Additionele informatie bij de multidisciplinaire richtlijn

Schizofrenie

Richtlijn voor de diagnostiek, zorgorganisatie en behandeling van volwassenen cliënten met schizofrenie

2005

Costs and effects of short-acting atypical and conventional formulations in the Netherlands

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ACT	Assertive Community Treatment
Atyp	Atypical antipsychotic (e.g. risperidone, olanzapine, clozapine)
Conv	Conventional antipsychotic (e.g. haloperidol)
DI	Disorganisation Index
Disc.	Disounted
DR	duration relapse
EPS	ExtraPyramidal Symptoms
m.s.	medium severe
n.s.	non-severe
PANSS	Positive And Negative Symptoms Scale
pSE	probability to suffer a side effect
pSwitch	probability to switch medication
QALY	Quality Adjusted Live Years
SE	Side Effect
TBR	Time Between Relapses
TD	Tardive Dyskinesia
Tx	Treatment
v.s.	very severe

OBJECTIVE: To estimate the costs and effects of short-acting conventional versus a short-acting atypical formulation over a five-year period in the Netherlands.
METHODS: A discrete event model was developed comparing two scenarios. In scenario 1, patients start with haloperidol, after which they may be treated with risperidone and clozapine. In scenario 2 patients start with risperidone after which they may subsequently be treated with olanzapine and clozapine. The model simulates individual patient histories accounting for age, gender, type and severity of disease, the potential to present a significant risk, and the propensity for side effects. Based on these patient characteristics, the model registers patient histories in terms of outpatient visits, psychotic episodes, symptom scores, treatment changes, compliance, actually presenting a significant risk, and treatment location. Outcomes are expressed in terms of the number and duration of psychotic episodes, QALY, the cumulative symptoms-score and costs. The scope of this economic evaluation is limited to the direct medical costs from the societal perspective, i.e. the costs of the medication, visits to the psychiatrist and costs associated with the treatment in various locations are included. Indirect costs, costs of the family and costs of the juridical system have not been included. Information on treatment alternatives, transition probabilities, model structure and health care utilisation were derived from literature and an expert panel. Subgroup analyses are performed for the most severe patients. Moreover, univariate sensitivity analyses are carried out.
RESULTS: It is estimated that starting treatment with an atypical compared to starting with a conventional has a positive effect on the outcomes, i.e. per patient in 5 years it avoids 0.02 relapses and decreases the cumulative symptom-score with 35 points (7%), while simultaneously yielding cost savings of approximately €5,977.
Sensitivity analyses show that the results are relatively robust and that they are mainly sensitive to estimates about compliance and to the estimated effectiveness of atypical and conventional formulations on the occurrence of symptoms.
CONCLUSION: Oral atypical formulations combine additional effectiveness with cost savings and are therefore the dominant therapy. Even more favourable results are obtained when treatment is limited to those patients in whom a further deterioration is expected.

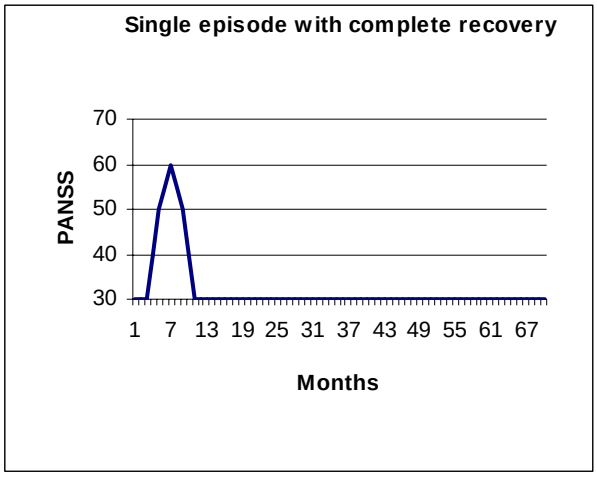
1 Introduction

1.1 Schizophrenia in the Netherlands

Schizophrenia is a chronic disease, which approximately affects 27,700 Dutch inhabitants.[1] The disease is characterized by the occurrence of positive symptoms (like hallucinations, delusions, incoherent speech, and catatonic behaviour) and/or negative symptoms (such as a restricted emotional experience, expression and social drive). Both types of symptoms have a devastating effect on the patient's ability to maintain (social) relationships, to get a job and to maintain the wish to participate in normal daily activities.

Figure 1 Disease profiles

A



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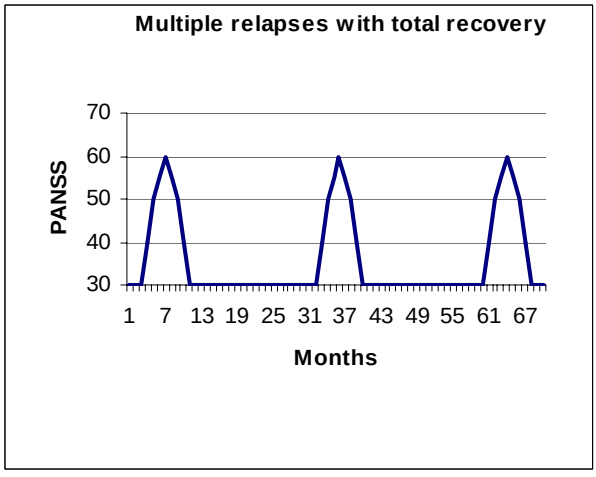

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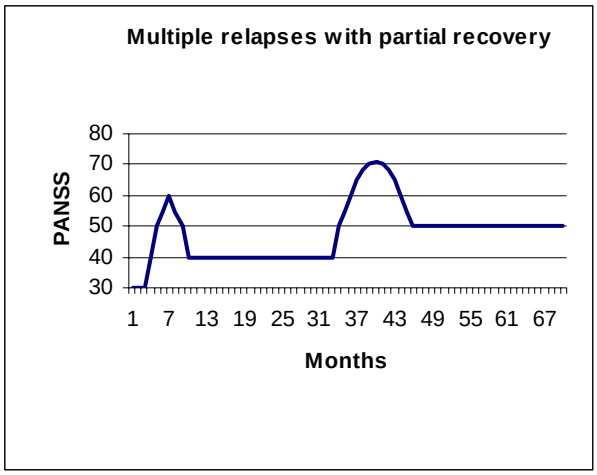

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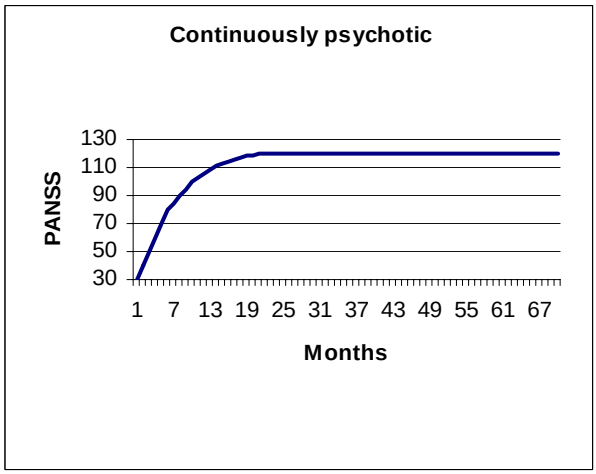


The number of episodes that a patient suffers during a lifetime varies considerably. Approximately 16% of the patients suffer only one episode, after which they completely recover (Figure 1A). Approximately 19% of the patients experience multiple episodes but are free of symptoms between episodes (Figure 1B). The largest group of patients (52%) consists of patients whose health state deteriorates continuously between episodes (Figure 1C). Finally, approximately 13% of the schizophrenic patients develop a continuously psychotic state (Figure 1D).[2] There is no curative treatment for schizophrenia. The available treatments reduce symptoms and delay the occurrence of episodes.

There are two types of medication: conventional agents like haloperidol and atypical agents like risperidone, olanzapine and clozapine. The conventional agents are effective in reducing the positive symptoms of schizophrenia (e.g. delusions and hallucinations), but they are not effective in reducing the negative symptoms. Moreover, severe side effects, like extrapyramidal symptoms (EPS) and tardive dyskinesia are observed.
The newer type of antipsychotic medications, like risperidone and olanzapine, are called atypical agents because they cause no or less typical side effects (like EPS). Another advantage of atypical agents is that they not only reduce the positive but also the negative symptoms.[3] Moreover, risperidone delays the occurrence of psychotic episodes more effectively than haloperidol.[4]
A relative disadvantage of the atypical formulations may be their high costs compared to the conventional antipsychotic agents. However, several economic evaluations per-

formed in Western countries have shown risperidone and olanzapine to be cost-effective when compared to conventional agents.[5,6,7,8] Thus far, no such economic evaluation has been performed for the Netherlands.

1.2 Perspective

The treatment of schizophrenia is costly. World wide, approximately between 1.5% and 3% of the total national health care expenditures is spent on schizophrenia.[9] The most important cost driver is inpatient care, as approximately between one third and two thirds of total health care cost for schizophrenia are spend on hospitalisation.[9] In 1993 Evers *et al*. estimated the total costs in the Netherlands at € 383 million.[10] Recently, the Dutch 'Schizofrenie platform' estimated the costs at € 496 million[2], of which € 448 million (90%) were associated with inpatient care (psychiatric hospital, general hospital and surveillance living). Medication costs were estimated at € 15 million (3%). These data suggest that the additional costs of new medications may easily be compensated if such medications achieve a decrease in the number of hospitalisations or institutionalisations.
The scope of this economic evaluation is limited to the direct medical costs from the societal perspective, i.e. the costs of the medication, visits to the psychiatrist and costs associated with residing in specific treatment locations. Direct non-medical costs such as travel expenses of the patient and the family are not considered. In addition, indirect non-medical costs such as productivity losses and juridical costs are not included in this evaluation.

1.3 Aim of this document

This document is written to inform the members of the workgroup who are participating in the development of the multidisciplinary CBO guideline Schizophrenia. In an earlier stage the following question was put forward: can atypical agents be preferred above conventional agents in the treatment of patients with schizophrenia.
In particular this document contains information regarding the cost-effectiveness of these alternatives which may be supportive to make choices in order to make recommendations in the guideline.

1.4 Report setup

The structure of this report is as follows. In chapter 1 all estimates and assumptions that form the model input are presented and justified. Chapter 1 reports the results of the simulations and the accompanying sensitivity analysis. In chapter 1 conclusions are drawn and the results are discussed. The detailed results of the univariate sensitivity analyses and the subgroup analyses are presented in the appendix.

2 Methods

This disease progression model was developed to provide numerical estimates of the expected costs and effects of different treatment strategies by combining knowledge about epidemiology, compliance, treatment patterns, the interaction between patient characteristics and treatment, and knowledge about the costs and effects of individual therapies.
Several articles have been published using models for schizophrenia.[5,6,7] Without exception these concerned Markov-chain models in which the disease was broken down into a number of disease states that had a direct link to estimates about costs and effects. Most often, these models started with a homogeneous cohort of 'average' patients. By using transition-probabilities it was calculated how many people moved from one health state to another at discrete time points. Models of this type have several disadvantages. In real life the transitions that patients make, depend on what has happened to that patient in the past. To implement such dependency in a Markov-chain often requires an impracticably large number of health states and or transition probabilities. Additionally, one may need many models when one wants to take account of the heterogeneity of a patient population. Most notably, such models do not reflect the psychiatrist's everyday practice.
It is aimed to circumvent the drawbacks of the previously build Markov-chain models for schizophrenia by using a discrete event simulation model. This approach implies that one doesn't start with a whole cohort of patients using average probabilities for the whole group. Instead individual patient histories are simulated with patient-specific probabilities. Moreover, there is no direct, average, link between being in a given health state but there are individualised relations between the events in a patient's life and the expected costs and effects.

2.1 Data collection

Previously this model was used to estimate the cost and effects of a long-acting atypical formulation over a five year period in the Netherlands versus a conventional depot and an oral atypical formulation. Consequently, information on treatment alternatives, transition-probabilities, assumptions, model structure and health care utilisation were already derived during this process from literature and from a panel of local experts on psychiatric diseases. The procedure of assembling the expert panel and the way consensus was reached is described below.
Dr. G. van Aalst was involved from the start of the project and helped to develop a first concept model. This model was described in a document containing questions about the structure of the model. The Dutch office of Janssen Cilag has an expert panel of psychiatrists which periodical assemble consisting of: P. Dries, Prof. dr. R. Kahn, J. Oolders, Prof. dr. J van Os and R. de Vries. The document was sent to the members of this panel and during a meeting the model was presented and discussed. The model was adapted on the basis of what was learned during the meeting and more specific questions were included in the document. Hereafter, the following experts were again interviewed with the help of the adapted document (containing a questionnaire): G. van Aalst, P. Dries, Prof. dr. J. van Os, dr. L. de Haan and L. Perquin. Moreover, Prof. dr. J. Urquhart was interviewed who is known for his specific knowledge on the subject of compliance. Each expert was interviewed individually, guided by the questionnaire, and was asked to evaluate the presented treatment alternatives, the model structure, the underlying assumptions and all estimates concerning transition-probabilities and resource utilisation. Furthermore, the experts were invited to provide information that they considered relevant in the development of the model and to discuss the results based on their clinical experience and knowledge of the literature. All estimates were implemented in the model and the results were

summarised in a report. This was sent to the experts to, once more, discuss the estimates and the results. Based on the final comments of the experts, some minor changes were made, and the report was finalised.

2.2 Modelling process in steps

The model was originally designed to simulate the histories of schizophrenic patients from their first episode at the age of onset until death. For its current purpose it was decided, guided by the expert panel, to limit the time horizon to five years. Additionally, patients enter the model at the moment they visit a psychiatrist for the treatment of a recurring episode. The model features two types of variables: 1) patient characteristics, which differ per patient and are fixed over time, and 2) time-dependent variables, which depend on the patient characteristics and change in time. The actual running of the model is characterised by four steps.

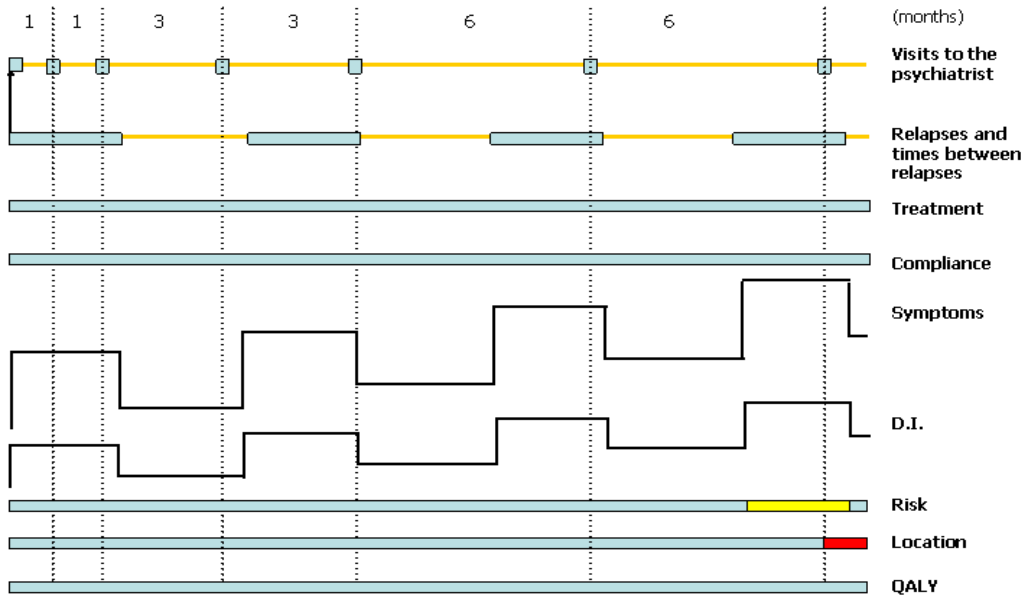
2.2.1 Step 1 Defining the relevant patient characteristics

The model simulates the histories of individual patients assuming certain treatment strategies. Subsequently, patient histories are assumed to depend on a number of baseline patient characteristics. The characteristics considered in the model are patient profile, severity, life expectancy, age, gender, probability of side effects and the 'potential to present a risk to society'. In order to account for the effects of these characteristics, the latter are determined per patient by random draws from predefined distributions at the beginning of a simulation run.

2.2.2 Step 2 Simulating a patient's history

A patient's disease progression is characterised by a number of variables that may change in time. These variables are the health state (being 'in relapse' or 'between relapses'), visits to the psychiatrist, treatment, compliance, symptoms, disorganization, risk to society, QALY and location. All time-dependent variables can be visualized on separate timelines that start at the same point in time and also end at the same point in time (Figure 2). The core timelines - indicated by the first two horizontal lines - are those that represent the alternating health states and the visits to the psychiatrists. The dependencies of the time dependent variables are presented in Table 1.

Figure 2 Model time lines



A patient enters the model when he visits the psychiatrist because he suffers from a relapse. At this visit the psychiatrist draws up a visiting scheme. Every time the psychiatrist sees the patient he will re-evaluate the patient's treatment and location. Furthermore, at each visit the psychiatrist will score the patient's symptoms on the Positive And Negative Symptoms Scale (PANSS). At any time (both during relapses and in the time between relapses) a patient can decide not to comply with his medication and to stop taking any next dosing.
The main strength of this type of modelling is that a patient's history is a determinant of future events.

Table 1 presents an overview of these dependencies. They will be described in more detail in the subsequent paragraphs.

Table 1 Overview of dependencies

Variable outcome	Depends on
Visits to the psychiatrist	Treatment switch Hospitalisation Number of relapses between visits
Relapses and times between relapses	Treatment Compliance Patient profiles Severity
Treatment	Number of relapses Side effects Current treatment
Compliance	Treatment Location Health state (in relapse or in between relapse)
Symptoms	Health state (in relapse or in between relapse) Duration relapse Treatment Compliance Patient profile
Disorganisation index (D.I.)	Number of hospitalisations PANSS
'Risk (to society)'	Potential risk PANSS
Location	Disorganization. Current location Risk to society
QALY	PANSS

2.2.3 Step 3 Calculation of the costs and effects per patient

The model registers how long a specific antipsychotic treatment was used in every patient, the number of visits that were made and the total time each patient has been 'in relapse' and 'between relapses'. Finally, the time is registered that patients spend in the various locations. The direct medical costs per patient in each treatment strategy are subsequently calculated by linking the registered information with the unit costs of medication, the locations where the patient has been treated and the number of psychiatrist visits. Expected costs and effects are presented with and without discounting.

2.2.4 Step 4 Calculation of the mean costs and effects of the patient population

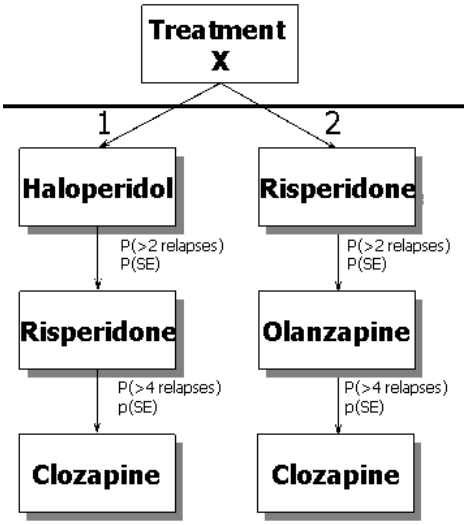
When the costs and effects per treatment strategy are calculated and registered for all individual patients, the model calculates the mean costs and mean effects per treat-

ment strategy. Additionally, estimates are obtained of the distributions of costs and effects, reflecting the individual differences in the patient population.
The model was built using Microsoft© Excel and @-Risk 4.5 by Palisade.

2.3 Comparators

The guidelines in the Dutch 'Farmacotherapeutisch Kompas' suggests that treatment should start with oral conventional formulations (e.g. haloperidol).[11] If negative symptoms prevail or if treatment with a conventional antipsychotic in the lowest dosing leads to adverse effects (e.g. EPS) treatment may be switched to an atypical. In case the treatment response is still not optimal, failure may be attributable to poor compliance. In that case, it is advised to consider a depot formulation (usually injected by a physician).
In current clinical practice, physicians have two main treatment options for the general schizophrenic population: 1) to remain treating patients with oral conventional formulations, and 2) to switch to an oral atypical formulation. Both options should be compared. Therefore the comparison, as outlined in Figure 3 (where the arrows represent treatment switches due to either relapses or side effects) is made for the general population. More specific populations are addressed in the subgroup analyses.

Figure 3 Treatment strategies



2.4 Fixed patient characteristics

2.4.1 Patient profile and severity

In the Netherlands it is estimated that the proportion of patients who suffer only one episode and who recover completely (see Figure 1) is approximately 16%. It is estimated that 71% suffer multiple episodes, of which 19% recover completely between episodes and of which 52% experience further deterioration after each episode.
It is estimated that approximately 13% is continuously psychotic.[2] Only patients with multiple episodes are considered in this economic evaluation. It is expected that the group that totally recovers after one episode (profile 1) will not need chronic treatment and the continuously psychotic group (profile 4) will predominantly be treated with clozapine. Consequently, the resulting distribution of patients who recover completely between episodes and patients who deteriorate is 25% and 75% respectively.

While the first profile may be considered the best and the fourth the worst, one may also find patients who are more severely and less severely ill within each profile (e.g. less symptoms, shorter relapses, more time between relapses). This patient characteristic is modelled with the so called 'severity index'. This variable can take three values: non severe, medium severe and very severe. Within each profile, the definitions are chosen in such a way that 10% is in the non-severe group, 80% in the medium severe group and 10% in the very severe group.

2.4.2 Age, gender and life expectancy (survival)

It is assumed that there is no difference in the percentage of females and males suffering from schizophrenia. Consequently, there is a 50% chance in the model that the considered patient is a man and a 50% chance that the patient is a woman.[12]
The evaluation only considers patients that already suffer from schizophrenia and it is estimated that patients enter the model at an average age of 34.4 (± 11.0) years. (The actual age of onset of schizophrenia is lower). After correcting for suicide (with a lifetime probability of 11%[2]) the average life expectancy is estimated at 61 years for males and at 65 years for females.[13]

2.4.3 Side effects

The probabilities that a patient will experience side effects due to one of the therapies are modelled as fixed patient characteristics. The model considers agranulocytosis, Tardive Dyskinesia (TD), Extrapyramidal Symptoms (EPS), sedation, and weight gain. Table 2 presents the estimated probabilities for the treatments under consideration. For example, it is estimated that a patient who is treated with haloperidol has a 17.6% chance of suffering from EPS, 2.7% for TD, 25.0% for sedation and 10.0% for weight gain.
There are few clinical trials in which haloperidol, olanzapine and risperidone have been compared for safety. Therefore, the EPS incidences of haloperidol and risperidone were estimated with the help of the Csernansky trial. The EPS incidence of olanzapine was estimated with the help of the relative risk on EPS while treated with haloperidol, as reported by Csernansky compared to Tollefson *et al.* [4,14]

Table 2 Probabilities of side effects

	EPS [4,14]	**TD**[4]	**Agranulocytosis** [15]	**Sedation (CNOMSS)**[16]	**Weight gain** [17]
haloperidol	0.176	0.027	0.00	0.250	0.100
risperidone	0.090	0.006	0.00	0.070	0.120
olanzapine	0.070	0.006	0.00	0.140	0.320
clozapine	0.000	0.000	0.01	0.270	0.450

The incidence of TD with risperidone and olanzapine are estimated not to differ (there are very few comparative long-term safety trials from which a difference can be derived). The estimates concerning the incidences of sedation associated with the different treatments were based on the CNOMSS database.[16]

2.4.4 'Potential risk'

From the experts it was learned that decisions about where to treat a patient (location) was highly influenced by whether the psychiatrist considers the patient to present a significant risk to oneself and others. Key risk factors are: being male, young, low social economic class, history of previous violence, substance abuse, the presence of acute psychotic symptoms, and specifically certain types of delusions. [18]
To model this, the variable 'risk' is introduced, which depends on the fixed patient characteristic 'Potential risk'. The relation between potential and actual risk is outlined

in section 2.5.6. Guided by the expert panel it is estimated that 30% of the male patients and 7.5% of the female patients have the potential to present a risk to society.

2.5 Variables changing in time

2.5.1 Visits

Patients enter the model at a visit to the psychiatrist, while suffering a relapse. Based on the interviews with the expert panel it was modelled that a subsequent visit to the psychiatrist would be planned one month after initiating treatment. Hereafter, the following visits are planned with intervals of one month, two months, two months and subsequently at a six months interval. This schedule is restarted after each treatment switch, after each stay in a hospital and when a patient has suffered too many relapses. It is modelled that the patient will visit the psychiatrist before the scheduled visit when he has experienced two new relapses since his last visit to the psychiatrist. Additionally, it is modelled that when a patient is referred to a hospital that he will stay there for a fixed period. In the current model the mean duration of hospitalisation of 62.7 days was used, as described in the RODOS report for the Netherlands.[19]

2.5.2 Health state and PANSS

A second core variable of the model is the health state of a patient, defining whether the patient is in a psychotic episode (relapse) or not. The health state can take two values: 'between relapses' and 'in relapse'.
Unless mentioned otherwise the estimates mentioned in this paragraph are based on expert opinion. The length of time between relapses (TBR) is drawn from a distribution, of which the parameters are dependent on the patient profile, severity, the treatment that is actually taken and compliance. Csernansky *et al.*, found that patients who are treated with risperidone or haloperidol were free from relapses for approximately 15 and 13 months respectively.[20] Based on the latter, it was concluded that the occurrence of relapses is delayed by risperidone relative to haloperidol. Additionally, this is assumed to be a 'class-effect'. Further, it was estimated that, when patients do not take any medication that the relapse risk increases with a factor 4.3 in comparison to haloperidol and with a factor 5 in comparison to atypicals.[21,11,22]

Very little data are available on the effect of treatment on the duration of a relapse. Therefore, in accordance with the expert panel, the duration of a relapse is assumed to be independent of the treatment.

The PANSS score is used as the main estimator for the seriousness (symptoms) of a patient's condition in the model. It may change in time taking values between 30 and 210. Guided by the expert panel it is modelled that the PANSS score depends on the patient's profile, health state, duration of the relapse, the treatment and compliance. For example, patients who are in relapse will on average have a higher PANSS score than patients who are in between relapses. Also guided by the expert panel it is estimated that relapses with a long duration increase the PANSS score more than a relapses with a short duration. Additionally, it is estimated that atypical agents reduce the PANSS more effectively than conventional formulations, based on the evaluations from the Dutch expert panel, Csernansky *et al*., Bouchard *et al.*, Bondolfi *et al*., Geddes *et al.* and Davis *et al.*[3,4,23,24,25,26] Moreover, it is estimated that the PANSS rises back to the no-treatment level as soon as the patient becomes non-compliant.
As the PANSS score and the duration of the relapses and the times between the relapses differ per patient profile, a discussion follows of their estimates per patient profile.

2.5.2.1 Estimates of total recovery patients

Figure 4 visualizes a typical history of a total recovery patient with medium severity. The picture is determined by four parameters: the PANSS in between relapses, the PANSS during relapses, the time between relapses (TBR) and the duration of the relapses (DR).
For the medium severe patient, it is estimated that the patient has a baseline PANSS score, drawn from a Pert distribution (a truncated beta-distribution defined by its upper and lower limit and its most likely value) with an average of 60. During an untreated relapse, the PANSS rises to 102. The relapse PANSS score is estimated to decrease with 11% by conventional antipsychotics and with 17% by atypical antipsychotics. The relapse lasts on average 5 months (drawn from a Weibull distribution), after which an event-free period starts. The length of this event-free period is also drawn from a Weibull distribution with an average of 13.3 months when treated with a conventional and 15.4 months when treated with an atypical. When the patient is non-compliant, these durations are reduced with a factor 4.3 when treated with conventional formulations and with a factor 5 when treated with atypical formulations to 3.1 months. [21,11 22] The corresponding estimates for non-severe and very severe patients are presented in Table 3 and Table 4.

Figure 4 PANSS score and health states

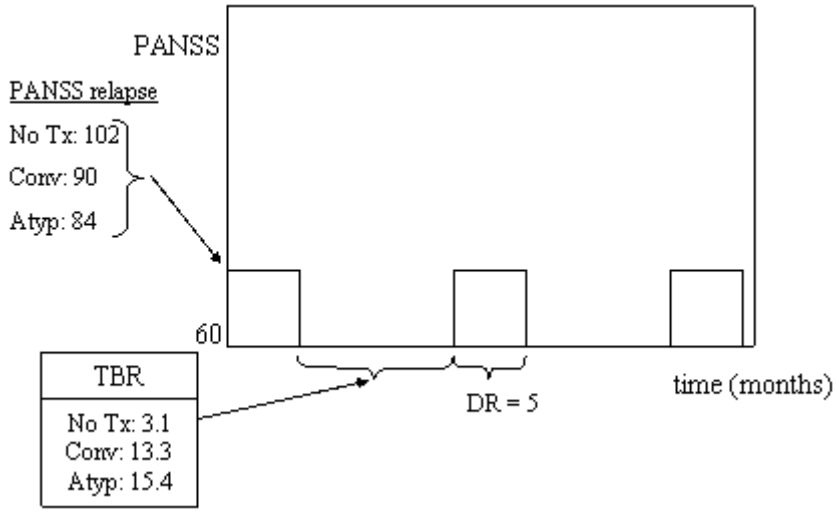


Table 3 PANSS during treatment

Treatment	Non severe	Medium severe	Very severe
No treatment	77	102	118
Conventional agents	68	90	105
Atypical agents	64	84	98
PANSS between relapses	60	60	60

Table 4 Times of and between relapses

	Non severe	Medium severe	Very severe
TBR Conventional	15.4	13.3	12.0
TBR Atypical	17.0	15.4	13.9
TBR Non Compliant[21]	3.5	3.1	2.8
Duration of relapse	2	5	7

2.5.2.2 Estimates of partial recovery patients

Figure 5 represents the typical history of a partial recovery patient with medium-severity of illness. When the patient is not treated during his first relapse, the PANSS score is on average 144. A patient who is treated with an atypical will have a PANSS decrease of 17% relative to no treatment, and an 11% decrease with conventional medication. After the relapse, the patient does not return to the baseline PANSS score. The recovery is only partial and the decrease in medium-severe patients is 30 points. The time until a next relapse is once again drawn from a Weibull distribution with an average of 11.3 months when treated with a conventional and with an average of 13.1 months when treated with an atypical. When the patient is non-compliant, these durations are reduced with a factor 4.3 when treated with conventional formulations and with a factor 5 when treated with atypical formulations to 2.6 months. [21,11] [22] It is calculated that the PANSS score of the second relapse is on average 168 points when a patient is not treated and the decrease due to treatments is similar as in the first relapse.
The corresponding estimates for non severe and very severe partial recovery patients are presented in Table 5 and Table 6.

Figure 5 PANSS and health states

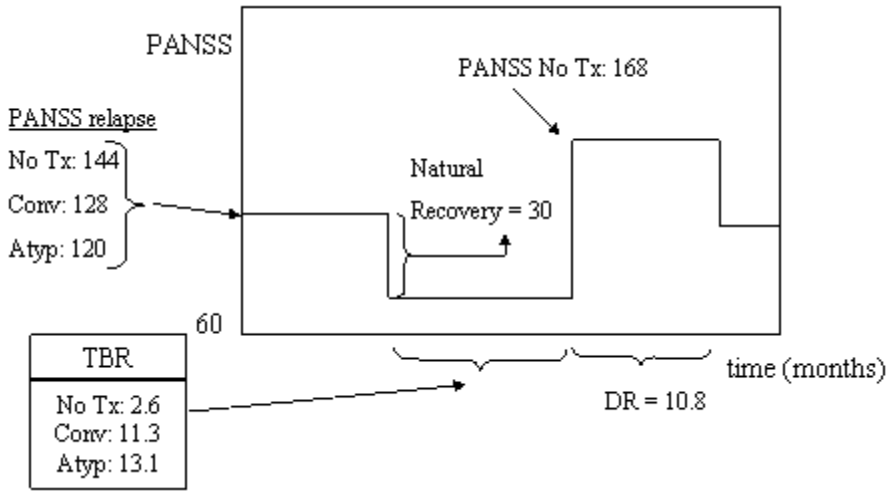


Table 5 PANSS during Tx

Treatment	Non severe	Medium severe	Very severe
No treatment (1st relapse)	138	144	150
Conventionals (1st relapse)	123	128	134
Atypicals (1st relapse)	115	120	125
Natural recovery	$PANSS_{during\ relapse}$-40	$PANSS_{during\ relapse}$ –30	$PANSS_{during\ relapse}$ -20
PANSS NT (2nd relapse)	146	168	190

Table 6 Times of and between relapses

	Non severe	Medium severe	Very severe
TBR Conventional	12.5	11.3	10.2
TBR Atypical	14.4	13.1	11.8
TBR Non-Compliant [21]	2.9	2.6	2.4
Duration of relapse	9.6	10.8	12.0

2.5.3 Treatment

The treatment variable identifies the treatment that is prescribed to the patient at each moment in time. The treatment is re-evaluated at each visit to the psychiatrist. It is assumed that the psychiatrist may decide to switch medication when a patient suffered more than a fixed number of relapses on a medication or when the patient suffered from side effects. Which treatment the psychiatrist subsequently prescribes, is dictated by the scenarios as described in Figure 3.
Each scenario contains three medications that are subsequently prescribed after that the former medication has not been successful in terms of either the occurrence of side effects or the prevention of relapses. However, psychiatrists may not always decide to switch treatment when a patient suffered from too many relapses or after a side effect has occurred. Therefore, these decisions are modelled by probabilities. The probability of switching is estimated to be 100% in case of agranulocytosis and tardive dyskinesia. If a patient suffers EPS due to treatment with a conventional, there is a 53% estimated probability that the psychiatrist will change the medication to olanzapine (and consequently a 47% chance that the patient remains treated with a conventional). If EPS occurs during atypical medication, this probability is 12%. When sedation occurs, the estimated probabilities of switching are 35% in both conventional and atypical medication. Moreover, according to the expert panel, psychiatrist will switch treatment with a probability of 47% in case of weight gain during atypical treatment. Contrarily, they estimated this probability to be zero when the patient is receiving conventional treatment. Further, it is estimated that when a patient suffers more than two relapses during a specific treatment that psychiatrists decide to switch the treatment in 90% of the cases.

2.5.4 Compliance

It is estimated that when patients are compliant, they are assumed to take all prescribed dosages and when patients are non-compliant, they are assumed to have stopped taking their medication. Thus, in this model compliance equals persistence and non-compliance equals non-persistence.
The probability that a patient is compliant is estimated to depend on the health state, the treatment and the location. Moreover, when patients in the model decide to be non-compliant, they remain so until their next visit to the psychiatrist. For instance, a patient who is treated in a hospital with an oral atypical has a 0.85 probability to comply and a patient who is treated at home with an oral atypical has a 0.70 probability to comply during episodes (Table 7).

Table 7 Probabilities of compliance during relapse distinguished by treatment and location

During episode	Conventional	Atypical
Home	0.70	0.70
ACT	0.75	0.75
Sheltered living	0.75	0.75
Hospital/Institute	0.85	0.85

The probability that a patient is compliant in between relapses is estimated not to differ between the various atypical agents. Compliance of the conventional agent is estimated to be 5% lower (absolute) in between relapses. For instance, it is estimated that patients, who are treated at home in between relapses with a conventional agent, have a 0.65 probability to be compliant.

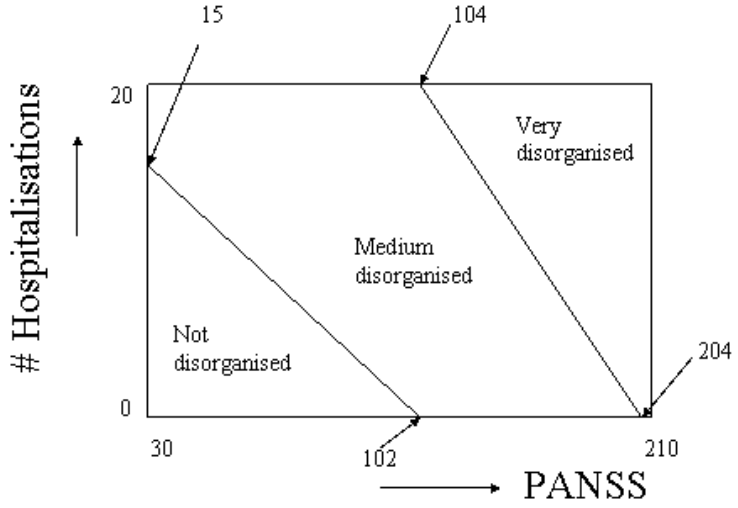
2.5.5 Disorganisation index

Interviews with experts learned that especially the decisions about the location are driven by social and environmental factors. To take these factors into account a variable was introduced indicated as the 'disorganisation-index' (D.I.) reflecting the pa-

tient's ability to take care of himself. In the model the D.I. is introduced as a score ranging from 0 to 10 and is calculated from the PANSS score and the number of previous hospitalisations.[27] This relationship can be graphically represented as presented in figure 6. It is based on the following equation:

$$DI_{(tv)} = (PANSS_{(tv)} + \alpha * \int_{t_0}^{tv} Hosp) / \beta$$, in which α = 5 and β = 31

Figure 6 The disorganisation index



In Figure 6, the lines that are drawn between the coordinates divide the figure in three domains: not disorganised, medium disorganised and very disorganised.

2.5.6 'Risk'

As opposed to the 'potential risk', which is a fixed patient characteristic throughout the model, the variable 'risk' is time-dependent. This variable takes the value 0 for 'no risk' and 1 for 'risk'. A patient who does not have the potential to present a significant risk to oneself or others will remain to present no risk throughout the model. Patients, who do have a potential to present a risk, may also remain without risk to themselves or others. However, it is estimated that they will be considered at a significant risk, when their PANSS score rises above 120 points.[28,29] Below this threshold the patient presents no risk and it is assumed that when a patient returns to values under this threshold that they again present no significant risk to themselves and/or others.

2.5.7 Location

The location of the patient is re-evaluated at each visit to the psychiatrist. The model considers five locations: at home, Assertive Community Treatment (ACT), sheltered living, hospital and institute.
The decision to switch between locations is dependent on the patient's current location, his disorganization index and his current 'risk'.

2.5.7.1 Patients who present a significant risk to themselves and others

The estimated probability that the psychiatrist will move a patient, who presents a significant risk, from one location to the other have been estimated by the expert panel and are presented in Table 8. It is assumed that patients who present a significant risk to society have a very high probability of being referred to a hospital and

subsequently to institutional care. Moreover, patients who present a risk and who are located in an institute have a high probability of staying there.

Table 8 Probabilities of a location switch for patients who are felt to present a significant risk to society

Patients who present significant risk		Previous location				
		Home	ACT	Sheltered living	Hospital	Institute
New Location	Home	0.00	0.00	0.00	0.02	0.02
	ACT	0.00	0.00	0.00	0.00	0.00
	Sheltered living	0.00	0.00	0.00	0.00	0.00
	Hospital	0.80	0.80	0.80	0.40	0.00
	Institute	0.20	0.20	0.20	0.58	0.98

For example, patients who live at home and present a significant risk have a 0.8 probability to be referred to a hospital and a 0.2 probability to be admitted to an institute at each visit to the psychiatrist.

2.5.7.2 Normal patients

For patients who present no significant risk, it is assumed that the probabilities of location switches depend on the current location and the disorganisation index. It is estimated that a patient who is at home with a high D.I. will have a higher probability to be referred to an intensive treatment location than patients who are at home and who are able to take care of themselves (low DI). Patients with a high D.I. who are treated in sheltered living have a higher probability of staying there than patients with a low D.I.
The probabilities of location switches for each domain c.q. level of disorganisation are presented in Table 9 to Table 11.

Table 9 Probabilities of location switch for patients with a low DI

Not disorganised		Previous location				
		Home	ACT	Sheltered living	Hospital	Institute
New location	Home	0.98	0.80	0.05	0.80	0.00
	ACT	0.00	0.20	0.15	0.20	0.00
	Sheltered living	0.02	0.00	0.80	0.00	0.30
	Hospital	0.00	0.00	0.00	0.00	0.00
	Institute	0.00	0.00	0.00	0.00	0.70

Table 10 Probabilities of location switch for patients with a medium DI

Medium disorganised		Previous location				
		Home	ACT	Sheltered living	Hospital	Institute
New location	Home	0.30	0.00	0.05	0.60	0.00
	ACT	0.50	0.80	0.05	0.30	0.15
	Sheltered living	0.10	0.00	0.85	0.05	0.00
	Hospital	0.10	0.20	0.05	0.00	0.00
	Institute	0.00	0.00	0.00	0.05	0.85

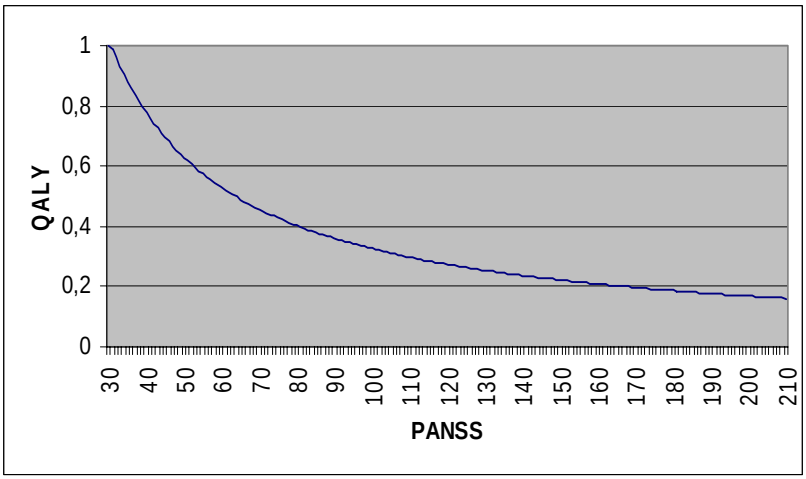
Table 11 Probabilities of a location switch of patients who have a high DI

Very disorganised		Previous location				
		Home	ACT	Sheltered living	Hospital	Institute
New location	Home	0.00	0.00	0.00	0.05	0.00
	ACT	0.20	0.20	0.00	0.35	0.05
	Sheltered living	0.00	0.00	0.50	0.00	0.00
	Hospital	0.20	0.20	0.25	0.00	0.00
	Institute	0.60	0.60	0.25	0.60	0.95

Quality of life

The primary outcomes of the model are in terms of symptoms, the number of psychotic episodes and the duration of being free from psychotic episodes. Some readers may prefer to see the outcomes in terms of quality adjusted life years (QALY's). Here, this is done by linking outcomes in terms of the PANSS with utility values as on the results of the study of Chouinard *et al.* [30] Using this study, the relationship was estimated between the PANSS and the quality index as pictured in Figure 7.

Figure 7 Estimated relationship between PANSS and utility



2.6 Costs

The model considers the medication and location costs (including visits), based on the principle opportunity costs. The estimated unit costs for medication are presented in Table 12 together with the location costs. The medication costs were retrieved from the 'Farmacotherapeutisch Kompas 2002'.[11]

Table 12 Medication and location costs

Medication	Costs (/month)	Location	Costs (/month)
haloperidol	€ 8.89	Home (per outpatient visit)	€ 47.22
risperidone	€ 118.88	ACT (per hour)	€ 42.50 *
Olanzapine	€ 118.88	Sheltered living (per day)	€ 72.27
Clozapine	€ 65.83	*Hospital (per day)	€ 225.49
		**Institute (per day)	€ 189.35

*Admittance in psychiatric ward of general hospital, **Admittance in psychiatric hospital

The location costs are based on Oostenbrink *et al*.[31] These are 1999 costs and were corrected for 2002 using the average health care are specific inflation rates of '96-'00. It was estimated that treatment at home without ACT only compromises outpatient visiting costs and medication costs. With ACT, treatment also includes the nursing costs based on two hours per patient per week. Treatment in a sheltered living location, hospital and institution includes the daily location costs for every day they spend in the location and the medication costs.

2.7 Outcomes

Outcomes are defined by:
- the average cumulative direct medical costs over a five year period per treatment strategy.
- the average cumulative number of relapses that each individual patient suffers per treatment scenario.
- the average cumulative PANSS score calculated as the sum of the annual average PANSS score of the five subsequent years.
- the average cumulative time spent in psychosis per treatment scenario.
- the average cumulative QALY per treatment scenario
- the average incremental costs per time-unit a patient has spent 'in relapse'.
- the average incremental costs per QALY

2.8 Sensitivity analysis

To evaluate to what extent the results depend on the underlying assumptions, univariate sensitivity analyses were carried out. Additionally, it was analysed what the results are if treatment is limited to subgroups.

2.8.1 Univariate analyses

The following estimates were addressed.

2.8.1.1 Patient compliance

First, the sensitivity of the model outcomes to patient compliance was investigated. The difference between the compliance probabilities of the atypical and the conventional agents was reduced to 0% and subsequently increased with twice the base case difference.

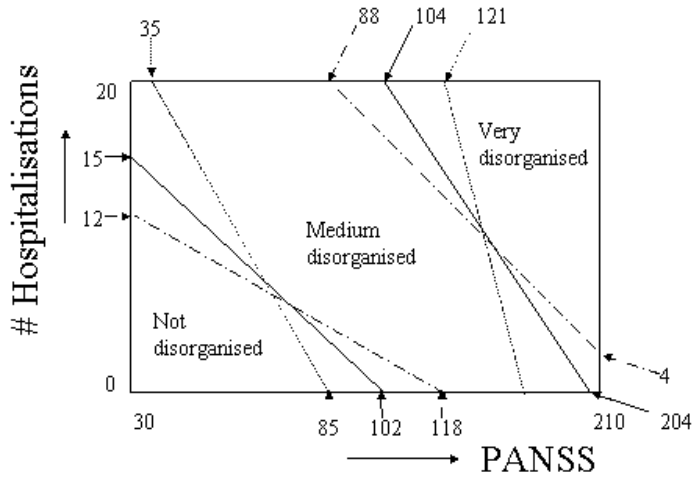
2.8.1.2 The effect of atypical agents on the PANSS

In the base case it was estimated that the reduction in PANSS due to atypical agents was 17%. It is analysed what the results are at 11% and 23%.

2.8.1.3 The disorganisation index

To analyse the sensitivity to the patient's disorganisation index, the criteria that define to which disorganisation group a patient belongs was changed (Figure 8). In the equation that defines the D.I. α was varied from 2.5 to 7.5 and ß was varied between 26 and 36 respectively, thereby increasing the weight of the number of hospitalisations and decreasing the influence of PANSS score on the D.I and visa versa.

Figure 8 Alternative definitions of the DI



2.8.1.4 The potential to present a significant risk

In the base case it was estimated that the potential to present a significant risk is present in 30% of the males and 7.5% of the females. This is varied to 60% and 15% and to 0% for both genders.

2.8.1.5 Unit costs

The costs per location are varied with plus and minus 20%.

2.8.1.6 The PANSS threshold to present a significant risk to society

In the base case an estimate was used of 120 PANSS points for the threshold of actually presenting a risk. It is tested what the effect is of varying this threshold from 110 PANSS points to 130 PANSS points.

2.8.1.7 The PANSS calculation

The PANSS during relapses is calculated by multiplying the duration of the relapse with a specific factor (α) the result of this calculation is added to the PANSS of the previous time between relapses. During this sensitivity analyses α was reduced and increased with 10%. By increasing α, the PANSS during relapses increases and by reducing α, the PANSS during relapses reduces.

2.8.1.8 The probabilities to have side effects

It is analysed what the results are when all medications have the same side effect profile as risperidone such that there are no difference in the side effect profiles of the various medications.

2.8.1.9 Medication switches

It is analysed what the results are when patients will not switch from their first-line medication. Consequently patients remain for 5 years on haloperidol or risperidone.

2.8.1.10 The effect of non-compliance on the time between relapses

In the base case analysis it is estimated that non compliance decreases the time between relapses with a factor 4.33 for conventional agents and with a factor 5 for atypical agents. It is analysed what the results are when this factor is only 2 for conventional agents and 2.3 for atypical agents.

2.8.1.11 The difference between atypical and conventional formulations regarding the time between relapses.

In the base case analysis it is estimated that the time between relapses was 15% shorter on conventional than on atypical agents. It is analysed what the results are when both are equal.

2.8.1.12 The duration of relapse

In the base case each patient profile and each severity group have a specific duration of relapses. It is analysed what the results are when only one fixed duration of relapse of 7 months is used for each patient profile and each severity group.

2.8.1.13 First line Tx

In the base case it is estimated that risperidone is first line treatment in scenario 2. It is analysed what the results are if olanzapine is used as first line treatment option in scenario 2 (Figure 3) instead of risperidone.

2.8.2 Subgroup analyses

The main results consider the whole population without distinguishing between more or less severe patients. It is envisaged that the balance between costs and effects may further improve when the treatment with atypical formulations is aimed at the more severe patients. Therefore, it was analysed what the results are for the non, medium and very severe patients separately, both for the complete recovery patients as well as the partial recovery patients.

2.9 Summary of model estimates

The estimates that were made to design the model-structure and to define the input are summarized in Table 13 and Table 14.

Table 13 Overview of estimated patient characteristics

	Table / Figure	Paragraph	Expert panel	Literature
Gender		2.4.2		12
Age		2.4.2		19
Potential to present a significant risk to society		2.4.4	Yes	
Incidence of side effects	Table 2	2.4.3		4,14,15,16,17
Patient profile	Figure 1	2.4.1		2
Severity index		2.4.1	Yes	
Life expectancy		2.4.2		2,13

Table 14 Overview of estimated time dependent variables

	Table / Figure	Paragraph	Expert panel	Literature
Duration of relapses		2.5.2	Yes	
Time between relapses		2.5.2	Yes	4,11,21,22
Visiting scheme		2.5.1	Yes	
Treatment switch		2.5.3	Yes	
Non-compliance	Table 7	2.5.4 and 0	Yes	32
Location switch		2.5.7	Yes	
Duration of hospitalisation		2.5.1		19
PANSS	Figure 4, Figure 5, Table 3, Table 5	2.5.2	Yes	
Treatment influence on PANSS	Figure 4, Figure 5, Table 3, Table 5	2.5.2	Yes	24,25,33
Disorganisation Index	Figure 6	2.5.5	Yes	27
Present risk to society		2.5.6	Yes	28,29
Costs	Table 12	0		11,31

3 Results

The medical and economic outcomes are generated by running the model for 3000 randomly selected hypothetical patients from the baseline distributions of patient characteristics. In accordance with the Dutch CVZ guidelines, a 4.0% discount rate is used for costs and effects.[34]

3.1 Effectiveness

Figure 9 displays the distribution of the number of relapses a patient suffers in 5 years per treatment scenario. The results show that the atypical formulations are expected to avoid very few relapses compared to the conventional formulations.

Figure 9 Distribution of patients according to relapses

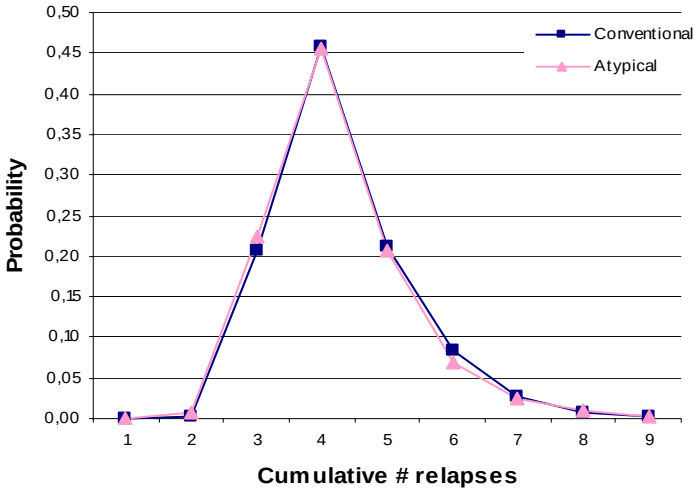


Figure 10 presents the distribution of the cumulative PANSS. This is the sum of the annual average PANSS score in the simulated five years. Starting with an atypical formulation is estimated to result in an increased number of patients with a cumulative PANSS score below 700 and a decreased number of patients with a cumulative PANSS over 700 relative to starting with a conventional formulation. The two peaks are the results of modelling two different populations; the total recovery population and the partial recovery population (see Figure 18).

Table 15 presents the average PANSS score during and in between relapses. Here, it can be seen that starting with an atypical agent reduces the average PANSS score during a relapse and in between relapses compared to starting with a conventional agent.

Figure 10 Distribution of patients according to the cumulative PANSS

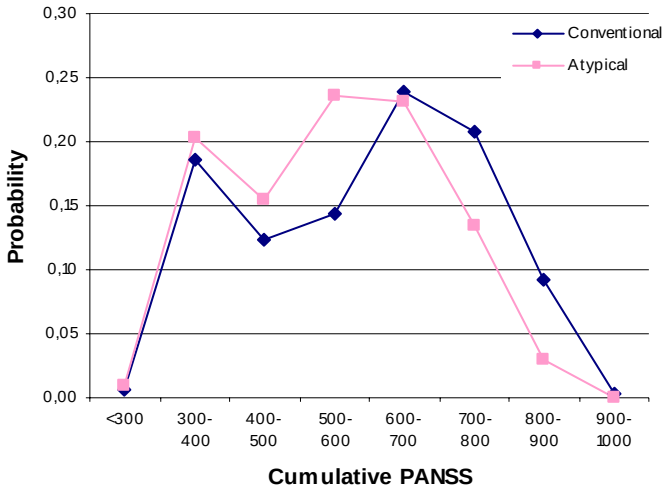


Table 15 Average PANSS distinguished by health state

Average PANSS	Start with conventional	Start with atypical
During relapses	138	130
In between relapses	89	83

Figure 11 presents the distribution of the total time patients are expected to spend in a psychotic episode. It shows that starting with an atypical formulation is estimated to reduce the time in psychosis only slightly.

Figure 11 Distribution of patients according to the time in psychosis

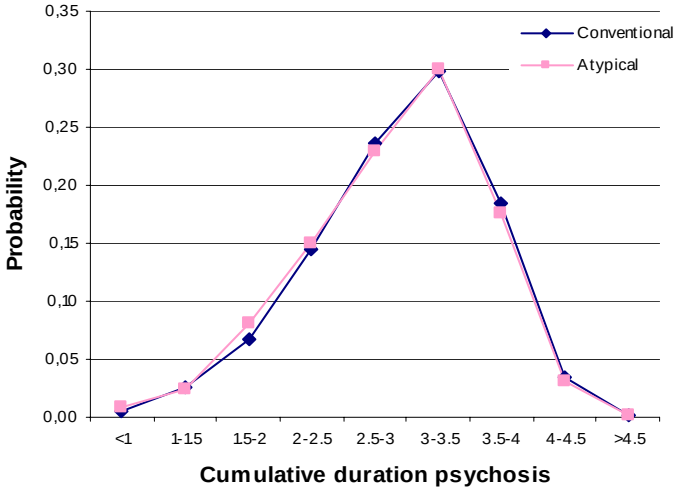
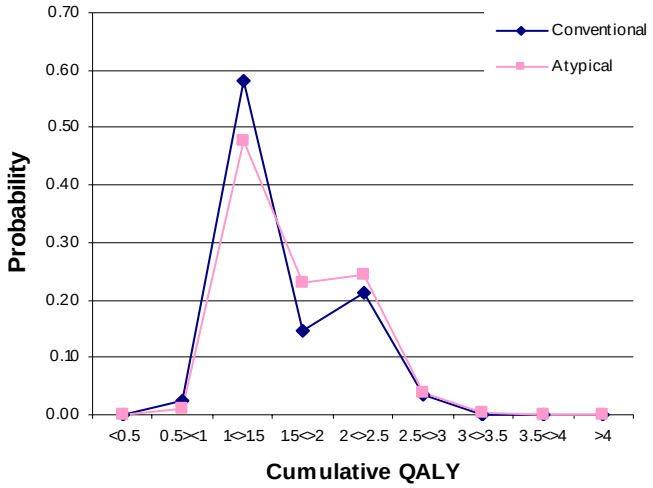


Figure 12 displays the estimated distribution of the cumulative QALY per patient. It is estimated that starting with an atypical increased the cumulative QALY per patient.

Figure 12 Distribution of patients according to QALY



3.2 Costs

Figure 13 shows the estimated distribution of costs per patient. It is estimated that approximately 61% of the patients who start with a conventional have 5-year costs lower than € 65,000 compared with 65% of the patients who start with an atypical formulation. Moreover, it is estimated that 19% of the patients who start with a conventional have 5-year costs higher than € 230,000 compared with approximately 16% of the patients who start with an atypical formulation.

Figure 13 Distribution of cumulative costs per treatment strategy

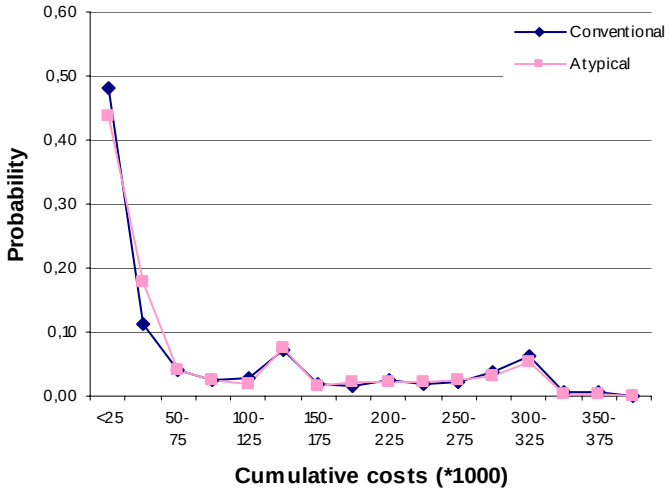


Table 16 displays the contribution of the individual location cost items and the treatment costs to the total medical costs. For instance, the treatment costs of starting with an atypical are € 6,792.

Table 16 Direct medical costs after 5 years

Costs	Start with conventional	Start with an atypical
Medication	€ 3,308	€ 6,792
Home	€ 402	€ 437
ACT	€ 6,184	€ 5,923
Sheltered living	€ 10,486	€ 10,589
Hospital	€ 29,934	€ 29,521
Institute	€ 45,502	€ 35,624
Total	€ 95,817	€ 88,885

3.3 Cost effectiveness

Table 17 shows the average 5-year costs and effects per patient with and without discounting. It is concluded that by starting with an atypical, one is expected to save approximately € 5.977 compared to starting with a conventional. Moreover, starting with an atypical is estimated to decrease the cumulative PANSS and to slightly decrease the number of relapses, the total time spend in psychosis and it is expected to increase the number of QALY's. This combination of negative incremental costs and additional effects would yield a negative cost-effectiveness value. Therefore, no incremental cost-effectiveness ratios are calculated.[35]

Table 17 Estimated cumulative (discounted) costs and effects

	Start with conventional	Start with an atypical
Costs	€ 95,817	€ 88,885
Costs (4% discount rate)	€ 88,366	€ 82,142
# of relapses	4.26	4.24
PANSS	588	551
Years in relapse	2.91	2.90
QALY	1.57	1.66
# of relapses discounted	3.99	3.97
PANSS discounted	545	510
Years in relapses discounted	2.72	2.71
QALY discounted	1.46	1.54

3.4 Treatment

Table 18 presents the expected number of months that patients are treated in an inpatient setting (hospitalisation and institutionalisation) and in an outpatient setting (home treatment, ACT and sheltered living) according to first, second and third line treatment. The total sums up to 59.0 months instead of 60 as a result of the probability to die (e.g. suicide and natural death). Additionally, Table 18 presents the average period that patients are treated with their first line treatment and the percentage of patients that remain on this treatment for the whole period of 5 years. It is seen that patients who start with a conventional spend on average 46.9 months in outpatient settings of which approximately 24.8 months during 1st line treatment. Additionally, these patients spend 12.1 months in inpatient settings of which approximately 4.9 months during 2nd line treatment. Moreover, they remain on average for 30.8 months on first-line treatment and 9.1% of the patients stay for the whole time horizon on a conventional formulation.

Table 18 Expected number of months in in- and out-patient settings and on first line treatment

	Start with conventional	Start with an atypical
Time spend in outpatient setting (months)	46.9	48.7
1st line Tx	24.8	29.2
2nd line Tx	15.9	14.3
3rd line Tx	6.2	5.2
Length of stay in inpatient setting (months)	12.1	10.3
1st line Tx	6.1	5.9
2nd line Tx	4.9	3.5
3rd line Tx	1.1	0.9
Time remaining on first-line treatment (months)	30.8	35.1
% patients remaining of first line Tx	9.1%	10.4%

3.5 Dynamics

Figure 14 shows the probabilities that a patient is treated in a specific location over the modelled five year period for patients who start with a conventional agent. Patients enter the model while treated at home and suffering a relapse. Consequently, after the first month the patients have a high probability to be referred to another location, because they have a high PANSS score and as a consequence a high disorganisation index. From month five to approximately seventeen, there is an increase in patients who are treated at home. The reason for this is that most patients progressed to the 'in between relapses' health state in that period. After month nineteen, the distribution of the patients becomes more stable. It can also be seen that the percentage of patients that are institutionalised increases over time, as the health state of the partial recovery patients deteriorates. Similarly, Figure 15 shows the percentage of patients treated in a specific location when starting on an atypical.
Figure 16 to 17 show the percentage of patients treated with a conventional, risperidone, olanzapine, and clozapine. In the first scenario patients start with a conventional and are subsequently treated with risperidone and clozapine. Approximately 20% of the patients switch immediately to risperidone because they suffer from one or more of the considered side effects. The increased probability of a treatment switch after the eighteenth month is the result of the number of relapses that the patients suffered (psychiatrist switches the patient's medication in 90% of the patients suffering more than two relapses on a medication).

Figure 14 Location distribution: start with a conventional

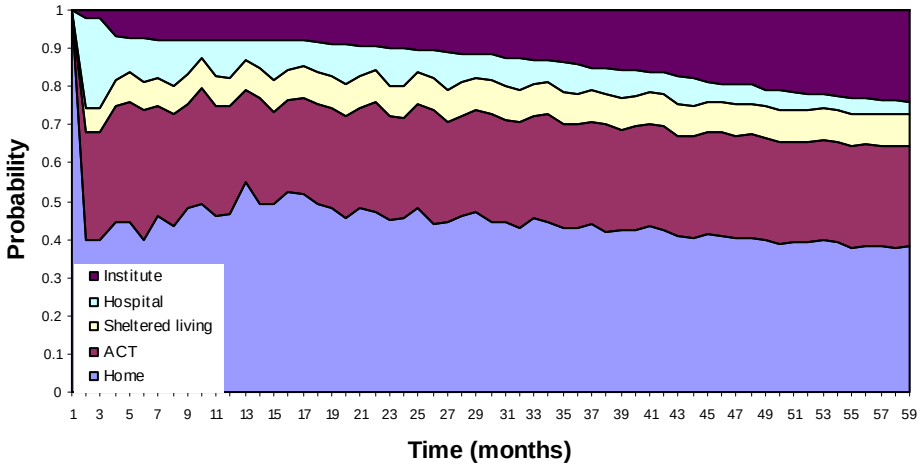


Figure 15 Location distribution: start with atypical agents

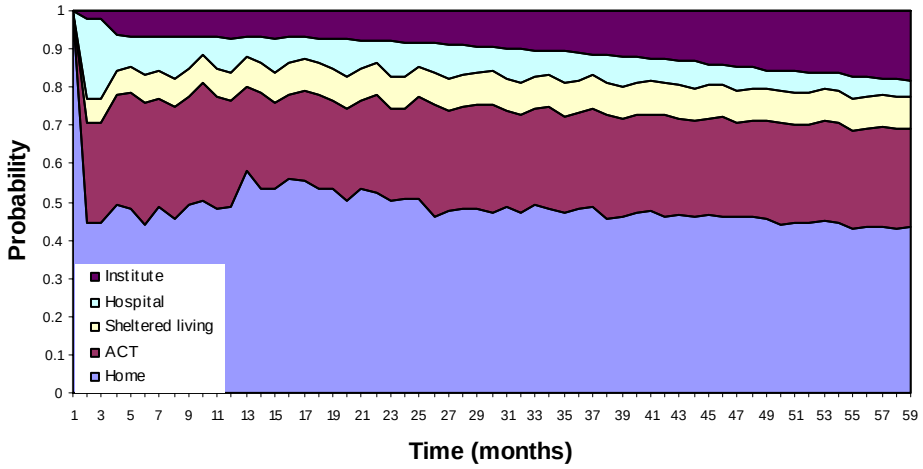


Figure 16 The treatment dynamics of the conventional treatment scenario (1).

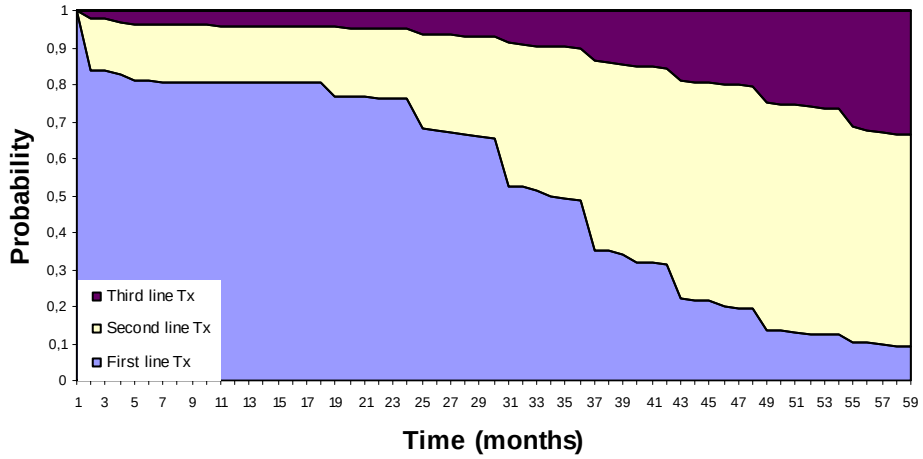
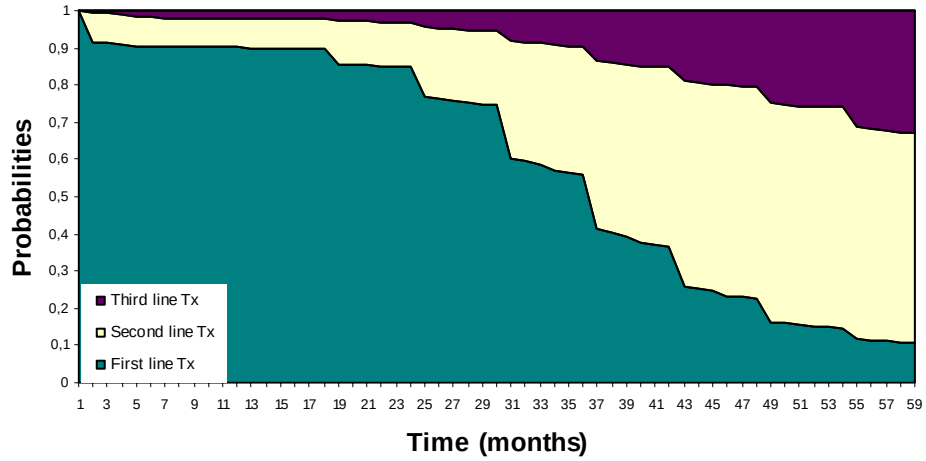


Figure 17 The treatment dynamics of the atypical treatment scenario (2)



3.6 Sensitivity analyses

3.6.1 Univariate sensitivity analysis

In the base case analysis, it was estimated that starting with the atypical formulations increases the effects and decreases the costs. Here, the dependency was analysed of that outcome with respect to the underlying estimates. The detailed results of the univariate sensitivity analyses can be found in appendix 1. Table 19 shows the incremental costs and effects of all sensitivity analyses.
Starting with an atypical is expected to lead to a reduced cumulative PANSS within all the uncertainty margins that are considered here. Additionally, starting with an atypical is expected to lead to no additional or to slightly reduce the number of suffered relapses. This is with the exception of when it is assumed that the compliance probabilities of the conventional and atypical formulations are equal. One might have expected that the atypical formulations would also under these circumstances avoid relapses, as the Csernansky *et al.* showed that risperidone delays the occurrence of relapses compared to haloperidol.[4] The explanation why the results differ from the expectations is bipartite. First, patients who start with a conventional are likely to be switched to an atypical during the five year time horizon (Figure 3). Consequently, the comparison is not five year treatment with an atypical vs 5 year treatment with a conventional. Second, patients who start treatment with a conventional are treated longer in inpatient settings (Table 18) than patients who start with an atypical. Subsequently, as the expensive inpatient settings assure a higher compliance than outpatient settings (Table 7), patients treated with a conventional may have on average a higher probability to be compliant than patients who start with an atypical. Consequently, the difference in suffered relapses is lower than one might have expected and even becomes negative when it is assumed that both antipsychotic formulations have equal probabilities to be compliant. It should be noted that in the base case only a very small difference in compliance probabilities (<5%) is estimated between atypical and conventional formulations, whereas several studies showed that patients are more likely to comply with atypical antipsychotic formulations.[32,36] Additionally, the atypical formulations are almost always considered to be cost saving. However, there are no savings expected when the additional efficacy of atypical agents compared to conventional agents on the PANSS is decreased from 6% to 0%. It should be noted that the estimate of 6% is rather conservative and that a smaller difference is unlikely.[3,26]

Table 19 Effect of sensitivity analyses on incremental discounted outcomes of scenario 1 and 2

Parameters	Ranges*	Incremental savings	Incremental # of re-lapses	Incremental PANSS
Base case analysis		€ 6,224	0.02	35
Compliance	No difference	€ 5,898	-0.03	35
	Twice base case difference	€ 8,343	0.08	40
PANSS reduc-tion atypical agents	0.89	-€ 3,102	0.06	3
	0.77	€15,999	0.01	68
DI	α = 2.5 β =26	€11,545	0.01	36
	α = 7.5 β =36	€ 4,790	0.02	36
Potential risk	♀ = 0 ♂=0	€ 2,883	0.02	35
	♀ = 60% ♂=15%	€ 6,831	0.01	33
Location costs	+20%	€ 8,989	-	-
	-20%	€ 4,823	-	-
PANSS risk threshold	110	€ 6,825	0.03	37
	130	€ 5,412	0.01	36
PANSS calcula-tion	+10%	€ 7,874	0.01	35
	-10%	€ 6,167	0.01	35
pSE, pSwitch→ atyp=conv		€ 7,097	0.00	36
No Tx switches		€ 3,136	0.06	47
Effect nc=2 (4.3 base case)		€ 5,207	0.01	37
TBR atyp=conv		€ 5,713	0.03	36
DR equal (7 months)		€ 8,847	0.03	31
Olanzapine 1st line Tx (scenario 2)		€ 5,026	0.02	35

*nc=non compliance, TBR=time between relapses, pSE=probability on side effect, pSwitch=probability to switch due to a specific side effect ,Tx=treatment, atyp= atypical, conv=conventional

3.6.2 Subgroup analyses

The detailed results of the subgroup analyses can be found in appendix 1. Table 20 presents the incremental results when the model is restricted to subgroups. No savings are expected when treatment is restricted to non-severe total recovery patients. Contrarily, savings are expected when treatment is limited to the medium severe and very severe total recovery patients and patients with partial recovery. It may be noted that the total treatment costs of non severe total recovery patients are approximately € 7,000 and that the probabilities to be hospitalized and to get institutionalized are relatively low.
It is therefore, unlikely, in these groups, that the additional costs of atypical agents can be recouped by savings in a five year horizon.
As there are no cost savings expected when using atypical agents in the non-severe total recovery subpopulation, it may be useful to calculate cost-effectiveness ratios. Here, costs per avoided relapse are estimated at approximately € 21,000 and costs per QALY are estimated at € 223,000.

Table 20 Effect of subpopulation analyses on incremental discounted outcomes of scenario 1 and 2

	Subgroups	Incremental savings	Incremental # of relapses	Incremental PANSS
Base case analysis		€ 6,224	0.02	35
Patient profiles	Total recovery population	€ 160	0.05	5
	Non severe	-€ 2,234	0.10	2
	Medium severe	€ 756	0.07	6
	Very severe	€ 1,469	0.03	7
	Partial recovery population	€ 9,733	0.01	49
	Non severe	€ 9,492	0.01	44
	Medium severe	€ 9,337	0.00	46
	Very severe	€ 10,382	0.00	45

4 Conclusions and discussion

A disease progression model was used to assess the costs and effects of oral atypical formulations in comparison to oral conventional formulations.
In the general population the atypical formulations are dominant compared to a conventional, as they decrease costs and increase effectiveness (Table 17).
The conclusion of dominance is confirmed by the sensitivity analysis, which showed that only when the input parameters take implausible values no cost-savings and incremental effects are expected. Moreover, subgroup analyses showed that further cost benefits may be expected when starting with an atypical is aimed at patients in whom a further deterioration is expected.

4.1.1.1 Validation

In the Netherlands the total direct costs of schizophrenia were estimated at between € 353 and € 454 million of which approximately 80% is spent on inpatient services and between approximately 1.1 and 3% is spent on drugs. [2,9] Moreover, the annual direct costs per patient are estimated at approximately between € 11,046[2] and $ 17,000.[9]
Table 12 displays the contribution of the individual location cost items and the treatment costs to the total medical costs. For instance, in scenario 1 the treatment costs are € 3,308, which is approximately 3.4% of the total direct costs. This is only slightly more than the previously reported 3% by the 'Schizofrenie Platform'. Moreover, in scenario 1 the inpatient costs (day care, hospital and institute) account for approximately 78% of the total costs, this is only slightly more than previously reported.[2,9]
Additionally, the direct cost per patient per year is estimated at approximately € 19,163. This is higher than the previously reported € 11,046 and $17,000.[2,9] The difference can partly be explained by the introduction of the expensive atypical formulations and partly by increasing health care costs over the last eight years.

4.1.1.2 Mechanism of action

Although the structure appears to be complicated there is a rather simple mechanism of action that underlies the expectations. When one compares starting with a conventional to starting with an atypical formulation, the difference is caused by a difference in the effect on the symptoms, a small difference in compliance and a difference in the duration until the next relapse. These effects cause a decrease in the occurrence of symptoms and having fewer symptoms decreases the likelihood of needing more intensive care. Additionally, fewer symptoms are associated with a decreased probability that one becomes disorganised or that one presents a significant risk, again implying a decreased need of more intensive care. Additionally, it is noted that once being treated in a more intensive treatment setting, the likelihood decreases to be treated in less intensive settings and as such, short-term benefits accelerate in the long run.

4.1.1.3 Model simplifications

In the mean time, the model still holds a number of simplifications. Some of those concern the way that non-compliance is modelled. Overall, a patient's drug exposure is dependent on persistence and compliance. Persistence defines whether a patient is taking its medication or not, while compliance is a qualitative measure of the accuracy with which a persistent patient is taking its medication. The majority of patients will have some degree of non-compliance in the sense that they don't take the drugs at a fixed hour every day, sometimes forget a daily dosage or even have a 'drug-holiday' of several days. These omissions may influence the effectiveness of the drug to some

extend, and differentially so between competing agents, but little is known about the quantitative effects of these various degrees of non-compliance for any of the pharmaceuticals used in today's treatment for schizophrenia. It was, therefore, decided to model patients as being either compliant or not, as no data are available and the experts are very reluctant to offer estimates. Consequently, in this model compliance equals persistence and non-compliance equals non-persistence. Naturally, more subtle approaches would have been possible, but it is questionable, with neither data nor expert opinion, that different results would be obtained.
Another simplification is that, in clinical practice, psychiatrists may not only switch treatment because the patient suffers too many relapses or a side effect. Psychiatrists may also switch because the duration of a psychotic episode is too long. Even though treatment will probably reduce the duration of episodes, there is very little data about the effect of treatment on the duration of an episode. Therefore, in accordance with the expert panel, the duration of a relapse is assumed independent of treatment. Consequently, the duration of psychosis could not be implemented as a parameter that influences the patient's treatment.
Further simplification concerns the fact that the number of treatment modalities was limited to three mediations, disregarding changes in dosage and all kinds of combinations.
Moreover, the concept of presenting a risk is defined very loosely, as is the concept of all those other factors such as being disorganised. Additionally, it should be noted that the estimation of the QALY is rather rough, as the study by Chouinard only estimated the QALY's corresponding with three types of patients. Also, in this study the QALY's were estimated by experts, whereas from a societal perspective this is preferably done by general public.
The analysis as carried out here has neglected a number of beneficial effects. The costs of treating adverse events (e.g. EPS), the indirect costs (e.g. costs of the family and costs of the juridical system) have not been included. It is highly likely that including them would have strengthened the conclusion in favour of the atypical formulations.
A major limitation of our study is that the conclusions are based on structured combination of all kinds of data and expectations and that direct data to support the conclusions are lacking. One may also feel that the complexity of the model is a limitation. However, it is felt that this way of modelling captures the disease process much better than Markov Chains. Moreover, it has been surprisingly easy to clarify the model to psychiatrists and it is worthwhile noting that the responses from the individual psychiatrists were surprisingly homogeneous.

4.1.1.4 Conclusion

Even tough the researchers were conservative in all their estimates, the conclusion still indicates that using atypical formulations combines additional effectiveness with cost savings.

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Appendix 1 Sensitivity analyses

This appendix presents more detailed estimates of the results of the sensitivity analysis as reported in 1.1.

Compliance
To analyse the effect of changes in the estimates concerning compliance, two alternative estimates are used, in which the difference between the compliance of the atypical and the conventional agents is was reduced to 0% (1) and subsequently increased with twice the base case difference (2). Table 21 and 22 present the results.

Table 21 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,198	€ 3,391	€ 6,776	€ 6,769
Home	€ 400	€ 402	€ 439	€ 439
ACT	€ 6,435	€ 6,373	€ 5,993	€ 6,066
Sheltered living	€ 10,429	€ 9,857	€ 10,978	€ 9,901
Hospital	€ 31,068	€ 30,780	€ 29,169	€ 27,719
Institute	€ 41,577	€ 45,717	€ 33,222	€ 36,465
Total	€ 93,106	€ 96,520	€ 86,577	€ 87,359

Table 22 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 93,106	€ 96,520	€ 86,577	€ 87,359
Costs (4% discount rate)	€ 85,881	€ 89,066	€ 79,983	€ 80,723
# of relapses	4.22	4.35	4.25	4.27
PANSS	587	589	549	545
Duration relapses (year)	2.88	2.95	2.92	2.89
QALY	1.58	1.57	1.67	1.68
# of relapses discounted	3.95	4.08	3.99	4.00
PANSS discounted	544	546	509	506
Duration relapses (year) discounted	2.69	2.76	2.72	2.70
QALY discounted	1.46	1.46	1.55	1.56

PANSS reduction medication
In the base case, the atypical formulations reduce the PANSS with 17%, while the conventional formulations reduce the PANSS with 11%. It is analysed what the results are when the PANSS reduction of the atypical formulations is subsequently lowered to 11%

and increased to 23%. In both cases, the PANSS reduction of the conventional formulations remains 11%. Table 23 and 24 present the results.

Table 23 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,314	€ 3,290	€ 6,769	€ 6,785
Home	€ 392	€ 404	€ 397	€ 472
ACT	€ 6,442	€ 6,148	€ 6,348	€ 5,490
Sheltered living	€ 10,470	€ 10,975	€ 10,283	€ 11,211
Hospital	€ 30,953	€ 28,907	€ 30,728	€ 24,964
Institute	€ 45,262	€ 45,107	€ 45,564	€ 28,477
Total	€ 96,833	€ 94,831	€ 100,089	€ 77,400

Table 24 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 96,833	€ 94,831	€ 100,089	€ 77,400
Costs (4% discount rate)	€ 89,248	€ 87,544	€ 92,350	€ 71,546
# of relapses	4.29	4.30	4.23	4.29
PANSS	600	577	597	504
Duration relapses (year)	2.91	2.94	2.87	2.93
QALY	1.55	1.61	1.55	1.82
# of relapses discounted	4.02	4.03	3.96	4.02
PANSS discounted	556	535	553	468
Duration relapses (year) discounted	2.72	2.74	2.68	2.73
QALY discounted	1.44	1.49	1.44	1.68

DI calculation

To analyse the effect of changes in the estimates concerning the disorganisation index, two alternative estimates are used. The first, with α=2.5 and ß=26, reflect a situation in which the effect of the PANSS score on the DI and therefore the location switches is increased, compared to the number of hospitalisations.

The second, with α=7.5 and ß=36, reflects a situation in which the effect of the number of hospitalisations on the DI and therefore the location switches is increased compared to the PANSS. Table 25 and 26 present the results.

Table 25 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,317	€ 3,355	€ 6,806	€ 6,773
Home	€ 338	€ 460	€ 374	€ 502
ACT	€ 6,428	€ 5,345	€ 6,465	€ 4,735
Sheltered living	€ 9,977	€ 9,052	€ 10,569	€ 9,093
Hospital	€ 31,656	€ 27,416	€ 31,985	€ 26,181
Institute	€ 74,566	€ 35,735	€ 57,333	€ 28,959
Total	€ 126,282	€ 81,363	€ 113,532	€ 76,243

Table 26 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 126,282	€ 81,363	€ 113,532	€ 76,243
Costs (4% discount rate)	€ 116,103	€ 75,260	€ 104,558	€ 70,470
# of relapses	4.21	4.29	4.21	4.27
PANSS	585	591	546	552
Duration relapses (year)	2.89	2.94	2.88	2.92
QALY	1.58	1.56	1.68	1.66
# of relapses discounted	3.95	4.02	3.94	4.00
PANSS discounted	543	547	507	512
Duration relapses (year) discounted	2.70	2.74	2.69	2.72
QALY discounted	1.46	1.45	1.55	1.54

Risk

To analyse the effect of changes in the estimates concerning patient's potential to present a significant risk, two alternative estimates are used in which first a zero probability to present a significant risk for males and females is assumed and second in which males have a 0.6 and females a 0.15 probability to present a significant risk to self and/or society. Table 27 and 28 present the results.

Table 27 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,366	€ 3,272	€ 6,770	€ 6,796
Home	€ 424	€ 371	€ 467	€ 407
ACT	€ 7,265	€ 5,348	€ 6,673	€ 5,082
Sheltered living	€ 11,104	€ 9,376	€ 11,305	€ 10,573
Hospital	€ 21,595	€ 39,429	€ 23,453	€ 36,013
Institute	€ 22,578	€ 70,575	€ 13,452	€ 57,457
Total	€ 66,331	€ 128,372	€ 62,120	€ 116,329

Table 28 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 66,071	€ 128,372	€ 62,120	€ 116,329
Costs (4% discount rate)	€ 60,940	€ 118,622	€ 57,250	€ 107,551
# of relapses	4.31	4.26	4.29	4.24
PANSS	598	590	553	548
Duration relapses (year)	2.96	2.92	2.92	2.89
QALY	1.55	1.56	1.66	1.67
# of relapses discounted	4.04	4.00	4.02	3.97
PANSS discounted	554	547	512	508
Duration relapses (year) discounted	2.76	2.73	2.73	2.70
QALY discounted	1.44	1.45	1.54	1.55

Location costs

To analyse the effect of changes in the location costs, two different estimates are used, in which the location costs are subsequently reduced and increased with 20%. As only costs are varied, the effects will not change compared to base case. Consequently, here, only cost figures are presented (Table 29).

Table 29 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,308	€ 3,308	€ 6,792	€ 6,792
Home	€ 322	€ 483	€ 349	€ 524
ACT	€ 4,947	€ 7,421	€ 4,738	€ 7,108
Sheltered living	€ 8,389	€ 12,584	€ 8,471	€ 12,707
Hospital	€ 23,947	€ 35,921	€ 23,617	€ 35,426
Institute	€ 36,401	€ 54,602	€ 28,499	€ 42,748
Total	€ 77,316	€ 114,319	€ 72,466	€ 105,304

PANSS risk threshold

To analyse the effect of changes in the estimates concerning the PANSS threshold at which patients who have the potential to present a risk actually present a significant risk, two alternative estimates are used in which the PANSS threshold is estimated at 110 and subsequently at 130. The results are presented in Table 30 and 31.

Table 30 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,292	€ 3,289	€ 6,777	€ 6,766
Home	€ 392	€ 405	€ 426	€ 438
ACT	€ 6,286	€ 6,639	€ 5,949	€ 6,245
Sheltered living	€ 9,527	€ 10,069	€ 10,058	€ 10,039
Hospital	€ 32,398	€ 30,555	€ 30,692	€ 28,771
Institute	€ 49,758	€ 39,488	€ 40,179	€ 32,144
Total	€ 101,653	€ 90,445	€ 94,080	€ 84,402

Table 31 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 101,653	€ 90,445	€ 94,080	€ 84,402
Costs (4% discount rate)	€ 93,892	€ 83,343	€ 87,067	€ 77,931
# of relapses	4.27	4.26	4.24	4.26
PANSS	589	591	549	552
Duration relapses (year)	2.93	2.94	2.90	2.93
QALY	1.57	1.56	1.67	1.66
# of relapses discounted	4.00	4.00	3.97	3.99
PANSS discounted	546	548	509	512
Duration relapses (year) discounted	2.73	2.75	2.71	2.73
QALY discounted	1.46	1.45	1.55	1.54

Calculation PANSS

To analyse the effect of PANSS score, two alternative estimates are used in which the α's of the calculation of the PANSS score of the total recovery and partial recovery patients are subsequently reduced and increased with 10%. By doing so, the average levels of the patients PANSS are reduced and subsequently increased. The results are presented in Table 32 and 33.

Table 32 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,585	€ 3,334	€ 6,768	€ 6,791
Home	€ 435	€ 370	€ 469	€ 403
ACT	€ 5,956	€ 6,424	€ 5,643	€ 6,275
Sheltered living	€ 10,573	€ 10,319	€ 10,714	€ 10,580
Hospital	€ 28,208	€ 30,708	€ 26,233	€ 29,283
Institute	€ 35,522	€ 56,390	€ 27,576	€ 45,514
Total	€ 84,279	€ 107,546	€ 77,403	€ 98,846

Table 33 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 84,279	€ 107,546	€ 77,403	€ 98,846
Costs (4% discount rate)	€ 77,766	€ 98,979	€ 71,600	€ 91,105
# of relapses	4.28	4.26	4.27	4.24
PANSS	551	622	513	585
Duration relapses (year)	2.92	2.90	2.92	2.90
QALY	1.66	1.50	1.77	1.59
# of relapses discounted	4.01	3.99	4.00	3.97
PANSS discounted	511	576	476	542
Duration relapses (year) discounted	2.73	2.70	2.72	2.70
QALY discounted	1.54	1.40	1.64	1.47

Side effects and switches

To analyse the effect of the probabilities of the occurrence of side effects and the probabilities to switch due to suffered side effects, one alternative estimate is used in which the incidence of the considered side effects and the probabilities to switch due to a suffered side effect of the conventional agents are assumed to be equal to the base case probabilities of risperidone.
Secondly, it is analysed whether the results are sensitive to medication switches. Therefore, it is assumed that patients will not switch from their first-line medication. The results of these assumptions are presented in Table 34 and 35.

Table 34 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 2,729	€ 525	€ 6,794	€ 7,120
Home	€ 400	€ 337	€ 436	€ 371
ACT	€ 6,292	€ 6,411	€ 5,938	€ 5,907
Sheltered living	€ 10,565	€ 10,751	€ 11,282	€ 10,768
Hospital	€ 30,810	€ 31,262	€ 29,755	€ 30,707
Institute	€ 45,474	€ 43,470	€ 34,196	€ 34,391
Total	€ 96,271	€ 92,756	€ 88,400	€ 89,264

Table 35 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 96,271	€ 92,756	€ 88,400	€ 89,264
Costs (4% discount rate)	€ 88,730	€ 85,535	€ 81,633	€ 82,399
# of relapses	4.25	4.31	4.25	4.24
PANSS	589	604	549	552
Duration relapses (year)	2.93	2.95	2.91	2.92
QALY	1.57	1.53	1.67	1.66
# of relapses discounted	3.98	4.03	3.98	3.97
PANSS discounted	545	558	509	511
Duration relapses (year) discounted	2.73	2.75	2.71	2.72
QALY discounted	1.46	1.42	1.54	1.54

Time between relapses

In the base case it is assumed that when a patient is non-compliant that the time between relapses (TBR) of this patient is reduced with a factor 4.3 for the conventional agents and a factor 5 for the atypical agents. To analyse the effect of the TBR reduction, two alternative estimates are used in which the base case TBR reductions of 4.3 and 5 are reduced to 2 and 2.3 respectively. By doing so, the times between relapses of non-compliant patients are increased.

Second, the effect of the differences in times between relapses between atypical medication and conventional medication is estimated by assuming no difference in time between relapses.

Table 36 and 37 present the results.

T**able 36 Direct medical costs after 5 years**

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,050	€ 3,384	€ 6,860	€ 6,720
Home	€ 394	€ 401	€ 429	€ 434
ACT	€ 6,232	€ 6,473	€ 5,893	€ 6,080
Sheltered living	€ 11,265	€ 9,933	€ 11,294	€ 10,521
Hospital	€ 28,985	€ 30,152	€ 28,458	€ 28,335
Institute	€ 41,785	€ 46,349	€ 32,979	€ 38,285
Total	€ 91,711	€ 96,691	€ 85,912	€ 90,374

Table 37 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 91,711	€ 96,691	€ 85,912	€ 90,374
Costs (4% discount rate)	€ 84,626	€ 89,149	€ 79,419	€ 83,436
# of relapses	3.88	4.51	3.88	4.47
PANSS	578	593	538	554
Duration relapses (year)	2.69	3.05	2.68	3.04
QALY	1.60	1.55	1.70	1.65
# of relapses discounted	3.64	4.22	3.63	4.19
PANSS discounted	536	550	499	513
Duration relapses (year) discounted	2.51	2.85	2.50	2.83
QALY discounted	1.49	1.44	1.57	1.53

Effect of duration relapse and first line Tx

To analyse the effect is of a constant duration of relapses for both patient profiles and their severity groups, one alternative estimate is used of 7 months for each patient profile and severity group. Second, to analyse whether there is a difference between olanzapine and risperidone, one alternative scenario is used in which olanzapine is used as first line treatment option in scenario 2 (

Figure 3) instead of risperidone.

Table 38 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,743	€ 3,470	€ 6,682	€ 6,878
Home	€ 496	€ 404	€ 541	€ 432
ACT	€ 5,243	€ 6,294	€ 4,635	€ 5,979
Sheltered living	€ 12,150	€ 10,870	€ 12,183	€ 10,651
Hospital	€ 25,061	€ 28,789	€ 18,930	€ 27,561
Institute	€ 19,986	€ 42,756	€ 14,123	€ 35,487
Total	€ 66,680	€ 92,583	€ 57,095	€ 86,989

Table 39 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 66,680	€ 92,583	€ 57,095	€ 86,989
Costs (4% discount rate)	€ 61,856	€ 85,402	€ 53,009	€ 80,377
# of relapses	4.78	4.27	4.76	4.25
PANSS	458	585	425	547
Duration relapses (year)	2.67	2.91	2.65	2.89
QALY	1.97	1.58	2.13	1.68
# of relapses discounted	4.48	4.00	4.45	3.98
PANSS discounted	427	542	396	507
Duration relapses (year) discounted	2.49	2.72	2.47	2.70
QALY discounted	1.81	1.47	1.96	1.56

Appendix 2 Subgroup analyses

Patient profiles
To estimate the effect of the individual patient profiles, the costs and effects of eight different subpopulations were calculated. Table 40 and 39 and Figure 18 present the results of the total recovery patients and subsequently of the partial recovery patients. Table 42 and 41 present the results of the non, medium and very severe total recovery patients and Table 44 and 43 present the results of the non, medium and very severe partial recovery patients.

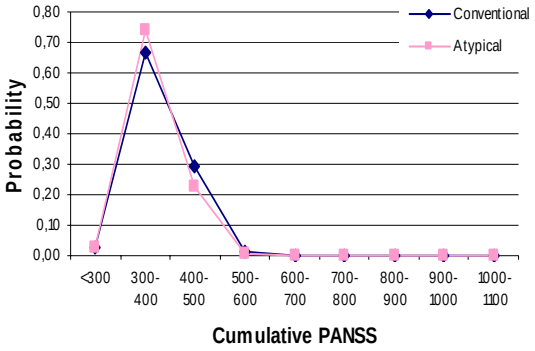
Table 40 Direct medical costs after 5 years

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Medication	€ 3,665	€ 3,165	€ 6,485	€ 6,878
Home	€ 662	€ 314	€ 675	€ 357
ACT	€ 2,875	€ 7,274	€ 2,666	€ 7,007
Sheltered living	€ 8,296	€ 11,197	€ 8,080	€ 11,571
Hospital	€ 8,891	€ 38,741	€ 7,491	€ 35,968
Institute	€ 5,757	€ 58,036	€ 4,498	€ 46,286
Total	€ 30,147	€ 118,727	€ 29,896	€ 108,067

Table 41 The (discounted) costs and effects generated per patient per treatment scenario over a five year period

Costs	Start with conventional		Start with atypical	
	1	2	1	2
Costs	€ 30,147	€ 118,727	€ 29,896	€ 108,067
Costs (4% discount rate)	€ 27,711	€ 109,584	€ 27,551	€ 99,851
# of relapses	5.45	3.87	5.40	3.86
PANSS	381	660	376	607
Duration relapses (year)	2.09	3.19	2.08	3.18
QALY	2.26	1.34	2.27	1.47
# of relapses discounted	5.09	3.63	5.04	3.62
PANSS discounted	354	612	349	562
Duration relapses (year) discounted	1.95	2.98	1.94	2.97
QALY discounted	2.09	1.24	2.10	1.36

Figure 18a Cumulative PANSS total recovery patients



b Cumulative PANSS partial recovery patients

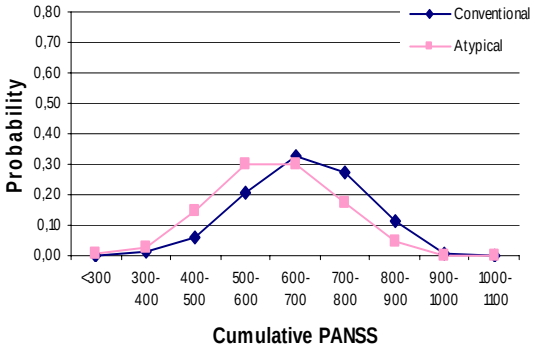


Table 42 Cost distribution of non, medium and very severe total recovery patients

Costs	Start with a conventional			Start with an oral atypical		
	n.s.	m.s.	v.s.	n.s.	m.s.	v.s.
Medication	€ 3,724	€ 3,735	€ 3,625	€ 6,027	€ 6,531	€ 6,688
Home	€ 819	€ 646	€ 517	€ 821	€ 667	€ 538
ACT	€ 25	€ 3,146	€ 5,163	€ 27	€ 2,770	€ 4,808
Sheltered living	€ 2,233	€ 9,904	€ 11,596	€ 2,229	€ 8,872	€ 11,341
Hospital	€ 0	€ 8,745	€ 21,454	€ 0	€ 7,186	€ 19,429
Institute	€ 0	€ 4,332	€ 18,968	€ 0	€ 3,574	€ 16,992
Total	€ 6,799	€ 30,507	€ 61,322	€ 9,104	€ 29,601	€ 59,797

Table 43 Costs and effects of non, medium and very severe total recovery patients

Costs	Start with a conventional depot			Start with an oral atypical		
	n.s.	m.s.	v.s.	n.s.	m.s.	v.s.
Costs	€ 6,799	€ 30,507	€ 61,322	€ 9,104	€ 29,601	€ 59,797
Costs (disc.)*	€ 6,253	€ 28,010	€ 56,669	€ 8,487	€ 27,254	€ 55,200
# of relapses	7.02	5.33	4.77	6.91	5.27	4.74
PANSS	310	382	445	308	376	437
Duration relapses (year)	1.13	2.15	2.65	1.12	2.11	2.64
QALY	2.53	2.24	2.03	2.54	2.27	2.05
# of relapses disc.	6.55	4.99	4.47	6.44	4.92	4.44
PANSS disc.	287	355	413	286	349	406
Duration relapses (year) disc.	1.06	2.00	2.48	1.04	1.97	2.46
QALY disc.	2.35	2.08	1.88	2.35	2.10	1.90

*disc=discounted

Table 44 Cost distribution of non, medium and very severe partial recovery patients

Costs	Start with a conventional			Start with an oral atypical		
	n.s.	m.s.	v.s.	n.s.	m.s.	v.s.
Medication	€ 3,279	€ 3,226	€ 3,093	€ 6,865	€ 6,872	€ 6,900
Home	€ 403	€ 314	€ 245	€ 446	€ 357	€ 276
ACT	€ 6,133	€ 7,515	€ 7,322	€ 5,710	€ 7,175	€ 7,492
Sheltered living	€ 12,446	€ 11,299	€ 9,234	€ 12,254	€ 11,615	€ 9,775
Hospital	€ 34,719	€ 37,702	€ 40,768	€ 29,990	€ 36,013	€ 40,895
Institute	€ 35,616	€ 55,303	€ 92,683	€ 26,984	€ 42,995	€ 76,379
Total	€ 92,596	€ 115,359	€ 153,345	€ 82,249	€ 105,028	€ 141,716

Table 45 Costs and effects of non, medium and very severe partial recovery patients

Costs	Start with a conventional			Start with an oral atypical		
	n.s.	m.s.	v.s.	n.s.	m.s.	v.s.
Costs	€ 92,596	€ 115,359	€ 153,345	€ 82,249	€ 105,028	€ 141,716
Costs (disc.)*	€ 85,998	€ 106,383	€ 140,644	€ 76,506	€ 97,047	€ 130,262
# of relapses	4.03	3.88	3.71	4.01	3.88	3.72
PANSS	532	659	768	484	610	720
Duration relapses (year)	3.00	3.20	3.39	2.97	3.20	3.40
QALY	1.72	1.33	1.12	1.92	1.44	1.20
# of relapses disc.	3.78	3.64	3.49	3.76	3.64	3.49
PANSS disc.	495	611	710	451	565	665
Duration relapses (year) disc.	2.80	2.98	3.16	2.77	2.98	3.17
QALY disc.	1.58	1.23	1.05	1.77	1.34	1.12

*disc=discounted