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Alzheimer's Disease: Evaluation of the effectiveness of currently used pharmacological treatments

Critical appraisal of the literature on evidence-based effectiveness of pharmacological treatments in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease manifested by cognitive and memory deterioration; and a decline in the ability to perform activities of daily living. It is the most common form of dementia in elderly. Therapeutic interventions are currently symptomatic at best, whereas research focuses on disease modifying treatments, which will hopefully be available in the near future.

The review objective was to evaluate the effectiveness of pharmacological interventions in Alzheimer's disease by critical appraisal of published randomised controlled trials, systematic reviews, and meta-analyses. The working group searched and evaluated trials and reviews on five main interventions in AD treatment; cholinesterase inhibitors, memantine, antipsychotic agents, antioxidants, and ginkgo biloba.

INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder manifested by cognitive and memory deterioration, progressive impairment performing activities of daily living (ADL), and neuropsychiatric symptoms such as depression, psychosis, and behavioural disturbances, which in turn leads to a reduced quality of life[1]. It is the most common form of dementia in elderly, accounting for about 60% to 80% of cases[1]. The classic clinical features of AD are amnesic type memory loss, deterioration of language, and visuospatial deficits, while motor and sensory abnormalities, gait disturbance, and seizures occur later in the disease[1, 2]. Behavioural disturbances, such as agitation and psychosis, also progress over the course of the illness[2]. Treatment of AD includes five major components: neuroprotective strategies; cholinesterase inhibitors; nonpharmacological interventions and psychopharmacological agents to reduce behavioural disturbances; health maintenance activities; and a multidisciplinary approach to care for patients[1, 2, 3].

While there is no cure for AD and no proven treatment to slow its progression, there are treatments available that may help improve symptoms[2]. Treatment may also, if given early enough, enable patients to maintain independence or manage at home for a longer period of time before hospitalisation is required [2,3]. The need for additional treatments to manage the troubling psychological and behavioural symptoms is not to be ignored [2,3].

Our review critically appraises some of the published randomised controlled trials, systematic reviews, and meta-analyses on the efficacy of pharmacological interventions in Alzheimer's disease patients. The working group searched and evaluated trials and reviews on five main interventions in AD treatment; cholinesterase inhibitors (ChEIs), memantine, antipsychotic agents, antioxidants, and ginkgo biloba.

Case Summary and Research Question

Mrs E, an 85 year old female, with a diagnosis of AD in November 2008, presented with ongoing deterioration of memory, cognition and functional activity; and acute delirium in March 2009. Her delirium was precipitated by dehydration, acute renal impairment, existing chronic renal failure and increased thyroid function. Her delirium was resolved with rehydration.

Prior to her hospital admission, Mrs E was very independent – she lived by herself in her own home with no external help. An occupational therapist and social worker's needs assessment found increasing difficulty with functional activities such as managing finances, cleaning, cooking, taking medications, and remembering to eat.

Mrs E returned home and received 'meals on wheels', twice daily home support, and follow-up visits by the district nurse. She has additional home help and shopping assistance through a private arrangement. However, no treatment for her progressive AD was considered.

Mrs E's case allowed us to consider the current available treatments for AD and their evidence based effectiveness. Our review examined evidence-based literature on the effectiveness of currently available pharmacological agents in the treatment of Alzheimer's disease when compared with placebo.

Effectiveness was assessed in terms of outcomes such as improved quality of life, cognitive function, memory, ability to perform ADLs, physical performance decreasing behavioural disturbance, and depression.

Search, studies review and results analysis

Search strategy

We searched MEDLINE from 1996 to 2009, Cochrane Collaboration Library, EMBASE from 1947 to 2009, PsycINFO, and EBM reviews.

Our search terms included Alzheimer's disease and - cholinesterase inhibitors, vitamin E, selegiline, antioxidants, Ginkgo biloba, antidepressants, anxiolytics, selective serotonin reuptake inhibitors (SSRI), antipsychotics, and agitation/aggression/psychosis.

Inclusion and exclusion criteria

Our systematic review objective was to look at the effectiveness of pharmacological treatment for mild, moderate or severe AD. Thus, we only included systematic reviews and meta-analyses that used randomised controlled trials. We restricted our search to published, full text English articles, with more than 20 human subjects, with at least one stated objective measure as listed below and published from 1996 onward. Studies included in our evaluation are randomised, double-blinded, placebo-controlled trials in people with AD and with specified duration. Members of the work group reviewed search results and the bibliographies to identify any articles that may be of interest. All articles found and analysed were submitted to the same inclusion/exclusion criteria.

All patients in the trials we evaluated were diagnosed with Alzheimer's disease using NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's disease and Related Disorders Association) or DSM criteria (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association).

Appraisal process

To critically appraise the literature found we used an appraisal format taken from the website of Centre for Evidence-Based Medicine (available from: http://www.cebm.net/index.aspx?o=1157).

Outcomes assessment methods

- The primary research outcomes of interest were:
- Cognitive function
- Functional performance (ADL)
- Behavioural disturbance
- Clinical Global Impression
- Quality of life
- Dependency and Institutionalisation

A variety of scales are used to measure these outcomes; Clinician's Interview-Based Impression of Change (CIBIC+) or Clinical Global Impression of Change (CGIC) scale to assess global status, Alzheimer's Disease Assessment Scale (ADAS-cog) to assess cognition or Severe Impairment Battery (SIB) to assess cognition in advanced AD, Mini Mental State Examination (MMSE) to assess memory, Alzheimer's Disease Cooperative Study ADL (ADCS-ADL) scale to assess function, Clinical Dementia Rating (CDR), and Neuropsychiatric Inventory (NPI) to assess behaviour.

RESULTS

Pharmacological intervention in AD has two main strategies aiming to provide symptomatic relief; one targets cognitive and functional symptoms and primarily includes ChEIs, memantine and antioxidants, whereas the other is psychopharmacological intervention which aims to alleviate behavioural symptoms[3, 4]. Ginkgo biloba, which can also be considered alternative medication, is prescribed in an attempt to improve both cognitive and behavioural symptoms[3, 4].

Cholinesterase inhibitors (ChEIs) (donepezil, galantamine, rivastigmine)

Search terms "Alzheimer's disease (drug therapy/therapy)" and "cholinesterase inhibitors", limited to the predefined criteria detailed above, yielded 116 results in EMBASE, 119 in All EBM Reviews, 103 in Medline, and 75 in PsycINFO with search limited to outcome/treatment study.

Cholinesterase inhibitors (ChEIs) delay the breakdown of acetylcholine released into synaptic clefts by inhibiting cholinesterases, and so enhance cholinergic neurotransmission [4,5]. The ChEIs available in New Zealand (donepezil, galantamine and rivastigmine) are considered by clinicians to be the first line of treatment for mild to moderate AD [3,4]. In addition, donepezpil was approved in 2006 for the treatment of severe AD [2,4]. Despite the slight variations in the mode of action,[9] side-effect profile, and ease of administration [2,6] of these three ChEIs, there is no evidence of any differences with respect to effectiveness [6].

The review looked at five systematic reviews [5-9] and thirteen placebo-controlled trials[10-25] that met the inclusion criteria, and were designed to evaluate the effectiveness and safety of ChEIs in patients with AD dementia. Overall there were 7298 patients randomised in the RCTs and the mean age was 72-75 years, with the exception of one study[16] which had a mean age of 86 years. The systematic reviews [5-9] divided dementias into mild to moderate and moderate to severe. One RCT [25] was also designed to compare two ChEIs. All RCTs specified duration of 6 months or longer and reported intention-to-treat (ITT) analysis of all randomised patients that started the study and had at least one follow-up observation. There was a 29% drop-out rate in the treatment group compared with 18% in the placebo group due to adverse effects such as abdominal pain, nausea, anorexia, dizziness, vomiting, diarrhoea, headache and insomnia, which were more common in the ChEIs group. The trials showed a beneficial effect of ChEIs on cognitive function and clinical global impression at 6 months or more. Moreover, although there was less data on the effect of ChEIs on functional performance and behaviour, the trials that measured this showed a small, statistically significant benefit [6]. The one trial [25] comparing donepezil and rivastigmine also demonstrated donepezil is associated with less adverse events. A risk of bias stems from the fact that most of these studies were funded by the pharmaceutical company that manufactures or markets the drugs on trial, and that only the method of randomisation, rather than the process, is specified. The RCTs' results were supported by the systematic reviews conclusions.

Memantine

Search terms "Memantine" and "Alzheimer's disease", limited to the predefined criteria detailed above, yielded 25 articles in Medline, and 110 in All EBM Reviews, while "Alzheimer's disease (limited to drug therapy/therapy)" and "Memantine" yielded 62 results in EMBASE.

Memantine is a NMDA (N-methyl-D-aspertate) receptor antagonist, inhibiting glutamate, the main excitatory neurotransmitter, from binding to the receptor. It is used in the treatment of moderate to severe AD to alleviate symptoms [4, 25]. Moreover, memantine's mechanism of action renders it neuroprotective, although clinical use has failed to demonstrate this [4].

Four RCTs on memantine efficacy [26-29] and one systematic review [30] matched our predefined criteria. These RCTs were of 6 months or more in duration and included mild, moderate or severe AD patients. As with ChEIs trials, these trials were funded by pharmaceutical companies that manufacture or market memantine, which can lead to bias in the results. Additionally, only two studies [27, 29] described the method of concealment. We used one study [26] that included vascular (VD) and Alzheimer's dementia as 50% of participants had AD diagnosis and the study clearly separated VD and AD treatment. The number of participants ranged from 80 to 404. The trials' conclusions, supported by the wider systematic review analysis, suggest that in moderate to severe AD, memantine provides a statistically significant and clinically detectable beneficial effect at 6 months on cognition, ADL, and behaviour. However, in mild to moderate AD, marginal non-statistically significant benefit is indicated at 6 months on cognition, with no effect on behaviour and ADL. It was also indicated that memantine was well tolerated with the number of adverse effects similar to the placebo group, and fewer than cholinergic agents. Drop-out rates in the RCTs were low and similar in both placebo and treatment groups with no specific adverse events in the memantine groups. Moreover, a consistent effect of reduction in the incidence of agitation in moderate to severe AD patients taking memantine arises in the trials. Although the effect of memantine on already present agitation is an important factor, no beneficial evidence was found.

Antioxidants (Vitamin E and Selegiline)

Search terms "Alzheimer's disease" and "antioxidants" yielded 15 results in All EBM Reviews. Searching "Alzheimer's disease" and "Vitamin E" and "selegiline" with additional limit to articles in EMBASE yielded 188 results and 61 results respectively, while searching the same terms in Medline yielded 25 results each.

A feature of AD is the existence of oxidative stress and accumulation of free radicals in the brain [4]. Therefore, Vitamin E (α-tocopherol) and Selegiline

(monoamine oxidase inhibitor), which contain antioxidant properties, have been studied in relation to AD. We reviewed one systematic review [31] and the largest and most influential study in the area - the first Alzheimer's Disease Cooperative Study (ADCS) that compared selegiline, α-tocopherol, or both, with placebo [32]. The trial was limited to moderate dementia and examined 341 patients. Possible biases did not arise when evaluating the trial, which described a clear selection and research strategy. Drop-out rates were small (6%) and similar in all study groups. The trial's principle outcomes measured were death, institutionalisation, loss of ability to perform ADLs, and progression to severe dementia on a CDR scale. Following results adjustment to baseline MMSE differences between the groups, the researchers showed a delayed progression to all outcomes measured in the treatment groups when compared with placebo in a 2 year follow-up period. Treatment with α-tocopherol (2000 IU/day) alone provided the longest delay, followed by selegiline alone, while a combination of the antioxidants resulted in the shortest progression-to-outcomes period. However, there was no improvement in cognitive tests in any of the treatment groups. Furthermore, a meta-analysis published in 2005 [33] suggested that high-dose (>400 IU/day) vitamin E may increase all-cause mortality, which has not been noted in the earlier large ADCS study and the systematic review.

We found three trials [34-36] and one systematic review [37] on selegiline efficacy that complied with our predefined criteria. The number of participants in the RCTs ranged from 25 to 98 patients and study duration was of 12 weeks or more. The trials and review concluded, irrespective of the outcome measured and contradictory to the ADCS study [32], that selegiline produces no significant benefit in AD. Thus, it will be unjustified to use it in the treatment of AD.

Antipsychotics

Search terms "Alzheimer's disease" and "antipsychotic" yielded 51 results in All EBM Review, 42 in Medline, 103 in EMBASE, and 102 in PsycINFO.

The majority of AD patients develop behavioural disturbances throughout the course of the disease. These behaviours are likely to be agitation, aggression, sleep disturbance, hallucinations, depression, delusions, apathy, aberrant motor behaviour, and wandering. The development of these disturbances can profoundly affect patients and caregivers and may hasten institutionalisation [5, 38].

Atypical antipsychotics, such as risperidone and olanzapine, and conventional ones such as haloperidol, are used in the treatment of aggression and psychosis. Our research found two systematic reviews [38, 39] and six trials [40-46] which looked at the efficacy of atypical antipsychotics in AD. These concluded that atypical antipsychotics offer reduction in the incidence of aggression and psychosis in AD dementia. There are potential advantages over typical antipsychotics such as a better side effect profile. However, the evidence is difficult to interpret as there are only six trials [40-46] published and systematically reviewed, while researchers in the area suggest there is additional data held by pharmaceutical companies [38, 39]. It appears there is a lowered incidence of extrapyramidal adverse effects but a specific increase in cerebrovascular events and death. This may offset the benefit and limit their effectiveness in AD treatment. Moreover, the primary outcome measures in the RCTs have been grouped together under behavioural and psychological disturbances (BPSD), making the drugs' impact on specific disturbances difficult to determine.

There is little evidence to support the use of other agents such as anticonvulsants, benzodiazepines, antihistamines, monoamine oxidase inhibitors, or selective serotoninre-uptake inhibitors (SSRIs) in the treatment of agitation or psychosis [2]. Anxiolytic agents are used to alleviate restlessness, agitation, and aberrant motor behaviours, while depression in AD tends to be treated with SSRIs with favourable tolerability when compared with other antidepressants [2, 5].

Ginkgo biloba

Search terms "Alzheimer's disease" and "Ginkgo Biloba" yield 25 results that comply with the predefined criteria in All EBM Review and Medline databases. "Alzheimer's disease" limited to drug therapy/therapy and "ginkgo biloba" yielded 2 results in EMBASE.

The complimentary, or alternative, treatment researched the most in relation to AD is the Ginkgo biloba extract EGb 761. Ginkgo biloba, a product of the maidenhair tree, has long been used in China as a traditional medicine for various health problems. An extract, EGb 761, is widely used in the West for the treatment of a range of conditions including memory and concentration problems, confusion, and depression. The mechanism of action stems from various actions of the extract; dilating blood vessels, reducing blood viscosity, modification of neurotransmitter systems, and reducing oxygen free radicals [2-4].

Our research found one systematic review [47] and four RCTs [48-51] on the efficacy of Ginkgo in AD treatment that complied with our predefined criteria. Participant numbers ranged from 20 to 513 and the duration from 12 to 52 weeks. These trials recognised funding from the company that manufactures the most widely used Ginkgo extract. It appears that ginkgo is safe to use, with no additional side effects compared with placebo. Adverse events with ginkgo use are similar to the ones arising with placebo, and there is no significant difference in the drop-out rates, which are accounted for in the ITT analysis. However, the trials demonstrated, and the systematic review supported, no consistent evidence for predictable and clinically significant benefit of Ginkgo biloba for people with AD dementia. Consistency, if any, appears to incline in direction of no difference between ginkgo and placebo groups.

DISCUSSION

Our critical appraisal reviewed class I evidence and literature from 1996 onward only. Although evidence for effective treatment for AD with ChEI can be traced to the early 1990s, when Tacrine was first approved by the Food and Drug Administration (FDA)[1, 2], 1996 was used as a cut-off year as we wanted to review commonly used and currently available AD treatments. All studies were subjected to the same inclusion and exclusion criteria as described above and reviewed by more than one assessor. Significant drop-out rates and biases, as well as the important issue of studies' funding, were accounted for and reported in our appraisal. These considerations strengthen the validity of the conclusions drawn in this appraisal.

We chose to review RCTs in addition to systematic reviews as AD intervention trials are vast and varied in their method, outcome measures, and conclusions. We felt a review of RCTs, used in the systematic reviews, would give us better understanding in the area and a greater ability to draw appropriate conclusions.

The reviewed studies used multiple outcome measures that, due to the word limit, we were unable to further discuss. Therefore our review can only comment on general trends of effectiveness rather than comparing individual studies' results. These considerations highlight the need, discussed in some of the literature [52, 53], to standardise outcome measures used in AD drug trials.

CONCLUSION

The results and conclusions drawn from this critical appraisal are relevant to Mrs E as she has been diagnosed with Alzheimer's disease. Mrs E predominantly has problems with activities of everyday function and cognition. The benefit of antipsychotics is not currently relevant to Mrs E as she has no documented history of psychosis or aggression.

The appraisal found that cholinesterase inhibitors are beneficial in mild to severe AD, while memantine produces significant results in moderate to severe AD. Both drugs target cognitive symptoms and provide moderate, but clinically significant, symptomatic benefit on cognitive, functional and behavioural symptoms, with no notable effect on disease progression. Atypical antipsychotic agents should be used to control aggression and psychosis, which commonly present as the disease progresses, whereas AD-associated depression could be managed with SSRIs. The antioxidant vitamin E was shown to delay progression to institutionalisation, severe dementia, inability to perform ADLs, and death, with no effect on cognition.

Selegiline and Ginkgo biloba showed no benefit in AD treatment.

In light of the evidence found and discussed above we would suggest a change in Mrs E's treatment strategy, and would like her treating physician to consider a more comprehensive and holistic approach and pharmacotherapy. Although benefit has been found with memantine, ChEIs, vitamin E, and antipsychotics, cost and the side effects have not been analysed. These important parameters should be considered before prescribing Mrs E any pharmacotherapy.

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