Modelling Approaches
The Case of Schizophrenia

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Abstract

Schizophrenia is a chronic disease characterized by periods of relative stability interrupted by acute episodes (or relapses). The course of the disease may vary considerably between patients. Patient histories show considerable inter- and even intra-individual variability. We provide a critical assessment of the advantages and disadvantages of three modelling techniques that have been used in schizophrenia: decision trees, (cohort and micro-simulation) Markov models and discrete event simulation models. These modelling techniques are compared in terms of building time, data requirements, medico-scientific experience, simulation time, clinical representation, and their ability to deal with patient heterogeneity, the timing of events, prior events, patient interaction, interaction between co-variates and variability (first-order uncertainty).

We note that, depending on the research question, the optimal modelling approach should be selected based on the expected differences between the comparators, the number of co-variates, the number of patient subgroups, the interactions between co-variates, and simulation time. Finally, it is argued that in case micro-simulation is required for the cost-effectiveness analysis of schizophrenia treatments, a discrete event simulation model is best suited to accurately capture all of the relevant interdependencies in this chronic, highly heterogeneous disease with limited long-term follow-up data.

In the context of ever-increasing healthcare costs, formal economic models evaluating healthcare technologies have become an 'unavoidable fact of life'.[1] Psychiatry, and particularly schizophrenia, has not escaped this trend.[2] The diversity of modelling methods used to support policy decisions on therapy choice in complex systems and disorders, such as schizophrenia, raises the question of their relative merits. This is of special relevance, since different model structures may produce different results and therefore different policy recommendations.

There are three main modelling approaches: decision trees, Markov models and discrete event simulation (DES) models. Decision trees provide a formal structure in which decisions and chance events

are linked from left to right in the order in which they would occur. A Markov model is a repeated decision tree in which events are modelled as transitions from one health state to another over time. Instead of having a probability to go from one health state to another during a fixed time period, a DES simulates the time to the next event directly.

In their review of modelling approaches, Karnon and Brown[3] observed that simple scenarios occurring over a short time period may best be modelled using a decision tree. Otherwise, cohort Markov models may suffice, unless what happens to patients after a certain cycle is dependent on their prior 'experience'. In that case, micro-simulation Markov models may be considered as the relevant modelling approach, but DES should also be considered.[3] More recently, Barton et al.[4] observed that the choice of model structure should be based on the following variables: patient interaction, the need for patient-level modelling, patient pathways and dimensionality. Finally, in 2006, Brennan et al.[5] proposed a taxonomy of model structures for economic evaluation of health technologies. Within the taxonomy, cohort and patient-level models were distinguished. Elements used to classify model structures were patient interaction, the timing of events, expected versus stochastic values, and the Markovian assumption. Underlying issues included the need for describing variability; the cycling of health states; population heterogeneity; dimensionality; interaction between co-variates and nonlinear associations between individual risk factors and outcome; and finally the need for probabilistic sensitivity and subgroup analyses. After determining what type of model would be appropriate, factors such as the availability of modelling software, the researcher's experience with the type of model and project time constraints also have to be taken into account.

By applying and discussing the criteria proposed by Brennan et al.[5] we intend to contribute to the dialogue on model structures, using the example of schizophrenia. This is a chronic and complex disease generating considerable treatment costs and where long-term follow-up data are scarce, consequently posing a challenge to researchers when trying to provide evidence in support of reimbursement decisions.

The structure of this article is as follows. First, each modelling structure (e.g. decision trees, [cohort and micro-simulation] Markov models and DES) is presented and illustrated with an example from the literature. Subsequently, these modelling approaches are compared based on a slightly adapted subset of relevant decision criteria as suggested by Brennan et al.[5] The three modelling approaches considered are ranked on each of the above criteria in table I.

Finally, the approaches are discussed in the light of (pharmaceutical) interventions.

1. Description of Modelling Approaches

1.1 Decision Tree Models

Decision trees have a 'root' decision, for instance, treatment 1 or treatment 2, on the left and branches for each (chance) event or secondary decision extending to the right. The sequential chance events and/or decisions are separated by chance nodes. At each chance node, probabilities of an event occurring (conditional on the previous event) determine the proportion of patients progressing down each unique path represented in the tree. Consequences such as costs and effects of events and decisions may be either attributed at each node of the tree or accumulated all at once at the end-nodes of the tree, depending on how the tree is set up. Sequential decision or chance nodes allow one to capture the relevant information required to compare the expected cost effectiveness of different treatment scenarios. The average effect and/or costs associated with each treatment option or branch can be estimated by 'rolling back' the tree, i.e. calculating the weighted averages for the outcomes of inter-

Table I. Definitions of criteria used to evaluate the appropriateness of three modelling approaches: decision trees, Markov models and discrete event simulation models

Criterion	Definition
Building time	The time required to programme the model
Data collection	The time required to collect the data necessary to fill the model
Experience	The number of publications using the (individual) modelling approaches in the medico-scientific literature
Simulation time	The time required to generate (probabilistic) results
Clinical representation	How well the chosen model structure reflects and is able to capture all relevant aspects of the underlying reality, and the corresponding uncertainties that exist, in a complex chronic disease such as schizophrenia
Ability to incorporate	
Patient heterogeneity	Ability to explicitly deal with different patient types in the model
Timing of events	Ability to allow for (recurrent) events over time and the possibility for (multiple) events to occur in any given time period
Memory	Possibility for present and future states to depend on past 'experience' (i.e. overriding the Markovian assumption)
Patient interaction	Possibility to incorporate interaction between patients (e.g. waiting lists before being admitted to a psychiatric hospital)
Interaction due to co-variates	Possibility to include co-variates that interact or have multiple effects causing interaction and/or nonlinear outcomes
Variability	Ability to incorporate and analyse first-order uncertainty (i.e. patient-level variability) within the model structure

est of the strategies compared at the root of the decision tree.

A specific problem in schizophrenia is noncompliance, which substantially increases the risk of psychosis and the related expensive hospitalizations. Depot or long-acting injection formulations are believed to increase compliance, and may therefore reduce the risk of psychosis and hospitalization. Glazer and Ereshefsky[6] tried to capture this process in their decision tree model comparing a conventional depot with oral conventional medication while using a time horizon of 1 year (figure 1). The model was also recently adapted by Edwards et al.[7] to evaluate the cost effectiveness of a newly introduced long-acting injection of an atypical oral antipsychotic, i.e. risperidone.

1.2 Markov Models

In a Markov model, events are modelled as transitions from one health state to another. Such transitions are assumed to be chance events, represented by model parameters reflecting actual event/transi-

tion rates over predefined time periods. The total time period covered by the model is attained by running the model for a finite number of set time cycles of equal length to which the event rates relate. A subject may transit to another health state once per cycle. If no specific time horizon is predetermined, the model continues until x% or 100% of the patients enter an absorbing state such as death. As in a decision tree, probabilities are conditional only upon the current health state. These probabilities may be allowed to vary over time to reflect the pattern of survival curves. Life expectancy is calculated by multiplying the cycle length by the percentage of patients in the health state, subsequently adding these results over time, and then summing across all states. Costs and QALYs can be estimated similarly. Accordingly, cohort Markov models basically simulate the average experience of the patients in a cohort (figure 2a).

Patients with schizophrenia are at risk of psychosis/relapses. During these relapses, patients display positive symptoms, such as hallucinations and delu-
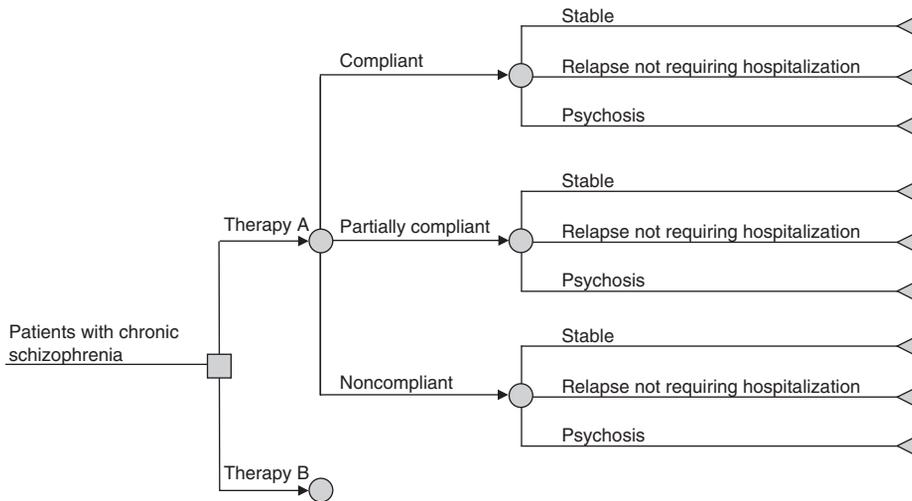
Fig. 1. Decision tree with time horizon of 1 year created for economic evaluation of pharmaceutical treatment for patients with schizophrenia.[6,7] Please note that the branch of therapy B repeats the branch of therapy A. The square represents a decision node and the circles represent chance nodes.

sions. Between relapses, in some patients negative symptoms prevail, some patients still experience positive symptoms and others have no symptoms. These symptoms clearly affect patients' quality of life (QOL) and use of healthcare resources. Also, between relapses patients may be at a different risk of being noncompliant, e.g. drop out and subsequently relapse. Palmer et al.[8] and Almond and O'Donnel[9] tried to capture this process in a detailed cohort Markov model, which was used to assess the value of olanzapine versus haloperidol (figure 3). In this model, a cohort was simulated through 20 quarterly cycles.

1.3 Discrete Event Simulation Models

The transition probabilities in Markov models are generally estimated by dividing the cumulative survival distribution in pieces with equal duration (cycle length) [figure 4]. The time a patient spends in a health state with DES is estimated based on the cumulative survival curve by random draws be-

tween zero and one (y-axis figure 4) and subsequently the corresponding time to event can be estimated (x-axis figure 4).[10]

Sets of equations are used to describe cumulative survival distributions, i.e. Gamma, Weibull and Gompertz. These equations can include several patient-level co-variates, such as age, sex and patient type. Depending on the software, life (and disease) histories of subjects are simulated one by one or simultaneously. Variables and outcomes are updated at the discrete timepoints at which the next event occurs.

Within Microsoft® Excel while using add-ons such as @Risk or Crystal Ball for first-order simulation, the structure of a DES model is quite similar to the structure of a Markov model. Columns represent health states and rows track the time spent in each health state. Rows may represent a constant amount of time similar to a cycle in a Markov model, but can also be programmed to reflect events such as outpatient visits with varying time intervals.

Several dedicated software packages such as Extend™ and Arena™ are available to develop DES models, and it is also possible to use Visual Basic for this purpose. One of the advantages of using a dedicated software package as opposed to Microsoft® Excel is that these packages allow a cohort of individual patients to be simultaneously processed through the model. Accordingly, these packages allow patient histories to affect each other more easily and thus may be used to evaluate actual patient flow and capacity issues.

We have previously reported on DES models for schizophrenia (see figure 5).[11-13] The models were designed to describe the history of patients who experience multiple psychotic episodes. First, patients were characterized by fixed variables (sex, patient profile, social and environmental factors, potential risk of harming self or others, treatment-related adverse effects and disease severity). Next,

based on these characteristics, the models generate time-dependent attributes throughout the simulation (relapses and time between relapses, symptoms, appointments, treatment, compliance, ability to take care of oneself, risk and care setting).

2. Comparison of Modelling Approaches

2.1 Decision Trees

2.1.1 Building Time, Data Collection, Simulation Time, Clinical Representation and Experience

A decision tree is generally considered to be the most simplistic modelling approach. Owing to its simplicity, the number of parameters to be estimated is small, and as a result the time needed for data collection, building the model and subsequently running it is relatively short. The need for expert input
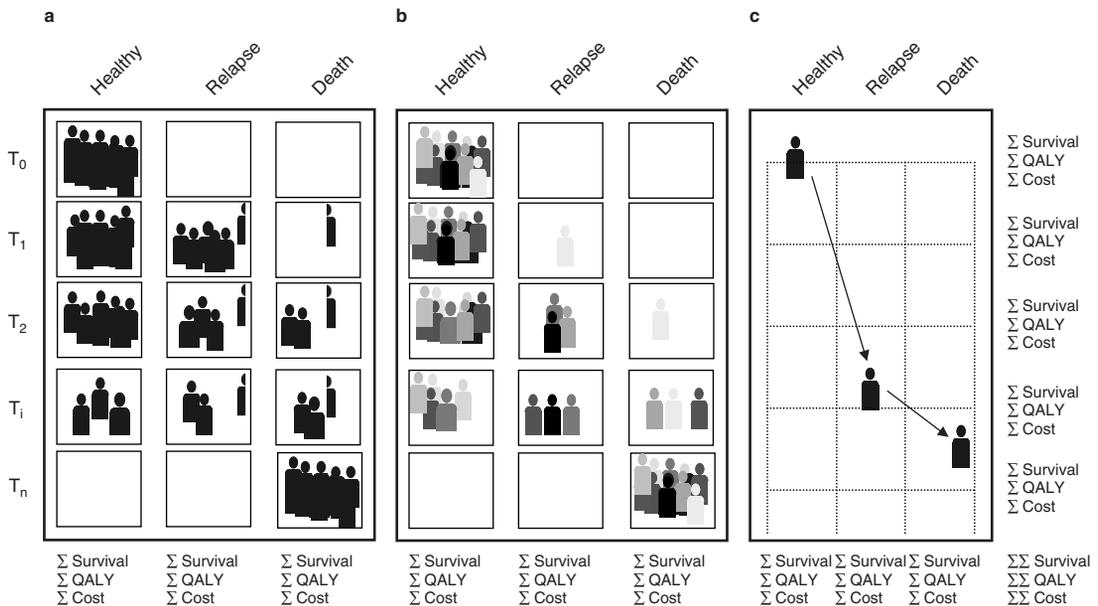
Fig. 2. Overview of the different (time-based) modelling approaches: cohort Markov modelling (**a**), first-order Monte Carlo (micro-simulation) Markov modelling (**b**) and discrete event simulation (DES) modelling (**c**). As in first-order Monte Carlo simulation Markov models, in DES models individual patient histories are simulated. Panel (**c**) shows only one patient in the DES model to emphasize that the time to event can occur at any discrete moment in time, whereas in Monte Carlo Markov models transitions may only occur once per cycle. The vertical time axis is actually continuous for DES, whereas in the Markov models a patient can only experience events (i.e. have relapses) during fixed time intervals. **T** = time.

is limited, since usually only few explicit assumptions are implemented. However, the number of assumptions required describing a complex and heterogeneous disease such as schizophrenia might be high. Conversely, when limiting complexity such as Almond and O'Donnel[9] and Glazer and Ereshefsky[6] did, several implicit assumptions had to be made. For instance, the latter authors appeared to have assumed that recurrent events, treatment switches and patient heterogeneity would not influ-

ence the results obtained. If these variables indeed may not be expected to affect the outcomes of the model, there would be no use in building a more detailed model that would more closely reflect clinical practice.

The size, time requirements and simplicity of such models, combined with the availability of easy-to-use dedicated software, make the decision tree a relatively popular modelling technique.
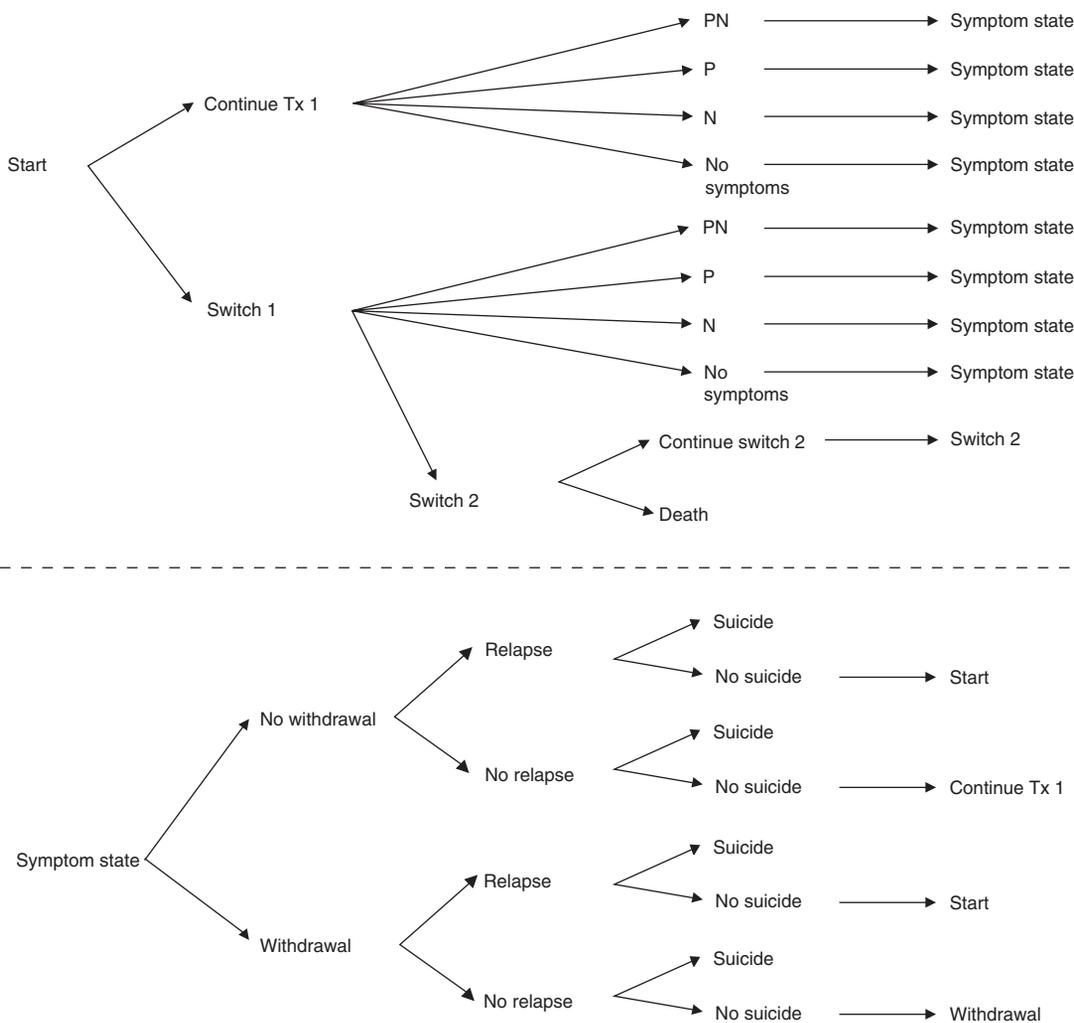

Fig. 3. Sections of the schizophrenia clinical decision Markov model by Almond and O'Donnel[9] and Palmer et al.[8] (each transition covers one quarter). **N** = negative symptoms; **P** = positive symptoms; **PN** = positive and negative symptoms; **Tx** = treatment.
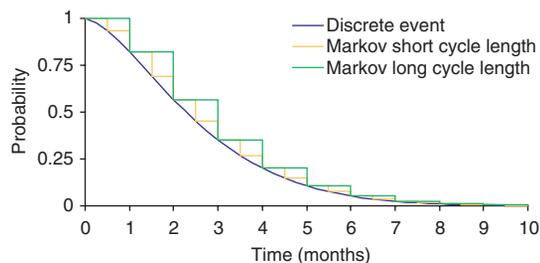
Fig. 4. Differences in estimating time to relapse between a Markov model with a long and short cycle length, and a discrete event simulation model.

2.1.2 Variability, Patient Heterogeneity and Patient Interaction

Technically it is possible to run a decision tree to simulate individual patients using first-order Monte Carlo simulation to assess the variability (or first-order uncertainty) of the results, caused by the variability in the input parameters. Generally, however, in decision analyses on a national level, variability is often not considered an important issue, contrary to second-order uncertainty. In a first-order simulation, one applies the standard deviation, reflecting patient uncertainty, whereas to assess second-order uncertainty one applies the standard error, reflecting cohort uncertainty.

Where a decision tree typically focuses on the average patient, patient heterogeneity may be explicitly incorporated either by analysing the model with separate sets of transition probabilities for each subgroup and then re-aggregating the results or by building separate branches for each different subgroup. Depending on the base-case size of the model and the number of subgroups, this might not be the ideal solution.

For instance, because actual time passing by is not reflected in the model, it is not feasible to include variability of patient characteristics over time, nor to evaluate patient interaction and allow for, for instance, waiting lists.

2.1.3 Timing of Events and Memory

In cases where long-term and recurring complications are relevant, analysts may feel restricted by the limitations of decision trees. The time horizon used in a model should of course depend on the impact of the technology over time on the development of a patient history. Since, in the case of schizophrenia, the impact of a treatment over time can be expected to vary considerably, the relevant time horizon is a very important consideration. The existing decision tree models of schizophrenia used time horizons varying from 1 to 2 years.[6,7,14] A longer time horizon to incorporate relapses might be implemented by breaking up the existing model into individual sequential time periods (figure 6),[6] but the consequences of this remedy would be that the size of the model would increase exponentially with each subsequent 'cycle'. For example, if this model were further expanded to cover 5 years, the number of branches would reach 118 098 (two main branches $\times$ 9^5 branches), which evidently is not optimal.

Similarly, including 'memory' is also likely to greatly increase the number of branches.

2.1.4 Interaction Due to Co-Variates

Interactions between co-variates to identify relevant subgroups for risk of relapse may be important (e.g. male and substance abuse). Treatment-related adverse effects such as weight gain may affect compliance and increase the risk of diabetes mellitus. This can be implemented in a decision tree by adding additional branches but again the increase in the number of branches in the tree can be prohibitive, especially in the latter case where timing of events is also important.
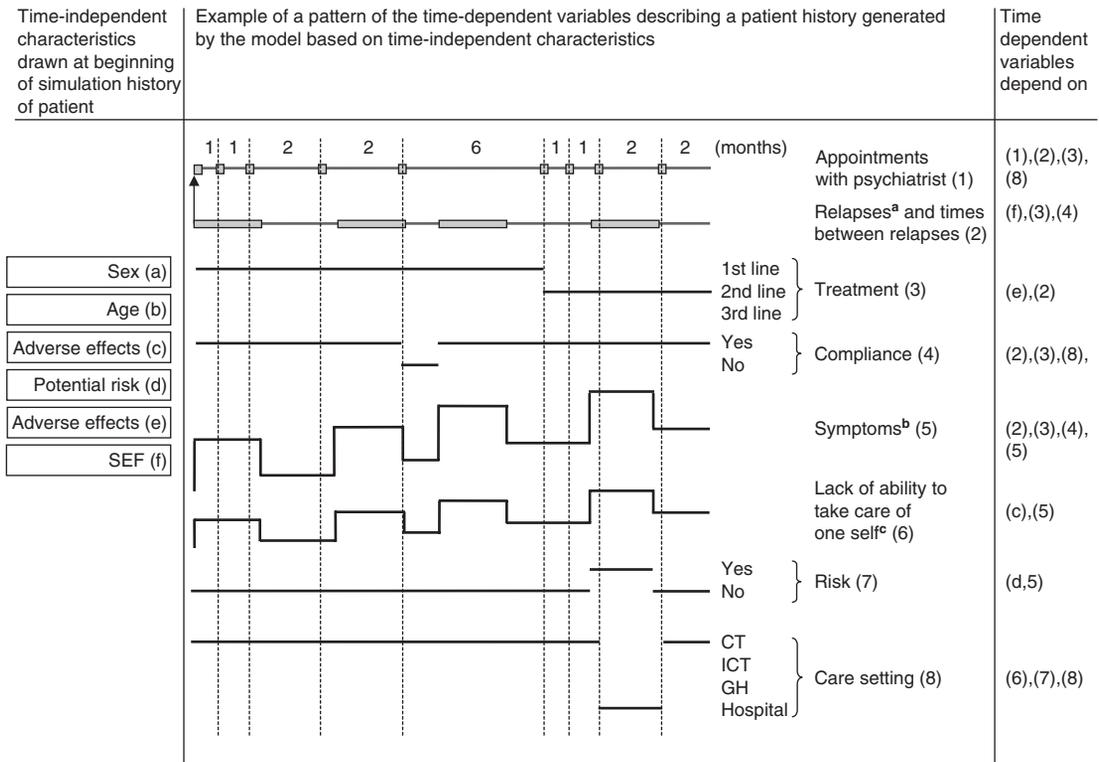
Fig. 5. Overview of a discrete event simulation for schizophrenia.[11] At the beginning of each simulation, the model draws patient characteristics from specified distributions of the six time-independent parameters (sex, patient profile, social and environmental factors [SEF], whether the patient will potentially present a risk to self or society, whether the patient will experience a treatment-related adverse effect) shown on the left. The time-dependent variables are shown on the right. Time is presented on the x-axis. The dependencies of the time-dependent variables are presented at the right. The dotted vertical lines each represent a psychiatrist visit. Compliance is affected by whether a patient is in relapse (2), treatment (3) and location (8). Risk of harming self and others depends on symptoms (5) and potential risk (d). For instance, the patient depicted in this figure has the potential to risk self and/or others, and when he/she reaches the threshold, the patient becomes an actual risk between the 6th and 8th visit. **a** Relapses are indicated by the shaded rectangles. The arrow at the beginning indicates that at the start of a relapse, the patient enters the model and visits a psychiatrist. **b** As time progresses, the patient experiences increasing symptoms. **c** As time progresses, the patient is increasing unable to take care of his/herself. **CT** = community treatment; **GH** = group home; **ICT** = intense community treatment.

2.2 Markov Models

2.2.1 Deterministic Markov Models

Timing of Events, Building Time, Data Collection, Simulation Time, Clinical Representation and Experience

Markov models offer a much more efficient approach to incorporate time in a decision model and are more suitable to incorporate more (temporal) detail, such as the occurrence of recurrent events. A higher level of detail will increase the model's building time and/or the number of parameters that needs to be estimated (data collection). The amount of time required to run the model will also increase with higher complexity. However, given the current generation of computers this may be a trivial factor. The structure of the Markov model of course enables the analyst to reflect reality more closely and therefore the clinical representation of the model is better than that of a decision tree.

Markov models have been applied extensively in assessment of medical treatments. For Markov

chains, ready-to-use software packages are also available (Treeage™). Moreover, the relative simplicity of the model design is an advantage of this modelling method.

Patient Heterogeneity

Similar to the decision tree, the inclusion of subgroups of patients can be accommodated either by running the model with separate sets of transition probabilities for each relevant subpopulation, and then re-aggregating, or by incorporating additional branches where the model becomes more complex. However, the same objections as were mentioned for the decision trees still apply.

Memory

The usefulness of Markov models is again limited by the Markovian assumption that reflects a 'lack of memory' associated with this type of modelling. In schizophrenia the Markovian assumption does not hold, as the risk of a new relapse or hospitalization and the symptom score depend on the number of relapses previously experienced. If one wanted to adapt the model of Almond and O'Donnel[9] and Palmer et al.[8] (figure 3) to incorporate this, one would need to differentiate the relapses according to the number of previous relapses/hospitalizations, and this requires additional health states and results in a large Markov model. The model becomes even larger if one also wants to allow for patient subgroups, such as sex and substance abuse. Even though it may still be technically possible to construct and analyse such a model, the number of health states does become so high that careful management of the model becomes a challenge, and other modelling options may prove more appropriate.

2.2.2 Individual Patient Simulation Markov Models

Variability, Memory, Interaction Due to Co-Variates

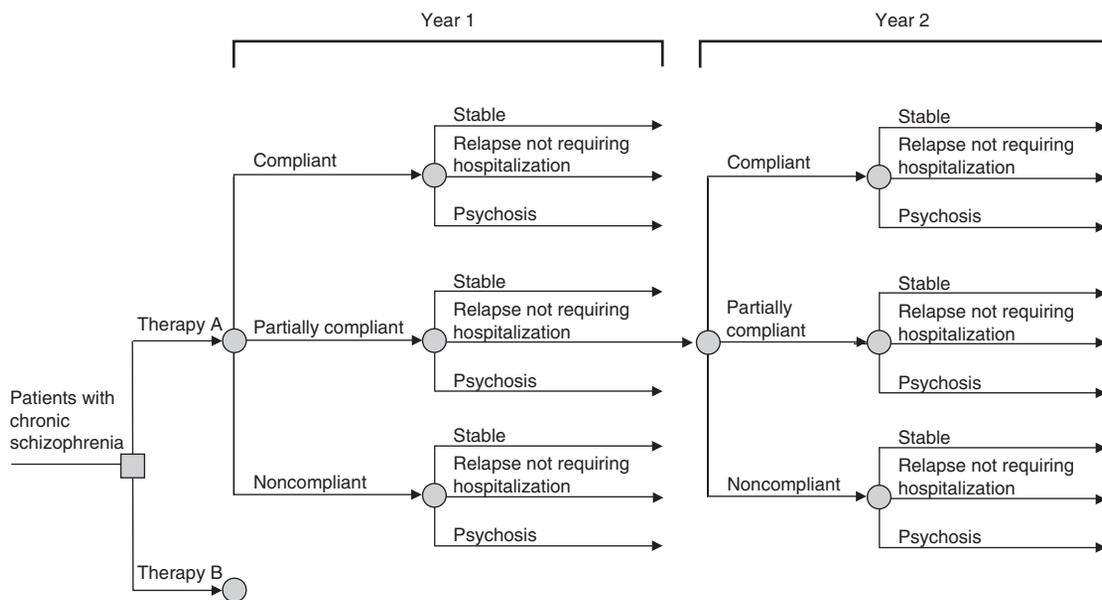An alternative to the cohort Markov model is the micro-simulation Markov model, which simulates

Fig. 6. Decision tree from figure 1 extended to 2 years. For simplicity, only a portion of the tree is depicted. The square represents a decision node and the circles represent chance nodes.

individual patient histories over time, thereby automatically including variability. Using first-order Monte Carlo simulations, the transition probabilities can be defined as functions of as many patient-level variables as desired. Such variables are called tracker variables.[15] For instance, a tracker variable can be used to keep count of the cumulative number of relapses a patient experiences over time. Only one example of a micro-simulation Markov model in schizophrenia has been found.[16,17]

The difference between cohort and micro-simulation Markov models is graphically displayed in figure 2a–b. In the example in figure 2b, a tracker variable would count, for instance, the number of relapses experienced. This tracker variable (the number of relapses) can be used to identify the pertaining probability of, for example, future hospitalization. For instance, one can decide to programme the model such that a second relapse is likely to be more severe than a first relapse and would therefore be more likely to lead to hospitalization. This enables using the simple Markov model structure without the need to expand it drastically to incorporate different patient types and pertaining health states.

Patient Heterogeneity

Clearly, by simulating individual patients and using tracker variables, the patient characteristics of these individual patients over time are more easily dealt with compared with simpler cohort Markov models or decision trees. Another advantage of using this approach is that the model structure can be maintained while including subgroups of patients and interaction between variables without the need for additional health/tunnel states.

Simulation Time

When evaluating a Markov model deterministically, as one would in a cohort model, the 'average' experience of the patients in the cohort is modelled. In contrast, when using first-order Monte Carlo sim-

ulation (micro-simulation) individual patient histories (e.g. 100 000) are (stochastically) simulated from one state to the next. This leads to a (potentially substantial) increase in simulation time. The simulation time of first-order Markov models increases exponentially when considering the second-order uncertainty of such models. This is because second-order uncertainty needs to be considered separately from first-order uncertainty.[18]

Interaction between Patients

In some cases, capacity constraints have to be taken into account and therefore what happens in one patient becomes dependent on the events happening in other patients. This question has not been frequently addressed. In micro-simulation Markov models, simulating patients one by one through the model and taking account of these interdependencies between patients is tedious. A simple solution would be to reduce the hospitalization transition probabilities to accurately reflect the number of patients hospitalized in clinical practice. Reducing the hospitalization transition probabilities is also applicable in cohort Markov models. Clearly, however, such an approach in a cohort Markov model does not fall under the definition of patient interaction. Reducing the hospitalization probabilities disregards the fact that the time spent on the waiting list may be associated with events occurring to that very patient subgroup. To accurately incorporate the latter process is likely to require micro-simulation, as the delay of hospitalization has to be associated with an increase of hazard rates on adverse events. Thus, the Markovian assumption does not hold any more.

2.3 Discrete Event Simulation Models

2.3.1 Timing of Events and Simulation Time

Even in a micro-simulation Markov model, analysts are limited in representing reality, since in those models patients can only experience one tran-

sition (between health states) per cycle. For instance, patients cannot have two relapses within one cycle. To ensure accuracy, one could decrease the cycle length. Since this will obviously increase computation time required, DES may be an alternative as it may reduce computation time compared with micro-simulation Markov models. The concept of DES as distinguished from the concept of the Markov approach is represented in figures 2 and 4.

In a DES model, the duration spent in a certain health state is directly drawn per patient from the corresponding cumulative survival distribution, whereas in Markov models the cumulative survival distributions may be used to estimate the transition probabilities over time.

The advantage of drawing directly from the cumulative survival distribution is that the DES model has to draw from as many distributions as the number of health states included, whereas in a micro-simulation Markov model, the number of distributions the model ultimately draws from is approximately equal to the number of cycles times the number of health states included in the model. For instance, when considering the model presented in figure 2 (programmed in Microsoft® Excel), per patient DES would need to draw once from three distributions, whereas the micro-simulation Markov model would need to draw from at least 15 distributions (three rows × five columns). This difference affects the simulation time. Still, simulation time in DES and micro-simulation Markov models remains a problem, especially when conducting probabilistic sensitivity analysis. Sometimes one has to resort to statistical approximations (meta models) by using, for instance, the Gaussian processes,[1] as has been proposed by Oakley and O'Hagan,[19] to diminish the computational burden encountered.

Another advantage of drawing from the cumulative survival distribution is that patients can proceed to another health state at any discrete moment in time, whereas in Markov models patients can only switch once during each cycle. Hence, DES models allow for a more precise handling of time than a Markov model (figure 4). Clearly, this does not necessarily produce substantially different results compared with a Markov model approach, as was demonstrated by Karnon.[20]

2.3.2 Model Building Time, Data Collection and Experience

As the model structure is similar, both micro-simulation Markov and DES are similar with respect to the required amount of detail and data collection. As such, depending of course on the experience of the model builder, it is likely that the time to build either type of model when using the same software such as, for instance, Microsoft® Excel will take about the same amount of time.

DES has been used extensively in industrial engineering, and dedicated software to run DES models has become available.[10] In technology assessment, DES models have been published since the mid 1980s.[21-23]

2.3.3 Patient Heterogeneity, Memory and Interaction Due to Co-Variates

Allowing for patient subgroups, memory and interaction due to co-variates can be incorporated quite easily (similar to micro-simulation Markov models) by specifying relevant tracker variables.

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1 A probabilistic simulation generally requires a minimum of 1000 simulations of cohorts. This may be quite time consuming for a patient-level simulation model, as each cohort requires a number of patient simulations to generate the cohort. If the probabilistic simulation takes too long, one could consider using a meta model. By using a meta model, one reduces one layer of simulations, i.e. the patient-level simulation, of the micro-simulation models. This substantially reduces simulation time of the probabilistic sensitivity analysis. A recently introduced meta-modelling approach is the Gaussian process. Gaussian process models have the advantage that they can be fitted on fewer probabilistic input and output combinations and that they can be applied for nonlinear models.

2.3.4 Clinical Representation

An important advantage of DES is that it allows for detailed modelling of the disease and its management over time, taking into account the enormous variability in the course of the disease and the different patient types. For instance, a DES model of schizophrenia will model appointments with psychiatrists, which are scheduled at variable time intervals depending on the state of the patient. During the appointments psychiatrists may decide on treatment setting and pharmacological treatment. This can be dealt with in a cohort Markov model, but will be cumbersome because of the explosion of the number of health states included. It could also be dealt with in a micro-simulation Markov model but would require adapting the cycle length and subsequently the corresponding transition probabilities, and again the corrections involved make it less attractive to use such a model. The greater flexibility of the DES approach allows for a representation of the patient history of schizophrenia that directly reflects the actual management of the disease in practice.

Micro-simulation Markov models and DES are able to include a greater level of detail than cohort Markov models. An important advantage is that the additional variables/parameters can now be subject to probabilistic analysis. The corresponding sensitivity analysis will give a better representation of the uncertainty that exists regarding the base-case values than with simpler models, in which many assumptions remain implicit, not quantified and consequently incontestable.

2.3.5 Variability and Patient Interaction

By simulating individual patients, DES inherently allows for inclusion of capacity constraints. Those constraints will be an important source of information for policy making in patients with schizophrenia, since post-acute psychotic patients in particular may be more likely to be put on a waiting list before being admitted to a psychiatric hospital, as healthcare systems try to decrease the length of hospital stay. As several dedicated software packages such as Extend® and Arena® allow for simulating patients simultaneously through the model, DES models allow for the inclusion of capacity constraints in an easy way.

2.4 Summary

Figure 7 summarizes the ability of each modelling approach to deal with the discussed modelling criteria.
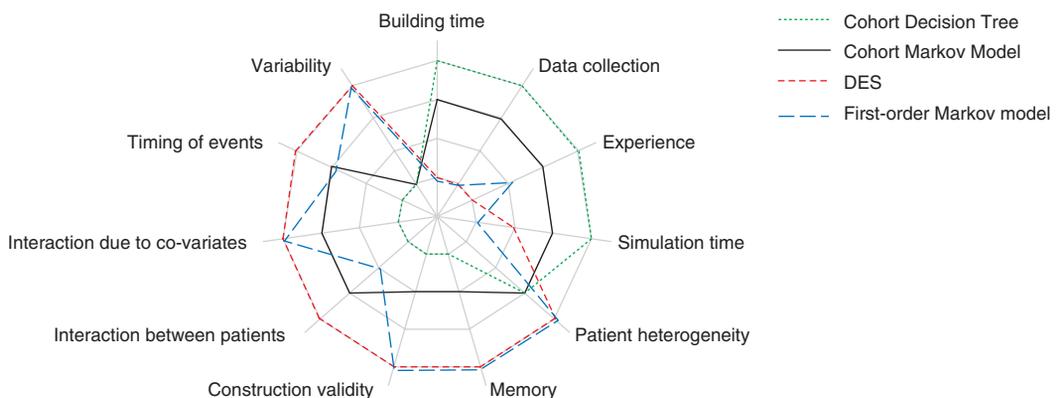

Fig. 7. A radar graph of the strengths and weaknesses of cohort decision trees, cohort Markov models, first-order Markov models and discrete event simulation (DES) models for application in a chronic complex disease such as schizophrenia. The further away from the centre the relevant line crosses the specific axis, the better this kind of modelling is than the others with respect to this particular modelling characteristic.

3. Considerations Relevant for the Choice of a Model for Schizophrenia

In theory, there are cases where an innovation is considered that has overriding implications for effectiveness and/or costs of treatment of patients with schizophrenia. If these overriding implications are very well documented in trials over a sufficiently long time horizon, and data are available to estimate differences in effectiveness in terms of QALYs and associated costs, a full-blown DES model or microsimulation Markov model might be superfluous.

However, in practice the literature on the safety and efficacy of the different antipsychotics is far from this theory and the ideal world.[24-38] Essentially, the pharmaceutical treatment of schizophrenia can be subdivided into two types of antipsychotics, conventional and atypical, and two types of formulations, oral and long-acting. In clinical practice many patients are being treated with a mixed set of antipsychotics. Very limited information on the effect of polypharmacy is available and clinical trials are focused on efficacy in a controlled setting, but for the assessment of a new intervention effectiveness in the context of the prescription of a new drug in practice has to be considered. The long-acting injectable antipsychotics obviously have the advantage of increased compliance versus the oral antipsychotics. The full benefits of this advantage are very difficult to capture in a clinical trial. With respect to the difference between atypical and conventional antipsychotics, it has been suggested[24,26,35] that the atypical agents have better efficacy and a different adverse effect profile than the conventional agents, which may affect compliance.

Given the uncertainties regarding differences between antipsychotics in effectiveness, compliance and adverse effects, a cost-effectiveness model should have the power to represent the different beliefs that may exist and their (long-term) economic and health-related consequences in clinical prac-

tice. Thus, when developing a model that allows for comparing oral and long-acting injectable atypical antipsychotics and oral and depot conventional agents, the model should be flexible. As cost per QALY is the preferred outcome of many health authorities, one should link symptoms and adverse effects to utilities.[39] The timing of events (e.g. psychosis) also becomes important, because if one drug has superior efficacy or compliance, the timing of the next episode may be delayed. In cardiovascular disease, an event (e.g. stroke or myocardial infarction) often has cost implications that are relatively straightforward. This is far less true in schizophrenia, and patients may experience several relapses of varying duration over a relatively short period. Moreover, patients with a psychosis are not always hospitalized (e.g. because they are in a stable environment). On the other hand, nonpsychotic patients might be hospitalized because neighbours are complaining. The impact of these social environmental factors on the hospitalization decision (the major cost driver in schizophrenia) differs by country or setting within a country. The model should be able to capture these differences. Moreover, patients who are often hospitalized have a higher probability of being treated in long-term institutions. Hence, a more effective drug may reduce not only the number of acute hospitalizations but also, eventually, long-term institutionalizations. This latter phenomenon can be considered if the time horizon of the model is long enough. A good model for schizophrenia should also have the power to analyse the implications of treatment in patient subgroups, as an expensive, more effective drug might be cost effective in severely ill patients but not in those with less severe disease.

Thus, the model structure should be chosen based on the available clinical evidence, the time horizon, number of co-variates, memory, patient heterogeneity and the required number of interactions between co-variates. Important for that choice is the

expected number of health states required to satisfactorily answer a research question. In theory one can model the cost effectiveness of antipsychotics using a cohort model; however, this type of model might require a high number of health states to represent the subtleties of treatment of patients with schizophrenia. If the skill of the researcher allows building a cohort model that reflects clinical practice such that the potential simplifications do not affect the outcomes, a cohort model should be preferred. However, if the researcher is not able to programme the required potentially large number of health states or needs to make assumptions that may affect the outcomes, other modelling options such as micro-simulation Markov and DES should be considered. However, these latter approaches are relatively new and may require substantial time to run the model simulations. In the end, micro-simulation Markov models and DES models may require a lot of simulation time, especially when conducting a probabilistic sensitivity analysis, but they allow for a more accurate representation of the complex clinical practice of schizophrenia.

4. Discussion

The cost effectiveness of pharmaceutical interventions for schizophrenia has been modelled with decision trees, deterministic Markov models, individual patient simulation Markov models and DES models. Several articles have been written on good modelling practice.[40-42] These articles address the quality of models by discussing the structure of a cohort model, input data and model validation. Weinstein et al.[40] concluded that the purpose of models is to synthesize evidence and assumptions in a way that allows end users to gain insight into the implications of those inputs for valued consequences and costs. Sculpher et al.[42] concluded that a model structure should be as simple as possible, consistent with the stated decision problem and a theory of disease, and not defined by data availability or health services input alone. The taxonomy proposed by Brennan et al.[5] adds to the literature in that it may help guide the choice of model structures for health economic evaluations. We used the taxonomy of Brennan et al.[5] in this article, with some adaptation, as a structure to discuss different model types used in the disease area of schizophrenia.

We explicitly included building time, data collection and programming experience, as these may be important decision criteria in certain situations. Furthermore, probabilistic sensitivity analysis was discussed under the headings of simulation time as well as clinical representation. Dimensionality is the consequence of several criteria and is therefore not distinguished separately. This article further combined the decision criteria 'time of events' and 'recycling of states', as these have similar consequences in terms of modelling requirements. Furthermore, we only distinguished between 'interaction between patients' and 'interaction due to co-variates'. 'Interaction due to co-variates' and 'individual risk factors' causing nonlinear outcomes were combined, as they are quite similar and have similar consequences. Interaction between patients directly or interaction in small populations were not considered, as this situation is unlikely in schizophrenia. Additionally, the concept of clinical representation was introduced to describe how successful different models were at capturing reality and the level of uncertainty that exists around point estimates.

It has also been suggested that the simplest model that addresses the objectives of the study and structure for the disease and treatment is the most appropriate.[42] However, simple models unavoidably involve many implicit assumptions and those will not be tested in the (probabilistic) sensitivity analyses. In the area of schizophrenia those implicit assumptions might result in an inaccurate analysis, which does not properly address the uncertainties involved in the treatment of patients with this disease.

5. Conclusions

In a complex disease such as schizophrenia, the research question will help identify the modelling approach that would be most appropriate. The presumed differences between treatments, the number of co-variates, patient subgroups, the interactions between co-variates, and simulation time all may be important to consider. Finally, it is argued that where micro-simulation is required for the cost-effectiveness analysis of schizophrenia treatments, a DES model is most flexible and may accurately capture all of the relevant interdependencies in this chronic, highly heterogeneous disease with limited long-term follow-up data.

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