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Rational decision making in mental health: the role of modelling

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Abstract

The use of decision analytic modelling techniques to assess the cost-effectiveness of drug interventions in mental health care has become more popular in recent years. A number of reasons have been suggested for their increased prevalence, namely (a) the need to rapidly assess the value for money of new pharmaceuticals; (b) the short time horizon of clinical trials and hence the need to extrapolate costs and outcomes to the longer term, (c) the lack of head to head comparison with alternative treatment strategies, and (d) the necessity to generalise the study results from setting to practice.

As simulation exercises become more widely accepted and used to inform policy-making decisions, a trend towards more sophisticated modelling structures is starting to emerge. While this is (sometimes) both desirable and necessary, it is also inevitable that new methodological issues arise. To illustrate the analytical and methodological challenges that health service researchers are facing when developing decision models in mental health care, we focus our attention on two clinical areas that have recently attracted the attention of the National Institute for Clinical Excellence (NICE): Schizophrenia and Alzheimer's Disease. Using these two clinical areas as examples, this paper will discuss a number of methodological issues that are intrinsic to economic evaluations of mental health, arguing that although these difficulties exist, the use of modelling is likely to represent a valuable tool for rational decision making.

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This paper is the result of joint work by the two authors. However, given the respective expertise of the authors in the clinical areas discussed here, AM was responsible for the sections specific to Alzheimer's Disease, and LG for those on Schizophrenia.

1. Introduction

Mental health covers a very wide spectrum of experiences and it becomes a serious problem when it interferes with a person's ability to cope or function properly on a day-to-day basis. It is estimated that approximately one in four people will experience a mental health problem in the course of year (Internet Mental Health). Only a small percentage of these however will develop a serious mental health problem (Internet Mental Health). Two of the most severe and life changing mental health disorders are Schizophrenia and Alzheimer's Disease. These disorders cause significant distress to the sufferer and their family, and impose substantial costs to the NHS. At a time of rising health care expenditure and budget constraints all health care systems require evidence about the relative value for money of health care. This includes comparisons of the relative costs and patient benefits for different diseases, and comparisons of alternative therapeutic strategies within specific disease areas. The UK National Institute of Clinical Excellence (NICE) has recently commissioned a rapid review of atypical antipsychotics for the treatment of schizophrenia, and has already issued guidance on drugs for Alzheimer's Disease (NICE, 2000). Starting from the available evidence on the value for money of drug treatments for Schizophrenia and Alzheimer's Disease, the present work will discuss a number of methodological issues surrounding the application of decision analytic modelling techniques in mental health care.

2. Economic implications of mental health

2.1 Alzheimer's Disease

Alzheimer's disease (AD) is a chronic and progressive disorder. The intrinsic characteristics of the disease and the absence of a simple and straightforward test to detect it exacerbate the difficulty of modelling the disease patterns. Deterioration is certain, but its progression is characterised by large heterogeneity in symptoms and evolutionary dynamics, with dementia sufferers differing in both their pattern of problems and the speed with which their conditions degenerate. Caring for a person with AD places a huge strain on both formal (paid, professional) and informal carers (Donaldson et al. 1997). People affected by senile dementia of the Alzheimer type and their carers require access to a variety of health and social care

services for treatment, information and counselling, community based support, respite care and long term residential care. Current treatment may include behavioural therapies or pharmacological treatment. It is expected that the progressive nature of the illness and the ageing of the population mean that many people with AD will require intensive support and/or long term residential or nursing home care. Estimates from the Alzheimer's Disease Society suggest that in the UK there are currently more than 700.000 people with dementia (Alzheimer Disease Society, 2000) with 70% of them having a diagnosis of AD. The costs of care for people with cognitive disability have been estimated at between £15,970 and £50,540 per person per year in 1999/00 prices, depending on severity of disability and setting of care (Kavanagh and Knapp, 1999; Kavanagh *et al*, 1993). Reports of the total costs of care for people with dementia in the UK range from £1 billion to £6 billion per year (Manca and Davies, 1999; Bosanquet *et al.* 1998; Gray and Fenn, 1993). These figures suggest that between 2% and 13% of total health and personal social services expenditure is for the care of people with dementia or Alzheimer's Disease. Concerns about the high cost of health and social care are compounded by the introduction of pharmaceutical products such as the anticholinesterase inhibitors. Second generation cholinesterase inhibitors (e.g. donepezil, rivastigmine, and galantamine) have reported similar efficacy and safety results, in terms of improved cognitive function, and delayed progression of disease in some patients. Currently, these drugs are considered the most successful agents for the management of Alzheimer's Disease (Burns *et al.* 1999). However, the value of the drugs to patients and carers in terms of improved quality of life is unclear, and uncertainty exists around the economic impact that the use of these drugs would have on the NHS and the society as a whole. In the attempt to investigate the economic impact of the introduction of anticholinesterase drugs on the care for people with AD a number of economic studies have been conducted. Overall, these suggest that the introduction of the new drugs might be cost neutral, while leading to modest improvements in the health-related quality of life (HRQOL) of patients and carers. However, the robustness of the economic evidence needs to be considered before concluding that any additional benefits of the new drugs for Alzheimer's disease are indeed worth the cost. The UK National Institute for Clinical Excellence (NICE) has recently published a report commissioned by the NHS R&D Health Technology Assessment Programme about the clinical and cost-effectiveness

of Donepezil, Rivastigmine and Galantamine for Alzheimer's disease (NICE, 2000). This report argues that "*The implications of the use of donepezil, rivastigmine and galantamine are unclear…"* and suggested a number of future research areas likely to bring valuable information to policy makers, such as *"…development of quality of life instruments for patients and their carers; comparisons of benefits from drugs with other interventions; identification of those patients likely to benefit from drug treatment; development of protocols of treatment withdrawal if not beneficial"*.

2.2 Schizophrenia

Schizophrenia can affect sufferers in their most prime years, with the age on onset around the late teens or early twenties. Approximately 1% of the UK population will have schizophrenia at some point in their lives (Institute of Psychiatry, 2001). In 1992/3, the direct costs of health and social care for people with schizophrenia was approximately £810 million in England, or 3% of total health service spending. Of this, £32 million was for pharmaceutical expenditure, mainly for antipsychotic drugs (NHSE, 1996; Knapp, 1997). There is no known cure for the illness although many of the positive and negative symptoms of schizophrenia are controlled or ameliorated with varying degrees of success through medication or psychosocial interventions. Antipsychotic or neuroleptic therapy is the primary method of symptom control and management for the majority of people with schizophrenia. The average cost per person of health and social care has been estimated at between £2140 and £36000 per year (Davies and Drummond, 1994, Aitchison and Kerwin, 1997). The 1990's have seen the introduction of new, so-called atypical antipsychotic drugs (e.g. Clozapine, Olanzapine, Quetiapine). Depending on dosage, the costs of clozapine are approximately £2500 per person per year, and the other newer atypicals, risperidone, olanzapine and quetiapine are approximately £1400 per person per year. The cost of older, conventional antipsychotics such as haloperidol or chlorpromazine is significantly lower, at less than £100 per person per year. The potential impact of these new drugs on pharmacy budgets is substantial. If their use continues to expand, they will add to the annual drug expenditure by between £86 million, if reserved for treatment-resistant or intolerant patients and £242 million if used for all patients. However, the new drugs may reduce the costs of other health care services, such as hospital inpatient care and may lead to significant improvements in patient outcome.

A large number of economic evaluations of schizophrenia drugs have been conducted, mainly using standard trial based analysis but with some using modelling techniques (e.g. Palmer 1998, Davies 2000). Recently the NHS Health Technology Programme has commissioned a systematic review and economic analysis of drug treatments for schizophrenia. This concluded that the expected costs and outcomes did not suggest that there was any significant additional benefit associated with the use of the atypical antipsychotics compared to the two 'typical' anti-psychotic drugs: chlorpromazine and haloperidol (forthcoming HTA report)

Given that evidence regarding atypical antipsychotics value for money is conflicting, the issue of what is an acceptable cost per QALY and uncertainty surrounding model parameters, the robustness of any conclusions drawn from model results is questionable, especially for the purposes of policy decisions.

3. Evidence of modelling in mental health

The economic evaluation of mental health interventions has become increasingly popular over the past decade (Knapp, 1999; Hargreaves *et al*, 1998). This reflects the increasing desire to provide the most cost-effective treatments to an increasingly large portion of society suffering from such disorders. The National Institute for Clinical Excellence has prioritised the evaluation of interventions for Schizophrenia and Alzheimer's Disease. The National Research Register lists 39 current projects looking at interventions for mental health that include an economics element. We focus here on those studies qualifying as "full economic" evaluations (Drummond *et al.* 1997) carried out within a decision analytic framework. A lack of good quality data, specifically for the UK population, is a major limitation to the standard of data analysis that can take place when applying modelling techniques. This is compounded by the observed heterogeneity of the methodological approaches when structuring the models and conducting the analyses. This paper will show that the majority of the published economic evidence produced in the last ten years using simulation models display some weakness in a number of aspects such as the choice of comparator, costing methodology, time frame and perspective of the analysis, target population, model structure, etc.

4. Methodological issues in the use of model in mental health

4.1. Anticholinesterase drugs for Alzheimer's Disease

We identified eight model-based published analyses qualifying as full economic evaluations of anti-cholinesterase drugs for AD. Five of these studies looked at donepezil, whereas three focussed on rivastigmine. No published economic evaluation was available on galantamine. The economic analyses of donepezil assessed the value for money of the drug in four different geographical settings: the United Kingdom (Stewart *et al.* 1998), Canada (O'Brien *et al.* 1998; Lanctôt *et al*. 1998), the USA (Neumann *et al.* 1999), and Sweden (Jönsson *et al.* 1999b). The studies on rivastigmine were set in the United Kingdom (Fenn and Gray *et al.* 1999), the USA (Hauber *et al*. 2000a), and Canada (Hauber *et al*. 2000b). Overall, the donepezil studies indicate that the drug is associated with a net improvement in the "number of years spent in a non-severe condition" of between 1 and 6 months. Three analyses suggested that donepezil is cost saving (O'Brien *et al.* 1998; Lanctôt *et al*. 1998; Jönsson *et al.* 1999b), while other two found that the drug was associated to a positive incremental cost (Stewart *et al.* 1998; Neumann *et al.* 1999). The studies on rivastigmine deemed the drug to be cost saving in their settings.

Perspective of the analysis

The perspective and range of costs included differed among the studies. Some authors included both direct costs and informal carers time (O'Brien *et al.* 1998; Neumann *et al.* 1999; Stewart *et al.* 1998; Hauber *et al.* 2000a; Hauber *et al.* 2000b), whereas others only considered direct medical costs (Jönsson *et al.* 1999b; Fenn and Gray 1999). If the new drugs are effective in preventing progression of the disease or in relieving symptoms, this may reduce the use of formal care services, captured by the costs of medical and social care, but increase the burden on family and friends. In this situation, excluding informal care costs from the analysis may result in over estimation of the relative cost effectiveness of the new drugs. Another element of heterogeneity in the resource use considered is the inclusion of the drug cost. Unlike the US- and UK-based models on rivastigmine, all the donepezil studies and the Canadian study on rivastigmine included the cost of the drug in the analysis.

Time frame of the analysis and treatment effect

It has been argued that the duration of AD from onset to death can be 8 to 10 years (Trabucchi M, 1999; Francis *et al.* 1999). The economic evaluations of donepezil and rivastigmine were based on effectiveness data from a limited number of trials, which were short in duration. This has a number of implications. First, the analysis can be limited to the effect of the drug to the period for which effectiveness data was available. In this case it may be assumed that the treatment effect to cease after 6 months (Stewart *et al.* 1998; O'Brien *et al.* 1998). This assumption would only be valid if donepezil were also discontinued at 6 months. If this is not the case, then the overall costs of the drug may be underestimated and the benefits overestimated. Alternatively, some studies used expert opinion to extrapolate the effectiveness of donepezil over a longer time period (Neumann *et al.* 1999). However, it is recognised that expert opinion can be the weakest source of evidence, which introduces additional uncertainty into the analysis and interpretation of the results. In this context, the correct assessment of the duration of the treatment effect of anticholinesterase drugs assumes a central role since it will affect the number of people having mild-to-moderate AD at each period of time. In a recently published re-elaboration of the donepezil study for the US, Claxton *et al*. (2001) have conducted a Bayesian value-of-information analysis alongside a probabilistic policy model of Alzheimer's disease. Among their findings, the authors showed that – in their model - the expected value of perfect information (EVPI) associated to the input parameter "efficacy duration" of the drug treatment was likely to justify additional research in this area. Finally, the cost-effectiveness of anticholinesterase inhibitors depends heavily on the distribution of the cohort of patients across different severity states. O'Brien *et al.* found that the results of their model were very sensitive to this variable.

Target population and comparator

The population considered in the analysis should be representative of the population to be treated. The trials and observational data used for the economic evaluations of donepezil and rivastigmine may not fully satisfy this criterion. Donepezil trials have been criticised (Birks *et al.*, 2001) for enrolling carefully selected sub-groups of patients with mild-to-moderate AD and excluding those with co-existing illness or concurrent treatment. This limitation seems not to apply to the rivastigmine trials

whose inclusion criteria for patient enrolment were more relaxed (NICE, 2000). In addition, the data obtained from non-randomised studies and used in some of the models might not be representative of AD patient population. These two factors reduce the generalisability of the results of the economic evaluations to patient groups outside the trial setting.

Since there are a number of drug therapies and non-pharmacological approaches to the management of people with AD, the relative cost-effectiveness of these needs to be assessed. A lack of head to head comparisons among the alternative anti-cholinesterase drugs is observed. Once established that one or more anti-dementia drugs are cost-effective it is crucial to compare their relative cost and consequences.

Measurement and valuation of costs

The published economic evaluations of anticholinesterase inhibitors used cost estimates obtained from different sources, such as retrospective analysis of available datasets (Jönsson *et al*. 1999b; Fenn and Gray, 1999), analysis of published literature (e.g. Stewart *et al*. 1998; Hauber *et al.* 2000a; Hauber *et al.* 2000b), and expert opinion (e.g. O'Brien et al. 1998; Neumann et al. 1999). This means that it is not clear whether any differences in costs were due to the anticholinesterase inhibitors, or other factors such as availability of services in different areas, living situation of the patient, sampling methods of the original study or disease severity.

All analyses directly or indirectly used the same measure of disease severity (i.e. Mini-Mental State Examination (MMSE) scale) to link treatment costs and disease progression. The MMSE was found strongly correlated to the costs of dementia care, but the robustness of this instrument as a cost predictor is uncertain. It has been suggested (Jönsson *et al.* 1999a) that there may be other tools that have strong correlation with costs, such as activities of daily living (ADL) indexes and behavioural disturbances measurement instruments, but – to our knowledge - their use as cost predictors has not been investigated yet.

Measurement and valuation of outcomes

Three of the five studies on donepezil measured the benefits of anticholinesterase inhibitors as "time spent in condition less than severe". Similarly, the three studies on rivastigmine measured health benefits in terms of "days by which cognitive decline is delayed". Whilst this provides a measure of health status, it does not give

an assessment of the value to patients or society of the health gained. In addition, the measure of disease severity based on the cognitive status of the patient is only one dimension of the overall health and non-health related quality of life. Other factors such as behavioural disturbances and general activities of daily living (such dressing, bathing, and handling finances) have a considerable impact on patients and carers quality of life. Two studies on donepezil used quality-adjusted life years (QALYs) to capture the range of health related dimensions that may affect the quality of life of patients (Neumann *et al* 1999; Lanctôt *et al.* 1998). QALYs provide an estimate of the value or preferences for changes in health status. Neumann *et al.* used the Health Utility Index Mark II (HUI:2) in a sample of patients and carers, which is a generic measure of the value of health related quality of life. Because only available in abstract form, no information was available regarding the methods used by Lanctôt and colleagues to estimate QALYs in their analysis.

Modelling the progression of the disease

Two different modelling approaches have been used in literature to mimic the evolution of the disease over time. The studies on donepezil adopted a Markov state transition model, while a Cox proportional hazard model was used to estimate the duration of incremental health benefits from rivastigmine treatment compared to placebo. The fundamental difference between the two methods is that the Cox proportional hazard model is a regression-based model which requires patient-level data, whereas the implementation of the Markov models for the donepezil studies were mainly based on secondary analysis of published data. The cycle-length of the Markov models used in the donepezil studies was six months. This was determined by the availability of the trail data, and the authors provided no explanation on whether the choice of having six-month length cycles was consistent with the underlying disease process. A common feature of these two approaches is that both used the decline in the cognitive function (i.e. MMSE score) as proxy for disease progression. It could be argued that even accepting the use of the MMSE score for this purpose, the use of deterministic Markov chain models in the donepezil studies could have been too simplistic. One possible improvement is to define probability distributions around the transition probabilities governing the Markov matrix. Using a probabilistic approach, Claxton and colleagues showed how the model developed by Neumann *et al*. could be refined to incorporate available

information into the decision model. Regarding the use of patient level-data to model the progression of the disease over time, one study recently argued that AD progression over time can be modelled using a cubic or logarithmic function of MMSE score (Mendiondo *et al*, 2000). The same authors showed that there are different rates of change for various ranges of the MMSE, where younger patients and more educated patients often progress more rapidly, while sex has little effect on disease progression. This seems a strong argument against the use of a deterministic time-invariant structure for the Markov model to describe disease progression. On the other hand, one limitation of the non-linear statistical models is that they can be "…even less appropriate than a linear model for extrapolation beyond the available data to the entire course of the cognitive or behavioural change in a patient population" (Mohs *et al.* 2000).

4.2. Antipsychotics for Schizophrenia

A literature review was conduced to identify full economic evaluations of antipsychotics. Studies were included if they met the following criteria:

1. Compare two or more antipsychotics and the antipsychotic regimen is clearly defined.
2. Data for direct costs of providing health and social care and the outcomes of care are reported for each comparator.
3. Sources of resource use, cost and patient outcome data are clearly specified and the estimates of costs and outcomes are calculated from observed data. Economic studies, which use expert opinion to derive estimates of resource, use or patient outcome will be excluded.

(Forthcoming HTA report)

Using these criteria 12 studies were selected for inclusion in this discussion. As this section primarily intended to highlight methodological issues arising from these studies a description of the evaluation results and study details have been omitted from this paper.

Handling of uncertainty and choice of model

A relatively large number of economic evaluations, of antipsychotics using modelling techniques have been conducted. Use of “state of the art” techniques, such as Bayesian analysis, probabilistic sensitivity analysis, missing data analysis however has been somewhat limited. The type of model used varied, and appears to follow a trend with regards to year of publication i.e. use of more sophisticated techniques has gained more widespread use in recent years.

Author	**Model type**
Palmer (1998)	Markov model
Launois (1998)	Markov model
Iskedjian (1999)	Deterministic model
Byrom (1998)	Deterministic model
Davies (2000)	Stochastic model
Almond (2000)	Markov model
Oh (1999)	Deterministic model
De Hert (2000)	Semi-Markov model
Glennie (1997)	Deterministic model
Davies. A (1998)	Deterministic model
Davies (1993)	Deterministic model
Glazer (1996)	Deterministic model

The majority (7/12) used a deterministic approach to assess the costs and outcomes associated with antipsychotics. Although uncertainty was explored using sensitivity analysis any interaction between uncertain parameters was not explored. In addition hypothetical ranges were often imposed.

The model by Davies (2000) used a probabilistic sensitivity analysis to analyse the uncertainty surrounding key costs and outcomes used in the model. Quasi confidence intervals were presented for costs and QALY estimated for the model for each therapy choice. Uncertain parameters were those derived from the review

process or literature, for which some information regarding their distribution was available. Although not all parameters were included in the simulation this type of analysis allowed a more thorough exploration of the uncertainty surrounding the model data and presented this uncertainty in the main results.

The use of Markov models in the economic evaluation of antipsychotics for schiziphrenia is becoming increasingly popular. Our review identified 3 full Markov models (Palmer 1998, Launois 1998, Almond 2000) and one semi-Markov model (De Hert, 2000). The Markov allows recurrent events that over time to be modelled (Gold, 1996), such as relapses. A decision tree models inability to account for this, apart from representing each event as a separate branch of the tree, is a major limitation of there use in this particular condition, which is characterised by periods of clinical improvement and periods of more severe symptoms or side effects.

Type of patients

An important issue is that of which patients to include in an evaluation. The most useful (in terms of making policy decisions) evaluation would be one which includes all schizophrenia patients eligible to be treated with atypcials in the real world. However, in order to make data collection more manageable, or to achieve statistical power with an affordable-size sample or because of expected difficulties achieving the informed consent of patients, many prospective trials have exclude certain patient groups. Hence the models based on these results (including those identified in the review) have also excluded them.

Common exclusions are patients with substance abuse problems or co-morbid anxiety problems (such as obsessive complusive disorder. Patient exclusions can make it difficult to generalise from research evidence, but this can generate problems for economics studies, if excluded patients impose costs which are out of the ordinary.

Overall the reporting of patient characteristics was particularly poor in modelling studies. Davies (1993) and Glazer(1996) gave a reasonable amount of detail on the typical patient used to model costs and effects. Patients were not first episode, and

were deemed to have significant severity of disease according to some clinical criteria, BPRS or CGI.

Perspective and costs included in the analysis

Most economic evaluations in the mental health field normally aim to measure costs comprehensively, not least because of the often wide impact that these disorders have on an individual's welfare which in turn can lead to the involvement of a multiplicity of agencies. The evaluator needs to choose the perspective for the evaluation, in particular whether to look only at those costs falling to the health service or to the public purse, or to the whole economy.

Costs other than health service and community costs have not been included in any of the model-based evaluations. Given that many of the costs associated with schizophrenia and its treatment fall on the sufferers family and/or caregivers (Magliano et al, 1998) the total cost over a patients lifetime estimated in these studies is likely to be extremely conservative.

Time frame and modelling of treatment effect

Schizophrenia, for many of its sufferers, is a lifelong disease. A patient may experience prolonged periods of well being, during which symptoms are controlled by medication, however there is always the possibility that the patient will suffer a relapse and may have to change dosage or drug in order to control symptoms once again. Economic evaluation of drug treatments for schizophrenia should therefore attempt to model the patient group, in question, over a lifetime.

The studies identified in the review used differing time periods over which to assess the costs and outcomes of antipsychotics. The time frames ranged from 1-year (Oh 1999, Glazer 1996, Iskedjian 1999, Byrom 1998, De Hert, 2000) to a lifetime (Davies 2000, Glennie 1997, Davies 1993). The 4 Markov models chose not to extend the timeframe to a patient’s lifetime and compared costs and outcomes over a 5-10 year period. Lack of long term data regarding alternative treatments was cited as the main reason for this. Given the chronic (and unpredictable) course of schizophrenia we might want to argue for longer duration studies that can capture relatively rare but

expensive events, such as hospitalisation. There is however a problem of sample attrition in long trials in schizophrenia, which could limit the reliability of longer-term data should it be available.

Measurement and valuation of outcomes

Studies have used alternative outcomes measures to illustrate the effect of an intervention. Davies (1993) used a measure common to schizophrenia trials Brief Psychiatric Rating Scale (BPRS) to compare patients before and after Clozapine, whereas Glennie (1997) used Quality Adjusted Life Years (QALYs) to compare interventions.

Although the use of QALYs to measure outcome allows comparison (in terms of a cost per QALY), which is not possible with a disease specific measure such as BPRS, the utility estimates used in this Glennie do cause some concern. Utilities were estimated from 7 schizophrenic patients using standard gamble and time trade off techniques, and are therefore likely to be subject to uncertainty due to the very small sample size. Davies (2000) also used these utilities to compare costs and outcomes of alternative treatments for first episode patients. It was argued that as the only other utility estimates available from Chouinard et al, 1997, were taken from psychiatric nurses and not from patients themselves, these were likely to represent the best estimates of the utility associated with given health states available.

Clearly there is a need to use utilities generated from a larger sample of patients than 7, however given the somewhat often disturbed state schizophrenic patients display (which may impact on there ability to answer TTO and SG based questions) it is unclear if patients, or a party acting on there behalf, should provide utilities to use in economic evaluation.

5. Future challenges for economic evaluation in mental health

The role of modelling in health economic evaluation is not an issue here, other authors have already clarified the redundancy of the debate *modelling vs clinical trials* (Brennan and Akehurst, 2000). As simulation exercises become more widely accepted and used to inform policy-making decisions, a trend towards more sophisticated modelling structures is starting to emerge. While this is (sometimes)

both desirable and necessary, it is also inevitable that new methodological issues arise. Using Alzheimer's Disease and Schizophrenia as examples we have illustrated the heterogeneity of modelling practice, and briefly discussed a number of existing and new methodological elements that can affect the results of simulation models in mental health. It has been already argued that although "*…all models may be 'wrong'* […] *some are useful…*" and it is both possible and necessary to develop a framework for assessing quality in decision models (Sculpher *et al.* 2000). Our conclusion is that in the context of the two clinical areas presented in the present paper the use of simulation modelling is particularly useful for a number of purposes, and it could be argued that their application has been somewhat sub-optimal. In particular, we found that stochastic modelling techniques were very rarely used. It could be argued that the use of this category of models is particularly suited in the evaluation of new drugs for schizophrenia and AD, in view of the fact that the course of disease as well as being difficult to predict is associated with heterogeneity of clinical patterns and repeated clinical events occurring over the patients' lifetime.

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