Cost-effectiveness of sertindole versus olanzapine or haloperidol: a comprehensive model

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Abstract

BACKGROUND: New drugs have become available to treat schizophrenic patients over the last 4 years. Their safety and efficacy with respect to conventional treatment has been well documented, although their economic impact in actual use has not yet been evaluated.
OBJECTIVE: The aim of this study is to evaluate new drugs in normal practice using a pragmatic Markov model of patients compliant with treatment.
METHODS: The model is based on a 6 month Markov cycle tree, divided into 4 sub-trees: M1, M2, M3 and M4. 1) M1 represents the drug strategies for schizophrenia: sertindole versus olanzapine versus haloperidol. 2) M2 lists the care structures. Five care management strategies are defined, depending on where the patients live (hospital, residential or private home) and the intensity of care (intensive or mild residential care, intensive or mild own home personal care). Care management depends on clinical status (relapse or non-relapse). Long stay hospitalisation is developed as a separate branch. 3) M3 represents clinical events. Each of the treatments has side effects which determine either compliance or non-compliance and the relapse frequency. The adverse events are extrapyramidal symptoms, drowsiness, weight gain and sexual dysfunction. Toxicity rates are estimated from three integrated safety studies. Adverse events occur less frequently with sertindole than with the other compounds. Sertindole produces particularly few extrapyramidal symptoms: 15% (177/1197) for sertindole versus 48% (237/489) for haloperidol versus 21% (52/248) for olanzapine. Drowsiness occurs less frequently in sertindole-treated patients: 10% for sertindole, versus 20% for haloperidol versus 26% for olanzapine. Weight gain and sexual dysfunction occurred more frequently than with the conventional anti-psychotics, but less frequently than the atypical anti-psychotics: 70 out of the 237 patients treated with olanzapine gained more than 7% of their initial body weight compared to 237 out of 1166 patients who gained weight in clinical trials on sertindole, i.e. 20% versus 30% for olanzapine. Sexual dysfunction occurs more frequently with sertindole than with haloperidol or olanzapine, although develops in, at most, 2.5% of patients. Anorgasmia occurred in 4/1197 men (76% of the treated population) and ejaculation or erectile dysfunction in 93 out of 913 patients studied in the Lundbeck short term clinical trials. Compliance and relapse rates were obtained by a meta-analysis of the literature and were calculated for the different patient situations. 4) M4 shows the patients' paths through the health care system. The corresponding transition probabilities were obtained from two French cohorts (2747 patients), a German cohort (294 patients) and a British cross sectional study (1051 patients). The model is based on 18 health states and 18213 nodes.
RESULTS: The relative risks of relapse on haloperidol or olanzapine compared to sertindole are 1.4 and 1.2 respectively. Sertindole is not only self-financing because of avoided hospital admissions (-15700$ compared to haloperidol and -80000$ compared to olanzapine), but it also produces modest net savings against these drugs.
Olanzapine and haloperidol are dominated strategies, which are less effective and more expensive. The robustness of these results was confirmed in a sensitivity analysis by varying adverse event, compliance, relapse and drop out rates.
CONCLUSION: Sertindole provides a benefit of 5 months without relapse compared to olanzapine and 13.5 months compared to haloperidol in the treatment of schizophrenia. This study clearly shows the benefits of sertindole in cost-effectiveness terms.

Key words: Schizophrenia, Database, Patient Path, Cost-effectiveness.

INTRODUCTION

Although drug costs are often the first things which come to mind to explain the increase in health expenditure, they actually represents only a very small part (approximately 13%) of total health expenditure. Another major factor is the medical and economic choices doctors have to make between many different management strategies, which may appear to offer identical efficacy in terms of survival, but which are different in terms of their side effect profiles. An economic evaluation of a choice of treatment is not straightforward and cannot be limited to the drug acquisition costs. It is impossible to avoid using special techniques which are becoming more and more precise and sophisticated, with the effect that medico-economics has become a discipline in its own right. Far from restricting health care, medico-economic analyses are designed primarily to extract the maximum benefit from available resources.

In order to provide clinicians with the necessary information to make management decisions, we have undertaken a medico-economic assessment of three management strategies in schizophrenia. The first was the comparator strategy which was found to be the most widely used in a psychiatric setting, daily administration of haloperidol, dose 10-20 mg/day. The second strategy was daily administration of sertindole at the recommended dose of 12-24 mg/day. The third was olanzapine, dose 10-20 mg/day.

This study consisted of several stages: estimating efficacy and adverse event rates for the three management strategies; measuring benefits to patients quantitatively (relapse free survival); quantitatively estimating the resources consumed, calculating costs associated with each of the management strategies and finally, a cost/effectiveness analysis.

1. METHODS

We have tried to follow the paths of schizophrenic patients on treatment, depending on whether or not they respond to treatment and as a function of the different management paths they may follow. The clinical benefits of treatment are measured by the time spent without relapse. Costs are calculated from the sum of the charges applicable to each of the management situations over time. All costs were calculated from the point of view of the psychiatric sector, and, as such, expenditure was limited to consumption of care and medical services. Transfer costs, direct non-medical costs and indirect costs were excluded from the remit of the analysis. The contribution of each of the clinical states to overall health costs and to the individual benefit gained by a patient were studied over a calendar period of 10 years.

Analytical framework

We decided to use a Markov model to simulate patients' outcome on each of the treatments and to calculate projected costs of care. This type of decisional analysis may be use to count events which may occur during the period of time examined. It records the distribution of a cohort of patients on treatment across different states of health associated with the clinical course of the disease, at regular intervals. Whether or not a patient passes from one state of health to another over time will depend on the transition probabilities which connect the states of health. These are calculated from observed frequencies in two large scale longitudinal cohorts, and from published clinical findings. These frequencies are defined as rates, i.e. as a number of events per unit of time and have a value from zero to infinity. Conversely, the limits of the transition probabilities are, by definition, zero and 1.

Observed rates must be converted into probabilities using the equation $_{Pi} = 1 - (1 - _{P(10t)})^{i/t}$, where $_{P(0t)}$ is the cumulative probability that an event may occur between time 0 and time t and i is the number of arbitrarily defined periods during this time interval (month, quarter, six month period over a calendar period of one year).

A basic feature of the Markov process is that it has no memory. Regardless of the patient's past history when he passes into a given state of health, all patients in that state of health are assumed to be subject to the same likelihood of developing potential subsequent events. In order to take account of the patient's own history, the different states of health through which the patient may have passed are taken from patient histories.

To illustrate the Markov process simply, it may be considered as a series of probability trees, the branches of which are linked together over time. Since Hollenberg's work, it has become conventional to describe this representation as a cyclical arborescence Markov process. The temporal horizon considered is from the start of treatment until death and is sub-divided into 6 month time periods called cycles. The decision to use a 6 month periodicity cycle was justified on clinical grounds: it is currently accepted that any schizophrenic deterioration which occurs within 6 months following a relapse should be considered as being part of that relapse (criterion D of the DSM III-R). Cycles run through the model are counted on a "started cycle" basis. A cycle counter was designed and set to take account of this rule. The counter is set in position 1 when treatment is started and moves to position 2 six months later, and thereon for 20 cycles (or 10 years).

Treatments

This model is applied to 3 types of patients; patients receiving sertindole, haloperidol or olanzapine.

These treatments are currently used in the management of schizophrenia and have well defined administration regimens:

- Sertindole (12-24 mg per day as a single dose)
- Haloperidol (10-20 mg per day in two divided doses)
- Olanzapine (10-20 mg per day in two divided doses)

The tree starts at a decision node (fig. 1-A). The three branches coming out of this node represent the three competing management possibilities: Sertindole versus Haloperidol versus Olanzapine. The bracket signifies that the same sub-tree is being used to evaluate the effects of the three treatments and describes the nature of the model being used. The Markov node shown on the right of the bracket by a rectangle containing two circles connected by an arrow indicates that the Markov process has been used.

Markov states

Each of the branches attached to the Markov node represents a Markov "state". The prognosis and consequences of schizophrenia occur as a result of interaction between medical and social factors. For this reason we have tried to integrate these two components simultaneously in order to characterise the outcome of schizophrenic patients managed in hospital, in a community care setting, or on a conventional outpatient basis. This is one of the original features of the process. The Markov states are defined both from clinical factors characterising the course of the disease, from the intensity of care required to manage the disease and from the premises in which the care is administered.

- Three clinical states are defined; relapse, non-relapse and chronic disease. Criteria used to define relapse vary depending on the author. Some define this as merely a deterioration in the patient's clinical condition, although other use psychometric scales such as the GCI, BPRS or PANSS. Hospitalisation of a patient is also a commonly used criterion to define relapse, although probably incorrectly so, as some authors rightly point out that 40% of relapsed patients are managed within the community and not in hospital. In view of the wide variety of approaches used, we have not endeavoured to harmonise definitions but, following Davis' recommendations, we have used published comparative rates to calculate the probabilities of relapse in different clinical settings. We have defined a chronic patient as any patient who has spent more than 120 days as a full inpatient during a 6 month follow up period, in whom there has been no significant change in consumption of resource from one 6 month period to the next.
- In order to evaluate intensity of care required by a schizophrenic patient, depending on his clinical condition, we constructed a global management indicator by weighting the number of days of full inpatient care, the number of days of partial hospitalisation and the number of outpatient episodes by 3 coefficients to reflect the extent of the resources mobilised for the patient. Three care groups were identified, depending on the score for each patient: high dependency inpatient management for patients who were admitted to hospital for more than 4 months, regardless of their clinical state; intensive management if a patient was admitted to hospital for more than 30 days in a 6 month period or if the global management indicator score was greater than 120 points with a smaller number of hospitalisation days, because of especially heavy outpatient care. Normal practice was defined by less than 30 days hospitalisation during a 6 month period or if the management indicator was less than 120. The care groups identified are not dissimilar to the management types in Gaëten Wagenaar's MALIN system, which differentiates full inpatient care, partial hospital care and one-off procedures. Neither case describes the structure of care activities but rather a clinical reality into which the patient's management falls. Outpatient management (either intensive or mild) were differentiated by the place in which the patient lives - either in a family home or in community care. There were therefore five patient treatment groups; high dependency hospital management, intensive home (*personal*) or residential (*collective*) care (IPC, ICC) and mild home or residential care (MPC, MCC). For reasons of simplicity, we usually defined care by its intensity without going into further detail about the structures through which the care was administered.

There are therefore 3 x 5 Markov states. Three other states were then added, one for patients lost to follow up, one for patients who may have seen a private primary care private physician and the third for death, making a total of 18 potentially usable Markov states (fig. 1-B). In view of the convention used to define chronic disease (global management indicator above 400), the mild care group, either at home or in community care, was not used for this type of patient. Due to a lack of information about primary care outpatient appointments, the same applied to the primary care group. Fifteen Markov states were finally, therefore, used.

Clinical events

The likelihood of patients finding themselves in any one of the fifteen states described above is governed by the development of chance events, the probabilities of which are shown on a probability tree for each of the initial states onto which the new situation is grafted. The bracket shown in front of the clinical events tree describes all of the outcomes which patients may experience, regardless of their starting situation (fig. 1-C). Patients may either survive or die on treatment.

In the former situation, treatment may be stopped (D0) either because it is ineffective (for example because a patient is resistant), or because the patient refuses to take the treatment. In all other cases treatment is continued.

Treatment is associated with side effects which may be either minor or major. The most serious are the extrapyramidal syndromes (EPS): Parkinsonism (muscle rigidity, dyskinesia and tremor), dystonia (bizarre involuntary movements) and akathisia (motor agitation). These problems usually develop after treatment for a few weeks. Other less serious conditions, but which are also incapacitating, are gathered together under the terms drowsiness, weight gain and sexual dysfunction.

The adverse event rates were taken from registration dossiers for the 3 compounds studied. These dossiers contained both short term trials (less than 60 days) versus either placebo or haloperidol, and long term follow up trials lasting more than one year, which were not randomised and did not contain a control group. We used the frequencies obtained from the pooled short term trials, all doses combined, i.e. 4 to 16 mg of haloperidol per day, 5 to 20 mg of olanzapine per day and 4 to 24 mg of sertindole per day. The numbers of extrapyramidal effects were defined using the Costard nomenclature and was far lower for sertindole: 15% (177/1197) than for its competitors: 48% (237/489) for haloperidol and 21% (52/248) for olanzapine. Weight gain and sexual dysfunction occurred more frequently with sertindole than with the first line neuroleptic agents, although the gain in weight was less for sertindole than for the other new anti-psychotic agents. Seventy out of 239 patients (30%) treated with olanzapine gained more than 7% of their initial body weight compared to 237 out of 1166 (20%) for sertindole. Conversely, more sexual dysfunction occurred with sertindole than with haloperidol or olanzapine, although this affected only 2.7% of patients treated. The majority of sexual dysfunction reports in sertindole-treated patients is decreased ejaculatory volume in male patients, which is generally not associated with decreased libido or impaired sexual performance. Orgasmic dysfunction occurred in a total of 4 out of 1197 patients (men and women combined), erectile dysfunction and ejaculatory disorders occurred in 33 out of 913 male patients from amongst the 76% of the total population who were male. We decided on a minimalist assumption, that these adverse event rates at 2 months could be used for treatment for 6 months without being extrapolated.

These problems will influence compliance, defining two categories of patients: compliant patients (com+) and non-compliant patients (com-). The risk of relapse (R+) increased with decreasing compliance of treatment. Probability of stabilisation (R-) increased with increased compliance. There was no systematic relationship however, between these findings: patients who complied strictly with their medication could still relapse.

In a meta-analysis of 44 trials which compared new generation anti-psychotic drugs to placebo, Baldessarini (1990) found the relapse rate in patients not receiving active treatment to be 55% after 10 months. An evaluation of 3 trials (n = 1260) of the long term follow up performed by the same group found that the relapse rate was 72% in non-compliant patients. In his article in 1992, Kissling summarised the results of 6 randomised, placebo-controlled trials lasting for 6 months, and estimated that the mean one year relapse rate was 74%. Weiden studied 5 trials and found the one year relapse rate of non-compliant patients to be 76%. Based on these figures, a 76% relapse rate one year after symptoms of schizophrenia have worsened appears to the be the upper limit of the confidence interval of the relapse rate in non-compliant patients. We used this worse case assumption in the model by applying a 6 month probability of relapse of 0.51. In order to calculate the lower likelihood of the relapse rate in compliant patients, we used results of comparative trials which examined relapse rates in patients treated with an optimal dose, in particular by depot injection of long acting neuroleptic drugs, or by continuous treatment, to those on conventional

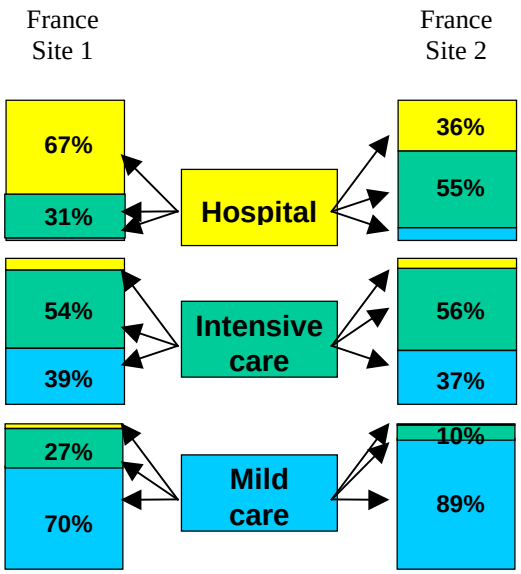
treatment or in whom treatment was interrupted. Gilbert (1995) analysed 66 trials containing 4365 subjects, 3141 of which had received interrupted treatment and 1234 had received continuous treatment, and found that the relapse rate in patients who received the optimal treatment dose was 15.6% at 9.7 months.

In a paired prospective trial, Johnson (1983) found that the one year relapse rate in patients whose treatment had been stopped was 65%. Figures published by Baldessarini (1990) and by Weiden (1995) are between these two extremes and found the relapse rate in compliant patients to be 35% for the first generation anti-psychotic agents and 22% for the atypical anti-psychotic agents (Weiden). It would therefore seem reasonable to use an annual relapse rate of 35% for compliant patients receiving conventional treatment and 22% for patients receiving 2nd generation anti-psychotic drugs as a best case scenario. These were the rates which were applied to the model, using 6 monthly relapse probabilities of 0.1937 and 0.1168 respectively.

Patient trajectories

Patient trajectories (fig. 1-D) by care group were calculated from two French cohorts (2747 patients), one German cohort (294 patients) and from a transverse English study (1051 patients). The French cohort was studied over two separate sites. 1884 patients were followed up in site 1, between 1993 and 1995 and 1863 patients in site 2, between 1990 and 1995. These dynamic cohorts were converted into closed cohorts and only those patients who had had at least one contact per 6 months with professionals or structures in the care sector were included in the analysis. A total of 400 patients were followed up in site 1 and 405 in site 2 over the period from 1993 to 1995. The other two fixed cohorts in site 2 (i.e. 238 patients) followed up between 1990 and 1992 and 171 patients followed up for 6 years from 1990 to 1995, were not used because of a lack of equivalent data for site 1. The populations in the databases studied were divided into the 5 care groups by 6 month period, depending on their clinical condition. Each clinical state (relapse, non relapse, chronic disease), the destination at a given time (t+1) of patients at a given time (t) in a given care group were identified by a cross-over grading by SPSS over four 6 month periods. The ratio of the sums of the total numbers in each of the starting states at t and those in the arrival states at t+1 over four 6 month periods may be used to calculate the mean transition probabilities between care groups (hospital, intensive home care, mild home care, intensive community care, mild community care) for each clinical state.

Figure 1: Transition probabilities for patients who relapsed



Resources consumed

The amount of resources consumed depend on the patient's clinical state. For a relapsed patient, relative changes in the global management indicator between two 6 month periods (t+1 and t) compared to the absolute value of the indicator at time (t) may be used to identify all of the resource programmes used which are associated with the patient's clinical condition, by following certain conventions. If consumption doubles from one six month period to the next, regardless of the initial value of the global management indicator at time t, all of the resource programmes used which are equal to or above this threshold value will be assumed to belong to the range of resources consumed by patients who relapse. If the value of the global management indicator at time t is between 50 and 400, all of the possible resource programmes used above a relative change of more than 20% from one six month period to the next, are assumed to belong to the same group. If the global indicator is over 400 points, an increase of just 10% from one six month period to the next in consumption will result in all of the resources used being allocated to patients who have relapsed. Combining these three sub-totals produces the overall consumption attributed to patients who have relapsed. Consumption by patients who have not relapsed is then calculated from the complementary figure. Consumption by patients with chronic disease did not form part of the analysis of relapsed and non-relapsed patients as, regardless of their clinical condition, these patients remain within hospital, (as defined by the magnitude of the global indicator (> 400) and the fact that values are stable from one 6 month period to the next (relative changes between +10 and -10%).

This analysis is performed on the two fixed French databases for each of the five 6 month periods to which the method could be applied. The first 6 month period of 1993 had to be abandoned in both cases, as it was not possible to calculate relative differences. The analysis was applied to the 5 patient care groups in order to determine the numbers of full inpatient hospitalisation days, partial hospitalisation (day hospitalisation, overnight hospitalisation) and the number of outpatient encounters for each professional category (doctors and nurses, psychologists and social workers) for each category of care. This information is summarised in table 1, which shows the mean consumption of resources during the follow up period in site 2.

Table 1: Average resource utilisation over 6 months by category of care group.

Catchment Areas	Hospital.	Intensive Care	Mild Care
FRANCE (2) - RELAPSE			
Full inpatient hospitalisation (days)	163.54	39.92	4.61
Day hospitalisation (days)	0.62	14.08	0.19
Overnight hospitalisation (nights)	0.00	0	0
Outpatient encounters	43.85	96.02	33.58
FRANCE (2) - NON RELAPSE			
Full inpatient hospitalisation (days)	141.50	16.3	0.42
Day hospitalisation (days)	0.00	17.61	0.04
Overnight hospitalisation (nights)	0.00	0.14	0
Outpatient encounters	23.50	157.08	20.11

Allocating values to costs

Full inpatient hospitalisation in psychiatric institutions, inpatient alternatives to hospitalisation (day hospital or overnight hospital) and non-inpatient alternatives to hospitalisation (Medical Psychology Centres (MPC), Day Care Centres (DC) and Halfway Houses) are from now on covered by a single financial structure. From this point, the institution which manages an overall budget for hospital activities and provides a health service within a community is no longer a hospital but a care network. In order for this to function correctly, careful decisions must be made between hospital and outpatient categories of care; global budgeting has introduced a problem into this area, countering good management within the system, as none of the procedures performed on a community basis are subject to tariff charges. Three types of value units were used to measure the costs of resources consumed:

- daily tariff charges (social security system) for full inpatient hospitalisation and for partial hospitalisation; day hospitalisation or overnight hospitalisation;
- actual costs of professional procedures performed within the community on the two sites studied, which were calculated from the financial accounting structures within the establishments;
- the public prices of neuroleptic drugs used within the sector.

The day costs were $232, $162 and $81 for full inpatient hospitalisation, day hospitalisation and night hospitalisation respectively. The unit cost of procedures performed on an outpatient basis was calculated from the combined salaries paid to the individuals concerned, after subtracting those parts of the salary paid with respect to their hospital activities and psychiatric training within the sector. The balance was then divided by the number of procedures performed in adults during the year being studied. The unit cost of a medical procedure (all combined) was $36 and the cost of a nursing procedure was $52. The cost of a psychologist's procedure was lower ($21) and that of a social worker higher ($66) (per encounter). The costs of outpatient anti-psychotic treatment were introduced into the analysis, based on a daily hospital cost for haloperidol (dose 15 mg/day) of $69 for 6 months. In France, the costs of sertindole (12-24 mg/day) and of olanzapine (15 mg/day) were provisionaly assume to be identical and equal to $1000 for a 6 month treatment period. At this time, no official price is available.

The cumulative cohort cost over a 2 year follow up period, the actual cost per care group per patient over a 6 month follow up period and the weighted cost of relapse and non-relapse as a function of the relative incidences in the populations in the different care groups were calculated from information available about the quantities and unit costs.

- The cumulative cost was the sum of the product of the quantities consumed per group multiplied by their unit value and by the number of patients affected in all of the groups over the five 6 month periods.
- The actual 6 month management cost per group was the cumulative cost per group divided by the number of patients, per five 6 month periods.
- The weighted cost of relapse was the actual cost of a patient followed up for 6 months, per group, multiplied by the number of patients who received this category of care.

The actual 6 month cost was the standard costs associated with each Markov state. The weighted cost of clinical states was obtained by calculating product of standard costs and the probabilities associated with the patient's trajectories within the care system.

Table 2: Six month average costs per care management group (US$$_{96}$)

Sites	Hospital.	Intensive Care	Mild Care
FRANCE (1)			
Relapse	38 996	17 289	2 472
Full inpatient hospitalisation	(97.7 %)	(57.1 %)	(55.5 %)
Day and overnight hospitalisation	(0.8 %)	(40.6 %)	(29.0 %)
Outpatient encounters	(1.5 %)	(2.3 %)	(15.5 %)
Non relapse	33 843	17 103	820
Full inpatient hospitalisation	(98.3 %)	(21.9 %)	(4.0 %)
Day and overnight hospitalisation	(0.7 %)	(76.1 %)	(45.2 %)
Outpatient encounters	(1.0 %)	(2.0 %)	(50.8 %)
FRANCE (2)			
Relapse	39 254	14 473	1 958
Full inpatient hospitalisation	(97;0 %)	(64.2 %)	(46.3 %)
Day and overnight hospitalisation	(0.3 %)	(15.8 %)	(1.6 %)
Outpatient encounters	(2.7 %)	(20.0 %)	(52.1 %)
Non relapse	33 883	10 421	742
Full inpatient hospitalisation	(97.2 %)	(36.4 %)	(13.2 %)
Day and overnight hospitalisation	(0.0 %)	(27.6 %)	(1.0 %)
Outpatient encounters	(2.8 %)	(36.0 %)	(85.8 %)

Incremental cost-effectiveness ratio

By definition, the three treatments being studied are mutually exclusive, i.e. they may not be given simultaneously for the same indication. Replacing one strategy with another results in a cost difference and in a difference in effectiveness.
In both cases, this produces a net increment in mean value. Increment because only differences between the strategies are measured. Mean value because it is a mathematical calculation of expectation, defined as the sum of the probabilities of events, weighted by costs and associated effectiveness. Net differential, insofar as the final figure is the algebraic sum of the positive and negative cost differences linked to the expenditure associated with the treatments in each of the care groups: mild, intensive or high dependency. The additional effectiveness of one treatment compared to another is measured in terms of gained months without relapse. The incremental cost-effectiveness ratio is defined as the quotient of these differences.

The calculation is represented by the following equation: $\Delta C/\Delta E = (\Delta CAC + \Delta CAI - \Delta CH)/ \Delta Q$

where C = total net medical cost per patient; E = total effectiveness; CMC = cost of mild care; CIC = cost of intensive care; CH = cost of inpatient hospitalisation care; Q = survival without relapse; Δ = difference.

The different strategies were then classified against each other based on effectiveness criteria. A strategy may be said to be strongly dominated by another if it less effective and more expensive or more expensive and equally effective. The strategy may be said to be efficient or cost-effective if no procedure can produce a better result at lower cost.

Sensitivity analysis

In order to confirm the validity of our conclusions, we examined the field of possibilities by introducing the worst and best extreme values obtained in clinical trials on the three treatment protocols which have been studied.

2. RESULTS

Description of the population

The initial distribution between different states in the model was the same as the distribution of the population by clinical state and by categories of care in the two French databases. Almost the same number of patients were followed up for 3 years in both sites: 400 in site 1 and 405 in site 2. The distribution of these patients' clinical states was however, different. Seventy-two patients (or 18% of the study population) were near-permanently hospitalised in site 1 compared to 2 (or 1% of the study population) in site 2. The mean relapse rate per 6 month period was only 13% on site 1 compared to 20% on site 2; an average of 51.8 patients relapsed per 6 month period at site 1 compared to 83 at site 2. Conversely, numbers of patients who did not relapse differed in the opposite direction: 276 patients did not relapse per 6 months at site 1 (69% of the population) compared to 316 patients at site 2 (78% of the population). The distribution of patients who either did or did not relapse in the different care groups reflected the diversity of approaches to care on the two sites: 22% of the relapsed patients received high dependency management at site 1 compared to only 6% at site 2. The incidence of intensive and mild outpatient management was consistent with the policy of systematic de-institutionalisation at site 2, in which 94% of relapsed patients were followed up in home care structures or in community care, compared to 78% at site 2. Not surprisingly, the category of care for non-relapsed patients was predominantly mild care at both sites (83% of these patients at site 1 and 88% at site 2).

Estimation of efficacy

The model may be easily used to calculate the time spent in relapse or non-relapse, for each of the three treatments, regardless of the care group involved.

The temporal horizon used in the model was 10 years, or 20 cycles. Seventy-two per cent of patients treated with sertindole remained on treatment during this period. Eighteen per cent were lost to follow up and 10% died. Two per cent of patients maintained on treatment (completers) were chronically institutionalised in a hospital; 32% relapsed and 66% stabilised. The likelihood of relapse on treatment was therefore 0.32.

Sixty-eight percent of patients treated with haloperidol remained on treatment during the same period, 10% gave up treatment and 10% died. Two percent of patients maintained on treatment (completers) were long term institutionalised in a hospital; 45% relapsed and 53% stabilised. The likelihood of relapsing on treatment was therefore 0.45%.

The relative risk of relapse on haloperidol compared to sertindole is therefore 0.45/0.32 or 1.4. The risk of relapse on haloperidol is therefore more than 40% higher than on sertindole. Similarly, we found that the risk of relapse on olanzapine was 20% higher than for sertindole.

The numbers of 6 month cycles without relapse after 10 years were 9.5, 9.21 and 7.22 for sertindole, olanzapine and haloperidol respectively, i.e. 57 months without relapse for sertindole compared to 51 months for olanzapine and 44 months for haloperidol. Patients on sertindole therefore benefit by 5 months and 20 days compared to olanzapine and by 13.5 months compared to haloperidol.

Measurement of projected costs

Total medical costs are defined as sum of all of the management costs for each of the categories of care involved, multiplied by the likelihood of requiring this category of care during the 10 years of the model.

The projected costs over the temporal horizon studied were $198,803 for sertindole, $205,298 for haloperidol and $205,482 for olanzapine at site 1. The corresponding figures for site 2 were $157,602, $157,643 and $158,513 respectively. It is reasonable to subtract the cost of managing chronic patients from these total costs, as we assume that these costs are almost identical regardless of the drug used, with the single reservation that slightly more patients gave up treatment with haloperidol. The projected costs for site 1 were $9817 for sertindole and olanzapine, and $9316 for haloperidol compared to $6461 for sertindole and olanzapine, and $6180 for haloperidol at site 2.

From these calculations, we obtained management costs of non-chronic patients, which may then be analysed by clinical state, (relapsers or non-relapsers), by management types (high dependency, intensive, mild) and by type of consumption (full inpatient hospitalisation, day or overnight hospitalisation, outpatient care) and drug consumption.

- If the medical expenditure on relapsers and non-relapsers who were treated with sertindole or haloperidol are compared (Table 3) we see that the costs of non-relapsers on sertindole are higher than those for haloperidol ($98,833 compared to $78,950; +$19,883).

Table 3: Expected 10 year costs per patient by clinical status (US $$_{96}$$)

Sites	Sertindole	Haloperidol	Olanzapine
FRANCE (1)			
Relapse	90 150	117 033	105 017
Non relapse	98 833	78 950	90 650
Chronic	9 817	9 317	9 816
Total	198 800	205 300	205 483

Conversely, relapsers on haloperidol were more expensive than those on sertindole: $117,033 versus $90,150; -$26,883), equivalent to a difference in cost of $7,000 between the two drugs in acute patients. The fact that more of the haloperidol patients dropped out of the study reduced the cost of managing chronic patients by $500 compared to sertindole. The difference in cost is therefore $6,500 in favour of sertindole. We have evidence to show that sertindole reduces the number of relapses and results in savings which should be analysed site by site: some of the funds released are, however, absorbed in the management of patients who do not relapse.

- If medical expenditure by category of care is compared on the same site (Table 4), we see that the costs of patients treated with sertindole who receive high dependency management in hospital are lower than those for haloperidol ($96,684 versus $108,966; -$12,282).

Table 4: Expected 10 year costs per patient by categories of care (US $$_{96}$)

Sites	Sertindole	Haloperidol	Olanzapine
FRANCE (1)			
Mild care	6 383	4 117	5 317
Intensive care	95 733	92 217	99 383
Hospital	96 684	108 966	100 783
Total	198 800	205 300	205 483

Conversely, the costs of intensive and mild care in the sector were higher [$95,733 versus $92,217 (+$3,516) and $6,383 versus $4,117 (+$2,266)]. Sertindole therefore reduces expenditure in the hospital inpatient group and produces a net saving of $6,500.

- If results are examined by professional service, we see that sertindole reduces the costs of full inpatient hospitalisation by $15,666 ([69,567 + 52,450] - [92,233 + 45,450]), compared to haloperidol for all relapsers and non-relapsers combined, although it increases the partial hospitalisation expenditure (+$4,701), the cost of outpatient care (+$232) and drug costs (+$3,733). Overall, the drug self-finances as a result of the savings it produces in avoided days of hospitalisation. It even produces slight savings to the social security system of $6,500 over 10 years or $650 per annum.

Table 5: Expected 10 year costs per patient by professional service (US $$_{96}$)

Sites	Sertindole	Haloperidol	Olanzapine
FRANCE (1)			
Relapse	90 150	117 033	105 017
Full inpatient hospitalisation	69 567	92 233	80 733
Day and overnight hospitalisation	18 367	22 433	21 867
Outpatient encounters	1 783	2 367	2 133
Incremental drug cost	433	0	284
Non relapse	98 833	78 950	90 650
Full inpatient hospitalisation	52 450	45 450	49 317
Day and overnight hospitalisation	39 850	31 083	36 500
Outpatient encounters	3 233	2 417	2 700
Incremental drug cost	3 300	0	2 133
Chronic	9 817	9 317	9 817
Total	198 800	205 300	205 483

Incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio highlights the differences between absolute values for costs and effectiveness. The denominator shows a benefit of 5 months and 20 days without relapse in favour of sertindole compared to olanzapine and 13.5 months compared to haloperidol. The numerator reveals a saving of $6,683 compared to olanzapine and $6,500 compared to haloperidol on site 1 after reducing the expenditure for chronic patients treated with haloperidol because of the higher number of patients lost to follow up.

	Treatment strategy		
	Sertindole vs Olanzapine	Olanzapine vs Haloperidol	Sertindole vs Haloperidol
Incremental effectiveness			
All countries	5.7 months	7.8 months	13.5 months
Incremental cost ($US, 1996)			
France (1)	- 6 683	183	- 6 500
Germany	- 4 912	- 159	- 4 753
France (2)	- 2 066	2 191	125
Great Britain	- 1 846	4 531	2 735
Incremental cost-effectiveness ratio			
France (1)	Sertindole dominates	Olanzapine dominates	Sertindole dominates
Germany	Sertindole dominates	Olanzapine dominates	Sertindole dominates
France (2)	Sertindole dominates	Olanzapine and Sertindole more effective, but more costly	
Great Britain	Sertindole dominates	Olanzapine and Sertindole more effective, but more costly	

CONCLUSION

First line treatment of a schizophrenic patient with sertindole produces a benefit of 13.5 months without relapse compared to treatment with haloperidol and 5 months and 20 days compared to treatment with olanzapine. Sertindole is self-financing as a result of savings in hospital admissions and produces savings compared to haloperidol and olanzapine. In this situation, sertindole provides greater effectiveness for a lesser cost compared to its comparators. It has a better cost-effectiveness ratio than its competitors. This study shows that this drug is economically beneficial.

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Figure 1 : Markov Model in Schizophrenia over 10 years

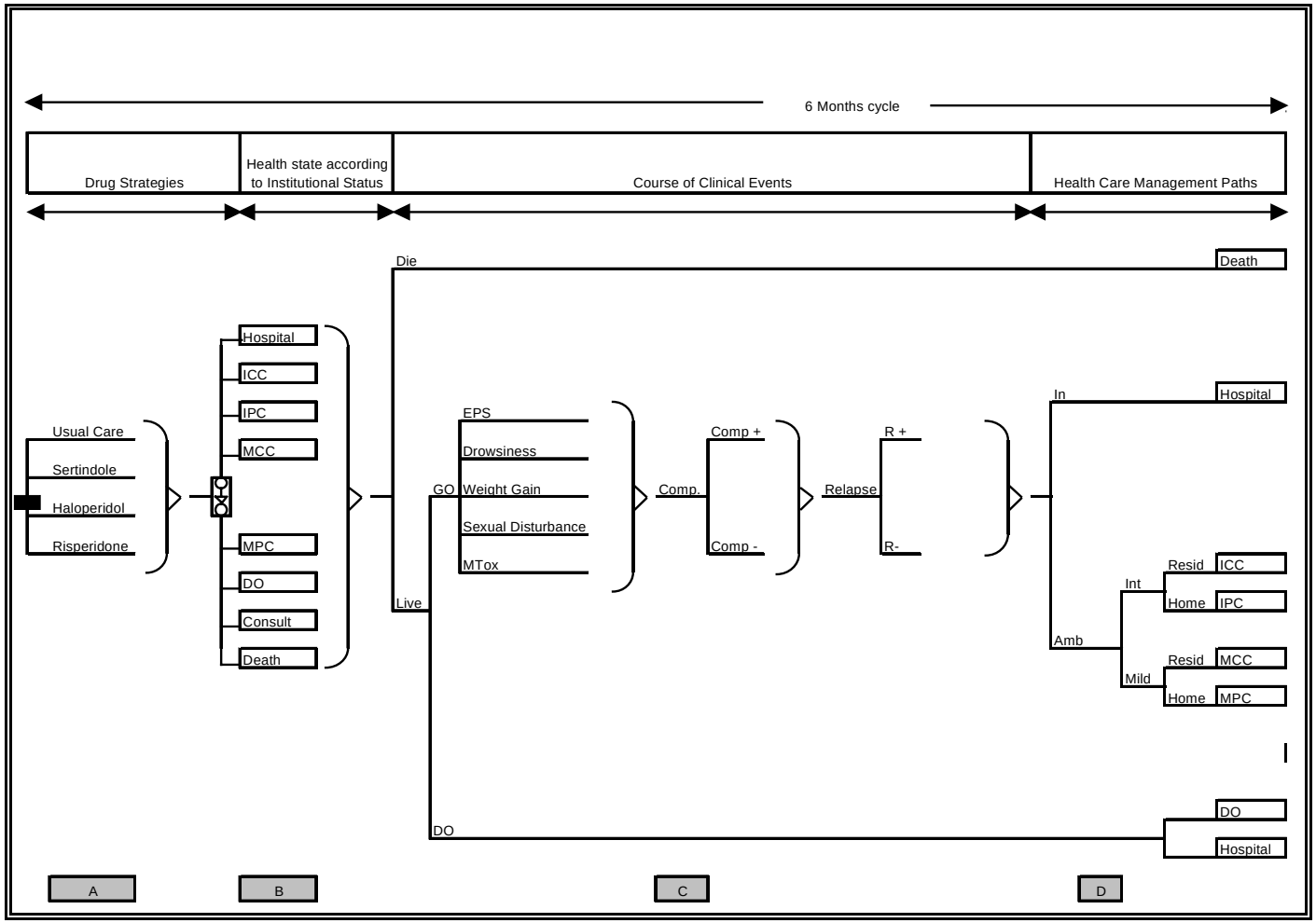

Figure legends

Figure 1

Abbreviations : EPS = extrapyramidal symptoms; MTox = minor toxicity; Comp+ = compliance; Comp- = non compliance; R+ = relapse; R- = non relapse; In = inpatient; amb = ambulatory care; Int = intensive care; Mild = conventional care; Resid = residential care; Home = domiciliary care; ICC = internsive collective care; IPC = intensive personal care; MCC = mild collective care; MPC = mild personal care.