A cost-utility analysis of cognitive behavioural therapy for patients with insomnia and chronic benzodiazepine use: preliminary results

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Abstract

The use of benzodiazepines (BZDs) in general practice reached almost epidemic proportions within general practice in the 1990s. This class of medicines includes drugs that principally help with either anxiety (anxiolytics) or insomnia (hypnotics), and are meant as short-term therapy. However, chronic use of BZDs is rife, and these patients are reluctant to come off medication as it can lead to acute withdrawal symptoms. A cluster randomised controlled trial was undertaken of cognitive behavioural therapy (CBT) delivered by counsellors in six sessions aimed at reducing BZD use. An economic evaluation was undertaken alongside the trial, collecting data on counsellor, primary care costs (incl. prescriptions) and health-related quality of life using the SF-36. Although these data are capable of producing a cost-utility analysis over one year, such an approach would not capture long-term outcomes or rare, high cost, events associated with BZD use. Consequently, a modelling approach is being pursued in parallel to the trial-based analysis which utilises epidemiological data describing increased risk of road traffic accidents, deliberate self-harm, falls in the elderly and premature death. Preliminary results are described and problems discussed.

Introduction

This paper describes the evaluation of an intervention to help patients who are chronic users of benzodiazepines who take their medication to counteract insomnia. The intervention - cognitive behavioural therapy (CBT) delivered by counsellors - has been widely evaluated in patient groups with insomnia (for example, Espie et al 1988, Tomeny and Morgan 1990). However, much of this evidence has been based in specialised clinics, and has not addressed

the parallel question of whether it reduces sleeping tablet usage. The aim of this study is to assess the cost-effectiveness of CBT when delivered in the mainstream health service and with the explicit purpose of reducing benzodiazepine use.

When designing the economic evaluation, two major causes of concern were identified. Firstly, that insomnia and its associated treatment are both associated with costly rare events that would not be captured within the trial. Secondly, the length of follow-up is critical, as benzodiazepine dependence is a chronic condition, and as such, any successful intervention will have long-term cost and outcome implications. The need for longer term follow-up has added importance in this situation as the costs of the intervention will not be offset to any significant extent in the short-term by reductions in the use of drugs (which cost around £9 per annum).

The economic evaluation needed to be built around a trial because no evidence from a pragmatic randomised controlled trial was available. Furthermore, the previous studies involved different patient groups, a different model of service delivery, and did not include the collection of cost or quality of life information. In order to capture the hidden costs of the condition and treatment, together with the longer term costs and outcomes, a modelling approach was used to supplement the trial. Patients will be followed-up within the trial for twelve-months, however, only 3 month data are currently available.

Insomnia and benzodiazepine use

Insomnia, or sleeplessness, is a common complaint which affects between 5-10 per cent of the adult population. It is a clinically ill-defined condition, with little agreement on what aspects of sleeplessness, or their severity, constitutes a case of insomnia. Causes of insomnia vary widely, although in up to 80% of cases seen in general practice, are related to anxiety or depression (Shapiro 1993).

The costs of insomnia have been highlighted in several cost of illness, and similar, studies (Leger 1999, Stoller 1994, Walsh 1999, Chilcott 1996). As well as drug costs and associated medical costs, other events were identified as being associated with insomnia. Stoller

(1994), for example, draws upon epidemiological data which points to a relative risk of 2-3 for accidents, 3-4 fold increase in hospitalisation and a 2-3 fold increase in office consultations. Further data relating morbidity and mortality effects to habitually short sleep are also used to estimate indirect costs associated with insomnia. Stoller concluded that "a conservative estimate of the total annual cost of insomnia [in the United States] was calculated at $92.5 to $107.5 billion" (price level unknown). However, there are several problems with many of these studies, for example, the definition of insomnia (which is confused with sleepiness in some studies) and the issue of determining cause and effect (i.e. is the insomnia caused by people having an accident, and not vice versa). Highlighting these difficulties, and the use of other extremely cavalier assumptions, Walsh (1999) explains that "in our judgement, the lack of relevant data preclude even preliminary estimates of either indirect or related costs….[and that the]……total direct costs in the United States for insomnia in 1995 were estimated to be $13.9 billion".

The treatment of choice for insomnia is the use of hypnotic drugs, and in particular, benzodiazepine hypnotics. Overuse of benzodiazepines led to patients becoming dependent on their medication, prompting action to reduce BZD prescribing. Consequently, there has been a 28% reduction in the number of benzodiazepine hypnotic prescriptions from 11.7 million in 1983 to 8.4 million in 1996 (Department of Health 1997). While recommendations vary, it is now widely accepted that hypnotic drug therapy beyond 4-6 weeks duration is undesirable at all ages (e.g. Committee on Safety of Medicines, 1988; Gillin, 1991; Ashton, 1994). A recent study of older people, however, found that despite the emphasis placed on these recommendations over the past 10 years, trends in the duration of hypnotic drug use showed a remarkably stable pattern for the period 1985-1993, with drug use which commenced after 1989 as likely to become long-term (i.e. ≥ 4 years) as that which commenced before (Morgan and Clarke 1997).

Epidemiological work has also highlighted associations between benzodiadepine use and increased risk of road traffic accidents (Thomas 1998), falls (Leipzig et al 1999), deliberate self-harm (Neutel and Patten 1997) and excess mortality (Kripke et al 1998). In general, these studies are of high quality, and by linking event to prescription data, are able to overcome the problem of reverse causation. Furthermore, many of these studies have

identified dose-response relationships between BZD use and events (Barbone 1998, Kripke 1998, Ray 1992, Leveille 1994), and other differences in risk associated with the type of drug use (Neutel 1996, Neutel 1998), which make the attribution of causation, rather than association, more robust.

Other costs are also associated with benzodiazepine use, such as utilisation of formal withdrawal programmes (Hopkins et al 1982, Brenner et al 1991), self-help groups (Brewsher 1995) and miscellaneous health service use (Burke et al 1995).

Methods

Trial-based economic evaluation

The trial was a cluster randomised cross-over trial. General practices were selected at random, and asked to participate within the trial. Practices were excluded if they were running, or are participating in, active benzodiazepine reduction or sleep management programmes. All practices had a six month period of recruiting patients to the intervention group, and a six month period recruiting to the control group. Patients were asked to participate within the study when they presented to the GP for any condition.

To ensure adequate representation of older patients (the most likely consumers of long-term NHS insomnia management), and to exclude those (generally younger adults) whose sleep disturbance is often lifestyle-related, the sample had a minimum age of 30, and was stratified at age 50 (50% 30-50; 50% 51+). All appropriately aged patients whose symptoms met DSM-IV/ICD-10 criteria for insomnia[*], and who are currently seeking repeat prescriptions for hypnotic drugs, were eligible for inclusion in the study.

The outcome measures used in the trial were; the Pittsburg Sleep Quality Index (ref), the Epworth Sleepiness Scale (ref), the Hospital Anxiety and Depression Scale (Zigmond 1983) and the SF-36 (Ware 1992). Included within these instruments were questions on hypnotic

[*] A persistent (i.e. for at least one month) complaint of difficulty initiating or maintaining sleep (or of non restorative sleep) which causes the individual significant distress and is associated with impaired social or occupational functioning.

drug use. All outcome measures were self-completed, and aimed to be gathered at 3, 6, and 12 months. Health-related utility was estimated using the SF-6D, an algorithm based on a sub-set of SF-36 responses (Brazier 2001).

Costs were estimated from the NHS perspective covering counsellor sessions, sleeping tablets, general practitioner (GP) and other primary care contacts. Hospitalisations associated with benzodiazepine use are very rare and were not considered within the trial. Resource use data were collected from self-completed questionnaires and counsellor diaries. Unit costs for counsellor sessions were estimated using a bottom-up methodology developed by a local provider (Psychological Health Sheffield) and information on national pay scales for counsellors (Pay and Workforce Research 1999). Other unit costs were taken from standard sources (British National Formulary 2000, Netten 2000).

Analysis of costs and outcomes was undertaken using analysis of variance. Changes in costs and outcomes were estimated with length of follow-up and treatment group as fixed factors, baseline measure of the dependent variable and age as covariates, and GP practice as a random factor.

Model-based economic evaluation

In order to incorporate the epidemiological information described above, and allow the extrapolation of results, a simple decision analytic model incorporating a Markov process was created using DATA 3.5. The model cycle was defined as three-months in order to fit in with the available trial data.

The Markov process uses four key health states;

- High dose BZD use (classified as 5-7 tablets per week)
- Low dose BZD use (classified as 1-4 tablets per week)
- No BZD use (classified as 0 tablets per week)
- Death

Following each of these health states, except death, there are three possible "clinical events";

- No accident
- Accident
- Die

Following the first two of these events, there are three possible "dose events"[†];

- Increase dose
- Maintain dose
- Reduce dose

The model structure is given in Figure 1. Initial population proportions (age and dose), transition probabilities at three months, and utilities were taken from the trial. Prescription costs and miscellaneous primary care costs associated with the three health states were also taken from the trial data. Annual mortality was taken from life tables (GAD 2001).

Epidemiological data were taken from the literature to estimate the excess mortality risk associated with the three levels of drug use. No compatible data describing dose-response relationships between BZD use and the other associated events (i.e. road traffic accidents requiring hospitalisation, falls requiring hospitalisation, and deliberate self-harm requiring hospitalisation) were available. Consequently, a single excess risk was applied to both the high and low benzodiazepine use groups. In the first stage of the analysis, the three "accidents" were combined into a single node, described by the sum of the three probabilities and their median unit cost. Costs associated with these events were estimated using length of stay data from Hospital Episodes Statistics for the relevant external causes codes, and per diem costs. No utility decrement was applied to the accidents.

The increased risk of the accidents were described by various measures; excess mortality was described by a Hazard Ratio, excess risk of falls was described by a Relative Risk, and

the excess costs of RTAs and DSH were described by Odds Ratios. However, when the incidence of the outcome of interest is uncommon (<10%), the adjusted odds ratio derived from a logistic regression approximates the risk ratio (Zhang 1998). For these very rare events, all three measures will produce similar estimates of excess risk. Additionally, the effect of uncertainty in the measures of excess risk was incorporated in the analysis by defining them as distributions.

Discount rates were applied at each cycle to produce annualised discount rates of 6% per annum for costs and 1.5% per annum for outcomes. The model was run for 20 cycles, or, 5 years. The model data are shown in Tables 1-4.

Monte Carlo simulations were used to estimate expected values, and incorporate the uncertainty associated with certain parameters. Distributions were sampled around the cost of the intervention, BZD costs for each dose group, primary care costs for each dose group, the cost of accidents, the relative risk of accidents and utility for each dose group. The distributions are described in Table 1-3.

Results

Trial-based economic evaluation

The intervention group reduced its consumption of hypnotics, and reported better quality of sleep and health related quality of life (as measured by the SF-36). The SF-36 and SF-6D results are shown in Table 5.

The cost of a counsellor session was estimated at £26.25, which includes typical overheads plus allowances for supervision, travel, training and general practice costs. This is considerably more than the figure of £11 per hour used in a previous trial of counselling in primary care, which was based purely on salary and employers on-costs (Harvey 1998). The mean cost of the counselling was £155 per patient (Table 6), however, there is evidence of

[†] The three possible dose events are contingent on the current dose. For example, when a patient has "no BZD use" they can increase to low use, increase to high use, or maintain no use. The three dose events shown in the main text relate to patients who are currently on low BZD use.

cost offsets due to reductions in sleeping tablet use (£1.40) and utilisation of primary care services (£35.60). The mean incremental cost per QALY is £17,376.

Model-based economic evaluation

Within the model structure, two sets of analyses were undertaken. The "continued effect" model was characterised by applying the 3-month transition probabilities to all successive cycles. The "single effect" model was characterised by applying the 3-month transition probabilities to the first cycle only, and then assuming all patients follow the transition probabilities of the usual care group. The results from these two models are shown in Table 7.

Under the continuous effect scenario, the treatment strategy dominates the usual care strategy, however, the assumption of continued effect is a strong one. The state probabilities for the two scenarios are given in Figures 2 and 3. Under the continued effect scenario, over 90% of patients will no longer use BZDs after two years – this is very unlikely to happen. Subsequent analyses used the single effect scenario.

The breakdown of the costs show that drug costs make up only a small proportion of total NHS costs associated with these patients. Costs of associated accidents are also quite small, although similar in magnitude to the drug costs. The vast majority of costs are primary care costs (Table 8), although not all of these are attributable to insomnia or BZD use.

Fifty simulations each with a population size of 100 were undertaken and the results shown in Table 7). Estimation of mean incremental cost-utility ratios revealed that 42% of the simulation produced negative effects and positive costs, and 2% of trials produced positive effects with negative costs.

Finally, the validity of the model can be directly tested by comparing the estimates produced by a single cycle against the actual results of the trial. This comparison shows sizeable

differences with the trial and model producing cost-per-QALY estimates of £17,376 and £14,865, respectively. Initial investigations have identified the following causes:

- Dosing data were not available for all patients, therefore, many of the parameters are based on a subset of patients.
- Approximations were used to describe the distribution of the trial data (e.g. triangular distributions) in order to simplify the modelling.
- Trial analysis was based on a fairly sophisticated analysis of variance, whilst inputs into the model were the product of simpler analyses. This was undertaken to simplify the production of parameter distributions.

Further work needs to be undertaken to reconcile the results produced by the two approaches.

Discussion

This paper presents preliminary results of both a trial and model evaluating the cost-effectiveness of CBT for patients with insomnia. Further analyses need to be undertaken, and a decision about how to proceed with the model needs to be made. However, some lessons can be learnt at this early stage of the work.

The model assuming a continued effect clearly produces very favourable results, however, this assumption is thought to be extremely over-optimistic. Consequently, a "single effect" scenario was used for the main analyses. However, these results should be treated with caution as longer-term follow-up data will come available shortly. It is possible that these data may show that patients only reduce their BZD dose temporarily, before returning to their pre-intervention dose. In such circumstances, a key variable will be the length of time before returning to pre-intervention doses. This would also raise the possibility of re-intervening in those patients who responded to the original course of treatment. The likely cost-effectiveness of such a strategy should be modelled prior to any decision is made about re-intervening. Whilst the cost per patient is likely to be lower for the second treatment (as fewer sessions are likely to be needed), the effectiveness of it may not be the same as the original intervention.

There are also some model developments that need to be considered. Firstly, disaggregating "accidents" into the separate events of RTA, DSH and falls, would produce more accurate results. Secondly, it would be possible to fit a dose-response curve to the accidents, perhaps based on the estimated relationship for mortality. Thirdly, there are evidence to show that falls in the elderly, accelerate the use of long-term residential care. This additional cost, could also be incorporated within the model. However, all of these of amendments are unlikely to alter the results of the model substantially.

There are also some problems regarding the use of the epidemiological evidence in the model, the estimation of treatment effect, the estimation of model parameters in the face of repeated measures and the choice of health states when structuring the Markov Process. All of these are discussed below.

Epidemiological evidence

The epidemiological evidence used to estimate accidents are only associations. This is highlighted by the results of studies that have examined the effectiveness of interventions aimed at reducing falls in the elderly. These studies have not shown a clear relationship between medication reduction and reductions in falls, due to the multifactoral nature of fall risk. These studies are in very selected groups of patients, and so do not in themselves prove the lack of an causal relationship, however, they serve as a warning to any over-reliance of any economic argument on such epidemiological data.

Estimation of treatment effect

The structure of the model implies that utility is a function of only dose. However, it is possible that the intervention could have an independent, positive, effect on well-being. For example, by empowering patients to take an active role in reducing BZD use, they may feel an added sense of achievement. Alternatively, patients may be able to find other facets of their life that can be helped by some of the techniques taught by the counsellors. This is an empirical question, and if such an effect could be identified, then it could be incorporated into the model.

Estimation of model parameters

The trial collected data at baseline, 3, 6 and twelve months, although only data for the first two time points are available. This allows the model parameters (e.g. mean utility for each dose group) to be estimated using more than one time point. This was undertaken for utility (Table 9). These results provide evidence that the monotonic relationship between dose and utility is not maintained after baseline.

These results may be due to:

- Small sample sizes and large standard deviations. In other words, the differences between the two time-points are not statistically significant.
- A non-representative sub-sample for whom dose group could be calculated leading to biases in the dose-utility relationship.
- The intervention having little effect on utility, but simply shifting "unhappy" patients from high BZD use to low BZD use.
- The intervention creating ill-health, for example, withdrawal effects or untreated insomnia.
- A lag in treatment effect (measured in utility). It may be that it takes time for patients to change their lifestyles, and hence QoL, following a change in their level of BZD use.

The final three explanations are not compatible with the fact that the trial data (which included a greater number of patients) produced a weakly significant utility gain. However, further work, needs to be undertaken to identify what is causing these differences.

Choice of health states when structuring the Markov Process

There is not a unique set of health states that can be used to structure a particular model. For example, previous models have defined possible 'health states' by:

- Clinical descriptions (e.g. symptomatic, asymptomic)
- Health state descriptions based on QoL scores (for example, Kobelt 1999)
- Care setting (for example, Langley-Hawthorne 1997)

In this study, health states were defined in terms of dose - in order to incorporate additional epidemiological data. Was this sensible? In terms of cost-utility analysis, the health states chosen to structure the model should be clearly related to utility and costs, and describe all major sources of utility changes in the patient population. If dose is not directly related to utility, or CBT provides a utility gain in its own right, then the current model structure is not valid.

Table 1: Unit costs (£)

	Mean (SD)	
Cost of intervention	154.5 (27.52)	*Source: Trial data*
	Likely (Min,Max)	
Cost of BZDs per quarter		
o No BZD use	0.9 (0.0, 1.8)	
o Low BZD use	2.7 (0.9, 7.3)	*Source: Trial data*
o High BZD use	8.2 (2.7, 9.1)	
Cost of other primary care services per quarter		
o No BZD use	9.1 (0.0, 91.3)	
o Low BZD use	45.7 (0.0, 91.3)	*Source: Trial data*
o High BZD use	22.8 (0.0, 137.0)	
Cost of RTA requiring hospitalisation	1,227	*Source: HES 1998/99 (ICD external causes V40-49).*
Cost of a fall requiring hospitalisation	2,408	*Source: HES 1998/99 (ICD external causes W01).*
Cost of DSH requiring hospitalisation	446	*Source: HES 1998/99 (ICD external causes X60-X84).*
Combined cost of accident	1,227 (446, 2408)	*Derived from the cost of the individual accidents.*

Table 2: Utilities

	Mean (SD)	
No BZD use	0.70 (0.13)	*Source: Baseline trial data*
Low BZD use	0.67 (0.14)	*Source: Baseline trial data*
High BZD use	0.64 (0.14)	*Source: Baseline trial data*

Table 3: Rates and probabilities

	Mean (95% CIs)	
Probability of death	-	*Source: GAD Life Tables for UK (females)*
Hazard ratio for death		
o No BZD use	1	
o Low BZD use	1.11	*Source: Kripke, 1998 (males)*
o High BZD use	1.35	
Rates of hospitalisation for falls	9.0 per 10,000	*Source: Neutel, 1996.*
Relative risk	3.6 (2.5 – 5.2)	
Rates of hospitalisation for RTA	1.2 per 10,000	*Source: Neutel, 1995.*
Odds Ratio	6.5 (1.9-22.4)	
Rate of hospitalisation for DSH	0.7 per 10,000	*Source: Neutel, 1997.*
Odds Ratio	8.2 (3.3-20.0)	
	Likely (Min,Max)	
Combined rate	10.9 per 10,000	
Combined OR	6.1 (1.9, 22.4)	

Table 4: Probabilities of dose changes

No BZDs	*Intervention*	*Control*
Probability of maintaining no BZD dose	1.00	0.67
Probability of increasing to low BZD dose	0.00	0.33
Probability of increasing to high BZD dose	0.00	0.00
Low BZDs		
Probability of decreasing to no BZD dose	0.57	0.14
Probability of maintaining low BZD dose	0.43	0.79
Probability of increasing to high BZD dose	0.00	0.07
High BZDs		
Probability of eliminating BZD dose	0.22	0.04
Probability of decreasing to low BZD dose	0.2	0.04
Probability of maintaining high BZD dose	0.58	0.92

Source: Trial

Table 5: Change in SF-36 and SF-6D scores between baseline and three months

Dimension	*Control Group*			*Clinic Group*			*Mean Difference (95% C.I.)*		*p*
	n	Mean change	SE	n	Mean change	SE			
Physical Function	72	-3.5	3.2	73	+2.7	2.4	+6.2	(-3.1 to +15.6)	0.19
Social Function	72	-17.2	5.6	73	+3.1	4.3	+20.3	(+3.6 to +37.0)	0.02
Role Physical	69	-3.6	8.7	72	-8.6	6.6	-5.0	(-30.9 to +20.8)	0.70
Role Emotional	69	-18.2	9.7	72	+6.4	7.6	+24.7	(-4.6 to +53.9)	0.10
Mental Health	70	-1.8	3.4	73	+5.9	2.7	+7.7	(-2.5 to +17.8)	0.14
Energy/Vitality	70	-9.0	3.4	73	+13.9	2.7	+22.0	(+12.8 to +33.2)	<0.01
Pain	72	-0.6	4.0	73	+1.3	3.1	+1.9	(-9.9 to +13.7)	0.75
General Health Perception	69	-2.0	3.5	73	+3.6	2.7	+5.6	(-4.8 to +16.1)	0.29
SF-6D	73	-0.03	0.02	72	0.02	0.02	+0.05	(-0.01 to +0.03)	0.12

Table 6: NHS costs between t1 and t2 (£1999/2000)

Dimension	*Control Group*			*Clinic Group*			*Mean Difference (95% C.I.)*		*p*
	n	Mean	SE	n	Mean	SE			
Primary care costs	69	81.3	13.5	73	45.7	10.1	-35.6	(-75.3 to +4.1)	0.08
Prescription costs	63	7.5	0.9	57	6.1	0.7	-1.4	(-4..0 to +-1.2)	0.29
Counsellor costs	-	-	-	74	154.5	3.2	+154.5	-	-
Total cost	60	105.6	13.2	57	214.2	10.9	+108.6	(+69.3 to +147.9)	<0.01

Table 7
Cost utility results of a deterministic Markov model of treatment

	CBT		Usual care		Incremental CPQ		
	Cost	QALYs	Cost	QALYs	Cost	QALYs	CPQ
Continued effect*	753	3.13	893	2.94	(140)	0.19	-
Single effect**	1,009	2.95	896	2.94	125	0.01	8,855

QALY = Quality Adjusted Life Years.
CPQ = Cost per QALY.
* = Expected value produced by DATA.
** = Mean value from 50 simulations of 100 patients.

Table 8
Composition of healthcare costs

	CBT	Usual care
Accident costs	6%	7%
Drug costs	7%	9%
Primary care costs	71%	84%
Clinic costs	16%	-
Total costs	100%	100%

Table 9
Utility estimates for the model at baseline and 3 months

	Baseline			Three months		
	n	Mean*	SD*	n	Mean	SD
No BZD use	5	0.71	0.11	28	0.65	0.14
Low BZD use	28	0.68	0.15	30	0.68	0.14
High BZD use	95	0.66	0.13	75	0.63	0.14

* These figures differ from those in Table #. The figures here have been re-estimated using only those patients who had three month utility and dose data available, in order to aid interpretation.

Figure 1: Model structure

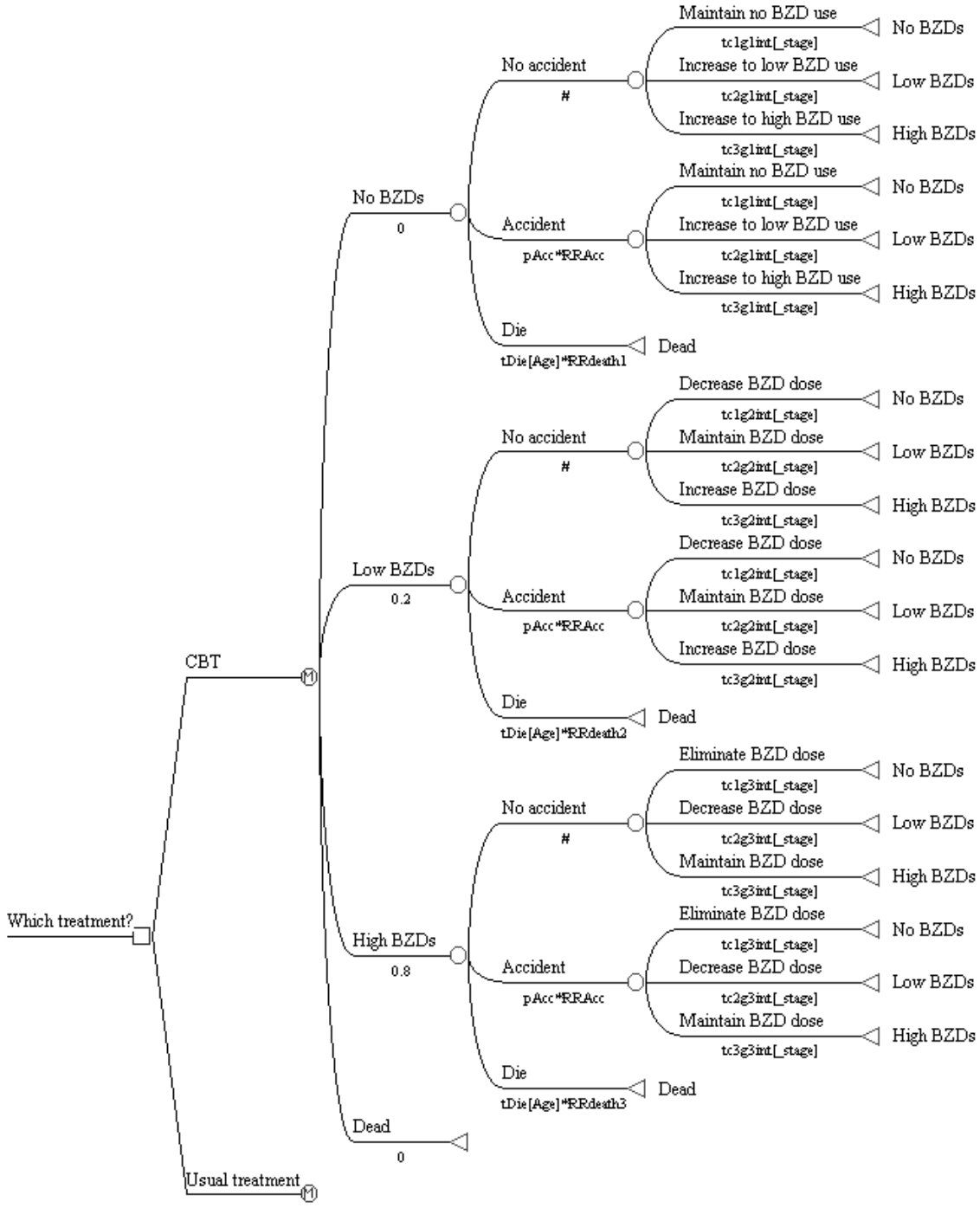


Figure 2
State probabilities for CBT (left) and usual treatment (right) assuming continued effect

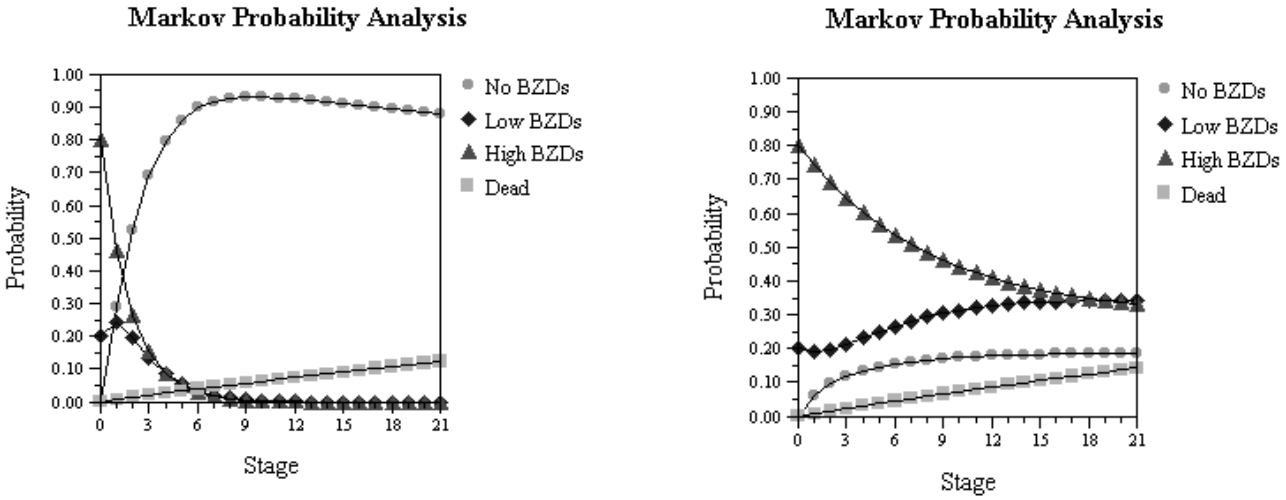
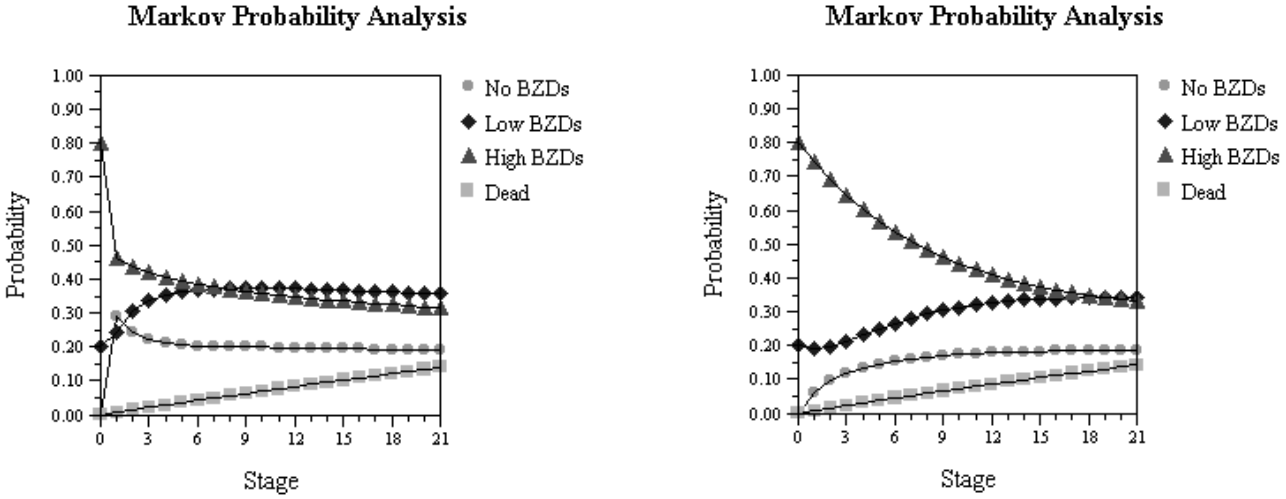


Figure 3
State probabilities for CBT (left) and usual treatment (right) assuming single effect



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