Cost-Effectiveness of Sertindole Versus Olanzapine or Haloperidol: a Comprehensive Model

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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 12-20 mg/day. The third was olanzapine, dose 10-20 mg/day. The fourth was Riperidone, dose range 4-5 mg a 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.

I. 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 $P_i = 1 - (1 - P_{(10t)})^{i/t}$, 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 4 types of patients; patients receiving sertindole,riperidone, 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)
  - Rispéridone (4-6mg per day as a single dose)

The tree starts at a decision node (fig. 1-A). The four branches coming out of this node represent the three competing management possibilities: Sertindole versus Haloperidol versus Olanzapine versus Rispéridone. 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, 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.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 the UK application, we have broadly followed this system of classification. However, it is also necessary to classify care into categories which are consistent with those used in the surveys from which the cost data are to be obtained. There is no point in defining a particular care category if there are no cost figures for it. Our categorisation is based on distinctions between different types of accommodation. Most of our cost data are from the Mental Health Residential Care Study (RCS) (Chisholm et al., 1997). This survey classified residential accommodation according to the structural characteristics of each facility - size and type and levels of staffing (Lelliott et al., 1996). We have adopted this classification but with aggregation of some categories and the addition of a category for people living in their own homes[1].

- ➢ The first category is long-stay hospital inpatient care. Since our classification is based on the nature of the client's **usual** place of residence, we do not identify acute inpatient care as a separate category. Instead, we include acute inpatient care as one of the services which may be utilised within any of the non long-stay inpatient categories of care. . In the UK, the minimum length of stay ever used in identifying " long-stay "

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[1] *The RCS did not include individuals living in their own homes.*

patients is 6 months[2]. We therefore assume patients in the long-stay hospital category remain inpatients for the full duration of each cycle. In the RCS, the National Health Service was the sole provider of this type of care.

An individual is considered to be in collective care if they are living in regularly **staffed** accommodation with other mental health patients. Personal care covers all individuals living in **non-staffed** accommodation[3].

➢ With respect to collective care, we distinguish between intensive and mild care on the basis of the type and levels of staffing of the residential facility. High-staffed hostels are defined as having 6 or more beds; waking night and constant day cover (hence 24 hour cover): and a staff resident places ratio of more than 0.5. In the RCS sample, these hostels had a typical staff resident places ratio between 0.95 and 1.0 and, on average, 15% of staff held a care qualification. There is supervision of basic living skills provided where necessary and meals cooked. This is a possible permanent home. Some degree of independence is expected, for example, the ability to go out during the day on occasions unaccompanied. The private sector is the main provider of this type of home (70% in the RCS), although funding is mostly public.

Staffed care homes are defined as having less than 6 beds; sleep-in night cover; constant day cove; and a staff resident places ratio of more than 0.5. In the RCS, the typical staff resident places ratio was 1.01 and, on average, 7% of staff held a care qualification. The main provider agencies in the RCS sample were private then local authority (52% and 36% respectively), although finance is again mostly from public funds. We combine these two types of facility to form our ICC category.

➢ Our mild collective care category corresponds to mid to low staffed hostels, as defined in the RCS.Mid-staffed hostels are defined as having 6 or more beds; sleep-in night cover; constant day cover; and a staff resident places ratio of between 0.3 and 0.5. In the RCS sample, the typical staff resident places ratio was 0.39 and, on average, 14% of staff held a care qualification. The main provider agencies are from the private and voluntary sectors (42% and 39% respectively in the RCS), with predominantly public finance.Low-staffed hostels have 6 or more beds; on-call or no night cover; regular day cover (usually 9am to 5pm) or regular part-time cover (usually morning or afternoon); and a staff resident places ratio of less than 0.3. In the RCS, the typical staff resident places ratio was 0.19 and 15% of staff held a care qualification. These hostels have independent rooms and some shared facilities. Residents have either a separate room in a house or a sheltered flat. Staffing includes a small amount of daily domestic input and on-call duty staff. Reasonable living and self care skills would be expected. The hostel may be a permanent home. The main provider agencies are from the private and voluntary sectors (56% and 39% respectively) and funding is mostly public. The number of patients in the MCC category is 320.

➢ In the UK mental healt system, clients living independently, i.e. not in staffed accomodation, can be disaggregated into those living with others in group homes and those living in family homes (either on their own or with friends/relatives). This

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[2] *In some statistics, 12 months is used.*
[3] *That is, not staffed on a regular basis.*

distinction is reflected in the cost data available. From the RCS, care costs for individuals living in group homes are available. The RCS did not include individuals living in family homes. However, we have access to another data set – the Daily Living Programme – from which costs of care can be calculated for individuals living in their own homes. The distinction we make in personal care is not therefore between intensive and mild care (based on the frequency of service utilisation) but between personal care in a group home setting and personal care in the individual's own home. To an extent, the latter distinction indirectly separates personal care according to intensity of use since, on average, clients living in group homes are expected to be more intensive users of mental health services than those living in their own homes. Our average cost figures do, in fact, indicate

Unsupported group homes provide residence with a few other clients but with minimum support – for example, up to one visit per week from care staff after a transitional period. Group homes are defined in the RCS as having less than 6 beds; on call or no night cover; no regular day cover – visits only (expected or ad hoc); and a staff resident places ratio of less than 0.3. In the RCS sample, there was typically a 0.16 staff resident places ratio and, on average, 33% of staff held a care qualification. The main provider agencies are the voluntary sector (56%) and local authorities (42%), with predominantly public finance.Our final category is care provided to individuals who are living alone or with a spouse, relatives, friends or even a landlady.

- 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. The probability of a schizophrenic patient dying is calculated from a decreasing exponential equation using the DEALE method.

The principle of the DEALE method involves firstly calculating mean natural mortality rates, adjusted for age, sex and race (μASR) from life expectancy (LE).

$$\mu ASR = 1 / LE$$

Secondly, specific mortality rates (μD) are calculated as the differences between observed mortality (μC) and the corresponding mortality for age and sex in the general population (μ pop).

$$\mu D = \mu C - \mu \text{ pop}$$

Finally, overall mortality (μT) is obtained by adding mean natural mortality (μASR) and specific mortality (μD) figures.

$$\mu T = \mu ASR + \mu D$$
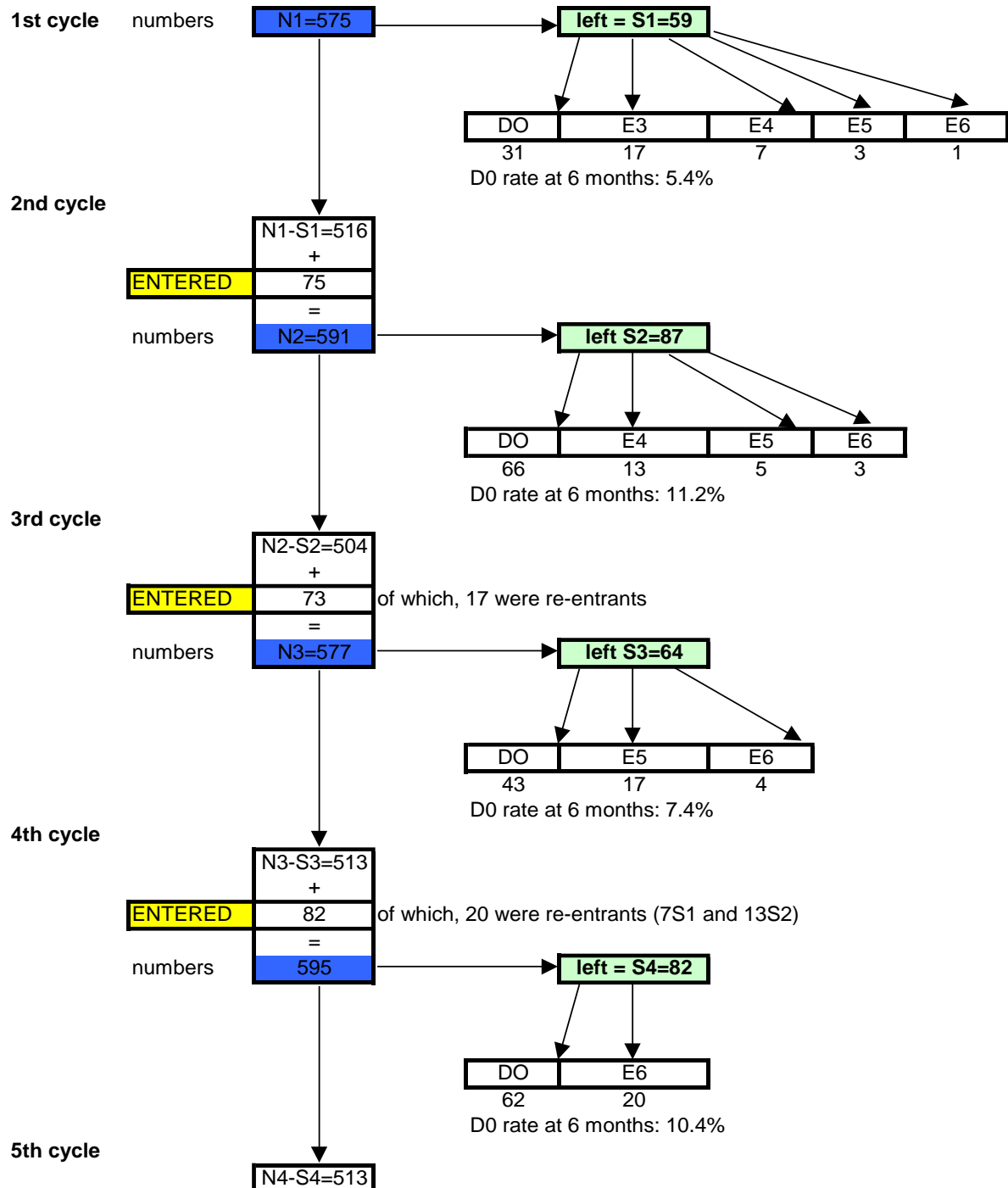
Survival S(t) is calculated from the equation e^{-rt} where r is the overall mortality rate and t is the length of the cycle (6 months). The six monthly probability of dying is calculated from the equation p = 1 - S(t).

When the patientsurvives,the 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.

Drop-outs were calculated from numbers in a french database. Patients were followed-up from one six month period to the next. Patients who entered and left and those still present during the previous six month period were calculated for each six month period. Of those who left the system, some re-entered the system during a six month period and others dropped-out of the study.

There were 575 patients present during the first six months of 1993. Of these 575 patients, 516 were followed-up to the second six month period of 1993. 59 patients left between the first and second six month periods of 1993 (575-516). The 59 patients who left were followed-up during the period 1993 to 1995; 17 re-entered during the first six months of 1994, and 7 during the second six months of 1994, 3 during the first six months of 1995 and 1 during the final six months of 1995. 31 patients dropped-out of the system permanently; these are the actual drop-outs during the first six month period of 1993. The drop-out rate in the first six month period of 1993 was 5.4% (31/575). This procedure was repeated during the subsequent six month periods.

Figure 1: **Follow-up of Pau patients**

1st cycle	numbers	N1=575		left = S1=59

	DO	E3	E4	E5	E6
	31	17	7	3	1

D0 rate at 6 months: 5.4%

2nd cycle

	N1-S1=516
	+
ENTERED	75
	=
numbers	N2=591

left S2=87

	DO	E4	E5	E6
	66	13	5	3

D0 rate at 6 months: 11.2%

3rd cycle

	N2-S2=504
	+
ENTERED	73
	=
numbers	N3=577

of which, 17 were re-entrants

left S3=64

	DO	E5	E6
	43	17	4

D0 rate at 6 months: 7.4%

4th cycle

	N3-S3=513
	+
ENTERED	82
	=
numbers	595

of which, 20 were re-entrants (7S1 and 13S2)

left = S4=82

	DO	E6
	62	20

D0 rate at 6 months: 10.4%

5th cycle

	N4-S4=513

Table 2: Calculation of drop-out rates (French data base)

	Year 1993 1st 6 months	Year 1993 2nd 6 months	Year 1994 1st 6 months	Year 1994 2nd 6 months	Mean
DO rate	5.39% (31/575)	11.48% (66/591)	7.45% (43/577)	10.42% (62/595)	8.69%

The drop-out rate applied to the model was the mean drop-out rate for each six month period.

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): Other less serious conditions, but which are also incapacitating, are drowsiness, weight gain and sexual dysfunction.

The adverse event rates were taken from registration dossiers for the 4 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: 19% (18/97) than for its competitors:28%(19/97) for Risperidone, 48% (237/489) for haloperidol and 28% (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 (20.6%) for sertindole and 15.7% and 11% respectively for Risperidone and haloperidol. Conversely, more sexual dysfunction occurred with sertindole than with haloperidol (2%)or olanzapine (1%), or risperidone(0%)although this affected only 2.8% of patients treated (3/54). 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.

These problems will influence compliance, defining two categories of patients: compliant patients (com+) and non-compliant patients (com-).The degree to which patients comply was assume to be the same across medication regimens but were differentiated according to the side effects they experienced. EPS and dizziness are more closely related to poor compliance (0.20) than other side-effects (0.40) 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 that 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

We require estimates of the probability an individual suffering from schizophrenia is in long-stay inpatient care and, for those who are not long-stay patients, the probability distribution across our remaining four categories of care, conditional on relapse status. These estimates provide the probabilities to be attached to the various decision tree nodes.

Kavanagh et al. (1995, Table 1, p.207) used various surveys to estimate the cross-sectional distribution of individuals with schizophrenia across the following locations: long-stay hospital inpatient wards, short-stay inpatients wards, specialist supported accommodation, prison, private residences and homelessness. We have used these estimates, together with data from the RCS, to derive the required probabilities. Since prisoners and the homeless are not included in our model, we have excluded these groups from the denominator and re-calculated the distribution of schizophrenics across the remaining locations.

A further problem to overcome in using the Kavanagh et al. (op cit) estimates is how to deal with individuals identified in short-stay inpatient care. In our model, individuals are allocated to their usual place of residence in each six month period and this cannot be short-stay (i.e. acute) inpatient care. Individuals identified as short-stay inpatients at a point in time must therefore be distributed across the other residential settings. This could be done with greatest accuracy if information were available on the distribution of short-stay psychiatric inpatients according to the type of accommodation from which they were admitted. Unfortunately, such information is not available. Given this data constraint, we presumed that, by definition, short-stay inpatients cannot be admitted from long-stay psychiatric care and assumed the proportion of short-stay inpatients admitted from private residences and supported accommodation

respectively are the same as the distribution of the non-inpatient population across these two types of accommodation.

With the above amendments, the Kavanagh et al. (op cit) figures provide estimates of the distribution of schizophrenics across long-stay inpatient care, specialist supported accommodation and private residences. In relation to our model, the term " specialist supported accommodation" covers the categories ICC, MCC and IPC and " private residences " is the category MPC. The distribution of individuals across the three locations - long-stay hospital, special supported accommodation and private residences - therefore, gives the probabilities of being a chronic or a non chronic patient. From the RCS, we observe the distribution of individuals across the categories ICC, MCC and MPC which allows disaggregation of the non chronic patient into the 4 community care categories

In the model, individuals who are not long-stay patients are split according to whether or not they experience a relapse within a six-month cycle. It is possible that relapse may change both the probability of locating in each of the remaining four categories of care and service utilisation, and so costs, within each of these categories. To obtain the estimates necessary to incorporate both effects, ideally one would examine a data set which identified relapse patients and monitored the impact of relapse on the distribution across residential setting (category of care) and service utilisation. Unfortunately, such a data set does not exist.

The closest correlate of relapse recorded in the RCS is whether the individual had a psychiatric inpatient stay in the previous 6 months[4]. We have identified relapse cases using this variable. That is, we assume, anyone who is not a long-stay inpatient, but who has had a stay in a psychiatric hospital in the previous six months has suffered a relapse[5]. Relapse has been defined as hospitalisation elsewhere in the literature (Lader, 1995). Since approximately two-thirds of schizophrenics relapse patients are hospitalised in the UK (Hale and Wood, 1996), use of this proxy will identify most, but not all, relapse cases. However, given that relapse has the greatest cost consequences when patients are hospitalised, using hospitalisation to define relapse means the proportion of the costs of relapse identified will exceed the proportion of relapse cases identified. If one is mainly interested in identifying relapse in order to estimate the cost consequences of relapse, hospitalisation may be a good indicator.

Using the hospitalisation rule for relapse, there are 59 patients in the relapse group (30 in MCC, 20 in ICC and 9 in PCGH) and 695 in the non-relapse group (290 in MCC, 280 in ICC and 125 in PCGH).

Every individual following the relapse branch of the model has a stay in an acute psychiatric ward irrespective of their usual residential setting (category of care). No data are available which allow one to establish whether relapse changes the distribution of individuals across the usual residential settings after discharge from acute inpatient care. We therefore assume the probability of an individual locating in each of the categories of care is the same whether or not they experience relapse (hospitalisation). This means, on average, patients are assumed to

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[4]   *The RCS was cross-sectional and so it is not possible to use a change in recorded symptomology or functioning to indicate relapse status.*
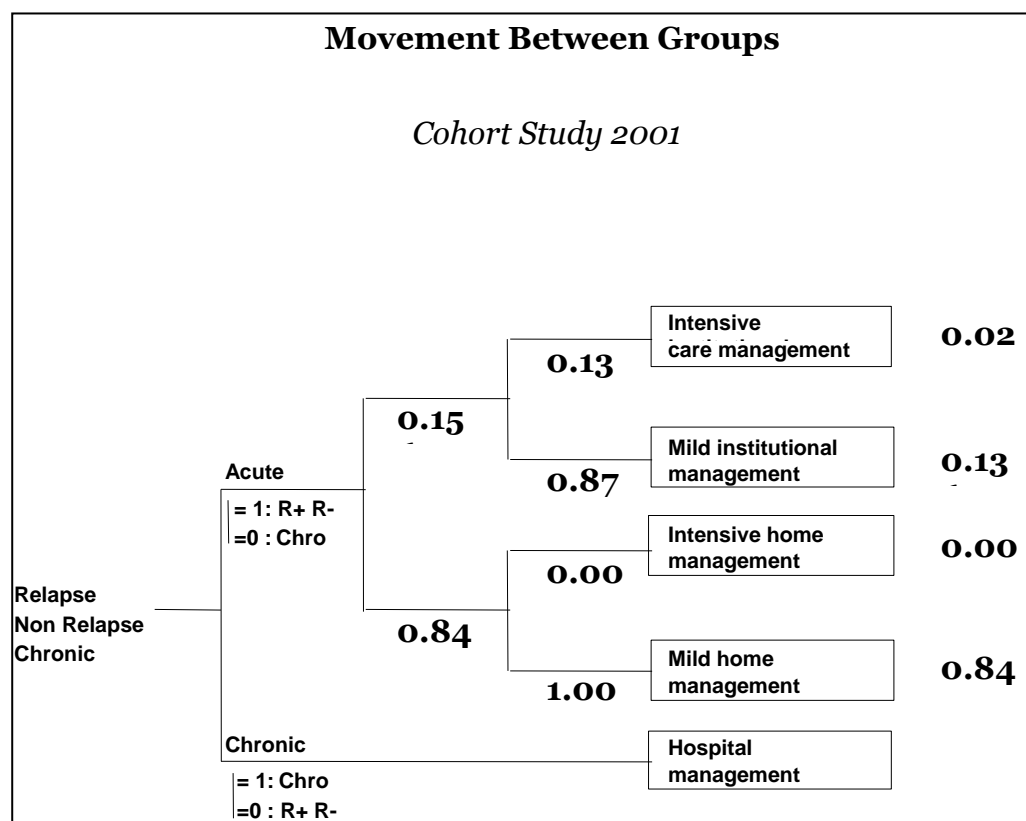
[5]   *The data set did not provide information on the duration of each inpatient stay and so it was not possible to identify relapse cases through an inpatient stay above a certain threshold.*

return to their original location of care after each period of acute inpatient care following relapse. The estimated probabilities for each of the categories of care are presented in Table 1.

Table 18: Probability distribution across categories of care[6]

L-S Hospital	ICC	MCC	IPC	MPC
0.	0.020	0.0136	0.000	0.844

Patient trajectories (fig. 1-D) by care group were calculated from a transverse English study (1051 patients).

Movement Between Groups

Cohort Study 2001

Acute

= 1: R+ R-
=0 : Chro

Relapse
Non Relapse
Chronic

Chronic

= 1: Chro
=0 : R+ R-

0.15

0.13 → Intensive care management — 0.02

0.87 → Mild institutional management — 0.13

0.84

0.00 → Intensive home management — 0.00

1.00 → Mild home management — 0.84

Hospital management

Resources consumed

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, month

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[6] *p_1 is the probability an individual with schizophrenia is in long-stay inpatient care. The remaining probabilities give the likelihood that schizophrenics who are not long-stay inpatients are located in each of the respective residential settings. The later probabilities sum to 1.*

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.

Table 1 Mean six-month service utilisation and costs (£, 1998) per patient by relapse status

Service	Non-relapse (n=68)		Relapse (n=77)	
	Mean	**Costs (£)**	**Mean**	**Costs (£)**
Inpatient (days)[**]	0.0	0.0	57.8	6,451.2
Outpatient – psychiatric (visits)[**]	1.4	135.3	2.1	209.1
Outpatient – other (visits)[*]	0.1	8.3	0.3	18.8
Day hospital (visits)[*]	2.3	132.8	2.1	125.7
Community mental health centre (visits)[1*]	2.4	43.7	1.4	25.2
Day care centre (visits)[**]	5.9	105.6	0.9	15.4
Group therapy[1*]	0.4	6.4	0.1	2.3
Sheltered workshop[*]	1.1	44.5	0.0	0.0
Specialist education[1*]	2.9	51.9	0.0	0.0
Other (not specified)[*]	0.6	11.6	0.0	0.0
Visits by:				
Psychiatrist[**]	2.5	102.6	2.3	269.4
Psychologist[*]	0.0	0.0	0.0	1.9
General Practitioner[*]	1.8	217.0	1.6	152.2
District Nurse[*]	0.1	0.9	0.0	0.0
Community Psychiatric Nurse[*]	12.6	1,014.3	5.2	791.0
Social Worker[*]	0.1	24.0	0.4	106
Occupational Therapist[*]	0.0	0.6	0.8	43.7
Home Help/ Care Worker[*]	0.4	0.0	0.6	0.0
TOTAL COSTS[**]		**1,899.3**		**8,212.0**

1 Costs not available – set equal to cost for day care centre
* Independent t-test not significant at p=0.05, ** significant at p<0.05 (similar results achieved using non-parametric tests)

Allocating values to costs

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 £65.61 for 6 months. the costs of sertindole (16 mg/day) was £582.40.The cost of risperidone(5 mg/day) was £590.86 and of olanzapine (15 mg/day) was equal to£951;21 for a 6 month treatment period.

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 (£$_{01}$)

Country	LS Hospital.	Intensive Collective Care	Mild Colletive Care	Mild Personnal Care
ENGLAND				
Relapse	25 632	4 476	8 285	8 285
Full inpatient hospitalisation	(100 %)	(70.23%)	(0.0 %)	(0.0 %)
Day and overnight hospitalisation	(0.0 %)	(1.87 %)		(5.00%)
Outpatient encounters	(0.0%)	(28.1 %)		(95.00%)
Non relapse	1071	1240	2 114	2 114
Full inpatient hospitalisation	0	0	(0.00 %)	(77.51 %)
Day and overnight hospitalisation	0	0	(47.17 %)	(1.53 %)
Outpatient encounters	(100 %)	(100 %)	(52.03 %)	(20.86 %)

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: $\Box C/\Box E = (\Box CMC + \Box CIC - \Box CH)/\Box Q$

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; $\Box$ = 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.

II. RESULTS

Description of the population

The initial distribution between different states in the model was the same as the distribution of the population by categories of care in a cross. The distribution of these patients' clinical states was the following. The mean relapse rate per 6 month period was 13% . Conversely, numbers of patients who did not relapse differed in the opposite direction: 276 patients did not relapse per 6 months at site 1 The distribution of patients who either did or did not relapse in the different care groups reflected the diversity of the clinical states s: 22% of the relapsed patients received high dependency management . The incidence of intensive and mild outpatient management was consistent with the policy of systematic de-institutionalisation, in which 94% of relapsed patients were followed up in home care structures or in community care. Not surprisingly, the category of care for non-relapsed patients was predominantly mild cares (83% of these patients).

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. Sixty tree per cent of patients treated with sertindole remained on treatment during this period. Twenty seven per cent were lost to follow up and 10% die. 36% of patients maintained on treatment (completers relapsed and 36% stabilised. The likelihood of relapse on treatment was therefore 0.36.

Sixty-tree percent of patients treated with haloperidol remained on treatment during the same period, 27% gave up treatment and 10% died.) were long term institutionalised in a hospital; 53% per cent of patients maintained on treatment (completers) relapsed and 27% were stabilised. The likelihood of relapsing on treatment was therefore 0.47 %.

The relative cumulative risk of relapse on haloperidol compared to sertindole is therefore 0.47/0.36 or 1.28. The risk of relapse on haloperidol is therefore more than 28% higher than on sertindole. Similarly, we found that the risk of relapse on olanzapine was 16 % higher than for sertindole.

The numbers of 6 month cycles without relapse after 10 years were 8.05, 7.95, 7 31 and 6.72 for sertindole, risperidone , olanzapine and haloperidol respectively, i.e. 48.3 months without relapse for sertindole compared to 47.6 months for risperidone ,43.9 months for olanzapine and 40 3 months for haloperidol. Patients on sertindole therefore benefit by 4.4 months and compared to olanzapine and by 8 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 £64472 for sertindole, £64491 for riperidone,£68494 for haloperidol and £68541for olanzapine ..

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 relapsers on haloperidol were more expensive than those on sertindole: £56,793 versus £47,959;, equivalent to a difference in cost of £8,900 between the two drugs in acute patients; some of the funds released are, however, absorbed in the management of patients who do not relapse but the costs of non-relapsers on sertindole is only sligtly higher than those for haloperidol (£16513 compared to £16241).

Table 3: Expected 10 year costs per patient by clinical status (£$_{01}$)

Country	Sertindole	Haloperidol	Olanzapine	Risperidone
ENGLAND				
Relapse	47 969	56 793	50 097	46 570
Non relapse	16 513	11 706	15 444	16 241
Total	64 472	68 499	68 541	64 911

- : If medical expenditure by category of care is compared (Table 4), we see that the costs of patients treated with sertindole who receive standard and intensive management in their home are lower than those for haloperidol, Olanzapine and Risperidone (£36, 825 versus 40,728; £40,728 £40,724; £37,238).

Table 4: Expected 10 year costs per patient by categories of care (£01)

Country	Sertindole	Haloperidol	Olanzapine	Risperidone
ENGLAND				
Mild care	36 825	40 728	40 577	37 238
Intensive care	3 414	3 538	3 731	3 440
Hospital	24 232	24 232	24232	24 232
Total	64 472	68 499	68 541	64 911

Hospital cost is the same for the three products because we considered that the four products had the same drop out rate and that relapse re-enter into the mental health sector two years later through a long stay hospitalisation for 6 months..

- If results are examined by professional service, we see that sertindole reduces the costs of full inpatient hospitalisation by £7 111 [[49502] -42,391], compared to haloperidol for all relapsers and non-relapsers combined, although it increases the cost of outpatient care (+$232) and drug costs (+£ 2 852) : ([352+2664] –[31+132]). 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 £4000 over 10 years or £400 per annum.

Table 5: Expected 10 year costs per patient by professional service (£01)

Country	Sertindole	Haloperidol	Olanzapine	Risperidone
ENGLAND				
Relapse	**47 959**	**56 792**	**53 097**	**48 670**
Full inpatient hospitalisation	42 391	49 502	46 362	42 953
Day and overnight hospitalisation	367	511	448	378
Outpatient encounters	4 848	6 746	5 908	4 998
drug cost	352	31	379	340
Non relapse	**16 313**	**11 706**	**15 444**	**16 241**
Full inpatient hospitalisation	0	0	0	O
Day and overnight hospitalisation	873	730	792	862
Outpatient encounters	12 976	10 845	11 786	12 807
drug cost	2 664	132	2 865	2 133
Total	64 472	68 499	68 541	64 491

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 Risperidone	Risperidone vs Olanzapine	Olanzapine vs Haloperidol	Sertindole vs Haloperidol
Incremental effectiveness				
Effectiveness *(discount rate 0 %)*	0.6 months	3.8 months	3.6 months	8 months
Utility				
Incremental cost (£2001)				
Cost *(discount rate 3%)*	-£439	-£3,630	+£41	-£4028
Incremental cost-effectiveness ratio	Sertindole dominates	Riperidone dominates	Olanzapine dominates	Sertindole dominates
ENGLAND				

CONCLUSION

First line treatment of a schizophrenic patient with sertindole produces a benefit of 1.8 months without relapse compared to treatment with haloperidol and 20 days compared to treatment with risperidone and 40 days compared to treatment with olanzapine. Over 10 years the sertindole relative advantage over its competitors seems to be modest.

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Figure 2: Markov Model in Schizophrenia over 10 years
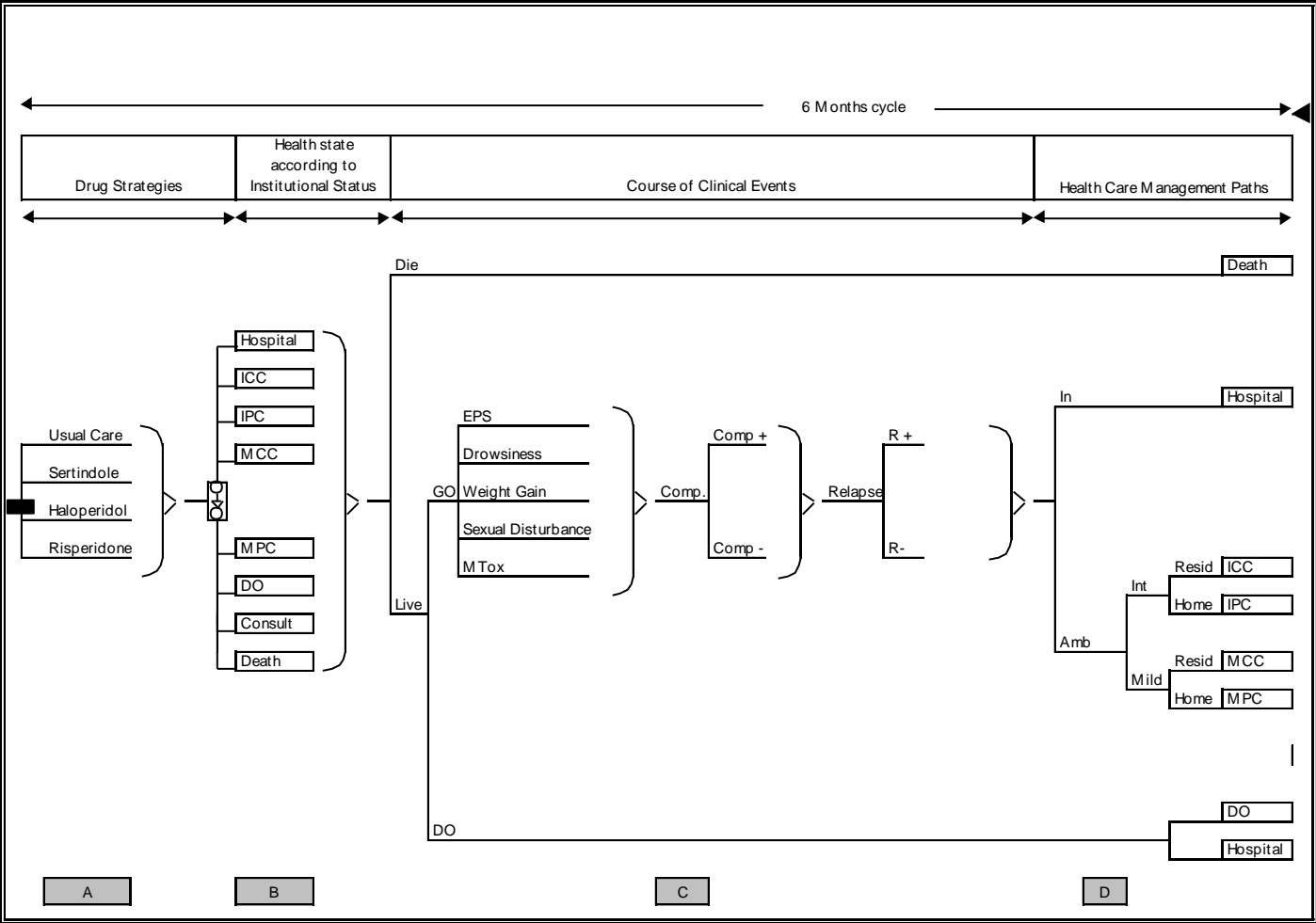
Figure legends

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.