1st International Pharmacoeconomic Conference on Alzheimer's Disease: Report and Summary

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Abstract

The 1st International Pharmacoeconomic Conference on Alzheimer's Disease (AD) was held in Amsterdam in July 1998. The meeting was held under the auspices of the International Working Group for Harmonization of Dementia Drug Guidelines (http://dementia.ion.ucl.ac.uk/harmon), bringing together academics, clinicians, purchasers and representatives from industry. Presentations were given on the methodology of pharmacoeconomic studies in AD, particularly focussing on caregiver burden, QOL and resource utilization.

Three economic models of AD were presented based upon data from the US, Canada and the UK. In two studies these data were then used to model the cost-effectiveness and effect on cost of treatment with donepezil. Both studies suggested a possible cost advantage for the use of donepezil, when compared to no placebo or treatment, particularly when it is used appropriately in mild to moderate AD. These data need to be interpreted with care as none of the cost or utility information were collected during the clinical trials and the analyses were based on non-verified assumptions about the long term benefits of treatment. An economic model of tacrine, based on long term open label follow-up of patients from a previous clinical trial also suggested a possible cost advantage for the use of this drug relative to placebo, although long term benefits hinged on similar non-verified assumption about the course of the disease. Additional data from a 2 year clinical trial of selegiline and vitamin E suggests that cognitive measures may be poor predictors of economic outcome, which are better measured directly. Both economic models of donepezil rely on short-term cognitive data to predict long-term outcome, which may not be useful in predicting economic savings. Further, long term open label follow-up may be misleading as other data suggests that participation in clinical research, regardless of the agent, may be sufficient to observe cost advantages such as delay in nursing home placement.

The issues facing pharmacoeconomists, researchers, clinicians and families in the future were addressed in a series of workshops using a method of Strategic Futuring. The workshops attempted to see 7 years into the future for a range of areas including: consumer and caregiver use of pharmaco-economic data; early detection and prevention; Japanese perspectives; activities of daily life and what will be daily life activities; caregiver burden; QOL at the end of life; new uses for new information and communication technology in clinical research; and physicians use of pharmaco-economic data. A range of exciting futures were predicted, although common themes that arose when considering barriers to achieving these futures included cost, education, political will, confidentiality, privacy and ethics.

The first conference was deemed to have been a success haveing attracted more than 160 delegates and many distinguished speaker. It is planned to hold a second conference in the year 2000. Over the next two years research needs to be broadened particularly in the methodological areas of resource utilization, Quality of Life (QOL) and caregiver burden. Data from clinical trials with relevant economic and QOL outcomes will be needed by purchasers if drug treatments for dementia are to gain widespread use. It is also hoped that the models described at the meeting may become more freely available to politicians, purchasers, clinicians and caregivers to help them make better decisions about treatment.

The Aging World

Increasing life expectancy is leading to expanding numbers of people worldwide suffering from dementia. It is now not uncommon for four generation or more of a family to be living simultaneously, with a major political challenge of maintaining equity and promoting QOL for all generations. The ethical challenges are also to ensure that economic pressures do not compromise the rights of the elderly to access skilled medical care, particularly in the areas of disease prevention and the treatment of chronic disease.

The main determinants of QOL in people over the age of 60 are health status, financial autonomy, contact with family, positive image, social role and personal responsibility. The major focus of the conference was on health status, the impact of economics and the outcome measures needed to carry out research in this area.

Integrating Care Systems

The goal of compressing of morbidity into the last few years of life remains a major medical and social challenge, with disability life expectancy growing more rapidly than the mean life expectancy. By contrast, we are now seeing a declining incidence in Europe and the United States of conditions leading to disability as preventive measures begin to take effect, particularly in the areas of cardiovascular disease, stroke and osteoporosis. The preventive approach is linked to the identification of risk factors, which for dementia include age, gender, education, genetics and cardiovascular disease. The evaluation of risk factors allows the identification of high-risk patients. Treatments such as estrogens, anti-inflammatory drugs, anti-hypertensives, anti-oxidants, and in the future, disease modifying compounds may be able to alter the risk of developing dementia.

A European working group has recently been established to identify expert dementia centers in Europe and to draw up recommendations for the ambulatory assessment of AD based upon their experience. Thirty-two centers in 15 countries participated in a recent workshop, where data from questionnaires and site visits to all centers were presented. The study examined the organization, facilities, functioning, financing, type of patients, diagnostic procedures, care plans and research in progress at each site. Although the results revealed great diversity resulting from the varied care systems in Europe, they also showed remarkable convergence in the type of patient need identified. The main recommendations to date are that care should be delivered through expert centers with multidisciplinary assessment, the use of formal care plans and adequate follow-up.

For people with dementia, bridging acute and chronic care is a key issue, guaranteeing a competent continuum of disease prevention, acute care, rehabilitation, long term care and end of life care. Chronic care systems need to be based on a biopsychosocial model rather than a medical model, and to focus more on function than diagnosis.

Evidence suggests that the frail elderly are best cared for by trained geriatricians. Nearly all countries face increasing economic pressure on health services for elderly people; specialist geriatric care has not been shown to increase costs, but may actually reduce cost in the long term. The effect of cholinergic treatment on cost of AD care has yet to be fully evaluated. The main reason for using anti-Alzheimer drugs should not only be to reduce costs, but should also be to maintain or improve QOL for the patient and caregiver.

In the US a number of organizations including the National Chronic Care Consortium, Social Health Maintenance Organizations, and the Program for All-Inclusive Care of the Elderly are working on models for bridging acute and chronic care. Other programs such as GITT (Geriatric Interdisciplinary Team Training) are facilitating multidisciplinary learning and communication.

Critical issues in bridging acute and chronic care include the need to move towards interdisciplinary cooperation, rather than a model of medical dominance. Care systems also need to become more efficient with more appropriate allocation of resources between community and institutional care. Maximization of resources will also require better integration of formal and informal home care. Finally there will need to be a greater social will to care for a growing aged population.

Economics of Alzheimer's Disease

A number of drugs for the treatment of AD have now gained regulatory approval worldwide. The issues now facing drug companies, purchasers and patients are whether there is adequate data to justify state purchasing of these treatments. Most purchasers have not accepted data submitted for regulatory approval as adequate to drive purchasing decisions even when entered into simple economic models.

A major part of the conference was spent reviewing the economics of AD together with the evolving guidelines and trends for pharmacoeconomic evaluation of anti-dementia drugs. The conference coincided with the publication of the first comprehensive textbook in this field (Wimo et. al., 1998).

Guidelines & Current Trends in Pharmacoeconomic Studies in Dementia

Four major sets of anti-dementia drug guidelines are available and tend to be the basis of decisions made by many health care purchasers. The FDA guidelines, published in 1990 have been very

influential, although developed primarily for drug regulators (Leber, 1990). They focus on the use of outcome measures, particularly cognitive and global function to evaluate the efficacy of a product and have had a major influence on anti-dementia clinical drug trial design.

The Canadian Health Technology Assessment Guidelines for Pharmacoeconomics (CCOHTA), last revised in 1997, are not specific to dementia however, while focusing on meta-analysis and epidemiological data, they also encourage the use of cost-benefit and cost-utility analysis. Australian guidelines are currently under review, with early indications suggesting that while randomized control trials will still be of major importance, there will be a greater emphasis on cost-benefit and cost-utility as an outcome. Within Europe, in addition to the European Medicines Evaluation Agency regulatory guideline on anti-dementia drugs, a number of individual countries are in the process of developing purchasing guidelines although none are yet in the public domain.

In Australia both tacrine and donepezil have been registered but neither is listed on the National Pharmaceutical Benefits Scheme, probably due to lack of data required to establish clinical benefit. A similar debate has arisen in the UK concerning the real clinical benefit of anti-Alzheimer drug treatments. The question of total cost to the UK National Health Service (NHS) and resource allocation decisions when balanced with other diseases and treatments has limited the use of these drugs. In Canada, the CCOHTA review of tacrine expressed uncertainty about effectiveness and was unable to perform a cost-effectiveness analysis of the drug with the available data. Overall the evidence suggests that anti-Alzheimer drugs are being licensed, but are not being purchased by health care systems. This may be because published studies rely on cognitive outcomes rather than 'real world' outcomes such as time to institutionalization, decline in activities of daily living (ADL), progression to severe dementia.

Well-validated surrogate outcomes can reduce the duration of clinical trials or reduce the sample sizes needed to show the benefit of a product. If an outcome measure is well-validated then purchasers will not have a problem using this data. The question faced by purchasers evaluating anti-dementia drugs is how well do cognitive scales in dementia fit the role of a validated surrogate outcome?

The stakeholders in the process of evaluating anti-dementia drugs include drug companies, investigators, regulatory authorities, and now purchasers, prescribers and patients. To evaluate an anti-dementia drug purchasers need clinical outcome data, reliable estimates of effect, estimates of cost per Quality Adjusted Life Year (QALY), and utilization estimates. Dementia is a 'system specific' disease, and it is thus important to capture costs both in clinical trials and in clinical practice. This raises the question of how this information can be provided to purchasers - whether randomized trials are needed rather than observational outcome studies - in reality probably both types of data are going to be important for purchasers.

The issues facing purchasers of both anti-dementia drugs, and drugs for chronic diseases in general are summarized in table 1. There is a growing need for better data, particularly as budgets are likely to remain a major issue for the future.

A US Cross-Sectional Economic Study of AD

The objective of this study was to assess health utilities, health status and the costs associated with AD patients and their caregivers in different disease stages and residential care settings. Previous QOL studies in AD have tended to focus on cognitive, behavioral and functional ability and on caregiver burden. They also tended to examine total disease cost alone, have had small sample sizes, and have not taken disease stage into account.

The study was based on a cross-sectional design and carried out in 13 US centers (Leon et. al., 1998). The patient sample was stratified by disease stage according to the Clinical Dementia Rating (CDR) (Berg, 1988; Morris et. al., 1993), and the residential setting (community or institution). Patients were diagnosed and staged by a clinician, and then economic and QOL data were collected in a telephone interview with the caregiver. The data collected for the study included demographics, the Health Utilities Index Mark II (HUI:2) (Neumann et. al., 1998b), the Short Form -36 (SF-36) (Ware and Sherbourne, 1992), health service utilization, caregiver time and caregiver burden. The HUI:2 does not ask the caregiver to directly assess utilities, rather, patients are assigned into a health state reflecting a unique combination of health attributes. Previously collected community-based preference weights are then used to assign a utility to the patients health state (for more details see Neumann et al (1998b)).

A total of 679 patients were recruited into the study with detailed stage and residential setting specific health utilities generated for both patients and caregivers (Neumann et. al., 1998a). The results showed a poor correlation between the SF-36 and patients HUI:2 scores, confirming the findings from other studies that simple health status measures cannot be used to reflect health utilities measurements. The stage of disease exerted a substantial influence on the patients HUI:2, while by contrast residential setting showed no independent effect. Moreover, caregiver utility scores were neither sensitive to the stage of the disease in the patient, nor to the residential setting.

Its cross-sectional nature and the use of proxies in the assessment process limited the study. There was also no direct utility assessment, and it is not clear how generic instruments such as the HUI:2 are sensitive to the AD-specific components of health related QOL.

The cost data generated by this study is summarized in table 2 (Leon et. al., 1998), and suggest that direct costs are 2-3 times higher in nursing home than in community-based patients. Costs rise with degree of impairment, although they are less than in previous studies, particularly Rice et al (1993).

This is likely to be due to the lower estimates of cost for informal care used in this study, together with somewhat lower estimates of formal care costs.

The Relationship Between Severity of AD and Costs of Caring in Canada

A secondary analysis of data on subjects with AD who were participating in the Canadian Study of Health and Aging (CSHA) (CSHA Working Group, 1994) was carried out to evaluate cost of care. Societal costs for four disease severity groups staged by Mini Mental State Examination (MMSE) (Folstein et. al., 1975) score (21-26, 15-20, 10-14 and <10) were estimated. The costs included those related to institutional care, medications, community support services and caregiver time.

The objectives of CSHA were to estimate the prevalence of dementia among elderly Canadians, determine risk factors and prevalence of AD, describe patterns of care for people with dementia and to provide a baseline for longitudinal follow-up (CSHA-II). A random sample of 9,008 community resident individuals and 1,255 in institutional care were screened using the modified MMSE (3MS). Of these, 1,125 were found to have dementia on clinical assessment, of which 747 were diagnosed with AD.

Those subjects were then included in a sub-study on patterns of caring where information was collected on use of community support programs, amount of direct caregiver time in the past month and the amount of indirect (supervision) time in the past month. Of the 747 patients with AD, a total of 601 were eligible to take part in the costs of caring study. The main reason for excluding patients from the study were lack of MMSE data. Detailed data on costs, disease severity and resource utilization have recently been published (Hux et. al., 1998).

A major finding was that annual cost per AD patient was strongly related to MMSE score. For patients of MMSE scores 21-26, the cost per patient per year was CA$9,451, rising to CA$14,054 for MMSE 15-20, CA$25,724 for MMSE 10-14 and CA$36,794 for patients with an MMSE score below 10. The proportion of the costs shifted significantly from the caregiver (76%) in the mild cases to health care costs (87%) in the most severe group.

The main conclusions were that costs of care for AD patients with greater cognitive impairment were higher than those with lower cognitive impairment, and that patients with lower MMSE scores have a higher probability of being in institutional care with associated higher costs.

A number of caveats need to be considered particularly since this is a secondary study based upon data collected for other purposes. The CSHA study did not include acute health care utilization, and caution is needed, as MMSE score is not the only predictor of institutionalization. As with the US study, the costs were influenced by the value placed upon caregiver time and it is not clear how this

should be quantified. Longitudinal cost modeling needs longitudinal data, which it is hoped will come from the 5-year follow-up of this cohort in CHSA II.

UK Cost of Illness Study in AD

An innovative and detailed UK cost of illness study in AD was recently completed by the Economists Advisory Group in collaboration with the UK Alzheimer's Disease Society (ADS) and Alzheimer Scotland: Action on Dementia, funded with a research grant from Pfizer Ltd. The study was based upon a postal survey of AD caregivers with the objective of generating data on annual direct and indirect costs of AD for different patient groups, identifying the main determinants of costs, and developing theoretical cost profiles over time for different patient groups. Intangible costs, utilities and QOL issues were not included in the study.

A random sample of 1,847 caregivers on the ADS database and the membership network of Alzheimer Scotland were invited to participate in the study, of which 655 evaluable questionnaires were included in the multivariate regression analysis. Cost profiling was carried out by age, diagnosis and years since diagnosis. Direct costs included institutional care, health services, social services, and private expenditure by patients and caregivers. Indirect (opportunity) costs included estimates of loss of earnings for working age patients and caregivers and loss of leisure time for caregivers.

The regression analysis indicated that the cost increase of institutionalization outweighs the reduction in opportunity costs of home caregivers, and thus long term care results in a net increase in total cost. The average cost of moving a patient into institutional care was £20,688 per year to the public purse alone. The average total costs of care rose from £21,000 per year in the first three years to £29,700 per year after nine years. Within this, the average direct costs of care rose from £12,600 per year in the first three years to £22,400 per year after nine years.

The major step change from home care to institutional care occurred in most cases 3-5 years from the time of diagnosis.

In terms of the total direct cost of AD for all age groups, 6% was accounted for by medical attention, 14% by social services, 18% by private direct expenditure and 62% by long term institutional care. The detailed finding of this study, and the cost profiles derived have recently been published (Holmes et. al., 1998).

An Alzheimer's Disease Map

Work in progress from Janssen Research Foundation, in collaboration with researchers from MIT, Harvard and Analysis Group/Economics, on developing an Alzheimer's disease map was presented. The disease map is intended to provide a unified framework for describing and simulating the natural history and evolution of the disease. The focus of the map is on the clinical and economic outcomes for periods of up to four years. The model was developed to describe and simulate the natural history of Alzheimer's disease using an innovative decision database methodology based upon published literature, clinical trial data and expert opinion. The decision model tracks several aspects of Alzheimer's disease including disease stage, participation in an intervention program, side effects, secondary conditions, clinical complications, institutionalization, and disease progression. This model estimates the number and percent of patients experiencing various disease outcomes and the total direct and indirect costs associated with treating those patients. The decision database methodology overcomes the "memory-less" limitation of Markov-based models, the extensive time requirement of Monte Carlo models, and the inability of standard decision tree software to deal with large, complex models. The decision database methodology enables researchers to examine clinical and economic aspects of Alzheimer's disease using a rigorous, probabilistic tool that is able to analyze the path-dependent nature of disease variables and the interaction amongst them.

The model is being developed for use by researchers, managers, decision-makers, health economists and market researchers. Its many possible uses include the prediction of outcomes such as institutionalization or disease progression in populations, and examination of the effects of co-morbidity on outcomes. The model could also be used to test various hypotheses before commencing clinical studies. Advantages of the model include the rich data set with approximately 150,000 nodes and a very large number of disease states. Caveats and limitations include the lack of effectiveness outcomes or utility measures, while work is still in progress to improve the quality of the data on which the model is based.

Economic Models of Drug Treatments for AD

In the absence of specific economic data collected during clinical trials of anti-dementia drugs, a number of attempts have been made to model the effects of these drugs on the economics of AD (Stewart et. al., 1998; Wimo et. al., 1998b; Knapp et. al., 1998). Three specific economic models of drug treatments for AD were presented at the meeting. Two models of donepezil were based upon the US and Canadian economic studies of AD, while a model of tacrine was based on long term follow-up of patients in an open label clinical trial.

The Economic Impact of Tacrine in the Treatment of AD

Tacrine is so far the most studied drug from a pharmacoeconomic point of view. Even if most analyzed scenarios present cost savings, there is a great span in the benefits, from about 1-17% (Lubeck et. al., 1994; Henke and Burchmore, 1997; Wimo et. al., 1997), indicating the effect of different methodological approaches.

A decision analytic model was constructed around milestones in the treatment of AD (Henke and Burchmore, 1997). The objective was to estimate the impact of tacrine use for patients with AD, with a primary outcome of the cost of caring for the patient from diagnosis to death.

The model was based upon data from 2-year follow-up for nursing home placement or death of patients who had received long term tacrine treatment, having taken part in a previous 30 week clinical trial (Knapp et. al., 1994; Knopman et. al., 1996). Mortality data was available for all 663 patients, and nursing home data for 595 patients. The long term open-label follow-up data suggest there was a significantly lower probability of nursing home placement in those taking more than 80mg of tacrine per day.

Comprehensive costs of community and nursing home care were obtained from Rice et al (1993). Assumptions in the model included the need for 4 physician visits in year 1, and 2 in each subsequent year together with liver function testing according to FDA guidelines. Probabilities of side effects were obtained from published reports and the package insert, with unit prices based upon Medicare rates. Table 3 summarizes the estimated average cost of caring for AD from diagnosis to death comparing patients treated or not treated with tacrine. A series of sensitivity analyses were performed to test the robustness if the model, suggesting that costs would always be lower for those patients starting tacrine compared to those who did not.

Overall, the model suggested that tacrine reduces the cost of caring for people with AD by more than $9,000 over their lifetime. The model contains many conservative biases such as including direct costs of formal services for the AD patient only, ignoring the informal caregiver burden of extensions in home-based care, and assuming that there would be no delay in nursing home placement for those patients discontinuing tacrine, or receiving less than 80mg per day. The study also assumed that tacrine delayed nursing home placement, but had no impact on patient survival. There are also issues of sample selection inherent in the long-term follow-up of a randomized controlled trial with an open-label extension protocol.

These results need to be interpreted with some caution as the reliability of the model is only as good as the data on which it is based. Better prospective data is needed to confirm these findings, with a careful examination of the nature of the critical events that drive the model. There is also no QOL

data, which is clearly important to maintain the perspective of the patient and caregiver, rather than basing decisions solely from the perspective of the reimbursement agencies.

An Economic Evaluation of Donepezil for the Treatment of AD in Canada

The objective of this model was to use secondary outcome data (MMSE) from a clinical trial of donepezil (Rogers et. al., 1998) to examine transitions in disease state over time and link these to cost information. Canada has an ageing population with a growing prevalence of AD. The economic burden of dementia in Canada was CA$3.9 billion in 1991 (Ostbye and Crosse, 1994), with the cost of care driven mainly by institutional care (CA$2.2 billion pa). Donepezil was seen as a promising new compound for treating AD, however, as purchasers were concerned about additional costs that might need to be included in their drug budgets. Some provinces of Canada also require economic evidence that the drug offers value for money before its use is reimbursed.

A decision analytic model was constructed comparing treating or not treating patients with 5mg donepezil per day. The effects of disease progression were examined by Markov model (Sonnenberg and Leventhal, 1998) examining transitions between MMSE groups, with 11 cycles of 24 weeks, equivalent to 5 years of disease progression. The costs per AD patient by MMSE group was obtained from the CSHA study described above. The primary outcomes were expected cost per patient and time maintained in non-severe AD (MMSE 10).

The key assumptions of the model were that drug effects impact in the first 24 weeks of treatment only, after which the treated group decline in parallel with the untreated group. The model also assumed donepezil would be discontinued at MMSE scores below 10 in line with the product data sheet, that mortality was independent of MMSE and treatment group with 62.9% survival at 5 years. Costs and outcomes were discounted at 5% per year.

The model suggested that there would be a net reduction in cost to society of CA$882 with the patient remaining for an average of 0.2 years in the non-severe stage of the disease. Over a 5 year time horizon, it further suggests that there will be a net reduction in cost to society of CA$882 per patient. Furthermore, patients not receiving donepezil are predicted to spend 2.21 years in non-severe AD (MMSE<10) compared to 2.41 years for treated patients (a gain of just under 2 months per patient). Sensitivity analyses were carried out to test the robustness of the model which showed that if donepezil is continued at MMSE scores less than 10, then net societal costs increase by CA$1,554 over 5 years.

This type of modeling has been necessary because short term trials cannot address the sort of policy questions that are of interest to purchasers. The available data and conservative assumptions suggest dominance for donepezil over placebo or no treatment, however, the reliability of the AD disease

progression 'trajectory' is unknown, and since no formal comparison was made with tacrine, dominance cannot be asserted. As with other studies, this model also lacks of data on QOL and caregiver issues, moreover, it also values caregiver time at a low value. The model suggests that for the drug to be cost saving it should be prescribed appropriately and discontinued below MMSE 10 when it is no longer indicated. This model also does not take into account the impact of drug therapy on survival, and assumes that it slows progression to nursing home placement, but not progression to death.

Estimating the Cost-Effectiveness of Donepezil in the Treatment of Mild to Moderate AD in the US

A second economic model of donepezil was presented based in part on the US cross-sectional study of AD described above. The objectives were to estimate the incremental cost per QALY gained in treating AD patients with donepezil. The target population were patients with mild to moderate AD. The study was based on a societal perspective, with a comparator of no treatment and a discount rate of 3% per year.

The inputs into the cost-effectiveness analysis were the natural history of the disease, the clinical effectiveness of the drug, costs and heath related QOL data. The data sources for the model were CERAD for natural history of the disease (Galasko et. al., 1995; Morris et. al., 1989), a 24 week clinical trial of donepezil (Rogers et. al., 1998), costs from a variety of sources and QOL weights from the HUI:2 data in the US cross-sectional study (Leon et. al., 1998).

As with the previous model, the outcomes were based on only 6 months of controlled data, however the results suggested that early drug intervention with mild patients was likely to be more cost effective than with moderately affected patients. Sensitivity analyses showed that the model was most susceptible to assumptions about the drug effect and time horizon. None of the cost or QOL data actually came from the clinical trials, and unlike the Canadian study, the source of cost/utilization data was not a nationally representative sample of US AD patients. With these caveats in mind, the model should be interpreted with caution. Overall the study confirmed that AD is costly, and that donepezil may be able to save some cost to society by keeping people out of nursing homes, particularly if the drug is used early in the disease.

The Effect of Disease Modifying Agents

Expanded data from the selegiline and vitamin E study on progression of AD (Sano et. al., 1997) were reviewed, particularly to examine how this could inform the economic treatment models that

have been presented. The trial was a two-year double-blind, placebo-controlled study, and is unique in terms of its length and the type of outcome measures selected for an AD study.

The choice of end-points were carefully selected to represent meaningful outcomes such as disease progression rather than acute worsening of the disease. The endpoints chosen needed to be relatively rare at the beginning of the trial and in the early stages of the disease, but then occur with sufficient frequency as the disease progresses (Sano et. al., 1996). The primary outcome chosen was that the patient reached any one of the following endpoints: death; institutionalization; loss of basic activities of daily living (ADL); or reaching a stage of severe dementia (CDR 3). The results of the study demonstrated a significant effect of treatment on delaying institutionalization and clinical decline with no effect on cognition. This lack of effect on cognition is important since other economic models use cognitive change as a surrogate for estimating economic benefit.

The outcome measures were then examined for their predictive effects on disease progression. Cognitive function at all stages of the disease and over varying time periods of 1 month, 3 months and 6 months showed no significant associations with the primary outcome measures chosen for the study. By contrast the outcome of reaching CDR 3 was highly correlated with nursing home placement, even when controlling for MMSE score, suggesting that these type of functional measures may be more important when modeling long term outcome in AD. Similarly, a loss of basic ADL was also a strong predictor of institutionalization.

The study also examined behavioral changes as rated by the CERAD Behavior Rating Scale for Dementia (Patterson et. al., 1997). The total score on this scale was not correlated with outcome, however the incidence of particular behavioral symptoms such as agitation and insomnia were correlated strongly with institutionalization. Other measures such as psychosis and depression did not show a relationship with outcome.

Outcome data collected from open label clinical trial extension studies, such as the tacrine study (Knopman et. al., 1996), may be misleading, since the effect of simply participating in a research clinical trial, whether or not the drug is shown to be effective, can have a significant effect on delaying nursing home placement (Albert et. al., 1997).

The conclusions of the review were that change measures, such as on cognitive or psychometric scales may not be the best outcome measures for studies examining economic value. Similarly, data from open trials need to be interpreted with caution.

Methodology of Pharmacoeconomic Studies of Dementia

The next section of the conference covered methodological issues in pharmacoeconomic studies of AD, with presentations on resource utilization, caregiver burden and QOL.

Resource Utilization

The design of economic studies in dementia needs to consider the perspective of who will be using the data that is generated. For some studies the societal perspective will be important, while in others the data will need to be relevant to a specific purchaser. A further issue to be considered is whether costs should be measured for the patient only, or for the caregiver as well.

Cost analyses in a clinical trials are based upon two steps; a measurement of resource utilization measured in physical units (days, hours) and a costing of this time in monetary units. The types of costs that can be included in a clinical trial are broad and include habitation, inpatient or outpatient care, formal home care, other care visits (day care, physiotherapy etc), , out of pocket costs, informal care by family members, and production losses (indirect costs). The decision on which costs to include and which to omit may have significant effects on the final outcome.

There are various ways of making time measurements of formal and informal home care including direct observation, dairy keeping and retrospective estimates. The choice of method will influence outcome, however, at present, the use of simple diaries or retrospective estimates is probably the simplest method to use without overburdening the caregiver.

Caregivers have many functions in a clinical trial. They are needed for completing of the Case Report Form, and are vital for collecting adequate data in a dementia study. Caregivers are also 'victims' of the dementia themselves, and experience caregiver burden, which influences outcome (Wimo et. al., 1992), can be measured, and may be amenable to treatment. Finally, the caregiver is a producer of unpaid informal care, which can be valued in monetary units.

The two main approaches to costing informal care are the replacement cost approach and the opportunity cost approach. The replacement cost approach assumes that if the caregiver were not there, then they would need to be replaced by formal staff. This replacement cost usually includes the value of supporting the patient in ADL's and IADL's, but may also include the value of the more difficult to define surveillance and supervision role. Problems in costing also occur with joint productivity, for example where the patient and caregiver do shopping together, and in estimating care productivity; a formal caregiver is likely to be much more efficient and take less time in supporting ADL tasks than an informal caregiver. With the opportunity cost approach, which means the forgone benefits because a resource is not used in its best alternative way (Drummond et. al.,

1987) , the valuation is for caregivers of working age in most cases based upon loss of income as a direct result of having to care for the patient. This significantly undervalues retired caregivers, and it is unclear how lost leisure time for the caregiver can be accounted for.

Some instruments are available to help standardize the measurement of resource utilization, e.g. the CATS (Caregiver Activities Time Survey) (Clipp and Moore, 1995) and the similar CAS (Caregiver activity survey) (Davis et. al., 1997) and the RUD (Resource Utilization in Dementia) (Wimo et. al., 1998a). The CATS surveys formal and informal home care, and also evaluates ADL, IADL and supervision of the patient by the caregiver. The RUD assess the use of a wide range of both formal and informal care for the patient and caregiver. The design of health economic studies, and the choice of instruments must take into account the amount of time required to complete them if the study is not to be exhausting for the study nurse, physician, study subject or caregiver.

Quality of Lives

Quality of life is a multi-dimensional, including cognitive, behavioral, functional, environmental, economic, social and spiritual dimensions (Whitehouse, 1998). All of these dimensions have subjective as well as objective aspects, of which the subjective aspect has posed problems when assessing patients with dementia. Although patients cognitive limitations may color their own perceptions of QOL, more recent scales have been developed to capture the patients view directly.

There are now more than 100 QOL instruments published, although very few are specific to dementia. Within the available dementia-specific scales, three approaches have been used to assess patient QOL; direct observation of the patients behavior (Beck, C. Unpublished; Volicer, L. & Hurley, A. Unpublished); obtaining information on QOL for the patient from the caregiver only (Rabins, P. and Kasper, J. Unpublished); and scales that ask the patient to rate their own QOL (Blau, 1977; Brod and Stewart, 1996; Logsdon et. al., 1998).

(Logsdon et. al., 1998; Brod and Stewart, 1996; Brod and Stewart, 1996; Logsdon et. al., 1998)Measuring caregiver QOL is also important, and for this generic QOL instruments are generally used. An important question is whether QOL for the caregiver is directly related to caregiver burden. Early data from National Institute on Aging studies and work in Cleveland suggests that the two are not directly linked and thus should be measured separately.

The Dementia QOL instrument (DQoL) (Brod and Stewart, 1996) is based on content derived from focus groups and asks patients to make self-ratings of their QOL. The instrument has recently been refined from 56 to 29 items, with the scale is linked to models of QOL covering the domains of aesthetics, positive and negative affect, self-esteem and feelings of belonging. Reliability in terms of internal consistency, re-test and inter-rater reliability have all been shown to be reasonable. By

comparison, the QOL-AD (Logsdon et. al., 1998) is based on a literature review and has 13 items making it quicker to complete. Its includes both patient and caregiver ratings of the patient covering the domains of physical health, energy, mood, living situation, memory, family, marriage, friends, chores, fun, money, self and life as a whole. Each of the domain items are rated as poor, fair, good or excellent. As with the DQoL it has been shown to be a reliable assessment.

A number of issues arise in the assessment of QOL, mainly focusing on whether QOL is really an emergent property, or whether it is simply the sum of various components such as function and affect. QOL is a highly individualized experience which may not be amenable to measurement in a composite scale. This self-experiential nature of QOL highlights the individual, cultural and generic issues involved. The cultural dimension of QOL is a particular issue in International studies. In designing a study a decision needs to be made on whether to use a generic or disease-specific QOL scales, though early evidence suggests that the disease specific instruments are more sensitive to treatment effects. Disease stage is also critical to QOL issues which change for both the patient and caregiver as symptoms progress.

QOL is closely linked to ethics in terms of autonomy and changes to the self in AD, beneficence in terms of whose responsibility is it to protect QOL, and justice in terms of what resources should be made available to people with dementia. These issues have formed part of a discourse-focussed community dialogue on ethics and QOL (Post et. al., 1994; Post and Whitehouse, 1995).

QOL is linked to economics since the way money is spent reflects a societies underlying values. QOL is intrinsic to cost-utility analysis, although the choice of utility weights is problematic since these are not usually made by the patient with dementia. Methods of calculation QALYs also varies, with the use of rating scales, time trade-offs and standards gambles; it is not known how well these different methods correlate in dementia. QALYs do however, allow dementia to be compared with other diseases in a direct way.

The translation and cultural committees of the International Working Group for Harmonization of Dementia Drug Guidelines (http://dementia.ion.ucl.ac.uk/harmon) are currently considering translating QOL instruments for use in international trials. Further research is urgently needed to directly compare drug interventions and psychosocial interventions using these scales.

Caregiver Burden

Caregiver burden is the physical, psychological or emotional, social and financial problems that can be experienced by family members caring for impaired elderly adults (George and Gwyther, 1986). Caregiver burden is associated with caregiver distress, poor caregiver health, increased use of health services, and predicts earlier institutionalization and death for the patient. What is not known is

how caregiver burden interacts with drug treatment - improving caregiver burden may interact positively with drug treatments to increase their effect, although conversely drug treatments may improve patient function but increase caregiver burden.

A caregiver (carer in UK and Australia) has been defined as a family member or friend helping someone, usually on a daily basis, with tasks necessary for independent living. A primary caregiver is someone with total responsibility for the provision of care. Burden on the caregiver can be divided into objective and subjective types. Objective burden is patient focussed and incorporates patient dependency, loss of cognition and other abilities, and the presence of problem behaviors or psychiatric disturbance. By contrast, subjective burden is self-appraised by the caregiver and usually covers areas such as demoralization, depression and feeling trapped, resentful, stressed, overloaded, unable to cope and exhausted. It may also relate to having other activities restricted, and to affecting outside relationships.

A number of models of caregiver burden have been developed e.g. Poulshock and Deimling's (1984) model which defines predisposing, exacerbating and protective factors. Caregiver burden may have a number of outcomes on the caregiver including psychological effects (depression, anxiety or general distress), effects on the caregivers physical health and use of health services, and an impact on the caregivers finances. All of these may lead to a yielding of the caring role usually associated with institutionalization (Pearlin et. al., 1990).

Measuring caregiver burden requires instruments that are specific to dementia, well validated, reliable and sensitive to change (Vitaliano et. al., 1991b). A number of factors confound the measurement of caregiver ratings including the caregivers own characteristics and their tendency to over- or under-estimate the patients disabilities. The positive aspects of caregiving are often ignored in existing scales; many caregivers report feeling useful and having higher self-esteem in their caring role. The trajectory of burden is non-linear and probably does not increase as dementia progresses, in some cases it may even decline as caregivers adapt to their situation. Particularly burdensome points in the course of the illness include diagnosis, occurrence of problem behaviors, incontinence and institutionalization. Depression in the caregiver itself may be burdensome and thus act as an additional confounder.

Table 4 summarizes the most common caregiver burden measures and indicates those that have demonstrated validity and reliability. Similarly a large number of generic scales are available to assess the psychological state and physical health of the caregiver (Schulz and Williamson, 1997).

Measuring caregiver burden is important. It is a significant predictor of institutionalization and this is the major driver of cost in pharmacoeconomic models. Caregiver burden should be measured on three levels: objective burden; subjective burden; and more distally such as through psychological

distress. Research need to examine linkage between these different levels, and the effects of other mediating factors such as the relationship of the caregiver to the patient. The choice of measure depends upon the anticipated outcome for the study, for example, in a trial examining the effect of a behavior-modifying drug, an objective behaviorally oriented scale should be used. The scale chosen should have adequate psychometric properties including demonstrated validity, reliability and sensitivity to change. Completion of the scale itself should not place excessive demands on the subject.

Strategic Futuring & Pharmacoeconomics in AD

In the final part of the conference a series of workshops applied the theory of Strategic Futuring to the further development of pharmacoeconomics in AD. The core concept of Strategic Futuring is to plan to create a specific, preferred future for a process and its stakeholders. A preferred future is emphasized so that the organization is focussed on its highest aspirations and values; a future that would be the best for all client stakeholders. There are three inter-related phases to strategic futuring: 1) Aspirations and Identity Clarification; 2) Environmental Assessment; and 3) Strategic Analysis.

The Aspirations Phase begins with the Institutes futurists guiding a process to discover a deeper vision of the preferred future. Participants articulate the organizations identity and role in creating the preferred future, its values for selecting actions and the specific missions necessary for achieving the preferred future. Then they can set specific goals associated with the vision, identity and mission. The Environmental Assessment Phase has participants identifying significant trends affecting the organization and its stakeholders. These trends are then used to develop alternative images of the future (i.e., scenarios). An important benefit of the environmental assessment phase is that it develops an extensive list of environmental risks and opportunities for the organization to consider. The final phase of strategic futuring is Strategic Analysis. After reviewing the scenario-specific strategies, the participants select several strategies for detailed analysis. The selection can be driven by a number of considerations including robustness (i.e., useful regardless of scenarios), risk, return, appeal or audacity.

Eight parallel workshops were convened in which the participants were first asked to briefly describe what state-of-the-art of economic and QOL research in AD would be like in the year 2005 with regards to their topic. In the second exercise the issues or barriers to achieving this future were examined. Brief summaries of the workshops are outlined below:

Consumer and caregiver use of pharmacoeconomic data

In the preferred future, caregivers will have access to easy-to-understand data on the effectiveness and costs of drugs, probably via the Internet. Electronic models will be publicly available, into which data about the patient can be fed, and predictions of costs and outcome of different treatments could be obtained. Policy makers and purchasers will have access to pharmacoeconomic data for a wide range of drugs, which could be used as lobbying tools. This will lead to just allocation of resources for the elderly, with comparison of utilities for different treatments across different diseases. The finances of the pharmaceutical industry will also be more transparent so that the public and purchasers are more aware of the equity of profits or losses being made.

The barriers to this future were seen as ageism, lack of political will for transparency of organizations and secrecy within the pharmaceutical industry. Policy makers were also felt to lack a vision for the future.

Early detection and prevention

Even by 2005 it will probably not be known whether there is an economic benefit to early detection of dementia, although prevention will certainly be a goal. There is likely to be a convergence of etiology, bringing together genetic factors, etiological mechanisms and channeling them into prevention. A second convergence would come from preventive strategies acting on more general mechanisms of aging, rather than disease-specific factors. Biological markers for the disease will be available, and will be particularly important as disease modifying drugs appear. The concept of a biological window will emerge, defined as the period in which an intervention could be applied before there was any clinical manifestation of evidence of the disease.

Of the barriers to this future, the main ones were seen to be time and changing demographics - would there be enough time to develop preventive strategies? Moreover, attitudinal barriers were seen to be equally important and will need to be overcome if preventive strategies are to be effective. Finally, other aging-related illnesses may overtake gains in the area of dementia, and will also compete for resources.

Japanese perspectives

In Japan the elderly population (over 65 years of age) will exceed a quarter of the total population by 2005. This is a major environmental challenge for Japan. Effective strategies against dementia will need reliable data on caregiving, epidemiology and economics of dementia. The system of caregiving for patients is poorly organized in Japan, with limited integration of GPs, nurses and caregivers.

Early diagnosis, and better diagnostic markers will be needed to target effective treatment. Coupled with this is the need for effective anti-dementia drugs - none of which are yet available in Japan.

Possibly the two major barriers to solving the problem of dementia in Japan will be lack of political will and the impending financial crisis.

Measuring activities of daily life and what will be daily life activities

By 2005 response to drugs will be enhanced by non-pharmaceutical interventions such as family education and cognitive training. More sensitive ADL checklists and biological markers will facilitate early diagnosis. Gender biases in ADL assessment will decline as traditional male and female roles continue to converge. Driving will be safer due to navigational aids, and there will be more group living for people who live alone. There will be more funding from the state, and better communication systems, such as videophones to allow distant family members to monitor and support elderly parents. Functional autonomy will be an important goal in aging.

Barriers to this future include issues of privacy, confidentiality, lack of political will, ignorance, lack of awareness, stigma of disease, ageism, lack of gold standards for family interventions, and lack of proven clinical trial designs for combination therapies.

Measuring caregiver burden

Small and large meetings will become virtual as the Internet is increasingly used to facilitate research and healthcare. Better communication between different payers will allow rational and equitable purchasing decisions to be made for patients. There will also be payment for caregivers in recognition of their role. The use of innovative caregiver support systems, and other techniques that have been shown to work will be implemented on a widespread basis. Technology will support education, training and the securing of the caregiving role. Leave from employment will be provided for caregivers, along with health promotion strategies.

The barriers to this future will be political, and the problems of dealing with a technologically un-empowered population. Social and political agendas will need to change to recognize the importance of caregiver burden. At a technical level informal care needs to be brought to political attention. Research needs to measure informal care more accurately, possibly by utilizing technology.

Measuring QOL at the end of life

The task of measuring QOL for this group may not change much by 2005. The primary dimensions will be dignity, freedom from pain and distress, perceived wellbeing and spirituality. There is likely

to be better agreement about the appropriate tools and instruments for measuring QOL for both patient and caregiver. Computerization may assist techniques for measuring QOL, possibly by using video systems. This may help to confirm that QOL is consistently maintained. QOL measurements will move from being cross-sectional to being measured in continuous time. Providers, decision-makers and others will facilitate the process of developing living wills and advance directives reliving the stress and emotional burden these decisions place on caregivers.

Barriers include massive economic pressure to restrain resources. Long term care is very labor intensive and technology may be able to reduce this cost. This may even include the transfer of elderly patients to areas where labor is cheaper and more available, particularly if communication links allows contact with family back home. The political process may also be a barrier in terms of planning priorities for long term care, and this is unlikely to be resolved until there is a major crisis which is unlikely before 2005.

New uses for new information and communication technology in clinical research

The future saw clinicians, researches and economists communication with each other using computer technology. This would be in the form of electronic messaging and video conferencing as well as access to databases and full-text electronic journals.

Healthcare data will be captured by computer in more detailed ways, evolving into data warehouses that track the medical course of a patient through their whole life. Linking healthcare and finance or banking systems would allow the direct and meaningful tracing of the effects of disease on personal finances and economics. Every home will have a videophone allowing continuous automatic monitoring of patients and caregivers - this will be particularly useful for measuring caregiver resource use. A community of up to 100,000 people linked up through this process would offer a rich system to studying the economic effects of disease and aging in general.

The barriers to this future are the issues of confidentiality, privacy and ethics. A major barrier will be the penetration of this technology, with the potential for establishing a two-tier society, where electronically connected individuals were not equivalent to those who had been left behind.

Physicians use of pharmacoeconomic data

As the use of cost benefit analysis becomes more widespread, there is the risk that it will be used inappropriately in making programmatic decisions. Therefore, program managers and medical decision makers will have to be educated about the limitations and appropriate use of such methods. Cost-benefit analysis is particularly useful when comparing different drugs or "cocktails", rather

than as at present comparing a intervention with a single drug (e.g. donepezil) with a "no treatment" option. Therefore even greater use of this technique is anticipated as new alternative drugs for the treatment of Alzheimer's disease are developed in the future. One version of this analysis namely "cost -utility" analysis will cause great friction as unequal utility weights are developed to differentiate the value of life at different ages. They may lead to a shifting of resources from the old to the young, unless ethical issues surrounding such a policy are resolved.

The boom in information technology will make it possible to continuously compile pharmacoeconomic data and to update cost-benefit estimates instantly as patients enter the system. At the moment the development of user-friendly statistical software and algorithms (e.g., to calculate confidence intervals of cost-benefit estimates) are lagging behind developments on the information processing side. In the future statistical technology will catch up with the information side, and become used more widely by physicians, consumers, and policy makers in making decisions. Given the convergence of all health care systems to a "gatekeeper" model, physicians and other providers will be asked to make decisions that will involve non-clinical criteria such as cost-benefit analysis. Providers are likely to continue to resist this trend. Human issues are more difficult to resolve that some of the technical issues and ongoing debate between providers and health systems manager may intensify.

Conclusions

The highly successful 1st Pharmacoeconomic Conference on AD attracted more than 160 delegates, and a wide variety of speakers. The second conference is now planned for 2000. Over the next two years many of the problems identified may be solved and the benefits of drug treatments may be better understood. However, the research needs to be broadened particularly in the areas of resource utilization, QOL and caregiver burden. It is hoped that the models described may become more freely available to politicians, purchasers, clinicians and caregivers to help them make better decisions about treatment.

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Tables & Figures

Table 1 - Issues Facing Purchasers Of Anti-Dementia Drugs

- The validity of scales used for testing interventions
- The definition of a clinical outcome
- The relationship between surrogate outcomes and clinical outcomes
- Impact of treatment on patient and caregiver
- The accuracy of the estimate of clinical benefit
- The system used to value the outcome
- Purchasers willingness to pay
- Conflict between the regulatory approach and the purchasers need for information

Table 2 - Annual Cost of AD in the USA ($1997). Adapted from Leon et al (1998)

Residential Setting/Severity	Formal Care	Informal Care	Total
Community			
Mild	7,008	7,452	14,460
Moderate	11,064	11,988	23,052
Severe	11,520	12,720	24,052
Institution			
Mild	41,832	420	42,252
Moderate	41,964	504	42,468
Severe	42,684	408	43,092

Table 3 - Average Cost of Caring for AD from Diagnosis to Death (US$) (Adapted from (Henke and Burchmore, 1997))

Component of Cost	People Starting Tacrine	People Not Staring Tacrine
Community care	$ 47,411	$ 45,909
Nursing home care	64,160	77,889
Tacrine acquisition	2,655	
Tacrine visits, monitoring	321	
TOTAL COST	$ 114,548	$ 123,798

Table 4 - Commonly Used Caregiver Burden Instruments

Scale	Reference	Number of Items	Assesses Subjective Burden	Assesses Objective Burden	Validated	Tested for Reliability
Burden Interview	(Zarit et. al., 1980)	22	✓		✓	✓
Problem Behavior Checklist	(Gilleard et. al., 1984)	28		✓		
Behavior and Mood Disturbance Scale	(Greene et. al., 1982)	34		✓		
Relatives Stress Scale	(Greene et. al., 1982)	15	✓		✓	✓
Rabins et al Structured Interview	(Rabins et. al., 1982)	52	✓	✓		
Caregiver Strain Index	(Robinson, 1983)	13	✓	✓	?✓	✓
Poulshock and Deimlings Model	(Poulshock and Deimling, 1984)	23	✓	✓	✓	?✓
Montgomery et al Inventories	(Montgomery et. al., 1985)	9		✓		✓
Caregiver Appraisal Measure	(Lawton et. al., 1989)		✓		✓	✓
Caregiver Hassles Scale	(Kinney and Stephens, 1989)	42	✓	✓	✓	✓
Screen for Caregiver Burden	(Vitaliano et. al., 1991a)	25	✓	✓	✓	✓
Caregiver Burden Inventory	(Novak and Guest, 1989)	24	✓	✓		✓
BEHAV-AD (1 item only)	(Reisberg et. al., 1987)	25		✓	✓	✓
Pearlin Interview	(Pearlin et. al., 1990)	94	✓	✓	✓	✓
Revised Memory and Behaviour Problem Checklist	(Teri et. al., 1992)	34	✓	✓	✓	✓
Neuropsychiatric Inventory	(Kaufer et. al., 1998)	12	✓	✓	✓	✓

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