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A cost-effectiveness analysis of AOTAL, a drug used to prevent relapse in weaned alcoholics

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A b s t r a c t

This paper offers a theoretical framework to evaluate the treatment of weaned alcoholics with a drug (AOTAL), used to prevent them from relapse. The model built is a Markov model. It describes the cyclical treatment history of alcoholics, moving between periods of treatment in an inpatient setting for detoxification or for complications, and periods with ambulatory treatment or periods without any treatment.

Transition probabilities (the probabilities for AOTAL and for a placebo to move from one treatment setting to another) are taken from the literature and from clinical trials.

Also the costs of the different treatment settings are calculated. The results of the model are obtained by linking treatment costs and treatment probabilities of AOTAL versus a placebo. In a most optimistic 'low boundary' variant, within a 3-year period, the use of AOTAL results in a net-benefit. The least optimistic 'high boundary' variant nearly always results in net-costs. In this case one calculates cost-effectiveness in terms of costs per additional life year.

In a sensitivity analysis, one measures the sensitivity of the end results for changes in important parameters : the relapse probabilities and the price of AOTAL.

1. Introduction

1.1. Alcoholism

From the literature we know that alcoholism is not an ordinary disease with a clear starting point, a treatment period and an end point. On the contrary, alcoholism is a complex phenomenon, with many possible medical conditions to be treated and with a cyclical course of development.

There is a variety of types of alcohol abuse (CARRIN and DE GRAEVE [1988]). The entire progression lies on a continuous spectrum from social drinker to heavy drinker to early alcoholic to moderate alcoholic. In our analysis we start from the observation that for most alcoholics there is an addictive cycle because of a physical dependence on alcohol. Withdrawal symptoms stimulate drinking which in fact has become irresistible.

The negative effects of alcohol abuse on the alcoholic's physical condition are many. Consumption of large quantities leads to organ damage (especially the liver), brain dysfunction, cardiovascular and mental diseases. The latter also explains why alcohol abuse has a significant effect on mortality rates. Alcohol abuse has also a large effect on society in general: alcohol is a major factor in divorce, and in automobile, motorcycle, home and industrial accidents. Clearly succesful treatment methods of alcoholism are very much warranted in view of the benefits (individual as well as societal) to be obtained from reducing morbidity, mortality and social damage in general.

1.2. Treatment

Once the addictive cycle is started, the alcoholic needs to be helped first in stopping to drink while controlling the withdrawal symptoms. In addition, medical illnesses (physical

or psychological) resulting from alcoholism have to be adressed.

On the whole one seems to accept that the ethiology of alcoholism is very complex; an array of various cultural, economic, relational, psychological and biological factors may be at the root of an alcoholic's problem. This complexity explains why treatment programs usually have a modest success rate. Marlatt and Gordon [1980], who made an extensive study on relapse rates and its determinants, find relapse rates of 78% in the first 90 days upon release from hospital. Therefore, a very broad treatment approach seems to be warranted. Drug treatment may of course be part of this approach.

1.3. A cost-effectiveness analysis

The question to be answered in this study, is whether the costs of treating alcoholics with the drug AOTAL (to prevent them from relapse) does outweigh the costs that can be avoided by the fact that more alcoholics are (temporarily) weaned. If there are no cost savings, the question becomes how much has to be paid to gain life years in alcoholics by treating them with AOTAL.

For the cost-effectiveness analysis, we will build a model in which **ex post** collected data concerning clinical probabilities and costs are linked together. These data are collected from earlier clinical trials, epidemiological research, a literature review and investigation of patient files.

Since alcoholics have relapses, moving between treatment periods in several settings and periods of abstinence[1], we decided to use a Markov model. Section two describes this model and discusses further the rationale behind the choice of this particular methodology.

In sections three and four we present all clinical data and cost data used in the Markov model. Section five discusses the results (net costs or net benefits). For the cases where net costs are obtained, incremental analysis is performed and cost-effectiveness is expressed in terms of costs per life year gained or costs per quality-adjusted lifeyear. The sensitivity of these results to some parameters (more specifically the price of the drug and its effectiveness) will be analyzed in section 6. The effect of these changes on final results gives useful information for interpreting the model. We conclude in section seven.

2. A markov model for alcoholism

2.1 Principles of a Markov model

From the previous, we know that relapse rates are particularly high in alcoholics. Most patients have a cyclical history of periods of treatment and no treatment. This complicates the modelling of alcoholism by a decision tree. We would obtain an extremely large decision tree with many repetitions and (uncertain) probabilities. Moreover, expert interviews to obtain probabilities and cost data would become quite complicated.

An alternative to the decision tree model is the Markov model (for the basics, see STOKEY and ZECKHAUSER 1978). A Markov model describes how a system evolves probabilistically over time. The system is at any given time in one of a finite number of states with a corresponding probability. To describe changes in the system over time, one needs to know the probability of making a transition from each possible initial state to each final state.

In general, **three conditions** are crucial to a Markov process.

1) There must be a finite number of well defined states. These states have to be exclusive. In our model this means that all treated alcoholics have to belong to one of the states we will define later. Nobody can enter or leave the process. However, a state can be defined from which it is not possible any more to move to another state (e.g. dead).
2) The transition probabilities remain constant over all periods. For instance, the probability to become weaned after hospital treatment is identical, whatever the history of the patient. It can also be said that the probabilities have no memory.
3) The sequential time periods must remain equal in length during the whole process.

2.2 The transition possibilities for the alcoholic

We distinguish eight different states for the alcoholics. First, the alcoholic can receive an ambulatory treatment (AT). Next, in Belgium there are three main inpatient settings for alcoholism treatment: 2) the psychiatric hospital (PH), 3) the psychiatric ward in a general hospital (PWGH), and 4) the general hospital (GH). It is important to distinguish between these 3 settings since they imply quite different treatment methods with different costs. In addition, an alcoholic can be in four other situations: 5) temporarily weaned (WA), 6) in hospital for a physical complication (PhCom) or 7) for a mental complication (PsCom) due to alcoholism, and 8) at last, he may be dead (dead).

Since there are eight states, we have 64 (8 x 8) transition probabilities. The transition probabilities are estimated for a time period of three months (section 3). We choose this duration since most relapse probabilities were available for 3 month periods.

3. Transition probabilities for the Markov model

In this section, all transition probabilities of the Markov matrix will be determined. The transition matrix of the alcoholics receiving AOTAL will be different from the matrix of alcoholics receiving placebo. With AOTAL, the probability to become weaned is enlarged. Since row probabilities have to sum to one, this will be reflected in the other transition probabilities as well. In section 3.1, probabilities derived from the results of the clinical trials will be calculated. We will first compute the transition probabilities to become weaned after inpatient detoxification[2]. We then calculate the probabilities to remain weaned. All remaining probabilities will be estimated in section 3.2.

Table 6 summarizes all calculated probabilities.

3.1 Basic clinical probabilities

Two clinical trials (LHUINTRE [1985], and PELCK [unpublished]) demonstrate that AOTAL is more effective than placebo to prevent relapse in weaned alcoholics.

The LHUINTRE-trial is a randomised double-blind trial including 85 severe alcoholics (>200 g/day), who are alcohol dependent. The treatment started with hospitalisation during 5 days for weaning, with standard supportive and preventive measures for withdrawal symptoms. No specific therapy was given. Afterwards, patients were randomly assigned to two groups, one receiving placebo and one receiving AOTAL. The patients were seen every month during three months.

The PELCK-trial is a randomised double blind trial in 5 Belgian psychiatric centres with chronic pharmacodependent[3] patients admitted for weaning. Placebo or AOTAL is given after hospital treatment of two or three weeks.

The results of the two trials are presented in the tables 1 and 2. Firstly, we give the results for the "intended to treat" cohorts including patients who do not comply ("lost" patients). Secondly, we give the results for the cohorts that remained in the trial until one of the evaluation times (excluding "lost" patients). Differences between placebo and AOTAL are significant (CHI^2 test with probabilities p = 0.068, p = 0.178 and p = 0.017 for days 30, 90, and 180 respectively for the Pelck Trial and p = 0.02 for the l'Huintre trial).

Table 1 : Results of the clinical trials for the "intended to treat" cohorts (probabilities)

PELCK :

Treatment group	Placebo			AOTAL		
Results on day	30	90	180	30	90	180
Lost	0.28	0.57	0.80	0.13	0.38	0.57
Relapse	0.30	0.15	0.11	0.24	0.20	0.11
Weaned	0.43	0.28	0.09	0.64	0.42	0.31
(N = 102)						

LHUINTRE :

Treatment group	Placebo	AOTAL
Results on day	90	90
Lost	0.14	0.21
Relapse	0.58	0.31
Weaned (N = 85)	0.28	0.48

Table 2 : Results of clinical trials for the group that remained in the trial until evaluation on day 30, day 90 or day 180 (probabilities)

PELCK :

Treatment group	Placebo			AOTAL		
Results on day	30	90	180	30	90	180
Relapse	0.41	0.35	0.55	0.27	0.32	0.26
Weaned	0.59	0.65	**0.45**	0.72	0.68	**0.74**

LHUINTRE :

Treatment group	Placebo	AOTAL
Results on day	90	90
Relapse	0.68	0.39
Weaned	**0.32**	0.61

The **basic transition probabilities** for the Markov model are the following :

- The probability of being weaned during a second three-month period, after treatment in a first three-month period, for the different treatment settings.
- The probability of remaining weaned in a second three-month period, after being weaned during a first three-month period.

For the calculation of these probabilities we use the data in table 2.

The probability of being weaned after treatment
We first calculate **the probability of being weaned during period 2, after treatment in period 1.**

The figures in table 2 are expressed as a percentage of all patients who did fully comply with the treatment.
In reality, a great deal of the patients do not comply however, as the figures in table 1 show. To deal with this problem we adjust the figures in the AOTAL group. We assign the probabilities of the placebo group to the patients who do not comply. The rationale is that these patients cannot benefit from the drug and therefore are assumed to experience the same effects as patients who simply take placebo. The new figures are given in table 3.

Table 3 : Results of clinical trials, adjusted for non-compliance

PELCK :

Treatment group	Placebo			AOTAL		
Results on day	30	90	180	30	90	180
Relapse	0.41	0.35	0.55	0.30	0.33	0.43
Weaned	0.59	**0.65**	0.45	0.70	**0.67**	0.57

LHUINTRE :

Treatment group	Placebo	AOTAL
Results on day	90	90
Relapse	0.68	0.45
Weaned	**0.32**	**0.55**

In our model we suppose that the LHUINTRE figures correspond to the Belgian general hospital setting where patients are admitted only during a short period without receiving specific therapy.

The probability to be weaned during a second period of three months after treatment in a first period of three months is given by figures on day 180. However, since we do not have such figures for the LHUINTRE trial we will use the figures on day 90. The latter (adjusted for non-compliance) costitute element 4E (table 6).

The PELCK figures correspond to psychiatric settings (PH, PWGH). The figures on day 180 constitute elements 2E and 3E (table 6).

The probability to remain weaned

We now calculate the **probability of remaining weaned in period 2 after being weaned during period 1.**
The best data we have for this probability are from the PELCK trial. Table 4 gives cumulative percentages of weaned alcoholics during successive periods, for the placebo group and the AOTAL group. The percentages are for the "intended to treat cohort".

Table 4 : Complete periods of abstinence. Cumulative percentages from the PELCK trial (percentages are for the "intended to treat" cohort)

Period of abstinence	Treatment group	
	Placebo	AOTAL
>30 days	0.45	0.66
>60 days	0.38	0.61
>90 days	0.26	0.48
>120 days	0.21	0.40
>150 days	0.11	0.28
>180 days	0.04	0.25

The probability that the patient remains abstinent during two consecutive periods, is given by the percentage abstinent patients on day 180, given abstinency on day 90. In the

placebo group this is **0.15** (0.04/0.26). In the Aotal group this is **0.52** (0.25/0.48).

When applying these probabilities to the transition matrix, we have to take into account that, in the AOTAL variant, not all patients in the "weaned" status have been treated with AOTAL in the previous period. More specifically, patients who have been treated ambulatory or for mental or physical complications did not receive AOTAL. Hence these patients, when transitted to the weaned status, will not receive the drug either. Their probability to remain weaned is the same as that of patients receiving a placebo, that is 0.15. More specifically this applies to 50% of the patients in the "weaned" status. The other 50% of the patients is taking the drug AOTAL, and hence experiences a probability of 0.52 to remain weaned in the next period. The average for all weaned patients is thus 0.33 (0.50 x 0.15 + 0.50 x 0.52), which constitutes element 5E in table 6.

3.2 Other probabilities

Calculations of the probability of readmission in a psychiatric ward or in a psychiatric hospital (element 2B, 2C, 3B, 3C), of being weaned after a period of ambulatory treatment (element 1E) or after treatment for complications (elements 6E and 7E), and of the probabilities of physical (1F, 2F, 3F, 4F, 7F) and mental complications (1G, 2G, 3G, 4G, 6G, 7G) and of death rates (1H, 2H, 3H, 4H, 6H, 7H) are all based on a literature review. Literature sources and specific hypotheses made for the calculations can be found in TORFS and DE GRAEVE [1990]. They are summarized in table 5.

For all remaining transition probabilities, no specific figures could be found. They are calculated mathematically. We proceed as follows. We sum the known probabilities in each row. Since we know the sum of all probabilities in a row should equal one, we can calculate the "rest probability". This rest probability

is distributed to the unknown probabilities weighted by the number of alcoholics in the several treatment groups.

Since most of the probabilities are not known with certainty, we introduce two variants. In a high boundary variant, we assume there is a maximum number of 65,909 alcoholics. As we have absolute numbers of physical and mental complications, this leads to rather low transition probabilities for these states. In a low boundary variant, the number of alcoholics is reduced to a minimum of 19,460. As a result transition probabilities for mental and physical complications increase. Since row probabilities sum to one, the change is reflected in the other transition probabilities as well.

Table 5 : Calculation of transition probabilities

Transition probability	Source / Comments
2E 3E 4E 5E	clinical trial data
8A 8B 8C 8D 8E 8F 8G 8H	transition from death to other states is not possible
1H 2H 3H 4H 6H 7H	SCHIPPERS [1982] death rate of alcoholics are 2.5 times the death rate of a normal population
5H	SHERLOCK [1982]
1E	LUDWIG [1988]
6E 7E	SHERLOCK [1982]
1F 2F 3F 4F 7F	epidemiological data based on DE ZWART [1989], HOOGENDOORN [1983b], National Cancer Registry [1989], LOBET [1986] . probabilities of complications are irrespective of the setting . low boundary estimation based on an absolute number of 19,460 alcoholics . high boundary estimation based on an absolute number of 65,909 alcoholics
5F 6F	. We assume that after a 3 month treatment for physical complications or being weaned the transition probability for physical complications is zero
1G 2G 3G 4G 6G	epidemiological data based on DE ZWART [1989] . probabilities of complications are irrespective of the setting . low boundary estimation based on an absolute number of 19,460 alcoholics . high boundary estimation based on an absolute number of 65,909 alcoholics
5G	we assume that after being weaned, the probability for a mental complication is zero
7G	we assume that 30% of all mental complications is chronical
2B 2C 3B 3C	BREDA AND VAN REGENMORTEL [1989] based on readmission rates for psychiatric patients in general . we assume that readmission probabilities reduce for the AOTAL group, when the probability of being weaned enlarges
all other probabilities	no data are available: mathematical calculation rest probability = 1 - Σ known probabilities rest probability is distributed to the unknown cells weighted by the number of alcoholics in the several treatment settings

Table 6 : Transition Matrices

a) Transition matrix for low boundary data. Placebo treatment

PERIOD 2

Period 1		AT A	PH B	PWGH C	GH D	WA E	PhCom F	PsCom G	Dead H
AT	1	0.590	0.066	0.016	0.027	0.13	0.157	0.01	0.0041
PH	2	0.249	0.10	0.02	0.010	**0.45**	0.157	0.01	0.0041
PWGH	3	0.268	0.03	0.07	0.011	**0.45**	0.157	0.01	0.0041
GH	4	0.430	0.048	0.012	0.019	**0.32**	0.157	0.01	0.0041
WA	5	0.716	0.081	0.020	0.032	**0.15**	0.0	0.0	0.0016
PhCom	6	0.621	0.070	0.017	0.028	0.22	0.0	0.01	0.0340
PsCom	7	0.107	0.012	0.003	0.005	0.08	0.157	0.632	0.0041
Dead	8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0

b) Transition matrix for low boundary data. AOTAL treatment.

PERIOD 2

Period 1		AT A	PH B	PWGH C	GH D	WA E	PhCom F	PsCom G	Dead H
AT	1	0.590	0.066	0.016	0.027	0.13	0.157	0.01	0.0041
PH	2	0.159	0.078	0.015	0.007	**0.57**	0.157	0.01	0.0041
PWGH	3	0.174	0.023	0.055	0.007	**0.57**	0.157	0.01	0.0041
GH	4	0.235	0.026	0.006	0.011	**0.55**	0.157	0.01	0.0041
WA	5	0.564	0.063	0.015	0.025	**0.33**	0.0	0.0	0.0016
PhCom	6	0.621	0.070	0.017	0.028	0.22	0.0	0.01	0.0340
PsCom	7	0.107	0.012	0.030	0.005	0.08	0.157	0.632	0.0041
Dead	8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0

c) Transition matrix for high boundary data. Placebo treatment.

PERIOD 2

Period 1		AT A	PH B	PWGH C	GH D	WA E	PhCom F	PsCom G	Dead H
AT	1	0.685	0.019	0.010	0.103	0.13	0.046	0.003	0.0041
PH	2	0.328	0.10	0.02	0.049	**0.45**	0.046	0.003	0.0041
PWGH	3	0.346	0.03	0.07	0.052	**0.45**	0.046	0.003	0.0041
GH	4	0.525	0.014	0.008	0.08	**0.32**	0.046	0.003	0.0041
WA	5	0.711	0.019	0.010	0.108	**0.15**	0.0	0.0	0.0016
PhCom	6	0.623	0.017	0.009	0.094	0.22	0.0	0.003	0.0340
PsCom	7	0.199	0.005	0.003	0.03	0.08	0.046	0.632	0.0041
Dead	8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0

d) Transition matrix for high boundary data. AOTAL treatment.

PERIOD 2

Period 1		AT A	PH B	PWGH C	GH D	WA E	PhCom F	PsCom G	Dead H
AT	1	0.685	0.019	0.010	0.104	0.13	0.046	0.003	0.0041
PH	2	0.246	0.078	0.015	0.037	**0.57**	0.046	0.003	0.0041
PWGH	3	0.260	0.023	0.055	0.039	**0.57**	0.046	0.003	0.0041
GH	4	0.333	0.009	0.005	0.05	**0.55**	0.046	0.003	0.0041
WA	5	0.560	0.015	0.008	0.085	**0.33**	0.0	0.0	0.0016
PhCom	6	0.623	0.017	0.009	0.094	0.22	0.0	0.003	0.034
PsCom	7	0.199	0.005	0.003	0.03	0.08	0.046	0.632	0.0041
Dead	8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0

4. Cost data

All costs are calculated for three month treatment periods.

4.1 Costs of the different treatment options

The costs of ambulatory treatment comprise the costs of GP-consultations, drugs and referrals. Since we know the total number of GP visits for alcohol problems in one year, the costs per alcoholic will vary according to the assumed number of alcoholics (LB, HB). Costs of treatment in a psychiatric hospital or in a hospital's psychiatric department are based on information about the average length of stay of alcoholics and of real total costs of alcoholics in a psychiatric department of one hospital. The same average daily cost is used for mental complications as well. Costs of treatment in a general hospital derive from a registration project in three university hospitals. The same holds for costs of some of the physicial complications. Various epidemiological data are used to weight the costs associated with the different complications. For weaned alcoholics, we used the same costs as for the ambulatory treatment. No specific costs are connected to the death state.

More detailed information on all hypotheses and calculations can be found in Torfs and De Graeve [1990]; a summary is provided in table 7.

Table 7 : Cost data: sources and hypotheses

Quantity	Cost/unit	Total costs	Source/comments
TREATMENT SETTING: AMBULATORY			
1.25 GP visits	388	425	LOBET [1986]: 65,909 GP-contacts per year deal with alcohol problems LB-number of alcoholics = 19,468
0.25 GP visits	388	97	idem, HB-number of alcoholics = 65,909
0.59 GP drugs	424	250	LOBET [1986]: 47% of contacts ends with a prescription LB-number of alcoholics = 19,468
0.12 GP drugs	424	50	idem, HB-number of alcoholics = 65,909
0.14 specialist visits	1,168	163	LOBET [1986]: 11% of contacts end with referral to a specialist LB-number of alcoholics = 19,468
0.03 specialist visits	1,168	35	idem, HB-number of alcoholics = 65,909
0.14 specialist drugs	424	59	assumption: all specialist visits end with a prescription LB-number of alcoholics = 19,468
0.03 specialist drugs	424	13	idem, LB-number of alcoholics = 65,909
TOTAL		879 195	LB-number of alcoholics = 19,468 HB-number of alcoholics = 65,909
TREATMENT SETTING: PSYCHIATRIC HOSPITAL			
60 days	4,215	252,900	average length of stay from expert interview; average price from patients files in one psychiatric ward of a general hospital
TREATMENT SETTING: PSYCHIATRIC WARD OF GENERAL HOSPITAL			
29 days follow-up TOTAL	4,215	122,000 4,000 126,000	average length of stay and price of one hospital average follow-up costs in one hospital
TREATMENT SETTING: GENERAL HOSPITAL			
		52,875	CLOSON [1988] average cost of DRG 435 (=alcohol dependent persons admitted for symptomatic treatment and detoxification) in three university hospitals
TREATMENT SETTING: DEATH			
		0	assumption
TREATMENT SETTING: WEANED			
		879 195	assumption: costs are the same as ambulatory treatment cost LB-number of alcoholics = 19,468 idem, LB-number of alcoholics = 65,909
TREATMENT SETTING: PHYSICAL COMPLICATIONS			
78% peptic ulcers	32,026	25,076	incidence of physical complications from literature review: DE ZWART [1989] HOOGENDOORN [1983b] NATIONAL CANCER REGISTRY [1989], LOBET [1986]
22% alc. liver disease + acute pancreatitis + cancers	155,000	33,635	costs peptic ulcer: CARRIN AND TORFS [1989] average costs of alcoholic liver disaese from three university hospitals: CLOSON [1988] same costs used for all other complications
TREATMENT SETTING: MENTAL COMPLICATIONS			
47.04 days	4,215	198,290	JAARBOEK VOLKSGEZONDHEID [1986]: weighted average length of stay in a psychiatric hospital and in a psychiatric ward of a hospital and in a psychiatric ward of a general hospital average price from patients files in one psychiatric ward of a general hospital

4.2 Cost related to the administering of AOTAL

AOTAL is given during three months to patients in the several hospital settings. Six unities is the daily intake of the drug. One package includes 100 unities and costs 930 Bef.
For three months AOTAL intake, the patient has to buy 6 Packages for a total price of 5,580 Bef.

In the model, in the AOTAl scenario, half of the weaned patients come from a setting where they received AOTAL during their treatment. Since AOTAL is given further after the first three months to patients who comply and did not yet relapse, we assign costs for AOTAL (3 months) to half of the patients who are weaned.

No clinical trials (placebo/AOTAL) have been performed with patients treated ambulatory or for complications. Hence in our analysis, these patients do not receive the drug, even in the AOTAL group.
All cost data are summarised in table 8.

Table 8 : Overview of costs

	Low boundary	High boundary	AOTAL
AT	879	195	0
PH	252,900	252,900	5,580
PWGH	126,000	126,000	5,580
GH	52,875	52,875	5,580
WA	879	195	2,790
PhCom	58,711	58,711	0
PsCom	198,290	198,290	0
Dead	0	0	0

5. Results

5.1 Net costs due to AOTAL

The costs given in table 8 will now be linked to the transition matrices presented in table 6. All costs will be discounted using a discount rate of 1.25% per three months.
Results are calculated for a period of 39 months, namely 3 months during which AOTAL treatment is initiated for the first time for patients in hospital settings, plus 3 years[4] during which AOTAL is given to each patient each time he is treated in a hospital. (Note that negative costs are savings)

Table 9 gives the results for the baseline analysis both for the low boundary and high boundary data.

Table 9 : Net costs due to AOTAL treatment, compared to standard treatment (discount rate of 1.25% per 3 months. Results are given for 39 months)

Initial state	Low boundary	High boundary
AT	- 7,894	+ 1,919
PH	- 11,201	- 280
PWGH	- 8,421	+ 2,532
GH	- 12,001	+ 3,380

In the low-boundary variant net savings are obtained for patients in each initial treatment setting, as a result of the use of AOTAL.

In the high-boundary variant net savings are only obtained for patients with initial treatment in a psychiatric hospital, however.

The evolution of net costs over time is shown in figures 1 (low boundary) and 2 (high boundary). In these figures it can be seen that net costs per period converge after some periods for all four initial treatment settings. Net costs per period become identical after some periods, whatever the initial treatment setting. For example in figure 2, patients in the psychiatric hospital have a high average cost in the first period, because they all receive AOTAL. In the second period they cause high savings because the effect of AOTAL on relapse rates is most pronounced. After 5 periods results are stabilised.

In figures 3 and 4 cumulative results are shown.

Figure 1 : **Net costs due to AOTAL treatment (baseline analysis; low boundary case)**

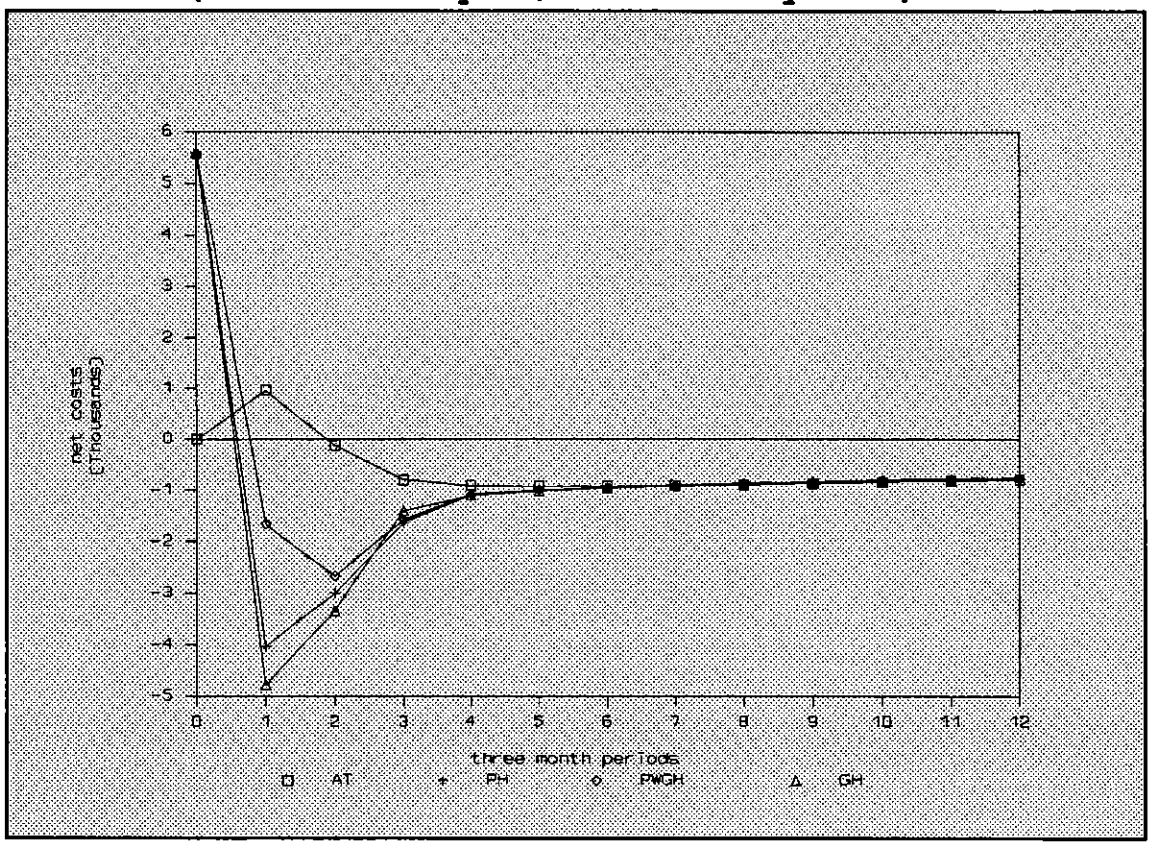


Figure 2 : **Net costs due to AOTAL (baseline analysis, high boundary case)**

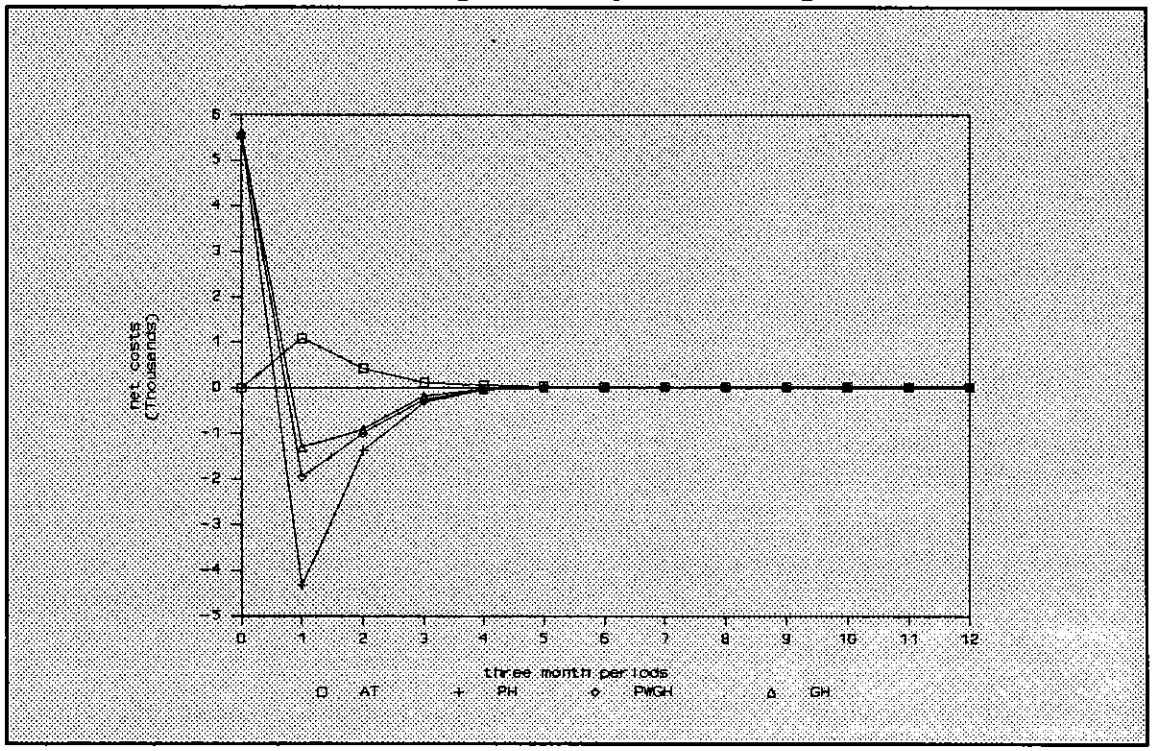


Figure 3 : Cumulative net costs due to AOTAL (baseline analysis, low boundary case)

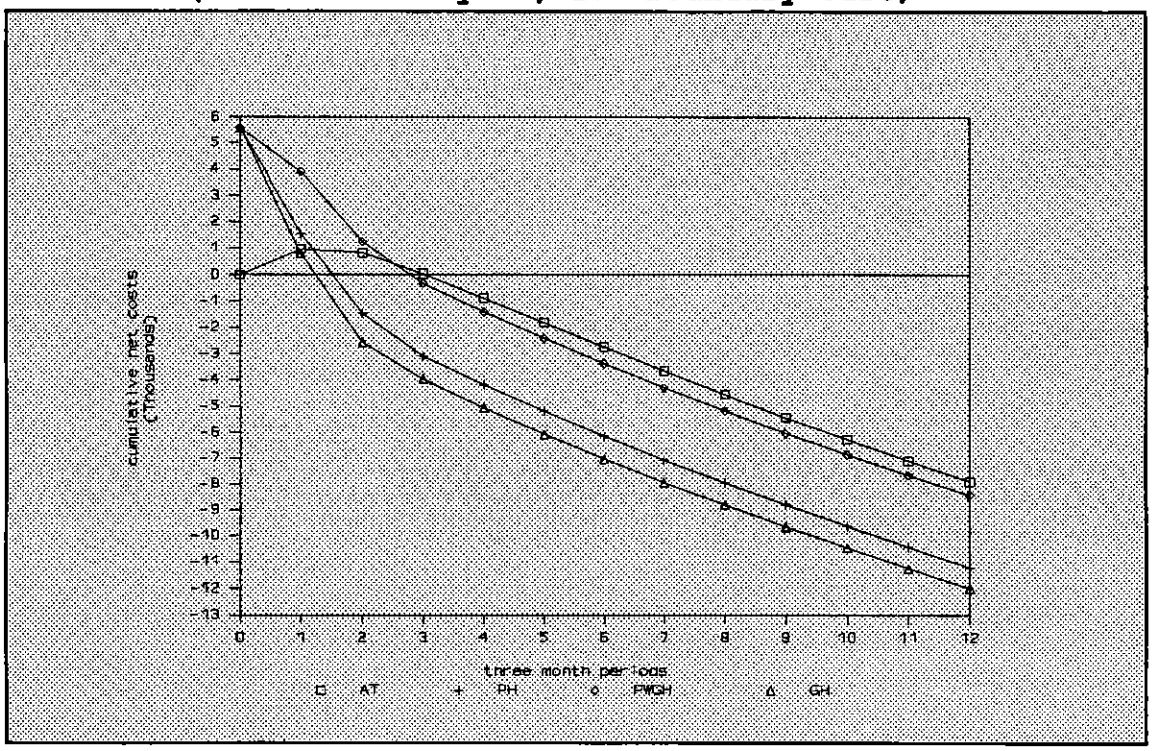
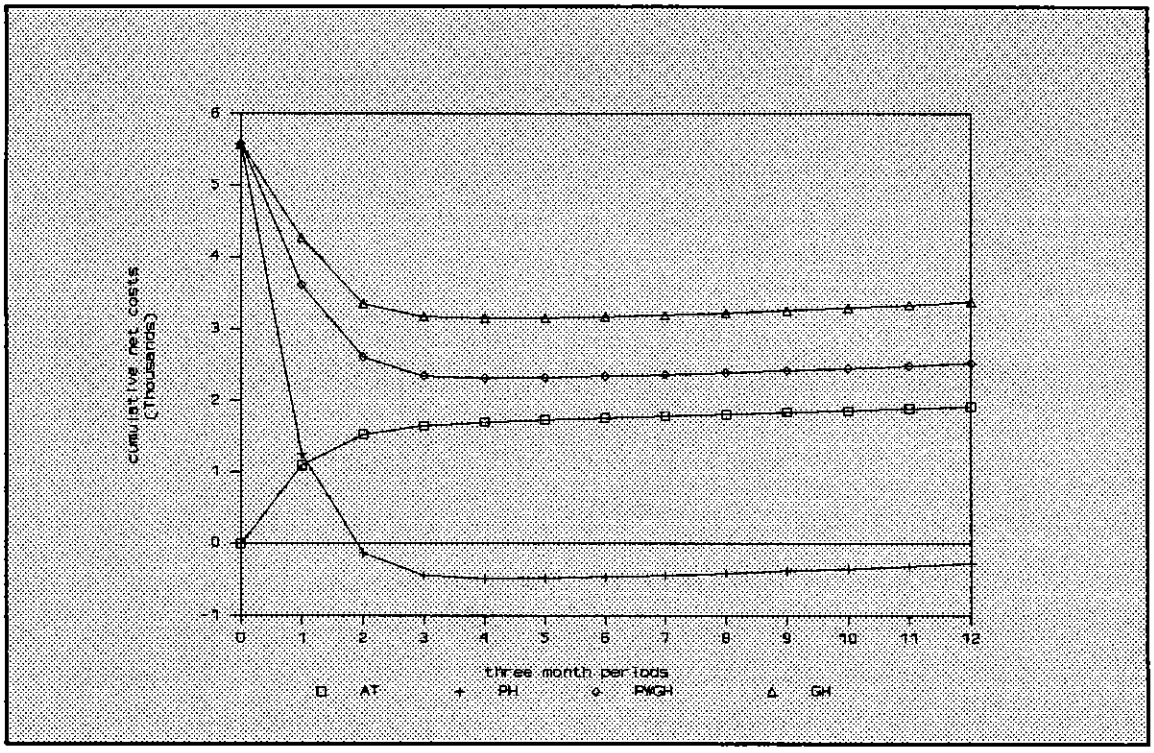


Figure 4 : Cumulative net costs due to AOTAL (baseline analysis, high boundary case

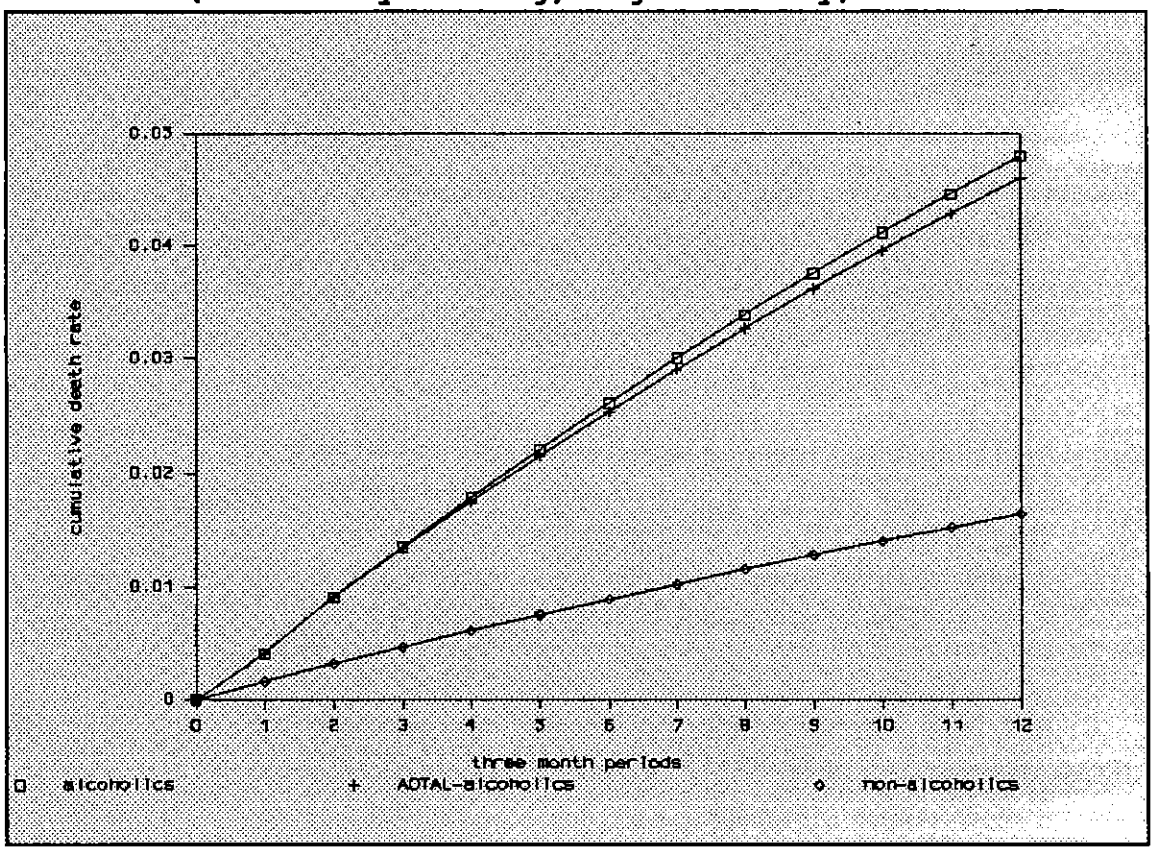


5.2 Cost-effectiveness ratios for the high boundary case

Since in the high boundary variant we obtained net costs instead of net benefits, cost-effectiveness ratios will give insight in the amount of additional money necessary to obtain an additional health effect. In this paper, the effect on health is measured by means of life-years gained.

The Markov model allows us, under the conditions in 2.2, to obtain an estimate of life years saved thanks to AOTAL, as compared to standard treatment.
In figure 5, differences in cumulative death rates between alcoholics receiving AOTAL and placebo are shown graphically, for a patient initially treated in an ambulatory setting (high boundary variant).

Figure 5 : Life-years gained due to AOTAL (ambulatory setting, high boundary)



In table 10 cost-effectiveness ratios are calculated.
The amount of money needed to gain one life-year is between 582,000 Bef and 728,000 Bef. For patients who are initially in the psychiatric hospital setting, one lifeyear gained is associated with money savings.

Table 10 : Cost-effectiveness ratios for the high boundary variant (39 months period)

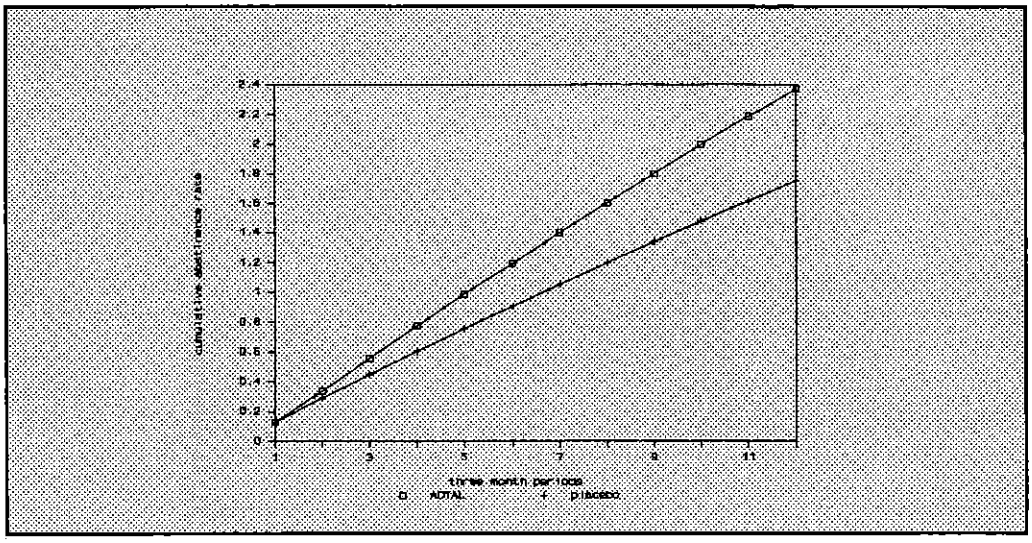
	(a)	(b)	(c)
Initial state			
AT	0.00264	1,919	728,237
PH	0.00436	- 280	- 64,294
PWGH	0.00435	2,532	582,337
GH	0.00527	3,380	640,880

(a) Gain in lifeyears per patient, due to AOTAL (39 months)
(b) Net costs due to AOTAL (39 months)
(c) Costs per additional life year gained (39 months)

Quality adjusted life-years

In our case, the primary aim of the drug is not to save lives, but to prevent alcoholics to drink. Instead of calculating lifeyears gained, we could also calculate the years of 'normal activity' added by the treatment. We compare the probability to be weaned for a patient taking AOTAL with the probability of a patient taking placebo, for each of the 12 three-month periods. We sum these differences. Figure 6 shows the difference in cumulative abstinence rates between a patient receiving AOTAL and placebo, for a patient initially treated in an ambulatory setting (high boundary setting).

Figure 6 : Periods of abstinence gained due to AOTAL (ambulatory setting, high boundary)



We would now like to convert weaned and addicted periods to 'quality-of-life' years. Utility values of the health states are totally lacking, however. We will therefore only calculate a few theoretical examples. We will first simplify the analysis and only differentiate between two states: "weaned" and "addicted" (no matter where treated). We rank our two states on a scale from 0 to 1, and attach a value of one to the weaned status. We further assume that a life-year in one of the addicted states has less quality and hence should obtain a lower value. Table 11 shows the total gain in quality adjusted lifeyears for several hypothetically postulated quality levels of an alcoholic state compared to a weaned state.

The total gain in quality adjusted lifeyears includes the pure gain in lifeyears on the one hand, and the gain in quality on the other hand. If one supposes there is no quality difference between the two states (each having a utility value of one), results of quality adjusted lifeyears do not differ from the results of lifeyears gained. The table shows however, that even a small gain in quality of life due to a weaned status, changes the cost-effectiveness ratios quite dramatically.

Table 11 : **Quality-adjusted lifeyears gained (39 month period, HB case)**

quality level of addictive state	1	.99	.97	.95
Ambulatory treatment: costs 1,919				
supplemental addicted years	-.1529	-.1514	-.1483	-.1453
supplemental weaned years	+.1556	+.1556	+.1556	+.1556
qualys gained	+.0026	+.0042	+.0072	+.0103
net cost/qualy	727,169	460,385	265,541	186,578
Psychiatric ward general hospital: costs 2,532				
supplemental addicted years	-.1999	-.1979	-.1939	-.1899
supplemental weaned years	+.2042	+.2042	+.2042	+.2042
qualys gained	+.0043	+.0063	+.0103	+.0143
net cost/qualy	582,337	398,950	244,780	176,553
General hospital: costs 3,380				
supplemental addicted years	-.2238	-.2216	-.2171	-.2126
supplemental weaned years	+.2291	+.2291	+.2291	+.2291
qualys gained	+.0053	+.0075	+.0072	+.0103
net cost/qualy	640,880	449,923	281,920	205,271

5.3 Sensitivity analysis

5.3.1 Changing relapse rates: lost patients are considered relapsed

In the baseline analysis we supposed that patients who were **lost** in the clinical trials, experienced the same probabilities to become weaned or to relapse as patients who remained in the trial till the day of evaluation, and as those who received placebo treatment

An alternative is to consider all patients who are **lost** in the clinical trials as **relapses.** Since less patients are lost in the AOTAL-group, the results will become more favourable for the drug AOTAL. The probabilities to become weaned can be derived directly from table 2.

For the psychiatric hospital and the psychiatric ward these probabilities become **0.09** (for placebo) and **0.31** for AOTAL. For the general hospital setting, these probabilities become **0.28** (for placebo) and **0.48** (for AOTAL).

When we use these probabilities in the transition matrices for the Markov model we obtain the results given in table 12.

Table 12 : Cumulative net costs due to AOTAL treatment (sensitivity analysis; lost patients=relapsed)

	Cumulative net costs	
Initial state	Low boundary	High boundary
AT	-12,886	+ 159
PH	-22,544	-10,345
PWGH	-16,761	-4,417
GH	-16,029	+2,019

When changing the probability of being weaned in this way we consistently obtain net savings due to AOTAL compared to standard treatment, except in the high boundary case when patients are initially in the general hospital treatment or treated in an ambulatory way.

5.3.2 Changing relapse rates: probability of relapse with AOTAL increases with ten percent

Relapse rates in the clinical trial are not known with certainty. Moreover, the artificial situation of the clinical trial may well lead to more favourable results compared to those that would be obtained in everyday practice. In a second sensitivity analysis, we therefore reduce the probability to become weaned with 10% for the AOTAL patients. Thus we get a probability to become weaned of 0.51 for patients treated in a psychiatric hospital or a psychiatric ward of, and of 0.50 for patients treated in a general hospital. The probability to remain weaned for a second three-month period becomes 0.30. Placebo probabilities are left unchanged.

Results are presented in table 13. Compared to the baseline case, savings due to the drug reduce by 65% to 101%, depending on the initial states. For the high boundary case net costs increase from 112% to 2483%. Results are thus quite sensitive to relatively small changes in the relapse probabilities.

Table 13 : Cumulative net costs due to AOTAL treatment (sensitivity analysis; probability of relapse with AOTAL increases with ten percent)

	Low boundary		High boundary	
initial state	cumulative net costs	% change vs baseline	cumulative net costs	% change vs baseline
AT	-2,305	- 71%	+ 7,149	+ 273%
PH	-1,289	- 88%	+ 6,674	+2,483%
PWGH	+ 62	-101%	+ 8,037	+ 217%
GH	-4,149	- 65%	+ 7,194	+ 112%

5.3.3 Changing the price of AOTAL

All calculations are thus far based on a price of 930 Bef per 100 unities of the drug AOTAL. Increasing or reducing this price will influence the results of our analysis. Figures 7 and 8 present the cumulative net costs of AOTAL compared to standard treatment, given different prices of AOTAL (for the low boundary and the high boundary case respectively).

In the low boundary case, we keep net benefits for the AOTAL treatment for all initial settings, up to a price increase of about 42%. In the high boundary case, on the other hand, net benefits are obtained for all initial settings, after a price decrease of 17%.

Figure 7 : Cumulative net costs due to AOTAL treatment (sensitivity analysis, price changes of AOTAL, low boundary)

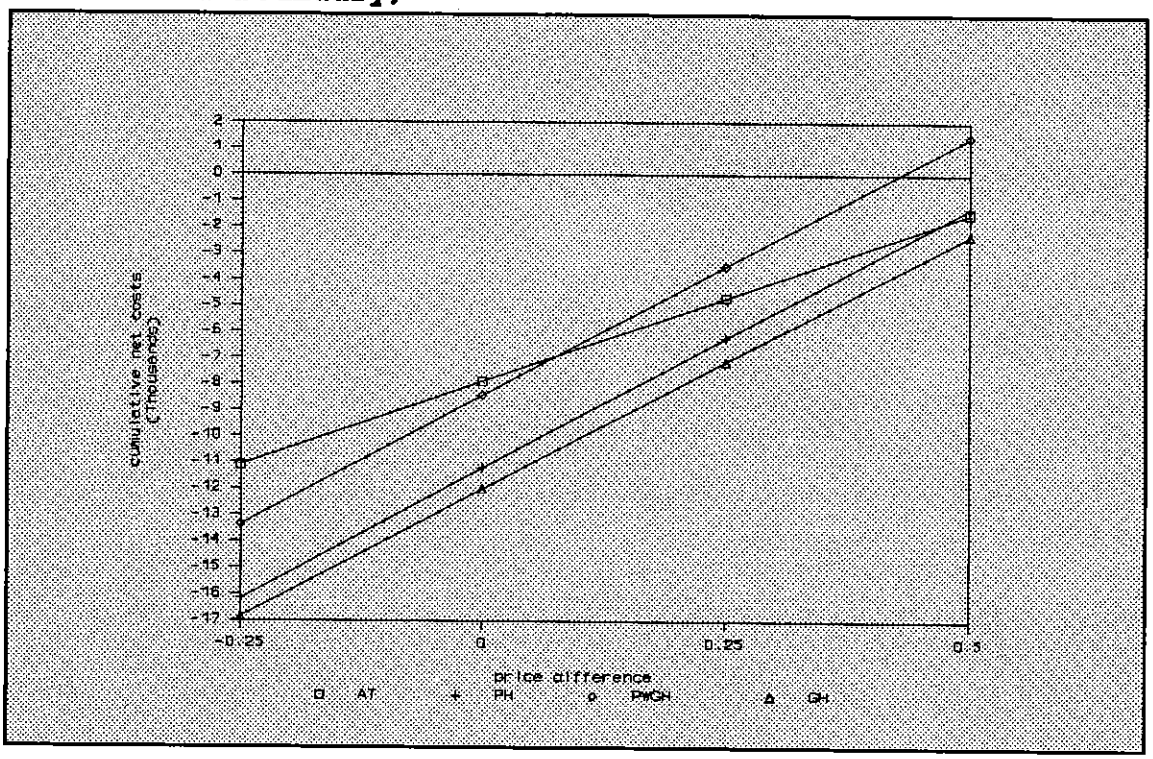
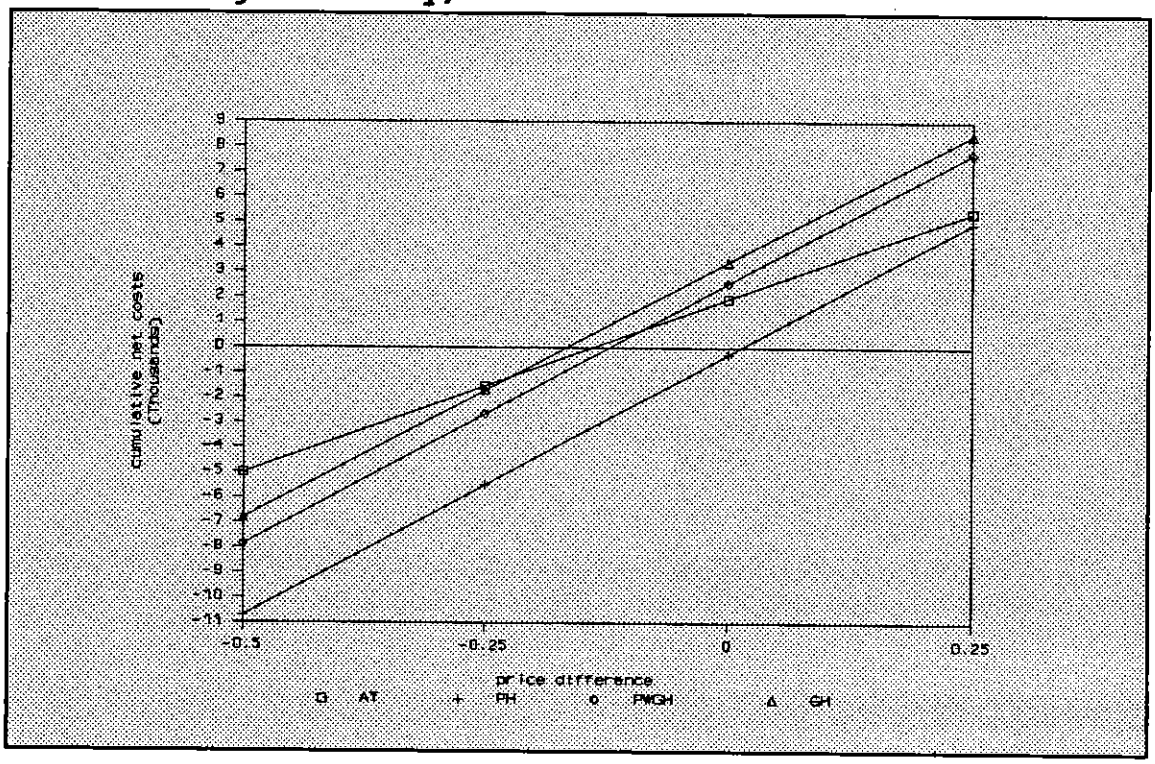


Figure 8 : Cumulative net costs due to AOTAL treatment (sensitivity analysis, price changes of AOTAL, high boundary)



6. Conclusion

In this paper we performed a cost-effectiveness study of AOTAL, a drug which can prevent weaned alcoholics from relapse.
We used a **Markov model** to reflect the medical history of an alcoholic population. The Markov model assumes that every treated alcoholic can at every moment be situated in one of 8 possible states : ambulatory care (including no treatment), psychiatric hospital, psychiatric ward of a general hospital, weaned, treated for physical or mental complications, or dead. The transition probabilities (probabilities to go from one state to another in two subsequent periods) are partly based on epidemiological data and partly on a literature review. However, the available data do not give absolute certainty about probabilities. We therefore proceeded with two alternatives : a low boundary estimate and a high boundary estimate. In the former we assumed mainly a relatively low number of alcoholics (19,460). In the latter alternative however we assumed a much higher number of alcoholics (65,909).

We restricted our analysis to **direct medical costs.** Inclusion of direct non-medical costs or indirect costs would necessitate large epidemiologic surveys or at least an intense follow-up of alcoholics by means of regular interviews concerning non-medical events. Nevertheless it must be stressed here that non-medical costs, especially in alcoholics, can be quite high (social problems, work loss, accidents...). Therefore results presented in this paper are likely to be conservative cost-effectiveness estimates.

Transition probabilities were then linked to the costs. This made it possible to assess the differences in total costs between treatment with AOTAL and standard treatment. The analysis was restricted to a period of three years but can easily be extended to a longer period.

In the **low boundary variant** the use of AOTAL entails net gains in a 3 year time scope of 8,000 to 12,000 Bef per alcoholic, depending on his initial state. It is important to keep in mind that in all scenario's AOTAL is given **only and each time** when the alcoholic is in an inpatient facility.

In the **high boundary variant** small net costs per alcoholic are obtained over a three year period, ranging from 1,900 Bef to 3,400 Bef depending on the initial state (except for the psychiatric hospital setting). These costs occur mainly in the first three months, when every patient in the inpatient settings receives the drug. After one year, the costs of the drug are fully compensated by the savings that it generates.

When comparing costs to **effects** in the high boundary variant, we see that, over a three year period, there is a gain of 2.6 to 5.3 lifeyears per 1,000 alcoholics. This relatively small change in life expectancy makes that, in the cases where we obtain net costs, the cost-effectiveness ratios vary between 582,000 Bef and 728,000 Bef per life year gained. By expressing effectiveness in terms of lifeyears gained, some comparisons with other programs are possible.
It must be noted that lifeyears gained do not constitute the most appropriate way to measure the effectiveness of an anti-alcoholism drug. Quality of life (for both the patient and his family) could constitute a better measure. Measures of the relative utility of a weaned status versus a treatment period are totally lacking, however. Hypothesizing that a period in one of the addicted states has only a quality level of 99% to 95% of a period being weaned, reveals that results are highly sensitive to inclusion of quality of life measures.

In a **sensitivity analysis** it is shown that savings due to AOTAL become larger, in the two variants, when all patients who were "lost" in the clinical trials, are considered as relapses. Results are very sensitive to changes in the relapse probabilities.

We will conclude now by summing up the **shortcomings** of this study and indicating future research possibilities.

All shortcomings of the study concern a lack of data.

Firstly there is a lack of epidemiologic data concerning medical history and behaviour of alcoholics. This was reflected in this study by working with a high and a low boundary variant. However the probabilities included in the Markov model remain somewhat uncertain.

Secondly, there is a lack of cost data. Some medical costs could not be accurately measured. This is e.g. the case for the complication costs. This causes no main problems since results are not sensitive to these costs. The lack of cost information for ambulatory treatment is more problematic. We solved this technically by assuming no cost differences between the two states "ambulatory treatment" and "weaned". Doing so we did ascribe no cost savings to a lower amount of ambulatory care due to AOTAL. We supposed in our study that a weaned patient is a patient who causes no medical costs (except ambulatory costs). This may be so in the majority of cases but there may be exceptions.
Non-medical costs are still more problematic. As a result, the analysis has been restricted to medical costs.

Thirdly, there is a lack of clinical trial results. Trial results were not available for every treatment setting during six months. Hence we had to make some assumptions concerning the applicability of existing clinical trial results to several settings. Moreover, the time scope of the clinical trials was rather short, with a relatively small number of patients reaching the end of the trial period. In addition, the clinical trials were restricted to specific groups of patients. Extrapolation of trial results to the total alcoholic population is uncertain. Finally, the definition given to relapse rate, may not coincide with the status 'weaned' in our Markov model. And there are of

course the more usual problems with clinical trial data. A clinical trial is always an artificial situation. The patient is more closely followed, receives more attention, and hence success probabilities might be higher. On the other hand, the clinical trials upon which basic probabilities in the model are based, were drug treatment against placebo. Of course in reality patients will never receive placebo. It can be hypothesised that the administering of placebo results in an overestimation of the effectiveness of standard treatment. Our cost-effectiveness estimates are hence conservative estimates.

These shortcomings might be solved by additional research. Some indications for this are given below.
Firstly, the medical and social history of some representative groups of alcoholics could be followed during 9 months. This could be done by regular interviews and file-investigation. Such research could provide basic probabilities for the Markov model as well as good cost estimates.

The same could be done in an environment where AOTAL is already an ingredient of treatment strategies, e.g. in a framework of fase III or fase IV studies.
The groups would have to be matched as well as possible.
Investigation of patient histories in a "traditional" environment and a "AOTAL" environment would deliver basic information on costs and probabilities in real life situations.

Secondly, the long term effects (6 to 9 months) in terms of clinical results, relapse rates, quality measures and costs could be compared between minimal (inpatient) or outpatient treatment combined with administration of AOTAL at one hand, and intensive inpatient treatment at the other hand.
Patient groups therefore would have to be matched or patients could be assigned randomly to the several groups.
Such a study would combine the accuracy of a clinical trial with the reality of real life situations.

Thirdly, registration surveys among GP's and interviews with alcoholics would provide useful information on direct and indirect costs.

Bibliography

- BREDA J. en VAN REGENMORTEL T. Evaluatie ziekenhuis-programmatie. Deel II : psychiatrische ziekenhuiszorg. Departement Sociologie en sociaal Beleid, UFSIA (University of Antwerp) 1989.

- CARRIN G. and DE GRAEVE D. A survey of economic evaluation of alcoholism treatment. Studiecentrum voor Economisch en Sociaal Onderzoek, UFSIA (University of Antwerp) 1988.

- CARRIN G. and TORFS K. Economic evaluation of the preventive use of misoprostol in osteoarthritic patients treated with NSAIDS. The case of Belgium. Studiecentrum voor Economisch en Sociaal Onderzoek, UFSIA (University of Antwerp) januari 1989.

- C.B.S. Nederlands statistisch zakboekje.

- CLOSON M.C. et al. Influence de la Structure des pathologies sur les dépenses des hôpitaux. Bruxelles, Centre d'informatique Médicale; Louvain la Neuve, Center for Operations Research and Econometrics, 1988.

- DE ZWART W.M. Alcohol, tabak en drugs in cijfers. Nederlands Instituut voor Alcohol en Drugs 1989.

- DRUMMOND M.F., STODDART G.L. and TORRANCE G.W. Methods for the economic evaluation of health care programmes. Oxford 1987.

- GALLANT D.M. Alcoholism, A guide to diagnosis, intervention and treatment. London, Norton & Company, 1987.

- GEIRNAERT M. en PEETERS R. Preventieprojekt voor alcohol- en andere drugproblemen in opdracht van de Vlaamse Gemeenschap. Rapport over het 1ste werkingsjaar. Deel II : registratie-opdracht. V.A.D., januari 1989.

- GIPS C.H. Alcoholgebruik en sterfte aan alcoholische levercirrose in Nederland. In : Tijdschrift voor alcohol en drugs 1982 (8) nr.3, pp. 105-108.

- GRUNDEMANN R.W.M. Alkoholgebruik onder de Nederlandse beroepsbevolking. In : Tijdschrift voor sociale gezondheidszorg 67 (1989), pp.61-66.

- HAAN G. en E. VAN DOORSLAER (1989), Onderzoek naar kosten-effectiviteit van geneesmiddelen in : G. Haan (ed.) Kosten-effectiviteit van geneesmiddelen; werking en bijwerking. Maastricht, pp. 17-36.

- HAYASHIDA M. e.a. Comparative effectiveness and costs of inpatient and outpatient detoxification of patients with mild-to-moderate alcohol withdrawal syndrome. In : The New England Journal of Medicine, vol 320 nr.6 (februari 1989), pp. 358-365.

- HILDERINK C. e.a. Alcoholhulpverlening in de gezondheids-regio Nijmegen : een inventarisatieonderzoek onder hulpverleners. In : Tijdschrift voor alcohol en drugs 1985 (11) nr.1, pp.1-7.

- HOLDER H.D. Alcoholism treatment and potential health care cost saving. In : Medical care, january 1987, vol.25, nr.1 pp. 52-71.

- HOOGENDOORN D. Opnamen in ziekenhuizen wegens overmatig gebruik van alcohol. In : Nederlands tijdschrift voor geneeskunde 1983a; 127 : nr. 23, p.1011.

- HOOGENDOORN D. Patiënten opgenomen wegens ongewenste gevolgen van het gecombineerde gebruik van alcohol en bepaalde geneesmiddelen. In : Nederlands Tijdschrift voor geneeskunde 1983b; 127 : nr.19 pp. 835-837.

- HOOGENDOORN D. Enkele statistische gegevens met betrekking tot het syndroom van Korsakow in de algemene ziekenhuizen. In : Tijdschrift voor alcohol en drugs 1985 (11) nr.3, pp. 117-123.

- KNIBBE R.A. en MEYERS J.M. Enkele aspekten van hulpverlening aan probleemdrinkers. In : Tijdschrift voor alcohol en drugs 1983 (9) nr.2, pp.68-74.

- KOK A.F.W. De hulpverlening aan Korsakow-patiënten in enige intramurale (geestelijke) gezondheidsvoorzieningen. In : Tijdschrift voor alcohol en drugs 1985 (11) nr.3, pp. 113-117.

- LHUINTRE J.P. et al. Ability of calcium bis acetyl homotaurine, a gaba agonist, to prevent relapse in weaned alcoholics. In : The Lancet, may 4, 1985, pp.1014-1016.

- LOBET M.P. Vraag naar hulp in verband met alcoholisme in de huisartsenpraktijk - 1984. Instituut voor Hygiëne en Epidemiologie, dienst epidemiologie 1986.

- LUDWIG A. M. Understanding the alcoholic's mind - the nature of craving and how to control it. Oxford, 1988.

- MENDELSON J.H. and N.K. MELLO. The diagnosis and treatment of alcoholism. London, 1985.

- Ministerie van Volksgezondheid en Leefmilieu, Statistisch Jaarboek Volksgezondheid.

- National Cancer Registry, Belgian Cancer Foundation, Ministry of Public Health and Environment, Cancer in Belgium 1986. Brussels 1989.

- N.I.S., Statistisch Jaarboek voor België.

- PELC I., LEBON O., VERBANCK P., LEHERT PH. and L. OPSOMER, Calcium-acetylhomotaurinate for maintaining abstinence in weaned alcoholic patients : a placebo-controlled double-blind multicenter study (1990).

- RICE D.P. and KELMAN S. Measuring comorbidity and overlap in the hospitalization cost for alcohol and drug abuse and mental illness. In : Inquiry 26 : 249-260 (summer 1989) pp.249-260.

- SCHIPPERS G.M. Rand Report 2: alcoholhulpverlening na vier jaar. In : Tijdschrift voor alcohol en drugs 1982 (8) nr.1, pp. 14-23.

- SHERLOCK S. Alcohol-related liver disease : clinical aspects and management. In : British Medical Bulletin (1982) vol.38 nr.1 pp. 67-70.

- STOKEY E. and ZECKHAUSER R. A primer for policy analysis, New York 1978.

- TAINTOR Z. WIDEM P. and BARRETT S.A. (eds.) Cost considerations in mental health treatment : settings, modalities, and providers. U.S. Department of Health and Human Services, 1982.

- TORMANS G. en CARRIN G. Inleiding tot de economische evaluatie van geneesmiddelen. Studiecentrum voor Economisch en Sociaal Onderzoek, UFSIA (University of Antwerp) 1989.

- VAN CASTEREN, V., LOBET M. en D. WALCKIERS, De morbiditeit in België in 1984, IHE, Ministerie van Volksgezondheid, april 1986, p. 16-17.

- VAN GINNIKEN S. and VAN IWAARDEN T. Alcohol control policy in the Netherlands. In : Health policy 13 (1989) pp.109-113.

- VAN NUFFEL R. Kencijfers registratiegegevens diensten geestelijke gezondheidszorg. Nationale resultaten 1986 en 1987. Samenwerkingsplatform Federatie van diensten voor geestelijke gezondheidszorg en Verbond der Medisch-Sociale Instellingen, december 1988.

- X, Belgische Senaat, zitting 89-90, 13-12-'89, Wijziging van de wet van 25-3-64 op de geneesmiddelen. Uiteenzetting van de Staatssecretaris voor Volksgezondheid. Ontwerp van programmawet. Verslag namens de commissie voor de Volksgezondheid en het Leefmilieu p. 2-3.

- X, Gecommentariëerd geneesmiddelenrepertorium 1989, Belgisch Centrum voor Pharmacotherapeutische Informatie 1989.

- X, LADIS 1988 (Landelijke registratie van de Centra voor Alcohol en Drugs), Nederlandse vereniging CAD's 1990.

- X, Registratieprojekt psychiatrie Limburg, resultaten 1985-86, Provinciale dienst voor volksgezondheid, Limburgse raad voor samenlevingsopbouw en A.C.C., juli 1988.

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