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REVIEW ARTICLE

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Systematic review of pharmacoeconomic models for schizophrenia

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ABSTRACT

Background: Economic models are broadly used in the economic evaluation of antipsychotics in schizophrenia. Our objective was to summarize the structure of these models.

Methods: Model-based economic evaluations of antipsychotics in schizophrenia were identified through Medline and Embase. General information was extracted including analysis type, model type, perspective, population, comparator, outcome, and timeframe. Model-specific structures for decision tree (DT), cohort- and patient-level Markov model (CLMM, PLMM), and discrete-event simulation (DES) models were extracted.

Results: A screen of 1870 records identified 79 studies. These were mostly cost-utility analyses (n = 48) with CLMM (n = 32) or DT models (n = 29). They mostly applied payer perspective (n = 68), focused on general schizophrenia for relapse prevention (n = 73), compared pharmacotherapies as first-line (n = 71), and evaluated incremental cost per quality-adjusted life year (QALY) gained (n = 40) with a 1-year (n = 32) or 5-year (n = 26) projection. DT models progressed with the branching points of response, relapse, discontinuation, and adherence. CLMM models transitioned between disease states, whereas PLMM models transitioned between adverse event states with/without disease state. DES models moved forward with times to remission, relapse, psychiatrist visit, and death.

Conclusions: A pattern of pharmacoeconomic models for schizophrenia was identified. More subtle structures and patient-level models are suggested for a future modelling exercise.

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Schizophrenia; pharmacotherapy; antipsychotics; pharmacoeconomics; economic model; model structure

Introduction

Schizophrenia imposes a great burden on both economics and quality of life. Its estimated societal cost ranges from 37% to 214% of GDP per capita [1], and it is ranked the sixteenth highest cause of years lived with disability out of the 25 most common diseases worldwide [2]. Many treatments are available for schizophrenia, with very different benefit/risk profiles. A network meta-analysis found that out of 15 antipsychotics, clozapine ranked first in symptom control, but lower than tenth in safety [3].

Economic evaluation produces data incorporating the benefits and risks of treatments. This approach to the evaluation of atypical treatments for schizophrenia has been used since 1990 [4]. In the current literature, model-based economic evaluations outweigh clinical trial-based analyses [5,6]. However, model-based studies may generate inconsistent conclusions on cost-effectiveness for the same comparison, even when the same modelling technique is used [7].

A comprehensive review of models used in the evaluation of treatment for schizophrenia can provide useful information for future model-based economic evaluations. Recent systematic reviews have not presented current models of pharmacotherapy for schizophrenia, as they have narrowed their search to long-acting/extended-release antipsychotics [5], newer second-generation agents [6], and the relationship between modelling technique and reported outcomes [7]. Although Nemeth et al [8]. did address models of pharmacotherapy, their study missed lots of model-based studies discussed by Scheele et al [7]., such as the NICE models from 2009 [9] (updated in 2014 [10]) and 2011 [11].

In view of the limitations in existing studies, we aimed to identify economic models of pharmacotherapy for schizophrenia and to present the structures of these models.

Methods

This systematic review considered all model-based economic evaluations of pharmacotherapy for schizophrenia published after 2000. The search was conducted using Medline and Embase via Ovid in April 2016. Search terms combining 'schizophrenia', 'economic evaluation', and

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Supplementary data present in this article can accessed here.

'model' were used as free term and medical subject heading (MeSH) term. The search strategy is presented in Supplement 1 and Supplement 2. Studies were excluded if they discussed aspects not related to treatment effect, the full text was unavailable, the study was later updated, or the study was not in English. Systematic reviews identified through the screening process were reviewed for manuscript inclusion. References in the studies identified were searched manually to find studies which might have been missed in the initial search.

To present the model structure, both general and model-specific information were extracted. General information included type of analysis, type of model, country/region, perspective, patient population, comparator, economic outcome, and timeframe. Model-specific information included branching points for decision tree (DT) models, health states and cycle length for cohort-level (CL) and patient-level (PL) Markov models (MM), and time approach methods for discrete event simulation (DES) models. For patient-level models, PLMM, and DES models, patient characteristics to be simulated were also extracted.

Within general information, type of analysis included cost-benefit analysis, cost-effectiveness analysis (CEA), cost-minimization analysis, and cost-utility analysis (CUA) [12]. CEA in this review referred to CEA using health outcomes other than quality of life, to differentiate these analyses from CUA, which was considered a special form of CEA using quality of life as health outcome. Cost analysis was also considered as a type of economic analysis, since while early economic evaluations primarily compared costs, they also presented health outcomes. Type of model included DT, CLMM, PLMM, DES model [7,13], and others. Perspective was classified into societal, payer, and patient perspective [14]. Patient population was classified into early, general and treatment resistant schizophrenia. According to NICE guidelines, there are 4 major areas of treating schizophrenia with antipsychotic drugs: initial treatment for early schizophrenia, treatment for acute schizophrenia, relapse prevention for stable schizophrenia, and treatment for resistant schizophrenia [10]. In this study, acute and stable schizophrenia were classified as general schizophrenia, since the timeframe of over 1 year covers both the acute and maintenance phase. Outcomes were classified into incremental cost per positive outcome gained, incremental cost per negative outcome avoided, and others. For positive and negative outcomes, 3 categories were considered: time spent in status, number of patients with an outcome, and number of outcomes per patient.

To present the general information, the studies that applied each category of each area considered under general information were summarized. Further information was presented, including the definition of perspective and patient population, and comparator and outcome options. Comparator options were the pharmacotherapy to be compared and the number of lines for switch.

To present the model-specific information, the statistics and options of the structures in the DT and CLMM models were summarized. For patient-level models, PLMM, and DES models, only the structural options in the original models were taken into account, since the number of original patient-level models was small, and the models adapting these original models would not involve a large change in the model structure.

Results

A screen of 1870 records identified 72 studies. By checking the references in these studies and the models included in previously published reviews, a further 7 studies were identified (Figure 1). The characteristics of the 79 studies [10,11,15–91] are presented in Supplement 3.

General information

A summary of study characteristics is presented in Table 1. The studies included were conducted in 28 countries/regions (mostly in United States: n = 17), usually applying CUA (n = 48) with cohort-level models (29 DT and 32 CLMM models). They mostly compared pharmacotherapy as first-line treatment (n = 71) for general schizophrenia (n = 73) in terms of incremental cost per quality-adjusted life years (QALY) gained (n = 40) over a 1-year (n = 32) or 5-year (n = 26) timeframe from the payer perspective (n = 68).

Perspective: definition

Different terms were used for payer perspectives, including terms related to payer (payer, third-party payer, health care payer, government payer), insurance (health insurance, general insurance), health service (ministry of health, health care system, health care service, health care provider) and others (health sector, direct cost).

Population: definition

In most studies, the term 'general schizophrenia' referred to non-treatment-resistant schizophrenia with a history of more than one relapse. Half the models specified the phase of disease at entry: acute phase (n = 15) and stable phase (n = 21). Twenty-seven studies further defined the patient population according

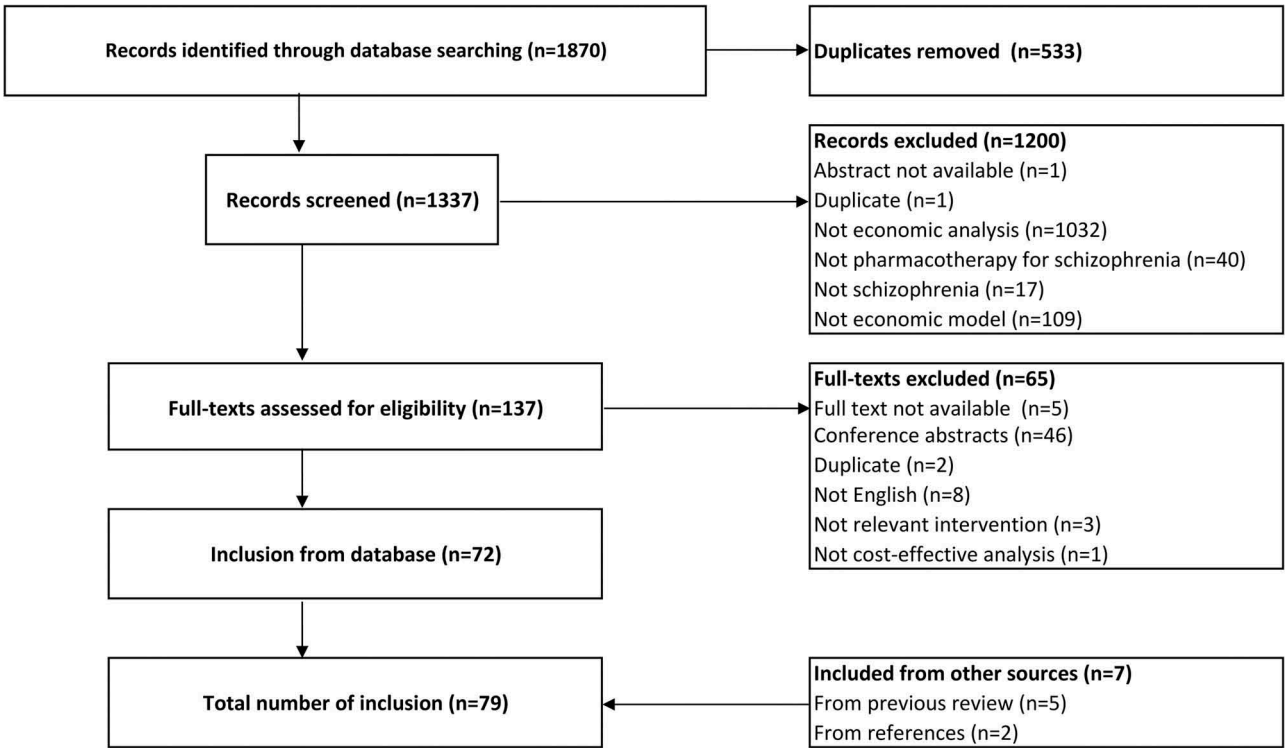

Figure 1. Screening process.

to current setting (n = 14; outpatient, inpatient), treatment status (n = 13; accept long-acting injection/oral treatment, naive to atypical antipsychotics, partially responsive), adherent status (n = 10; high risk of non-adherent, adherent), other disease status (n = 3; moderate severity, residual state, young schizophrenia with duration < 5 year). Treatment-resistant schizophrenia was classified as moderate/moderate to severe, stabilized on clozapine, or progressive deterioration.

Comparator options

Olanzapine and risperidone were the most common pharmacotherapies compared (n = 51 and n = 50). Groups of typical and atypical antipsychotics were considered in 9 and 8 studies. Only half of the studies on typical/atypical antipsychotics provided detailed information about the drugs included (typical treatment – haloperidol, chlorpromazine; atypical treatment – olanzapine, risperidone) using the weighted mean of market share. Treatment switch was allowed in most studies (n = 49), with 3 treatment lines most commonly used (n = 26), followed by 4, 2, and 5 treatment lines (n = 12, n = 8, n = 2 respectively).

Outcome options

The following positive outcomes were considered: QALY, life years, and being stable, compliant, or employable. Different terms for stable were applied: response, non-relapse, symptom-controlled. The following negative outcomes were considered: disability-adjusted life years (DALY) and occurrence of relapse and side effects. Relapse was further classified into inpatient and/or outpatient relapse in 6 studies. Side effects considered were extrapyramidal symptoms (EPS), metabolic syndrome, and diabetes as primary outcome. Other outcomes were a decrease in incremental cost per Positive and Negative Syndrome Scale (PANSS) score and difference in cost, remaining on first-line treatment, tardive dyskinesia, coronary heart disease, agranulocytosis, and death.

Other than QALY, the most commonly used outcome of time spent in state was the duration of stable phase (n = 9). Others were DALY, life-year, time spent in relapse, EPS, and duration of first-line treatment. For number of patients with outcome, the most commonly used outcome was relapse (n = 14), either requiring (n = 5) or not requiring hospitalization (n = 4). Others were number of patients being stable, experiencing relapse, metabolic syndrome, or diabetes, and remaining on first-line treatment or employable. For number of outcomes per patient, only relapse was considered.

Model-specific information

DT

DT models evaluated 2 to 64 outcomes and 1 to 12 branching points with increasing model complexity. Most DT models applied branching points at relapse

Table 1. Summary of studies included in the analysis.

Comparison area	Description	N
Type of analysis	Cost-utility analysis	48
	Cost-effectiveness analysis	26
	Cost analysis	5
Type of model	Cohort-level Markov model	32
	Decision tree model	29
	Discrete event simulation model	10
	Patient-level Markov model	4
	Other models	4
Country/region	United States	17
	United Kingdom	9
	Canada	6
	Sweden	6
	Germany	3
	Spain	3
	Belgium, Ethiopia, Finland, France, Greece, Thailand	Each = 2
	Australia, Brazil, China, Croatia, Czech Republic, Italy, Mexico, Norway, Portugal, Singapore, Slovenia, South Africa, South Korea, Taiwan, Uganda, Vietnam	Each = 1
	Multi-regions	3
	NR	1
Perspective	Payer perspective	68
	Societal perspective	5
	NR	7
Patient population	Patients with general schizophrenia	73
	• Patients entered model at acute phase	15
	• Patients entered model at stable phase	21
	• NR	37
	Patients with treatment-resistant schizophrenia	6
	Patients with early schizophrenia	1
Type of comparison	Pharmacotherapy comparisons	71
	• Olanzapine	51
	• Risperidone	50
	• Haloperidol	30
	• Aripiprazole	19
	• Paliperidone	19
	• Quetiapine	17
	• Ziprasidone	15
	• Clozapine	6
	• Amisulpride	5
	• Chlorpromazine	5
	• Sertindole	3
	• Lurasidone	2
	• Zotepine	2
	• Zuclopenthixol	2
	• Asenapine, Flupentixol, Fluphenazine, Sulpiride, Trifluoperazine, Placebo	Each = 1
	• Typical antipsychotics	9
	• Atypical antipsychotics	8
	• No treatment	5
	Scenario comparisons	8
	• Adherence-level comparison	4
	• Brand-generic switch comparison	2
	• Treatment sequence comparison	2
Economic outcomes	Time spent in status	
	• QALY	40
	• Duration of relapse	11

(*Continued*)

Table 1. (Continued).

Comparison area	Description	N
	• Duration of being stable	9
	• DALY	8
	• Life year	2
	• Duration of being on 1st-line treatment	1
	• Duration of EPS	1
	Number of patients with outcome	
	• No. of patients with relapse	14
	• No. of patients stable	8
	• No. of patients on 1st line treatment after 1 year	1
	• No. of patients employable	1
	• No. of patient with metabolic syndrome	1
	• No. of patients with type 2 diabetes	1
	Number of outcomes per patient	
	• No. of relapses per patient	14
	Others	
	• Difference in costs	6
	• Cost per score of PANSS decreased	4
Timeframe	16-week	1
	26-week	1
	1-year	32
	2-year	4
	3-year	2
	5-year	26
	10-year	4
	lifetime	12

DALY, disability-adjusted life years; EPS, extrapyramidal symptoms; No., number; NR, not reported; PANSS, positive and negative symptom score; QALY, quality-adjusted life years.

level (72%), response level (41%), discontinuation option (62%), or adherence level (38%).

The relapse branch was composed of no relapse (or stable) and relapse. Around half of the studies (57%) further classified relapse into inpatient and outpatient relapse. The response branch was composed of response and no response. The discontinuation branch was composed of continuation, discontinuation, and sometimes dose increase (n = 7). Discontinuation could be followed by a medication switch or just discontinuation. The adherence branch was composed of adherent, non-adherent, and sometimes partially adherent (n = 2).

CLMM

Twenty-nine (91%) CLMMs reported their structure, considering from 2 to 33 Markov health states. Common health states were stable and relapse (n = 22). Stable phase was replaced with response level (PANSS improvement: > 30%, 30%–20%, < 20%), more detailed symptom (mix/positive/negative/no symptom), or residual symptoms state in 2, 1, and 1 studies. The other elements of states were setting of care (inpatient, outpatient), treatment (lines of treatments and no treatment), adherence level (adherent, partially adherent, non-adherent), presence of side effect, and death.

The following cycle lengths were applied: 6 weeks, 18 weeks, 1 month, 3 months, 6 months, and 1 year. A 1-year cycle was most often used, with a lifetime (n = 7) and 5-year timeframe (n = 4). A 3-month cycle with 5-year timeframe was also used (n = 6). All these cycle lengths were used in the models using schizophrenia disease status as Markov states. For models using Markov states with long-term side effects, only a 1-year cycle length was used. For models using Markov states with only treatment sequences, 1-year (n = 2) and 18-week (n = 1) cycle lengths were used.

PLMM

Two PLMM models were original [75,77]. The other models adapted the model of Furiak et al [75]., with minor changes to the model structure (adding 2 side effects: hyperprolactinaemia and tardive dyskinesia). The model of Vera-Llonch et al [77]. had 6 health states (no chronic side effects, diabetes,

prolactin-related disorders, both of these, discontinuation, and death) with a 1-month cycle. They set the baseline body weight and body mass index to patients individually, and simulated the changes in body weight and possible adverse events (AE). The model of Furiak et al [75]. had 3 health states (stable with or without side effects, and relapse requiring hospitalization) and 3 adherence levels, with a cycle length of 3 months. They initialized the baseline adherence level for patients individually and simulated changes in their adherence level, disease progression, and possible AEs (weight gain, EPS, diabetes, hyperlipidaemia) and treatment sequence.

DES

Two DES models were original [80,81]. The other models adapted the model of Heeg et al [81]. by adding another compliance level and a line for treatment switch. The model of Heeg et al [81]. moved forward by times to remission, relapse, and psychiatrist visit, and ended at completion of timeframe or death. They initialized the following characteristics: age (on entering the model and at death), gender, disease severity, risk of self-harming or harming others, possibility of AEs, and social and environmental factors with impact on their treatment location. The model of Dilla et al [80]. moved forward with time to remission, relapse, AE, psychiatrist visit, and death. They did not report on the simulation of patient characteristics.

Discussion

Similarities between models

The pharmacoeconomic models analysed in this review addressed similar research questions. They primarily focused on the comparative cost-effectiveness from the payer perspective of different pharmacotherapies in terms of QALYs and relapse in general schizophrenia patients who required relapse prevention.

Among the models identified, DT and CLMM dominated. Within DT or CLMM, the models shared similar structures. Most DT models defined response as an outcome for acute phase treatment and relapse as an outcome for maintenance treatment, as well as discontinuation (switch or dropout) and adherence level as factors to adjust outcome probability. Most CLMM models transitioned between stable phase and relapse, with treatment status and adherence level as factors that may change transition probabilities, and with AE and setting/severity that may change QALY.

Differences between models

Some models addressed non-common research questions, such as patient population (e.g. early schizophrenia or treatment-resistant schizophrenia), comparison (e.g. different treatment regimen, compliance levels, and brand–generic switch), and outcome (e.g. long-term AEs and discontinuation). Some models also employed non-common structures. For example, some DT models included the additional branch points of suicide, AE, and employability. Some CLMM models did not have disease states. Instead, they focused on AEs (e.g. transition between no AE and long-term AE, short-term AE and/or death due to AE), settings (e.g. transition between outpatient and inpatient care), or treatment (e.g. transition between treatment lines).

The definition of framework in models with similar research questions and structure was another source of heterogeneity. Defining general schizophrenia across studies was associated with subtle differences in initial disease severity, acute or maintenance phase of disease, settings, and adherence. Pharmacotherapy comparisons included models with different subsequent treatments in terms of the number of lines and treatments available for switching. Calculation of QALYs was based on different ranges of disease status and AEs. Different definitions also existed for other common outcomes, such as relapse and response. There were sometimes differences in the methods of evaluation (PANSS scale or Brief Psychiatric Rating Scale) and the thresholds to determine response or relapse (20% or 30% changes).

Many DT models shared similar branching points with single-choice, binary, or multiple options, e.g. a patient could be classified as a responder or a non-responder, but in some models, the option of a partial response existed for patients with residual symptoms. There were also models which assumed that patients who received the last line treatment would respond to the treatment. The majority of CLMM models had similar health states and relations between them; however, important factors, such as current treatment, AEs, and adherence level were excluded from some models.

Limitations

The major limitation of this review is the necessity of making assumptions in cases where studies did not provide sufficient information. For example, in studies that lacked a description of the patient population, general schizophrenia was assumed. Secondly, this review aimed

to identify and present economic models of pharmacotherapy for schizophrenia, and so does not attempt to account for differences between schizophrenia models that could be rooted in different requirements existing in different countries, such as the preferences of different health technology assessment institutions, different treatment guidelines, and the availability of comparators and treatment lines.

Suggestion for future studies

Analysis on modelling studies

It would be interesting to conduct further studies to investigate whether the choice of model structure is influenced by the research question and if particular structures are chosen for particular treatments and/or patient populations, such as the antipsychotic treatments to be compared or patient populations with special features.

It would also be interesting to investigate the impact of structural choices on modelling results. Developing economic models to test this impact is needed. The impact will be difficult to identify through review of existing economic models, as they are different not only in model structure but also in the inputs and assumptions used. Our review summarizes the options for model structures, and this may help future modelling studies to identify alternative modelling options that could be tested.

Modelling studies

We have also identified several areas that need further research for modelling. First, modelling for treatment-resistant schizophrenia should be addressed, due to the limited number of studies focusing on this area. Many studies have involved long-term simulations that inevitably reached the late stage of the disease, but these studies used assumptions instead of more subtle modelling techniques.

Another area relates to treatment sequence. Despite the fact that some models allowed treatment switch, most of them did not consider the reasons for switching. In addition, only 3 studies considered treatments with better attributes had a higher probability of being switched to.

Future models should also consider more detailed outcomes. Due to the variety of benefit and risk profiles among available treatment options, economic models that do not take account of residual states in natural disease progression, detailed adherence levels, or long-term AEs are prone to bias.

Finally, patient-level models are recommended, as the complexity of schizophrenia limits the use of cohort-level models. By increasing the complexity of the model, DT models can have tree structures with 64 outcomes, and CLMM models can have Markov structures with 33 health states, making them inconvenient as a model. Additionally, cohort models cannot take into account patient heterogeneity, which may possibly make their results less precise and their uncertainty analysis less complete. However, patient-level models require more data and better modelling skills.

Conclusions

Current patterns and structures for modelling pharmacotherapy in schizophrenia focus on general schizophrenia using cohort-level models. Future modelling should concentrate on rare cases, such as treatment-resistant schizophrenia, and on details of treatment sequences and outcomes. Employing patient-level models may provide the complexity needed for schizophrenia modelling.

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