THE EFFICACY OF TACRINE
AND THE MEASUREMENT OF OUTCOMES
IN ALZHEIMER’S DISEASE

prepared by Dr. Judith Glennie, FCSHP
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The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization, funded by the federal, provincial and territorial governments. It was established to encourage the appropriate use of health technology by influencing decision-makers through the scientific evaluation of medical procedures, devices and drugs. The effectiveness and cost of technology and its impact on health are examined.

This overview has been prepared by staff at CCOHTA and is based in part on a study commissioned by CCOHTA: A Study of the Efficacy, Effectiveness and Economic Impact of Tacrine in Alzheimer’s Disease conducted by Wolfson C.¹, Moride Y.², Perrault A.³ and Vida S.⁴ This overview attempts to put the original study into a clinical perspective.

Due to the complexity of the issues surrounding this topic, this document contains more detail than has traditionally been provided in previous overviews. Your comments on the value of this additional material would be appreciated.

This overview does not necessarily reflect the opinions of the original investigators.

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<tr>
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<th>Name</th>
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<td>Health Sciences Center</td>
<td>McMaster University</td>
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<td>Hamilton, Ontario</td>
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SUMMARY REMARKS

BACKGROUND

Alzheimer’s disease (AD) is a disorder associated with progressive decline in memory and cognitive function. It is the most common cause of dementia in the elderly, with no known cure. The burden of illness on patients and families, as well as the economic impact of this disease, make it an important health care and societal problem.

Studies using Tacrine (tetrahydroaminoacridine: Parke Davis) have demonstrated the drug’s efficacy in mildly to moderately impaired AD patients. The clinical impact is not dramatic and adverse events limit the usefulness of the drug. Overall, Tacrine is considered primarily palliative in its effect, as it does not alter the ultimate course of disease. Significant controversy exists regarding the measurement tools used to evaluate AD therapies, as well as translation of efficacy results into effectiveness data.

Given the potential burden of disease as our population ages, and the uncertain role of Tacrine in disease treatment, a study was commissioned by CCOHTA to carry out an assessment of Tacrine for the treatment of AD\(^1\). Given the limitations of the data available in the public domain, the study’s scope was limited to a critical appraisal of the evidence of Tacrine’s efficacy in AD. This overview summarizes the findings of the commissioned study.

CONCLUSIONS

Based on a Best Evidence Synthesis of 5 cross-over trials and 5 parallel trials of Tacrine judged to be scientifically acceptable (published since 1990 and available in the public domain):

1) Tacrine was shown to have modest efficacy in mild-to moderate AD, with small but clinically unimportant improvements in cognitive status in 3 trials. The remaining 7 clinical trials demonstrated no differences in the outcome measures related to cognition.

2) There are challenges presented by the interpretation of clinical trial results in terms of Tacrine’s efficacy in this patient population. There is significant variability in the degree to which the outcome measurement tools used in the Tacrine trials have been assessed for validity, reliability and responsiveness; and very few scales have been developed specifically for AD. Clearly, more research and development is needed in the area of measurement scales suitable for the evaluation of treatment in AD.

3) The modest efficacy of this drug must be balanced by:

   a) the frequency of Tacrine’s adverse effects (e.g. hepatotoxicity, gastrointestinal events) in study subjects who, apart from suffering from AD, were healthy with no other medical conditions and free from potentially interfering/interacting medications; and,

   b) the inability to identify initially which subjects may respond to Tacrine without experiencing
side effects.

4) Given the small proportion of study subjects who were able to complete the trials reviewed, the effectiveness of Tacrine within the overall cohort of subjects eligible for trial entry has not been established. The authors were unable to predict the potential effectiveness of Tacrine in the population of AD subjects for whom physicians may consider this drug.

5) Using data from the Canadian Study of Health and Aging (CSHA) and the Régie de l’assurance-maladie du Québec (RAMQ), it appears that community-dwelling AD subjects have a lower use of formal medical services (e.g. physician visits, medications prescribed) than the normal elderly. (This is consistent with other reports that indicate that formal medical care does not contribute significantly to additional costs incurred by AD patients living in the community.) Of the annual net cost of treating dementia in Canada, community costs represent 32% while long-term care institutions represent 56% of this total. (Remaining costs include drugs, hospitalization, diagnosis, research, and treatment of patients under age 65.)

6) The results of this evaluation are limited by: access to and problems with the data available in the public domain; a cost analysis which focused solely on community-dwelling AD patients; and the continued absence of information regarding the cost of informal care for AD patients in the community.
INTRODUCTION

Alzheimer’s Disease

Alzheimer’s disease is a dementia related to aging, with a progressive increase in risk with each decade after 40 years. The prevalence of AD is increasing dramatically as our population ages. It is anticipated that the number of cases in Canada will more than double current levels, to over 387,000 by the year 2020 (see Table 1). Medical science’s efforts to understand AD and to develop effective treatments have had limited success. It is believed that the underlying defect in AD involves a decrease in the production of acetylcholine (ACH) in the brain. Acetylcholine is a neurotransmitter with a central role in a wide variety of neurologic functions, including movement, thought processes and behavioural control.

The clinical presentation of AD manifests over an extended period of time, in a highly variable manner. Typically beginning with subtle impairment of short-term memory and attentiveness, AD progresses slowly and gradually, often going unnoticed for several years. Patients’ ability to think and perceive are gradually affected, and they often develop behavioural and psychiatric problems (e.g. depression, anxiety, delusions, hallucinations). Ability to speak and move are affected in advanced stages of AD, and patients eventually become bedridden.

The consequences of AD for the patient, family and society overall are multi-dimensional. In addition to the clinical manifestations, the quality of life and economic impact on both patient and care giver is an issue, especially in later stages of the disease. Progressing memory impairment results in patients being unable to care for themselves. Family members step out of the workforce to meet ever increasing support requirements. Institutionalization is often required as it becomes no longer feasible to fulfill these patients’ constant care needs in the home. Society is directly as well as indirectly affected by AD, as productive members are lost to disease and health care costs increase with institution-based support requirements.

TABLE 1: Prevalence of AD in community dwelling elderly in Canada (1991)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Age standardized prevalence per 1,000 population</th>
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<tr>
<td>65-74</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>4</td>
</tr>
<tr>
<td>female</td>
<td>11</td>
</tr>
<tr>
<td>total</td>
<td>8</td>
</tr>
<tr>
<td>75-84</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>39</td>
</tr>
<tr>
<td>female</td>
<td>46</td>
</tr>
<tr>
<td>total</td>
<td>43</td>
</tr>
<tr>
<td>85 and over</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>121</td>
</tr>
<tr>
<td>female</td>
<td>147</td>
</tr>
<tr>
<td>total</td>
<td>138</td>
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<tr>
<td>Overall</td>
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<tr>
<td>male</td>
<td>22</td>
</tr>
<tr>
<td>female</td>
<td>30</td>
</tr>
<tr>
<td>total</td>
<td>27</td>
</tr>
</tbody>
</table>

Treatment

As noted above, many of the clinical manifestations of AD appear to be related to a deficit in the
cholinergic system due to an unknown mechanism. This has resulted in the development of treatment regimens aimed at improving ACH transmission. Drugs, like lecithin and choline, have been administered in an attempt to directly increase ACH levels but with very limited success. A number of other products, such as donepezil, varenicline, besipirdine, selegiline, and xanomilene, are at various stages of investigation. Tacrine derives its activity in AD from its ability to increase ACH levels primarily through indirect means (blocks breakdown of ACH; i.e. acetylcholinesterase inhibition), although there appears to be some direct activity (i.e. increased ACH release and synthesis). Tacrine also appears to modify other neurotransmitters which may explain the improved neurologic and psychologic performance seen in some AD patients treated with this drug.\(^2\)

Since the 1980's, clinical trials involving Tacrine (as well as other potential AD therapies) have been criticized on various scientific fronts: from study design, to measurement tools, problems during the study process, all the way through to the interpretation of study results. The focus of this overview document is on the measurement tools and efficacy outcomes specific to Tacrine studies.

**BEST EVIDENCE SYNTHESIS**

The investigators set out to complete a review of those clinical trials with the methodological potential to provide useful evidence of the efficacy of Tacrine in AD. The following outlines the methods used in the evaluation process, as well as an introduction to some of the issues which had to be considered in assessing the literature in this area.

**Methodology**

A comprehensive literature search was carried out in June-July 1996 to identify human studies (English and French) published since 1990 and concerned with the efficacy of Tacrine in the treatment of AD. All material used was in the public domain, except the following unpublished material obtained from CCOHTA: i) letter to Parke-Davis regarding the Clinical Interview-Based Impression of Change (CIBIC) (Dr. Leber, personal communication, 1991); ii) Guidelines for the Clinical Evaluation of Antidementia Drugs (P. Leber, First Draft, 1990); and, iii) The Progressive Deterioration Scale (PDS).

A total of 21 randomized controlled trial (RCT) articles involving Tacrine and employing clinical (i.e. cognitive or functional) outcomes were identified. These represented 14 separate studies, of which one was eliminated because it focused on sleep disturbance as a primary outcome (not considered relevant for the issue at hand). The methodologic review focused on the remaining 13 RCTs involving Tacrine. Only 10 of the 13 RCTs met the pre-defined criteria for scientific quality. The Best Evidence Synthesis was based on 5 cross-over and 5 parallel design studies which passed the initial review process. A classical meta analysis was not justifiable, as these 10 studies were so variable in dose, treatment duration and outcome measures that to combine them would not be appropriate. However, the patients enrolled in the trials did have AD of similar severity. Concurrent with this review process, the validity and reliability of the primary outcome scales used in Tacrine trials were evaluated, along with the adverse event and responder literature regarding this product.

Subsequent to the Best Evidence Synthesis, the investigators attempted to carry out an economic evaluation of Tacrine in AD.
Scales Used to Assess Outcomes in Patients with AD

Scales for Describing Severity of AD

Part of the evaluation process focused on the measurement tools used to describe the severity of AD in those patients participating in Tacrine trials. This is pertinent, as one needs to ensure that the evaluation is based on studies looking at patients with the same baseline severity of disease.

There are two broad types of scales for determining severity of AD: global staging scales (based on clinical symptoms, behaviour problems and functional status; e.g. Global Deterioration Scale [GDS] and Clinical Dementia Rating Scale [CDR]); and cognitive scales (reflecting cognitive status of patient; e.g. Mini Mental Status Examination [MMSE]). These scales have demonstrated adequate validity and reliability in this patient population. Combined use of these scales has been recommended for increased precision of staging.

Other Issues

The Tacrine AD studies excluded a number of patients based on concomitant disease (including liver or kidney disease) or treatment with medications thought to affect cognition or to have central nervous system activity. With the study participant population limited to otherwise healthy AD patients, and given the age group at risk for AD, this eliminated a large number of “typical” AD patients.

Properties of Outcome Measurement Tools

Before discussing the outcomes used in the Tacrine AD studies, the concepts of validity, reliability and responsiveness must be reviewed (see Figure 1). These are three properties which describe the ability of a tool/instrument (as reflected in its psychometric properties) to measuring “soft” outcomes, such as quality of life, cognition, ability to carry out activities of daily living, etc. Each one of these properties can be assessed within a given tool in order to make a determination as to the usefulness of that tool.

The validity and reliability assessment of a given instrument is specific to the situation and population being examined. If an investigator intends to use that tool in a new setting (e.g. change from the North American to an Asian culture) or in a different patient population (e.g. different disease state) from which it was originally tested, both of these properties need to be reassessed.

One must look critically at the instruments used in the AD clinical trials (to determine whether or not appropriate tools were used to measure efficacy) before making a determination as to whether or not Tacrine had an effect in these studies. The multidimensional nature of AD requires the use of multiple, complex instruments.

Figure 1. Definitions of Validity, Reliability and Responsiveness
VALIDITY
- An instrument’s ability to measure what it is intended to measure
In AD, the ability to accurately measure domains affected by the disease (i.e. cognition, behaviour, function)

RELIABILITY
- The instrument’s ability to consistently give, with repeated measurements in clinically stable patients, the same scores for each individual
Note that this is a function not only of the instrument itself, but also of the raters who apply the instrument (i.e. reliability in measurement) and the population to which the instrument is applied

RESPONSIVENESS
- The instrument is capable of detecting change (over the short and/or long term)
This is particularly important in assessing differences in response (i.e. improved outcomes) to treatment (e.g. drug studies)

Outcome Measures

Three domains of outcome are compromised in patients with AD: cognition, behaviour and function. Each of these domains can be measured by a scale from a specific group of instruments, and each scale must be valid, reliable and responsive to changes in those domains in AD patients. It is necessary to use indirect assessment scales to measure the impact of an intervention in AD because there is no biochemical marker (e.g. indication of improvement in ACH transmission) which can be measured directly in patients undergoing AD treatment.

a) Cognitive Scales

Domains measured by cognitive scales include memory, language, constructional ability, attention and calculation, and higher cognitive functions. Several different scales were used in the 10 Tacrine trials. As part of the review, the authors evaluated the psychometric properties of four primary scales (Table 2).

b) Global Assessment of Change Scales

These scales are intended as measures of the overall functioning (i.e. performance, behaviour) of the patient as compared to baseline. Global scales have been favoured outcome measures in psychiatric research. The ratings, carried out by a skilled clinician, are believed to represent an unbiased determination as to whether or not the patient has changed in a clinically important way. In 1990, in recognition of the potential pitfalls of the sole use of cognitive scales in clinical evaluation of antidementia drugs, the American FDA issued guidelines which made the use of global assessment of change scales mandatory.
Table 2: Properties of Cognitive Scales used in Tacrine Alzheimer’s Disease Studies

<table>
<thead>
<tr>
<th>Scale</th>
<th>Validity</th>
<th>Reliability</th>
<th>Responsiveness</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State Examination (MMSE)</td>
<td>Adequate (1)</td>
<td>Adequate/high (3)</td>
<td>Not as useful at low end of the scale in longitudinal studies Low sensitivity and not as useful at high end of the scale in cross-sectional studies</td>
<td>Discriminative (4)</td>
</tr>
<tr>
<td>Alzheimer’s Disease Assessment Scale - cognitive (ADAS-c)</td>
<td>Adequate (2)</td>
<td>Adequate/high (3)</td>
<td>Shown in longitudinal studies Some subsets of scale may be insensitive to change in mild dementia</td>
<td>Evaluative Only scale developed and validated specifically for AD Inconsistent information on age, education as confounders (5)</td>
</tr>
<tr>
<td>Cambridge Mental Disorders of the Elderly Examination - cognitive (CAMCOG)</td>
<td>Adequate Most comprehensive of the 4 scales assessed</td>
<td>Fair to adequate, but limited data (3)</td>
<td>Shown in one longitudinal study</td>
<td>Discriminative (6)</td>
</tr>
<tr>
<td>Abbreviated Mental Test Score (AMTS)</td>
<td>Adequate (1)</td>
<td>Adequate/high (3)</td>
<td>Shown in only one longitudinal study</td>
<td>Discriminative (4)</td>
</tr>
</tbody>
</table>

(1) scale does not assess higher cognitive function or all components of memory
(2) scale does not assess executive functions (such as attention and calculation)
(3) inter-rater reliability for all scales high, but criticized on various aspects in the literature
(4) adequate validity and reliability; not designed to measure subtle aspects of cognition; demonstrate little or no change over time; not ideal outcome measure for antidementia drug trials
(5) limited ability to detect change at extremes on severity continuum; most appropriate as a measure of drug efficacy for mild to moderate AD
(6) superior in range of cognitive functions and sensitivity at extremes of severity; insufficient description of psychometric properties
The authors reviewed 3 global scales used in the 10 studies evaluated: Clinical Global Impression of Change (CGIC), Clinical Interview-based Impression of Change (CIBIC) and Visual Analogue Scale for Improvement (VAS). They were unable to assess the psychometric properties of these scales due to insufficient studies involving demented patients. These scales have been incorporated into clinical trials (per the FDA directive) while their psychometric properties have yet to be fully evaluated. Until more research is available, it will continue to be difficult to determine whether these scales reflect a drug’s antidementia efficacy.

c) Functional Scales

Functional scales are intended to evaluate improvement in day to day functioning as measured by changes in basic Activities of Daily Living (ADL; e.g. eating and bathing) and Instrumental or more complex Activities of Daily Living (IADL; e.g. shopping, traveling). ADL and IADL are considered clinically meaningful outcomes because some cognitive skills are required to carry out ADL and IADL tasks, and because the measures reflect the level of assistance provided by care givers. As part of their review, the authors evaluated the psychometric properties of four scales for assessing functional outcome (see Table 3).

d) Behaviour and Mood Scales

A complex relationship exists amongst behaviour problems, cognitive status and functional status. The behaviour domain was not measured as a primary outcome in the 10 studies reviewed. Study subjects were usually selected for the absence of behaviour problems (low baseline scores on both behaviour and mood problems), so the trial would not be expected to measure behavioural changes in the Tacrine group. Five behavioural scales were briefly reviewed and described by the authors: Alzheimer’s Disease Assessment Scale - non-cognitive (ADAS-nc), Behavioural Pathology in Alzheimer’s Disease (Behave-AD), Behavioural Problem Checklist (BPC), Stockton Geriatric Rating Scale (SGRS), London Psychogeriatric Rating Scale (LPRS). All scales showed adequate reliability and some responsiveness to change, while validity was noted to be limited for BPC, SGRS, and LPRS.

e) Quality of Life Evaluations

Quality of life (QOL) was not specifically measured in most of the Tacrine trials evaluated, although many of the scales utilized indirectly measure aspects which likely have an impact on the patient’s QOL. The care giver’s QOL is also an issue which must be considered in AD. There is no formal definition of QOL in AD per se, and research into this issue is in its early stages.

Summary of Scales used in Tacrine AD Studies

The outcome scales used in the Tacrine studies relate to domains of interest in AD, but most have limitations in terms of validity and responsiveness and, consequently, in their ability to detect change. This has implications for the decision-making process: it is difficult to assess the clinical importance of an improvement in AD status via a drug intervention if it is not clear what is being measured. Of the scales reviewed, those developed specifically for AD were judged most apt to identify improvement of clinically significant importance.
Table 3: Functional Scales used in Tacrine Alzheimer’s Disease Studies

<table>
<thead>
<tr>
<th>Scale</th>
<th>Validity</th>
<th>Reliability</th>
<th>Responsiveness</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive Deterioration Scale (PDS)</td>
<td>Adequate</td>
<td>Adequate</td>
<td>Incompletely assessed (inferred)</td>
<td>Only scale developed and validated for AD (2) (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consistency between raters has not been assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instrumental Activities of Daily Living Scale (IADL)</td>
<td>Adequate (1)</td>
<td>Fair to adequate</td>
<td>Unable to assess</td>
<td>(3) (4)</td>
</tr>
<tr>
<td>Rapid Disability Rating Scale (RDRS)</td>
<td>Fair to adequate (1)</td>
<td>Adequate</td>
<td>Unable to assess</td>
<td>-5</td>
</tr>
<tr>
<td>Functional Life Scale (FLS)</td>
<td>Adequate (1)</td>
<td>Adequate Concern that consistency between raters not assessed accurately</td>
<td>Incompletely assessed (inferred)</td>
<td>-5</td>
</tr>
</tbody>
</table>

(1) concerns whether each domain of AD is sufficiently represented in the scale
(2) scale is unpublished to date; insufficient information on psychometric properties
(3) exclusively concerned with IADL
(4) captures AD patients earlier in disease than ADL; often used in conjunction with Physical Self-Maintenance Scale, which covers self-maintenance activities (ADL)
(5) also include items of basic ADL and other aspects of functioning (e.g. cognition, mood, sensory deficits)
EFFICACY OF TACRINE

Randomized Controlled Trials

Randomized controlled trials have been used to evaluate oral Tacrine in doses from 40 to 160mg per day. The studies of adequate methodology used in this review are summarized in Table 4. The 5 parallel trials were highly variable in their duration and the doses of Tacrine used. Two of these studies found no significant improvement; one found marginally significant results. These results were likely due to an inadequate washout period after a pre-trial enrichment phase (the latter phase used to determine tolerability and early signs of responsiveness). The two remaining studies showed statistically significant effects for Tacrine; one with possible selection bias and an analysis involving only those who completed the trial; the other demonstrated an outcome scale difference of marginal clinical importance.

The 5 cross-over trials reviewed involved small sample sizes and were, again, highly variable in duration and doses used. Only 1 of the 5 studies showed statistically significant improvement in cognitive status due to Tacrine. In general, when a carry-over effect is suspected (i.e. the effect of the drug lasts after it is discontinued, thus affecting the results achieved with the follow-up medication), cross-over trials are not as appropriate as parallel trials.

Thus, Tacrine has demonstrated modest improvements in cognitive function and behavioural deficits in a subgroup of patients with AD in 3 of 10 methodologically adequate RCTs. The efficacy of Tacrine in clinical trials is accompanied by a high drop out rate (40 to 60%), mainly due to adverse effects (see below).

Adverse Events with Tacrine

There are two possible sources of adverse events with Tacrine: those induced by drug interactions and those side effects inherent to the drug itself. The pharmacokinetic properties of Tacrine (i.e. low bioavailability and a route of metabolism affected by many other drugs) make it an agent theoretically susceptible to drug interactions. Data documenting the risks are not available as patients on medications known likely to interact with Tacrine were excluded from clinical trials.

Adverse events or side effects due to Tacrine fall into two major categories: hepatotoxicity (liver) and autonomic or cholinergic effects (mainly gastrointestinal), with the former being the most potentially serious, especially in the elderly population. Depending on the definition used, studies reported overall adverse effect rates of 48 to 94%, with 12% of these being described as “severe”.

Withdrawal rates due to adverse effects varied from 18 to 25%. Autonomic/cholinergic adverse effects (mainly gastrointestinal; i.e. nausea, vomiting, diarrhea, abdominal pain, cramps, discomfort, dyspepsia, anorexia, weight loss) were dose dependent and occurred in 72% to 94% of trial participants.
<table>
<thead>
<tr>
<th>Study author, year</th>
<th>Type</th>
<th>Study Information</th>
<th>Outcome Measures (primary = *)</th>
<th>Results</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinstein et al., 1991</td>
<td>parallel (1)</td>
<td>n = 12 4 wk dose titration 8 wk study + lecithin</td>
<td>Cognition Behaviour/Mood Function/QOL</td>
<td>NS difference on cognition scale</td>
<td>Small sample Timing of dose titration and actual trial duration?</td>
</tr>
<tr>
<td>Farlow et al., 1992 (2)</td>
<td>parallel</td>
<td>n = 468 entered - 237 after dropouts - 217 completed 12 wk study</td>
<td>Cognition* Global Impression of Change Behaviour/Mood Function/QOL Global Assessment</td>
<td>Dose-dependent increase in cognition scale at 6 wk (marginal), and 12 wk (significant); Global Impression of Change at 12 wk = 3.4 (T) vs. 3.9 (P)</td>
<td>Significant, dose-related dropouts Efficacy analysis only; no ITT analysis</td>
</tr>
<tr>
<td>Davis et al., 1992 (2)</td>
<td>parallel</td>
<td>n = 632 entered enrichment - 563 best dose possible - 231 best dose established - 215 randomized (evaluated: 198, 209 ITT; 187, 195 efficacy) 6 wk enrichment phase, 2 wk w/o 6wk study</td>
<td>Cognition* Global Impression of Change Behaviour/Mood Function/QOL Global Assessment*</td>
<td>ITT analysis: significant on one of two cognition scales, as well as on two functional scales; no difference in Global Impression of Change Modest benefit</td>
<td>Only 36.5% of subjects starting enrichment phase could have best dose established w/o too short? Overestimate of cognition scale change?</td>
</tr>
<tr>
<td>Knapp et al., 1994 (2)</td>
<td>parallel</td>
<td>n = 650 enrolled - 279 completed - 263 evaluated 30 wk</td>
<td>Cognition* Global Impression of Change Behaviour/Mood Function/QOL Global Assessment</td>
<td>Efficacy and ITT analysis: cognition and Global Impression of Change marginally better with T</td>
<td>59% withdrawal rate</td>
</tr>
<tr>
<td>Maltby et al., 1994</td>
<td>parallel</td>
<td>n = 53 - 41 randomized - 32 evaluated Dose finding (8 wk + 4 wk w/o) 36 wk study</td>
<td>Cognition* Behaviour/Mood Function/QOL</td>
<td>NS effect at 6 wk or 36 wk</td>
<td></td>
</tr>
<tr>
<td>Study author, year</td>
<td>Type</td>
<td>Study Information</td>
<td>Outcome Measures (primary = *)</td>
<td>Results</td>
<td>Problems</td>
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<tr>
<td>Gauthier et al., 1990⁹</td>
<td>cross-over</td>
<td>n = 52 dose-finding - 46 f/u study - 39 evaluated</td>
<td>Cognition*</td>
<td>Significant increase on cognition scale at 4 wk (but not at 8 wk)</td>
<td>Authors noted carryover effect even after 4 wk w/o</td>
</tr>
<tr>
<td>Chatellier et al., 1990¹⁰</td>
<td>cross-over</td>
<td>n = 67 (dropouts) - 60 dose-finding - 52 in f/u study - 49 evaluated</td>
<td>Cognition*</td>
<td>NS difference on cognition scale</td>
<td>Small sample</td>
</tr>
<tr>
<td>Molloy et al., 1991¹¹</td>
<td>cross-over</td>
<td>n = 34 dose-finding - 27 in f/u study - 22 evaluated</td>
<td>Cognition*</td>
<td>No overall benefit on cognition, function or behaviour</td>
<td>Small number completed study</td>
</tr>
<tr>
<td>Eagger et al., 1991¹²</td>
<td>cross-over</td>
<td>n = 89 ITT - 65 evaluated</td>
<td>Cognition*</td>
<td>Significant increase in cognition scores</td>
<td></td>
</tr>
<tr>
<td>Wilcock et al., 1993¹³</td>
<td>cross-over</td>
<td>n = 79 - 72 ITT - 41 completed dose-finding phase during RCT</td>
<td>Cognition*</td>
<td>NS difference on cognition scores (using 2 different scales)</td>
<td></td>
</tr>
</tbody>
</table>

(1) all outpatients; excluded patients with other major disorders or on medications with a central nervous system effect

(2) significant author overlap amongst studies; supported in part by pharmaceutical manufacturer; similar eligibility criteria and primary outcome measure; differing dosage and study duration

ITT  intention to treat analysis
NS  not statistically significant
T Tacrine; P = Placebo
PPP placebo-placebo-placebo; PPT = placebo-placebo-Tacrine; PTT = placebo-Tacrine-Tacrine
w/o washout
f/u follow-up

Canadian Coordinating Office for Health Technology Assessment
Hepatotoxicity most commonly presented as elevations in liver enzyme levels in 12 to 64% of patients taking usual doses of Tacrine. Tacrine-induced enzyme elevations are usually reversible on discontinuation of the drug and many patients are asymptomatic. There are, however, reports of patients developing significant symptoms concurrent with enzyme elevations; and the few liver biopsy studies carried out to date have demonstrated liver cell damage (i.e. necrosis) in some individuals with increased enzyme levels. As the onset of this phenomenon is variable (usually within the first 12 weeks of therapy, although 10% of elevations occur thereafter) and prediction of those likely to experience severe toxicity is not possible, close enzyme level monitoring is mandatory.

These adverse event rates occurred in relatively healthy AD patients taking Tacrine. The rate and/or severity of such events in the “typical” AD patient is not known. In addition, the safety of Tacrine in patients with pre-existing renal and hepatic disease has not been established, since these patients were also excluded from drug trials.

Efficacy Summary

Overall, there was great methodologic diversity and no clear pattern of findings amongst the Tacrine studies reviewed. There was no obvious association between the dosage of Tacrine and clinical benefit, and Tacrine did not halt the progression of disease. The relationship between dose and adverse effects or treatment withdrawal repeated itself in the trials reviewed. Only modest efficacy was demonstrated in an unpredictable subgroup of patients, in the context of important side effects. Neither dosage titration nor enrichment successfully screened for those patients likely to have problems with or respond to Tacrine, respectively. Most of the study participants were healthy elderly, who continued to experience significant side effects with this drug. Elderly patients having concurrent diseases and/or taking certain medications (i.e. likely more representative of the “typical” AD patient) were excluded from these trials.

EFFECTIVENESS

The authors were unable to translate the efficacy data from the clinical trials into an impression of the effectiveness of the drug in the real world. Obstacles were found in three main areas: the uncertainty in interpreting the various outcome instruments in this population (as noted above); the small number of methodologically adequate trials available, which showed only modest impact (as noted above); and the inability to compare the characteristics of those who did not complete the trial to those who did. The authors concluded that Tacrine was not likely to be effective in AD as an overall treatment approach until such time as it is possible to identify the subgroups of patients who could benefit the most from this medication.
COSTS

Given that the efficacy and, thereby, the effectiveness of Tacrine in AD could not be established, the authors could not justify carrying out a complete economic analysis. They did, however, provide a review of the studies published between 1980 and 1996 which evaluated the costs of AD. The perspectives, AD populations (community versus institutionalized), data sources, costing methodologies, countries of origin, and numerous other factors varied significantly amongst these studies, thus impeding the transportability of information. Only one full economic evaluation was reported, that by Lubeck et al (1994) based on data from the clinical trial by Knapp et al (1994). The study suggested that the use of Tacrine represented savings of 17% over the costs that would normally be incurred in the absence of this medication. (Note that there were several limitations to the methodology used in the evaluation.) A more recent analysis of the 2-year open-phase portion of the study by Knapp et al (1994) suggested that Tacrine may reduce the likelihood of nursing home placement (Knopman et al [1996]).

The authors made note of the one Canadian study carried out to date, which used estimates derived from interviews of 10,263 elderly patients and their care givers in the community and in institutions (i.e. the CSHA study population). Ostbye and Crosse estimated the total annual net cost of dementia, above and beyond the normal costs incurred by the elderly, at $CND3.9 billion ($13,900 per dementia patient per year). Thirty-two percent of these costs ($1.25 billion) were associated with patients in the community, whereas costs for patients in long-term care institutions accounted for 56% of the total ($2.18 billion). Remaining costs included drugs, hospitalization, diagnosis, research, and treatment of patients under age 65.

COST ANALYSIS

The authors carried out their own analysis of Canadian data. They conducted a descriptive study of the type and intensity of health services utilization of community-dwelling elderly subjects following a diagnosis of AD. All subjects resided in Quebec for the year 1991. Linkage of secondary data from the Canadian Study of Health and Aging (CSHA) and the Régie de l'assurance-maladie du Québec (RAMQ) databases allowed comparison of the utilization of formal care (i.e. outpatient prescription medications and medical services) for subjects with AD (n=39) compared to cognitively normal elderly subjects (n=837).

The average number of prescriptions per year for AD patients and normal elderly was 46.3 and 39.8, respectively, with a similar distribution of classes of medications within each group. The groups differed on a number of measures of medical service utilization. Patients with AD tended to have fewer visits for medical services, although a greater proportion of services were delivered in hospital (but with a shorter length of stay than their normal counterparts). While fewer AD patients had billings for laboratory tests overall, those who did require tests usually had twice as many as normal elderly patients. Both groups consulted with general practitioners more frequently than specialist physicians. Overall, the review demonstrated that the direct costs of formal care did not contribute significantly to the additional costs incurred by AD patients living in the community.

STUDY LIMITATIONS
The Best Evidence Synthesis methodology used an arbitrary grading scheme in evaluating the studies from the literature. The grading process was not used to weight the reviewed studies, but rather to assess the methodological issues important to the evaluation of Tacrine in AD. The limitations of the review’s results rest mainly in the information (or lack thereof) in the trials used in the evaluation process (e.g. absence of information re: patients not completing the studies). The time frame of the project precluded the reviewers from contacting the original investigators to obtain additional data. In addition, the wide variety of scales used for each outcome measure and the gaps in knowledge about scale properties had implications for the confidence with which the efficacy of Tacrine could be evaluated.

The cost analysis portion of the evaluation focused solely on community-dwelling AD patients. While the analysis did confirm previous research regarding formal care utilization, the cost of informal care (for community-dwellers) and the additional institutionalized care required by this group remains unanswered in the Canadian context.
REFERENCES


THE EFFICACY OF TACRINE AND THE MEASUREMENT OF OUTCOMES IN ALZHEIMER’S DISEASE


