Treatment of Moderate to Severe Alzheimer's Disease: Rationale and Trial Design

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ABSTRACT: Moderate to severe Alzheimer's disease (AD) is characterized by increasing cognitive, functional, and behavioural dysfunction that results in increased caregiver burden and, eventually, complete dependence. Despite its significance as a societal health problem, there are few treatment trials of cognitive enhancers or disease modifying agents for this stage of illness. Studies suggest the cholinesterase inhibitors, especially donepezil, may provide benefit. Several studies provide support for the use of the NMDA receptor antagonist memantine as monotherapy or added to a cholinesterase inhibitor for moderate to severe AD. While there are no published guidelines for the treatment of moderate to severe AD, these studies do provide guidance for recommendations for study design and outcome measures. Such studies are urgently needed.

RÉSUMÉ: Traitement de la maladie d'Alzheimer de modérée à sévère : justification et plan d'essais. La maladie d'Alzheimer de modérée à sévère est caractérisée par une dysfonction cognitive, fonctionnelle et comportementale progressive qui engendre un fardeau croissant pour les soignants et une dépendance complète éventuelle. En dépit de son importance comme problème de santé au niveau sociétal, il existe peu d'essais thérapeutiques portant sur des stimulateurs cognitifs ou des agents modificateurs de la maladie à ce stade de la maladie. Les études suggèrent que les inhibiteurs de la cholinestérase, spécialement le donépézil sont bénéfiques. Selon plusieurs études, l'utilisation de la mémantine, un antagoniste du récepteur NMDA, en monothérapie ou en association à un inhibiteur de la cholinestérase serait bénéfique dans la MA de modérée à sévère. Bien qu'il n'y ait pas de lignes directrices publiées concernant le traitement de la MA de modérée à sévère, ces études peuvent servir de guide pour formuler des recommandations sur le plan d'étude et les critères d'évaluation. Il est urgent de procéder à de telles études.

RATIONALE FOR TREATMENT STUDIES

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive and functional impairment and behavioural and psychological symptoms (BPSD). As the disease progresses, the patient becomes more functionally impaired with total dependence on caregivers being a hallmark of the more severe stages. The Canadian Study of Health and Aging (CSHA) estimated that 50% of individuals diagnosed with AD were already in the moderate to severe stages, while almost 90% of patients in long-term care facilities were moderate to severe.[1] As dependence on the caregiver increases, the degree of caregiver burden and stress increases, leading to an increased risk of institutionalization for the patient and increased medical and psychological morbidity for the caregiver.[2] Furthermore, the dependence leads to an increased demand on caregiver time, a major contributor to indirect care costs, while institutionalization comprises the most significant driver of direct costs for dementia care. The CSHA estimated that as a result of these factors, the cost of care for AD patients rises dramatically for mild to moderate to severe illness.[3] The Kungsholmen project noted that the severe stages of dementia account for 70–80% of the total costs.[4] Due to its prevalence, associated disability, contribution to caregiver burden, and stress,

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as well as direct and indirect costs, moderate to severe AD clearly represents an important societal health problem. This alone provides a strong rationale for the study of therapeutic interventions.

There are emerging data that suggest there are differences between mild and moderate to severe AD in neuropathology and neurochemistry, which may have important implications for pharmacotherapy. Stage-specific changes in amyloid plaque and neurofibrillary tangle burden have been documented,[5] as well as changes in neurotransmitters, such as catecholamines,[6,7] GABA,[8] and glutamate.[9] For example, in the cholinergic system (the best-studied of the neurotransmitter systems in AD) cholinergic markers, such as choline acetyltransference (ChAT), do not decline significantly until later stages of AD, while milder stages are characterized by relatively preserved ChAT.[10] This type of

data has led to the hypothesis that cholinesterase inhibitors may be more effective for moderate to severe AD than milder disease.[11] It also suggests that pharmacological agents studied in mild AD may be more or less effective in moderate to severe AD.

Unfortunately, at the present time, there are no clinical practice guidelines (CPGs) specific for moderate to severe AD. The cholinesterase inhibitors (ChEIs) are indicated for mild to moderate AD, but where provincial formularies reimburse their costs, payment is contingent on patients scoring between 10-26 on a Mini-Mental State Examination (MMSE).[12] Memantine has only recently received conditional approval for the treatment of moderate to severe AD in Canada. While many pharmacological treatment trials for BPSD have focused on moderate to severe AD patients,[13] there are very few trials on cognitive enhancers or disease-modifying agents for this stage of illness.

Table: Randomized Trials for Moderate-Severe AD

Study	Drugs	N	Inclusion Criteria	Baseline MMSE	Primary outcome measure(s)	Secondary outcome measures	Findings
Feldman et al 2001[11]	donepezil 10 mg vs placebo	290	- MMSE 5-17 - FAST≤6	≈12	CIBIC+	MMSE, SIB, DAD, IADL, PSMS, NPI, FRS, CSS, HRQLCQ, CUSTQ	donepezil>placebo on CIBIC+
Tariot et al 2001[27]	donepezil 10 mg vs placebo	208	- MMSE 5-26 - NPI at least 3-4 for frequency on at least 1 symptom	≈14	NPI-NH	MMSE CDR-SB PSMS	donepezil= placebo on NPI-NH. donepezil>placebo on some secondary measures
Winblad and Poritis 1999[29]	memantine 10 mg day vs placebo	166	- GDS 5-7 - MMSE<10	≈6	CGI-C BGP	Ferm's-D	memantine>placebo on primary outcome measures
Reisberg et al 2003[34]	memantine 20 mg BID vs placebo	252	- MMSE 3-14 - GDS 5 or 6	≈8	CIBIC + ADCS/ADL$_{SEV}$	SIB, MMSE GDS, FAST NPI, RUD	memantine>placebo on CIBIC +(p=0.06) ADCS/ADL$_{SEV}$ (p=0.02) and SIB (p<0.001)
Tariot et al 2004[38]	memantine 20 mg BID + donepezil vs placebo + donepezil	404	- MMSE 5-14	≈10	SIB ADCS/ADL$_{SEV}$	CIBIC, NPI BGP, FAST	memantine + donepezil >placebo + donepezil on all measures
Sano et al 1999[39]	Vitamin E 1000 IU BID vs selegiline 10 mg vs combination vs placebo	341	- CDR 2	≈ 11-13	Death, or institutionalization or loss of 2/3 key ADLs or CDR3	ADASCog, MMSE, BDS, DS, BRS, UPDRS	- No differences between treatments - when adjusted for baseline MMSE selegiline, vitamin E, and combination>placebo

MMSE = Mini Mental State Examination; FAST = Functional Assessment Staging; CIBIC+ = Clinician's Interview Based Impression of Change plus Caregiver Input; SIB = Severe Impairment Battery; DAD = Disability Assessment for Dementia; IADL = Instrumental Activities of Daily Living PSMS = Progressive Self-Maintenance Scale; NPI = Neuropsychiatric Inventory; FRS = Functional Rating Scale; CSS = Caregiver Stress Scale; HRQLCQ = Health-Related Quality of Life of Caregiver Questionnaire; CUSTQ = Canadian Utilization of Services Tracking Questionnaire; NPI-NH = Neuropsychiatric Inventory Nursing Home Version; CDR-SB = Clinical Dementia Rating Scale Sum of Boxes; GDS = Global Deterioration Scale; CGI-C = Clinician's Global Impression of Change; BGP = Behavioral Rating Scale for Geriatric Patients; ADCS/ADLSEV = Alzheimer's Disease Cooperative Study Activities of Daily Living-Severe; ADASCog = Alzheimer's Disease Assessment Scale Cognitive Subscale; BDS = Blessed Dementia Scale; DS = Dependence Scale; BRS = Behavior Rating Scale for Dementia; UPDRS = Unified Parkinson's Disease Rating Scale

METHODS

Despite the significance of moderate to severe AD, and evidence that treatments for milder illness cannot necessarily be assumed to be effective for more severe disease, there is a dearth of studies to date to inform treatment guidelines. In order to recommend appropriate trial designs for moderate to severe AD, a literature search was conducted with Medline using keywords: Alzheimer's disease, moderate, severe, and therapy. A review of the study methodologies highlighted the challenges associated with this area of research and provided guidelines for trial design and choice of instruments, which follows.

RESULTS

Cholinesterase Inhibitors

The pivotal ChEI studies included subjects with mild to moderate AD, generally with MMSE scores in the range of 10-26.[14] While there are several post-hoc analyses of rivastigmine- and galantamine-treated patients from these trials, who at baseline scored near the bottom of this range (e.g., MMSE ≤14),[15,16] only two studies with donepezil have been published using inclusion criteria specifically focused on moderate to severe AD (Table). In a 24-week randomized, double-blind, placebo-controlled, parallel group trial of donepezil, Feldman et al. studied 290 AD patients with moderate to severe AD.[11] Inclusion criteria included MMSE scores of 5-17 and a Functional Assessment Staging Test (FAST) score of ≤6.[17] This resulted in groups with average baseline MMSEs of approximately 12. The primary efficacy measure was the Clinician Interview-based Impression of Change with Caregiver Input (CIBIC+).[18] Secondary measures included: the MMSE and the Severe Impairment Battery (SIB) as cognitive assessments;[19] the Disability Assessment for Dementia (DAD), modified Instrumental Activities of Daily Living Scale, and Physical Self-Maintenance Scale (PSMS) for functional measures;[20,21] and the Neuropsychiatric Inventory (NPI) for behaviour.[22] A variety of other instruments were also used to assess global functioning (the Functional Rating Scale),[23] caregiver outcomes (Caregiver Stress Scale),[24] (Health-Related Quality of Life of Caregiver Questionnaire),[25] and a resource utilization scale (The Canadian Utilization of Services Tracking Questionnaire).[26] Donepezil therapy was associated with significant benefits on the CIBIC+, as well as both the MMSE and SIB. Because the placebo decline on the SIB was greater than the MMSE, the authors suggested the SIB was more sensitive to change in this population. The other secondary measures including the DAD and NPI also showed statistically significant differences favouring donepezil at endpoint. In their discussion, the authors noted that the CIBIC+ was chosen as the primary outcome measure given questions about the clinical relevance of small but significant changes in cognition at this stage of the illness. They also noted that unlike the floor effects encountered with the MMSE, the SIB demonstrated a 2.1 point improvement with donepezil compared with a 3.6 decline in the placebo group, demonstrating that measurable changes in cognition are possible at this stage of illness, as well as confirming the SIB's usefulness as an outcome measure.

The second study was a 24-week randomized, double-blind, placebo-controlled parallel group trial of donepezil in 208 nursing home residents.[27] Inclusion criteria included scores of 5-26 on the MMSE and at least one neuropsychiatric symptom from the NPI, which occurred several times per week. This resulted in a group with average MMSE scores of approximately 14, with 22-26% being severe and 60-62% being moderate. The primary outcome measure was the NPI-NH (nursing home version) with secondary measures, the MMSE, the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB),[28] and PSMS. There were no statistically significant differences noted at endpoint on the NPI-NH, MMSE and PSMS, though scores on CDR-SB suggested significant benefit for donepezil therapy. These authors also raise concerns about the sensitivity of the MMSE to detect decline in more seriously impaired patients.

Memantine

The best studied treatment for moderate to severe AD is the non-competitive NMDA-receptor antagonist memantine. In a brief 12-week randomized, double-blind, placebo- controlled parallel group design, memantine therapy was studied in 166 patients in a psychiatric hospital or in nursing homes.[29] Inclusion criteria included MMSE <10 and Global Deterioration Scale (GDS)[30] score of 5-7. Average MMSE scores were approximately 6 with over 96% of patients being staged as either severe or very severe. Fifty-two percent of subjects had high Hachinski Ischemic Scale scores, suggestive of mixed or vascular dementia. Primary outcome measures were the Clinical Global Impression of Change,[31] and the Behavioral Rating Scale for Geriatric Patients (BGP).[32] The Ferm's D-test was used as a secondary measure of functioning.[33] Treatment effects favoured memantine on all measures. In a 28-week double-blind, placebo-controlled, parallel group trial of memantine, 252 patients with moderate to severe AD were studied by Reisberg et al.[34] Inclusion criteria included MMSE scores of 3-14 and a GDS of 5 or 6. This resulted in a study population with an average MMSE score of approximately 8 with 44% staged as moderate (GDS=5) and 56% moderate to severe (GDS=6). Primary outcome measures were the CIBIC+ and Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for more severe dementia (ADCS-ADLSEV).[35] Secondary measures included the SIB and MMSE for cognition, the GDS and FAST for global staging, the NPI for behaviour, and the Resource Utilization in Dementia scale for health-related economic outcomes.[36] The ITT-LOCF endpoint analysis of the CIBIC+ demonstrated a trend favouring memantine (p=0.06) while the observed case analysis statistically favoured memantine (p=0.03). The ADCS-ADLSEV statistically favoured memantine, as did cognitive outcomes with the SIB. In this study, memantine treated patients declined by 4 points on the SIB compared to 10 points in placebo-treated patients (p<0.001). In contrast, there were no significant differences on the MMSE. Livingston and Katona have recently analyzed these two studies with numbers needed to treat analysis (NNT).[37] A responder analysis from the Winbald and Poritis study in severe dementia was statistically significant with NNTs of 3 and 4. Based on the Reisberg et al. study, the NNT for improvement or stabilization in the CIBIC+ and one of the secondary outcome measures (SIB or ADL) was 6 (p=0.004, 95% CI:4-12). The numbers needed to harm (NNH) for adverse outcomes were all similar except for agitation, with placebo having a significantly higher risk

(NNH=8). Finally, effect sizes from both studies ranged from 0.32-0.62. The authors concluded that given the low NNTs, a medium effect size, and an extremely benign safety profile, memantine appears to have clinically significant benefit in moderate to severe AD with a magnitude that is similar for ChEIs in mild to moderate disease.

In the third study, Tariot et al examined the use of memantine in 404 moderate to severe AD patients already treated with donepezil in a randomized, double-blind, placebo-controlled trial of 24 weeks duration.[38] Inclusion criteria included MMSE 5-14 and donepezil therapy for at least six months prior to randomization. Average baseline MMSE scores were approximately 10. The primary outcome measures were the SIB and ADCS-ADLSEV. Secondary measures were CIBIC+, NPI, and the BGP. All outcome measures favoured memantine with statistical significance.

Alpha-Tocopherol/Selegiline

In a two-year double-blind, placebo-controlled parallel group design, Sano et al studied 341 moderate to severe AD patients with alpha-tocopherol (vitamin E), selegiline, or the combination.[39] Inclusion criteria included a Clinical Dementia Rating (CDR) of 2 (moderate severity), resulting in groups with baseline MMSEs that averaged approximately 11–13. The primary outcome measure was time-to-occurrence of any of death, institutionalization, loss of two to three basic activities of daily living (eating, grooming, using the toilet) as measured by the Blessed Dementia Scale,[40] or a CDR rating of 3 (severe dementia). Secondary measures included the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) and MMSE for cognition,[41] the Blessed Dementia Scale and Dependence Scale for function,[42] and the Behaviour Rating Scale for dementia.[43] Unfortunately, there was a trend towards significant differences among the treatment groups in baseline MMSE scores. There was no difference in the primary outcome for any of the groups but, after adjusting for baseline MMSE, a significant delay in the primary outcome was noted for selegiline, alpha-tocopherol, and the combination. There were no significant differences in the cognitive measures, leading the authors to suggest that other aspects of moderate to severe AD, such as behavior and function, may make it difficult to assess cognition, and cognition may not be the best measure of disease progression at this stage.

COMMENT/SUMMARY

There are limited data supporting the use of pharmacological agents to treat moderate to severe AD. Use of donepezil appears promising based on one positive RCT and a second study with a positive secondary global outcome as measured by the CDR-SB. Post-hoc analyses of trials with galantamine and rivastigmine suggest the benefits may be a class effect, though further studies would be helpful. The positive clinical results are supported by neuropathological evidence, suggesting cholinergic markers are appropriate targets at this stage of illness.[10] Treatment with memantine – an NMDA antagonist – also seems promising based on three RCTs, including a study suggesting combined therapy with donepezil and memantine is better than donepezil alone. Finally, there is some evidence that the antioxidants alpha tocopherol and selegiline may delay the progression of the

illness, though significant methodological problems raise concerns about the validity of these results and further confirmatory studies are necessary.[44] While providing treatment guidelines for moderate to severe AD based on these few studies would be overly ambitious, they do raise important methodological issues for studying moderate to severe AD and can provide guidance for recommendations about appropriate trial designs.

TRIAL DESIGNS FOR MODERATE TO SEVERE AD

Inclusion Criteria

Moderate to severe AD can be reliably distinguished from milder disease by a combination of global staging and MMSE score.[45] GDS (and FAST) stages 5 (moderate), 6 (moderate to severe), and 7 (severe) or CDR stages 2 (moderate), 3 (moderate to severe), 4 and 5 (severe) would be appropriate stages and rating instruments for moderate to severe AD studies. The MMSE scores of 10–19 have generally been considered consistent with moderate AD and <10 severe AD. While the studies reviewed previously included a variety of upper limits for the MMSE (usually 10–17), it is recommended that average baseline MMSEs for studies of moderate to severe AD be no greater than 12.

Design

All moderate to severe AD trials should be randomized and double-blind. As mentioned previously, there are currently no CGPs for moderate to severe AD, though CPGs for mild to moderate AD have generally recommended a trial of a cholinesterase inhibitor.[46] It is, therefore, reasonable to recommend placebo-controlled trials, especially if the trial focuses on severe AD (GDS 7, CDR 4 or 5, MMSE <10). Trials that utilize an equivalency or non-inferiority design, with the investigational drug compared to cholinesterase inhibitors, are recommended, especially if moderate patients are included. Sample size calculations for these designs may necessitate a need for large sample sizes.[47] Another recommended design would include all patients being treated with "standard care" (e.g., ChEIs) using a parallel group design comparing the investigational drug to placebo. This design might result in an approved indication for combined therapy only (as opposed to monotherapy). A final design would include a parallel group design with three arms: standard care plus placebo, standard care plus investigational drug, and investigational drug plus placebo.

OUTCOME MEASURES

Outcome measures in moderate to severe AD trials will differ from mild to moderate AD trials because of psychometrics and different stage-specific goals.[48] Since small changes in cognitive function may have questionable clinical relevance at this stage of AD, it is recommended that primary outcome measures include a global rating and either a functional or behavioural measure. Cognitive, functional, behavioural, and measures of caregiver distress are all appropriate secondary measures. The CIBIC+ is one recommended global outcome measure that has been used in previous moderate to severe AD studies and appears to be sensitive to change. There is some suggestion that this instrument relies more heavily on ADL and behavioural change,

which would be appropriate for moderate to severe AD trials.[45] Function can be measured with the ADCS-ADLSEV or DAD, both of which are sensitive to change in this population. Unfortunately, these scales might be limited in long-term care institutions where patients frequently do not have the opportunity to demonstrate functional competence on all the activities of daily living assessed. Behaviour can be measured with the NPI. Cognitive measures such as the MMSE and ADAS-cog are limited by a floor effect, as noted in the previous moderate to severe AD studies.[48] The SIB has demonstrated excellent sensitivity in this population. The SIB appears to be most useful in patients with MMSE <10 and may suffer from a ceiling effect in patients with moderate disease (e.g., MMSE >15).[45]

Stabilization of function, behaviour, and cognition is a reasonable goal of therapy and possibly more realistic than significant improvement at this stage of illness. Pharmaco-economic outcomes are important and might focus on indirect costs, such as caregiver time, which make up a significant proportion of costs for community dwelling patients. Finally, while health-related quality of life is an important outcome, practical and theoretical issues have limited its measurement and there is no consensus about valid and reliable measures at the present time. This would be particularly problematic for moderate to severe AD where proxy measures would have questionable validity.

SUMMARY

In conclusion, moderate to severe AD represents a significant societal health problem with respect to prevalence, symptomatology, caregiver burden, and pharmaco-economics. There are emerging data that the cholinesterase inhibitors and memantine may be useful therapies at this stage of illness, though further studies are necessary. The clinical trials completed to date do provide evidence that there are specific rating instruments and trial designs that are valid and reliable in this patient population.

DISCLOSURE

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