantial proportion of patients with schizophrenia are treated with medications administered in depot form. This fact alone limits the applicability of the US results. Examples of probabilities not listed in the tables include "stay on agent" as well as "switch 1." The model construction is not specified. The BPRS score was used as one of the effectiveness measurements, but the appropriateness of this score for long-term modelling could have been considered.

Launois R, Graf von der Schulenberg M, Knapp M, Toumi M (1998) Cost-effectiveness of sertindole versus olanzapine or haloperidol: a comprehensive model. Int J Psychiat Clin Pract 2 [Suppl 2]:79–86 [35]

This study evaluated three competing antipsychotic drug strategies in normal practice using a 10-year cost effectiveness model based on a 6-month Markov cycle tree. The model incorporated five care management strategies defined by place of residence (hospital, managed care, or private home), intensity of care (intensive or mild), and clinical events (EPS, sedation, weight gain, sexual dysfunction, relapse). Dropout and direct medical costs associated with the above were also considered.

Assessment. This Markov model included almost all of the key confounding variables emphasised in previous sections. However, it did not include the possibility of switch. Additionally, probabilities were based on different trials and metaanalyses. The manner in which the metaanalyses were conducted was not specified, nor was the composition of the group constructing the model or the way in which they reached agreement. The institutionalisation specificity in this model was unique. It allowed for the grouping of diverse institutions in homogenous categories on an international level. Mixing clinical status with setting permitted the differentiation of the quality of life coefficients with accommodation and disease severity levels. The study's long-term timeframe was a novelty among the reviewed papers; however, it might have been interesting to assess lifetime impact as well.

Almond S, O'Donnell O (2000) Cost analysis of the treatment of schizophrenia in the UK: a simulation model comparing olanzapine, risperidone and haloperidol. Pharmacoeconomics 17(4):383–389 [36]

This analysis is based on the same 5-year Markov decision tree simulation model used in the authors' previously reviewed

article. However, by adding risperidone as a third initial treatment node, the authors extended the model. This was made possible by including newly released data from an international, multicentre, double-blind 28-week prospective study of 339 individuals.

Assessment. Because this model is a continuation of a previously published model, it was surprising to note that the authors did not correct its weaknesses. Consequently, the assessment does not differ from that of their 1998 paper [24], to which the interested reader should refer.

Lecomte P, De Hert M, Dijk MV, Nuijten M, Nuyts G, Persson U (2000) A 1-year cost-effectiveness model for the treatment of chronic schizophrenia with acute exacerbations in Belgium. Value Health 3(1):1–11 [37]

A 1-year semi-Markov model was constructed to simulate the cost-effectiveness of atypical (risperidone and olanzapine) and typical (haloperidol) antipsychotic treatments for schizophrenia. The model was based on data from the literature, guidelines from the American Psychiatric Association (APA), and the results of discussions with experts employing the Delphi method.

Assessment. The model improves upon the few existing economic analyses of atypical antipsychotics. The definition of response used was based on both the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) scores, providing a more global measurement compared with the BPRS used in other studies. Furthermore, the opportunity to decrease the dosage after 6 months in case of response was in accordance with APA guidelines. The use of shorter, more frequent cycles that more closely follow clinical practice for assessing patients permitted the model to respond to changes in patient state with a greater degree of sensitivity, thus better reflecting real-life conditions. However, the model did not incorporate indirect costs; they were obtained from official tariff lists, which beg discussion of the distinction between tariffs and charges.

Tilden D, Aristides M, Meddis D, Burns T (2002) An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics. Clin Ther 24(10):1648–1667 [38]

This study assessed the cost-effectiveness of quetiapine compared with haloperidol in partial responders with schizophrenia using a 5-year Markov model based on 3-month cycles. The different health states in the model were derived from a clinical trial of quetiapine versus haloperidol, and the remaining states were based on those in Almond and O'Donnell's 2000 model [36].

Assessment. The values and outcomes used in the analysis were derived from international clinical trial data, just as in Almond and O'Donnell's 2000 model [36]. There were UK centres in the trial, but the original article of the clinical trial [39] did not describe the percentage of patients from the UK. As was mentioned in the assessment of the model of Almond and O'Donnell [36], if one wants to establish the cost-effectiveness of olanzapine in a UK context, it would have been preferable to rely on UK data only to estimate parameter values and outcomes. As in the original model paper, the model construction is not specified. In contrast to the original model, the authors replaced the BPRS score with the PANSS score as an effectiveness measurement. Although PANSS is more widely recognised, its appropriateness for long-term modelling was not discussed.

Ganguly R, Miller LS, Martin BC (2003) Future employability, a new approach to cost-effectiveness analysis of antipsychotic therapy. Schizophr Res 63:111–119 [40]

This study used a decision analytic cost-effectiveness model to compare risperidone versus haloperidol over a 1-year period using the number of employable persons as a measure of effectiveness. This model is an extension of the model for schizophrenia outpatients by Glazer and Ereshefsky [30], to which the authors added terminal branches for assessing cognition and executive functioning. A Monte Carlo simulation procedure was used to generate the number of patients in each health state.

Assessment. The model is a simple decision analytic model that considers compliance and health states (stable, exacerbated, and hospitalised) and employability. It can be questioned whether "employability" is an accurate measure of changes in health status, as it is known that there is high unemployment among patients with schizophrenia. The chosen time horizon of 1 year was justified when considering compliance as the only variable. With the addition of employability, however, a longer period would have been suitable. The authors used Glazer and Ereshefsky's 1996 [30] estimates of resource utilisation, which were based on data from the latter's own institution. The question of whether these data were representative remains unanswered.

Discussion and limitations

The intention of the present review was to establish a reference point from which various attributes could be studied and to improve future pharmacoeconomic models. Confounding factors are rarely considered in modelling studies. Furthermore, attributes such as the structure of the model, expert panel use, sensitivity analyses, timeframes, type of analysis, and model design are not systematically employed. The most realistic and illustrative model design for chronic diseases such as schizophrenia would be a combination of the Markov process and a decision analysis tree. Markov models cover the possibility of patients transitioning back and forth between health states when they enter a new cycle, while decision tree analyses reveal distinct paths and probabilities. Few published studies have employed this technique.

The most common type of analysis recommended by official guidelines is a cost-effectiveness study [41]. The majority of studies reviewed conducted this type of analysis. One study even conducted a cost-utility analysis [42]. The ideal timeframe is one capable of projecting data throughout a patient's lifetime. In fact, sev-

Table 4

Literature review (√ indicates that the factor/variable was included in the model)

Study	Better cost-effective alternative	Compliance	Institution	Dropout	Switch	Mixed case	Source of probabilities		
							Hard data	Expert panel[a]	Delphi panel[b]
Davies LM, Drummond MF(1993)	Clozapine		√			√	Yes		Yes
Glazer WM & Ereshefsky L (1996)	Depot drug	√					Yes	Yes	
Glennie JL (1997)	Clozapine/risperidone			√			Yes	Yes	
Laurier C et al. (1997)	Zuclopenthixol						Yes	Yes	
Byrom B et al. (1998)	Atypicals	√	√		√	√	Yes		
Palmer CS et al. (1998)	Olanzapine			√	√		Yes	Yes	
Davies A et al. (1998)	Risperidone	√	√			√	Yes	Yes	
Almond S, O'Donnell O (1998)	Olanzapine			√	√		Yes	Yes	
Launois R et al. (1998)	Sertindole	√	√	√		√	Yes		
Almond S, O'Donnell O (2000)	Olanzapine			√	√		Yes	Yes	
Lecomte P et al. (2000)	Atypicals	√	√		√				Yes
Tilden D et al. (2002)	Quetiapine	√		√	√		Yes	Yes	
Ganguly R et al. (2003)	Risperidone	√					Yes	Yes	

[a] *Expert panel: collects probabilities through interviews based on personal belief and judgment;* [b] *Delphi panel: has the goal of obtaining the most reliable consensus of a group of experts by a series of intensive questionnaires interspersed with controlled feedback [42]*

eral guidelines recommend that the timeframe of an informative prediction model be 5 years, preferably with the ability to project throughout a patient's lifetime [15]. Yet in our review we noticed that the timeframe adopted depended on the perspective and data incorporated into the model. Most of the studies used short-term data with short-term results. Only four of the 13 studies considered a timeframe exceeding or equivalent to 5 years. Given schizophrenia's chronic nature and frequent lengthy duration, long-term timeframes would be preferable.

Most of the studies considered used some form of expert panel. There was often a lack of transparency as to composition and method of agreement; the authors simply stated the panel's existence or that a Delphi panel was employed. Evans and Crawford [43] suggest that the terms used to describe the process by which an expert opinion panel is created for pharmacoeconomic evaluation studies are fraught with inconsistencies and rank expert opinion use, stating that model validation is their most important function and probability estimation their least important role. In the published articles reviewed in this research, expert panel participation in either model validation or probability estimation was never specified.

Sensitivity analyses can only partially correct for biases in probability estimation inherent in expert opinion use. Under no circumstances can they repair biases generated by a faulty model [44].

Of the modelling studies reviewed in this research, only a few conducted sensitivity analyses, frequently in the form of different scenario analyses. The importance of sensitivity scenario analyses in pharmacoeconomic evaluations cannot be stressed enough because they permit robustness testing of the model as well as probability estimations. The literature review illustrated in **Table 4** reveals that most of the models studied did not include all key confounding variables. Inclusion or exclusion of variables important in a medical decision tree should be clearly cited when reporting modelling studies. Naturally, the inclusion/exclusion of certain variables depends on the objective and perspective of the model. It would have been interesting, nevertheless, to assess the results obtained in the studied models had the missing key confounding variables been included. This was not possible because missing probabilities in the published studies rendered reconstruction of the models nearly impossible.

Objectively, the ideal model would be one capable of reflecting usual practice. To date, no "gold standard" model exists, and all are based upon assumptions that are validated neither *a priori* nor *a posteriori*. Pharmacoeconomic modelling studies are further handicapped by limited empirical data necessary to construct the model, the validity of assumptions used, and whether or not one setting can be adapted to another. Finally, the use of expert panels is harshly criticised due to questionable reliability even though they are, at times, the only method available.

Conclusion

Our results argue in favour of standardised pharmacoeconomic models for

schizophrenia. The pharmacoeconomic model is a unique tool for testing hypotheses and identifying the key variables of cost drivers in schizophrenia. Associated environmental factors of a disease can be incorporated into it, thereby contributing to more precise calculations and accurate final analysis. In the field of mental health – and especially in schizophrenia – there are a large number of variables that contribute to determining drug treatment strategy. The probabilities used in a model as well as its very structure should be carefully reviewed. No single global intervention for the management of schizophrenia exists. Therefore, complementary strategies should be considered and the most relevant included in the decision tree when making economic evaluations. None of the published models studied in our research included nonmedical treatments such as psychotherapy, family therapy, or rehabilitation. Standardising modelling techniques will facilitate adherence to guidelines issued by decision makers charged with allocating limited resources. In the same manner as one can say that a clinical trial has been performed according to good clinical practice, it would be helpful to be able to state the equivalent with respect to pharmacoeconomic analyses. Omission of key confounding elements can only complicate the decision-making process. Although they do possess inherent biases, models remain the best method of obtaining realistic assessments of medical interventions. This article has been written with the hope that peer review will help refine our observations and take standardisation of modelling techniques one step further towards better cost-effectiveness analyses.

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References

1. Caroff SN, Mann SC, Campbell EC, Sullivan K (2002) Movement disorders associated with atypical antipsychotic drugs. J Clin Psychiatry 63 [Suppl 4]:12–19
2. Conley RR, Kelly DL (2002) Current status of antipsychotic treatment. Curr Drug Targets CNS Neurol Disorders 1:123–128
3. Möller HJ (2003) Management of the negative symptoms of schizophrenia: new treatment options. CNS Drugs 17(11):793–823
4. Genduso LA, Hakey JC (1997) Cost of illness studies for schizophrenia: components, benefits, results, and implications. Am J Manag Care 3:873–877
5. Salize HJ, Rössler W (1996) The cost of comprehensive care of people with schizophrenia living in the community – a cost evaluation from a German catchment area. Br J Psychiatry 169:42–48
6. Rouillon F, Toumi M, Dansette GY, Benyaya J, Auquier P (1997) Some aspects of the cost of schizophrenia in France. Pharmacoeconomics 11(6): 578–594
7. Masand PS, Berry SL (2000) Switching antipsychotic therapies. Ann Pharmacotherapy 34:200–207
8. Masand PS (1998) Weight gain associated with atypical antipsychotics. J Psychotic Disorder 2:4–6
9. Beasley CM, Tollefson GD, Tran PV (1998) Safety of olanzapine. J Clin Psychiatry 58 [Suppl. 10]:13–17
10. Wirshing DA, Maarder SR, Goldstein D, Wirshing WC (1997) Novel antipsychotics: comparison of weight gain liabilities [abstract]. In: Scientific Abstracts of the 36th Annual Meeting of the American College of Neuropsychopharmacology, Kamuela, Hawaii
11. Souêtre E, Martin P, Lecanu JP, Alexandre L, Lozet H, Gauthier JM, Camus C (1992) Economic assessment of neuroleptic strategies in schizophrenia: amisulpride versus halopéridol. L'Encéphale 18:263–269 [French]
12. Fichtner CG, Hanrahan P, Luchins DJ (1998) Pharmacoeconomic studies of atypical antipsychotics: review and perspective. Psychiatric Annals 28(7):381–396
13. Beck JR, Pauker SG (1983) The Markov process in medical prognosis. Med Decis Making 3:419–458
14. Sonnenberg FA, Beck JR (1993) Markov models in medical decision making: a practical guide. Med Decis Making 13:322–338
15. Drummond MF, O'Brien B, Stoddart GL, Torrance G (1997) Methods for the economic evaluation of health care programmes, 2nd edn. Oxford University Press, Oxford
16. Weiden PJH, Mott T, Curcio N (1995) Recognition and management of neuroleptic noncompliance. In: Shriqui CL, Nasrallah HA (eds) Contemporary issues in the treatment of schizophrenia. American Psychiatric Press, Washington, DC, pp 411–434
17. Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ (2000) Predicting medication noncompliance after hospital discharge among patients with schizophrenia. Psychiatr Serv 51(2):216–222
18. Rittmannsberger H, Pachinger T, Keppelmüller P, Wancata J (2004) Medication adherence among psychiatric patients before admission to inpatient treatment. Psychiatr Serv 55(2):174–179
19. Lundbeck H A/S. Data on file, available on request from corresponding author
20. Langley-Hawthorne C (1997) Modeling the lifetime costs of treating schizophrenia in Australia. Clin Ther 19(6):1470–1495
21. Mauskopf JA, David K, Grainger DL, Gibson PJ (1999) Annual health outcomes and treatment costs for schizophrenia populations. J Clin Psychiatry 60 [Suppl 19]:14–19
22. Foster RH, Goa KL (1999) Olanzapine: a pharmacoeconomic review of its use in schizophrenia. Pharmacoeconomics 15(6):611–640
23. Oh PI, Iskedjian M, Addis A, Lanctôt K, Einarson TR (2001) Pharmacoeconomic evaluation of clozapine in treatment-resistant schizophrenia: a cost-utility analysis. Can J Clin Pharmacol 8(4):199–206
24. Almond S, O'Donnell O (1998) Cost analysis of the treatment of schizophrenia in the UK: a comparison of olanzapine and haloperidol. Pharmacoeconomics 13(5 Pt 2):575–588
25. Glennie JL (1997) Pharmacoeconomic evaluations of clozapine in treatment-resistant schizophrenia and risperidone in chronic schizophrenia. Technology overview: pharmaceuticals. Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Ottawa, issue 7.0
26. Sacristián JA, Gomez JC, Salvador-Carulla L (1997) Cost effectiveness analysis of olanzapine versus haloperidol in the treatment of schizophrenia in Spain. Actas luso-españolas de neurologia, psiquiatría y ciencias afines 25(4):225–234 [Spanish]
27. Guest JF, Cookson RF (1999) Cost of schizophrenia to UK society. Pharmacoeconomics 15:597–610
28. Duggan A, Warner J, Knapp M, Kerwin R (2003) Modelling the impact of clozapine on suicide in patients with treatment-resistant schizophrenia in the UK. Br J Psychiatry 182:505–508
29. Davies LM, Drummond MF (1993) Assessment of costs and benefits of drug therapy for treatment-resistant schizophrenia in the United Kingdom. Br J Psychiatry 162:38–42
30. Glazer WM, Ereshefsky L (1996) A pharmacoeconomic model of outpatient antipsychotic therapy in "revolving door" schizophrenic patients. J Clin Psychiatry 57(8):337–345
31. Laurier C, Kennedy W, Lachaine J, Gariepy L, Tessier G (1997) Economic evaluation of zuclopenthixol acetate compared with injectable haloperidol in schizophrenic patients with acute psychosis. Clin Ther 19(2):316–329
32. Byrom B, Garratt C, Kilpatrick AT (1998) Influence of antipsychotic profile on cost of treatment of schizophrenia: a decision analysis approach. Int J Psychiatry 2:129–138
33. Palmer CS, Revicki DA, Genduso LA, Hamilton SH, Brown RE (1998) A cost-effectiveness clinical decision analysis model for schizophrenia. Am J Manag Care 4(3):345–355
34. Davies A, Langley PC, Keks NA, Catts SV, Lambert T, Schweitzer I (1998) Risperidone versus haloperidol: II. Cost-effectiveness. Clin Ther 20(1):196–213

35. Launois R, Graf von der Schulenberg M, Knapp M, Toumi M (1998) Cost-effectiveness of sertindole versus olanzapine or haloperidol: a comprehensive model. Int J Psychiat Clin Pract 2 [Suppl 2]:79–86
36. Almond S, O'Donnell O (2000) Cost analysis of the treatment of schizophrenia in the UK: a simulation model comparing olanzapine, risperidone and haloperidol. Pharmacoeconomics 17(4):383–389
37. Lecomte P, De Hert M, Dijk MV, Nuijten M, Nuyts G, Persson U (2000) A 1-year cost-effectiveness model for the treatment of chronic schizophrenia with acute exacerbations in Belgium. Value Health 3(1):1–11
38. Tilden D, Aristides M, Meddis D, Burns T (2002) An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics. Clin Ther 24(10):1648–1667
39. Emsley RA, Raniwalla J, Bailey PJ, Jones AM on behalf of the PRIZE Study Group (2000) A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. Int Clin Psychopharmacol 15:121–131
40. Ganguly R, Miller LS, Martin BC (2003) Future employability, a new approach to cost-effectiveness analysis of antipsychotic therapy. Schizophr Res 63:111–119
41. National Institute for Clinical Excellence (2004) Guide to the methods of technology appraisal. Oxford, Radcliffe Medical Press
42. Dalkey N, Helmer O (1963) An experimental application of the Delphi method to the use of experts. Man Sci 9(3):458–467
43. Evans C, Crawford B (2000) Expert judgement in pharmacoeconomic studies. Guidance and future use. Pharmacoeconomics 17(6):545–553
44. Nuijten MJC (1999) Measuring sensitivity in pharmacoeconomic studies–refining point sensitivity and range sensitivity by incorporating probability distributions. Pharmacoeconomics 16(1):33–41

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