The Use of Medications for Cognitive Enhancement

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ABSTRACT: **Objective:** To provide Canadian physicians and allied health care professionals with the evidence they need to help them make treatment decisions in the management of patients with Alzheimer’s disease or other dementias. **Options:** The full range and quality of diagnostic and therapeutic modalities available to Canadian physicians for the management of dementia. **Outcomes:** Improvement in the treatment of dementias, leading to reduced suffering, increased functional capacity and decreased economic burden. **Evidence and values:** The creation of these evidence-based consensus statements involved literature reviews of the subject by the authors; comparison of alternative clinical pathways and description of the methods whereby published data were analyzed; definition of the level of evidence for data in each case; evaluation and revision in a conference setting (involving primary care physicians, neurologists, psychiatrists, geriatricians, psychologists, consumers and other interested parties); insertion of tables showing key variables and data from various studies and tables of data with recommendations; and reassessment by all authors. **Benefits, harms, and costs:** A rational plan for the therapy of dementias is likely to lead to substantial benefits in both human and economic terms. **Recommendations:** Treatment decisions should be made taking into account the severity or stage of the disease, the availability of caregivers, the presence of disease affecting other bodily systems and the ability of the subject to pay the cost of the medications. Donepezil is considered to have positive effects upon certain tests of neuropsychological function and may produce some improvement in Alzheimer’s disease of mild to moderate severity as measured by rating scales. Its ability to improve quality of life remains uncertain. No other drug treatments* (apart from symptomatic therapies) are at present approved for the treatment of Alzheimer’s disease. **Validation:** These recommendations were created by a writing committee, evaluated and revised at a consensus conference and further reviewed and revised by the writing committee prior to publication.


Following the introduction of the first medication approved in Canada for the therapy of Alzheimer’s disease (AD), the Canadian Consensus Conference on Dementia (held in February 1998) felt it appropriate to survey agents for which therapeutic claims have been made in this field. At that conference, the authors produced a detailed document surveying anti-dementia

* See Brief Review: Rivastigmine, A Second Cholinesterase Inhibitor – pg S122

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METHODS

We performed a MEDLINE search of the literature from 1986 to March 1998 in order to identify all randomized controlled trials (RCTs) of tacrine, selegiline, vitamin E, donepezil or gingko and propentofylline. The search was updated in October of 2000. Only those trials with cognitive outcome measures were assessed. All studies evaluating combinations of therapies were excluded unless the results were presented separately for each therapy. Excluding articles that did not meet inclusion criteria, 24 remained for review. By contacting behavioural neurology experts we identified 15 further articles. All reference lists from the articles retrieved in the MEDLINE search were scanned and reviewed. Of the 44 original papers, 27 remained. We were unable to obtain three papers but included the information from the abstract of one of them, leaving 25 articles. Following the updated search an additional five RCTs were identified. In total, 30 trials were included in our sample.

Following the creation of an initial draft review, all authors had the opportunity to contribute further sections and then to review the whole draft paper, amending it as they saw fit. A final draft was circulated to the co-authors and agreed upon prior to the conference, in which all participated. The results of the review were presented to the conference and agreed as amended after debate. The principles and guidelines set out in this document were then adopted.

The criteria for assigning levels of evidence and grades of recommendation used in this manuscript were developed at the Canadian Consensus Conference on Dementia and are listed in Table 1. The committee used the Canadian Medical Association’s clinical practice guidelines and the rules of evidence used by the committee were consistent with the Canadian Task Force on the Periodic Health Examination as previously used. The full methods used in the consensus development process are published elsewhere.

### Therapies for Cognitive Enhancement

#### 1. Tacrine

In two early studies, tacrine did not lead to useful improvement in cognition, functional status or behaviour. Over 1100 patients, with mild to moderate probable AD, were randomized by Gracon to receive placebo or tacrine for 12 or 30 weeks. Outcome measures included objective assessments of cognitive function, qualitative assessments of treatment response from the caregiver and clinician perspective, and assessments of activities of daily living (ADL). Statistically significant treatment effects favoring tacrine were demonstrated in each domain but these tended to be subtle, ranging from improvement to stabilization or slowed decline.

Knapp et al evaluated the efficacy and safety of three doses of tacrine in patients with mild to moderate AD in a 30-week trial, using as primary outcome measures the Clinician Interview-Based Impression (CIBI), Alzheimer Disease Assessment Scale – Cognitive (ADAS-Cog) and a Final Comprehensive Consensus Assessment (FCCA). Only 263 of 653 patients included in an intent-to-treat (ITT) analysis had evaluable data at 30 weeks. The ITT analysis revealed significant (P≤.05) dose-response trends and between-group comparisons on the CIBI and ADAS-Cog but these were modest – on the CIBI, 23% improved on tacrine and 17% on placebo. In the evaluable patients, dose-response trends in favor of 160 mg/d of tacrine were observed for all three primary measures (P≤.001). The authors concluded that tacrine produced dose-related improvements on objective tests, global evaluations and measures of quality of life and that the large number of patient withdrawals did not bias the overall conclusions.

Raskind et al examined the effects of tacrine in patients with mild to moderate AD who had been enrolled in a previous trial and had taken placebo or 160 mg/d of tacrine. The main outcome measure was a change from baseline to last observation carried forward in discrete subscale scores of the ADAS, both cognitive and noncognitive. Improvement was defined as a decrease of at least one point from baseline. Compared with the placebo group the percentage of patients receiving tacrine whose conditions improved by one ADAS point or more, or stabilized, was significantly greater for eight psychological measures and on scores for cooperation, delusions and pacing.

Knopman et al assessed the possible association between tacrine dose and likelihood of nursing home placement or death in patients with AD in an unblinded study following a 30-week RCT. Patients who remained on tacrine at doses >80 mg/d for a minimum of two years were less likely to have entered a nursing home than were patients on lower doses.

Watkins et al showed that among 2,446 patients with mild or moderate AD exposed to tacrine in clinical trials conducted in...
the United States, Canada and France, serum alanine aminotransferase (ALT) levels greater than the upper limit of normal occurred on at least one occasion in 1,203 patients (49%), levels greater than three times the upper limit of normal occurred in 25%, and levels greater than 20 times the upper limit occurred in 2% of patients. Ninety percent of all ALT levels greater than three times the upper limit of normal occurred during the first 12 weeks of treatment. In all instances, discontinuation of tacrine therapy reversed any elevations in ALT levels.

**Recommendation:** The value of tacrine for symptomatic therapy in patients with AD is uncertain and its side-effect profile is cause for concern. While approved in the United States and in some European countries, we concur with the assessment made by the Health Protection Branch which rejected the drug on the grounds that the demonstrated benefits in certain test parameters did not translate into sufficient functional improvement to offset its potential risks. *Level 1, Class D.*

### 2. Donepezil

This agent has been evaluated in six RCTs, one with an open label extension. In a multicentre double-blind placebo-controlled RCT, Rogers et al.\[^{12}\] examined the safety and efficacy of 1, 3 or 5 mg of donepezil compared to placebo for 12 weeks in 161 outpatients with a diagnosis of probable AD. The subjects had a Mini-Mental State Examination (MMSE) score between 10 and 26, a mean age of about 71 years and no significant medical illness. Donepezil (5 mg. od.) significantly improved cognition, as measured by an adjusted mean decrement from baseline in the ADAS-Cog scale of 2.5 points, compared to placebo and an adjusted mean increase from baseline of two points on the MMSE scale (a secondary outcome measure) when compared to the 1 mg dose of donepezil (but not when compared to placebo). The Clinician’s Global Impression of Change (CGIC) was the primary outcome measure. Functional, quality of life, and disease severity parameters were not significantly affected. The incidence of adverse effects did not differ between the donepezil and placebo groups. Donepezil use was not associated with hepatotoxicity.

In an open-label extension of the above for up to 192 weeks, and using the same efficacy measures in 132 members of the original patient group, Rogers and Friedhof\[^{12}\] reported a reduction in the rate of cognitive and global decline of patients in mild-to-moderate stages compared to that expected in light of the natural history of the disease. Because the original RCT had demonstrated a large placebo effect, comparison with natural history controls may be inappropriate.

Rogers et al.\[^{13}\] evaluated the efficacy and safety of donepezil in patients with mild to moderate AD in RCT conducted at 20 investigational sites in the United States. Patients were assigned to either placebo or donepezil at a 5 or a 10 mg dose. The primary outcome measures included the cognitive portion of the ADAS, and the Clinician’s Interview Based Impression of Change-Plus (CIBIC-Plus). Cognitive function (measured using the ADAS-Cog) was significantly improved in the donepezil treated group relative to the placebo groups at 12, 18, and 24 weeks. Adverse effects appeared to be more common with increasing dose of donepezil.

In a similar study, Burns et al.\[^{14}\] evaluated the efficacy of donepezil in 82 sites internationally, including Canada and the United Kingdom, using a 30 week RCT. A total of 818 patients were randomized in this study. Again improvement were seen in the ADAS-Cog scores in patients receiving donepezil relative to those in the placebo group.

Rogers et al.\[^{13}\] evaluated donepezil in a randomized placebo controlled trial. This study was conducted at 23 centres in the United States and patients were randomized to placebo or donepezil at doses of either 5 or 10 mg for a period of 12 weeks. This study evaluated 468 patients with mild to moderately severe AD. Relative to placebo, donepezil produced statistically significant improvements in the ADAS-Cog, CIBIC-Plus and the MMSEs. The mean donepezil to placebo differences for the group receiving 10 mg of donepezil were 3.1 units for the ADAS-Cog (p<.001); 0.4 units for CIBIC-Plus (p<.008); and 1.3 units for the MMSE (p<.004).

Most recently, Greenberg et al.\[^{16}\] evaluated donepezil therapy at memory disorders units at the Massachusetts General Hospital and the Brigham and Women’s Hospital in Boston. In this study, 60 older adults with probable AD were randomized in a 24-week cross-over study to donepezil or placebo in one of two sequences. Donepezil was administered in a 5 mg dose. Test results using the ADAS-Cog were significantly improved during treatment with donepezil and slightly worse in the placebo group. Nine patients withdrew from the study after randomization. Of these, two were judged to have serious adverse events possibly related to donepezil (syncope and seizure). Of patients completing the study, gastrointestinal adverse effects were the most common reported problems.

**Recommendation:** At present, donepezil is the only drug approved for the treatment of mild-moderate AD. Donepezil has been shown to lead to improvements in certain cognitive tests and in clinical global assessments. However, long term clinical benefits of maintaining functional independence and improving quality of life remain unclear. The studies excluded patients with important medical illnesses, so effectiveness may have been overestimated and side-effects underestimated in terms of the likely outcome in clinical practice. *Level 1, Class B.*

### 3. Vitamin E

Only one double-blind RCT compared the use of vitamin E (alpha-tocopherol) to placebo in the treatment of moderate AD. Sano et al.\[^{17}\] compared 2000 IU of vitamin E vs. 10 mg/d of selegiline vs. both vs. placebo in 341 subjects over two years, to determine whether either or both of these antioxidants could delay disease progression. The primary outcome, defined as time to occurrence of any of death, institutionalization, loss of ability to perform activities of daily living or severe dementia, was negative (see following section). However, institutionalization was significantly delayed in the vitamin E group. Falls and syncope were notably more common in the treatment groups and there was no additive effect of combining therapies. Despite random assignment, the baseline score on the MMSE was higher in the placebo group than in the other three groups and this variable was highly predictive of the primary outcome. The study has been criticized\[^{18}\] on the appropriateness of the end points, the statistical adjustments and internal consistency.

**Recommendation:** While vitamin E is reasonably safe, the benefits shown by the methodologically flawed trial appear modest, so there is insufficient evidence to recommend it for the treatment of AD. *Level 1, Class C.*
4. Selegiline

Selegiline was compared to phosphatidylserine in 40 patients with mild to moderate AD in a three month RCT. The selegiline group showed significantly superior improvements compared to the others in most cognitive areas examined and appeared able to induce an increased degree of autonomy in day-to-day activities. Tolerability was good. Forty patients with mild-to-moderate AD were enrolled by Campi et al in a single-blind, RCT to assess the efficacy and safety of selegiline and L-acetylcarnitine in the treatment of AD over three months. Selegiline therapy led to a comparative global improvement in the processing, storage, and retrieval of given information, improvements in verbal fluency and visuospatial abilities.

Tariot et al examined the value to 10 mg and 40 mg of selegiline vs. placebo in 17 hospitalized patients with dementia and found decreases in anxiety and excitement and improvement in cognitive tasks with the 10 mg dose. A study of 20 outpatients with AD comparing 10 mg of selegiline to placebo, demonstrated improvements in memory and attention in patients followed for three months. Lawlor et al examined the behavioural and cognitive effects of selegiline in 25 behaviourally disturbed AD patients in a 14-week study of selegiline (10 mg) and placebo. In the primary analysis, improvement on the Brief Psychiatric Rating Scale, the Dementia Mood Assessment Scale (DMAS) and the ADAS-Cog scores with selegiline treatment did not reach statistical significance. In a secondary analysis, it improved behaviour and cognition in a subset of testable patients.

Sano et al studied 341 patients with moderate AD who received selegiline, alpha-tocopherol, both agents or placebo for two years. The primary outcome was the time to the occurrence of death, institutionalization, loss of the ability to perform basic ADL or attainment of a Clinical Dementia Rating score of 3. Despite random assignment, the baseline score on the MMSE was higher in the placebo group than in the other three groups, and this variable was highly predictive of the primary outcome. In the unadjusted analyses, there was no statistically significant difference in the outcomes among the four groups. However, in an adjusted analysis selegiline resulted in significant improvements compared to placebo. It was concluded that in patients with moderately severe impairment from AD disease, treatment with selegiline slows functional deterioration but that it has little effect on cognitive measures.

Following a six-month double-blind RCT, Finali et al concluded that selegiline improved cognitive functions and behaviour founded on memory efficiency and reported that selegiline significantly improves some memory parameters, probably through improvement in information processing abilities and in learning strategies at the moment of acquisition. Burke et al in a 15-month double-blind RCT on 39 subjects with mild AD, found that selegiline had a slight effect on a single measure of psychopathology but had no measurable impact on any other measure of behaviour or cognitive function and did not appear to slow the progression of the disease. Mangoni et al enrolled 119 patients with AD to assess the efficacy and tolerability of selegiline over three months and reported that it improved cognitive functions and reduced behavioural alterations. Freedman et al in a carefully-designed RCT found that oral selegiline provided no detectable benefit on general behaviour, neuropsychiatric symptoms or cognitive functions in patients with AD treated for six months.

Filip et al conducted a randomized placebo control study in nursing homes located in seven cities in Czechoslovakia to evaluate the benefit of selegeline relative to placebo in improving cognitive function. A total of 173 nursing home residents were evaluated. After 24 weeks of treatment, the subset of patients with normal results on the clock drawing test who were treated with selegeline had improved MMSE scores relative to those treated with placebo.

**Recommendation:** Selegiline has only been found effective in the treatment of AD when secondary analyses were performed. There is insufficient evidence that this agent leads to clinically important improvements in AD. *Level I, Class C.*

5. Ginkgo biloba

Two double-blind placebo-controlled RCTs compared the use of ginkgo biloba (a plant extract with antioxidant properties) to placebo in patients with mild to moderate AD or multi-infarct dementia. In a German study, Kanowski et al compared the use of 240 mg per day of a standardized ginkgo preparation (Egb 761) to placebo in 222 healthy outpatients for 24 weeks. Only 156 subjects (70%) completed the trial, but incomplete information is provided as to the reasons for dropout. Outcome measures were global assessment, attention/memory, and ADL scales. The primary outcome measure was the therapeutic responder rate, defined as a change in scale score of at least one standard deviation from the baseline mean on at least two of the three outcome measures. This is not a standard outcome measure in North America and its validity is uncertain. The rate in the ginkgo group was 28% (22 subjects) compared to 10% (eight subjects) in the placebo group (p<0.01). For individual outcome variables, statistically significant differences favoring ginkgo were found in the clinical global assessment and attention/memory scales, but not in the ADL scale.

In a North American study on this agent, Le Bars et al studied the safety and efficacy of 120 mg per day of a standardized ginkgo preparation (Egb 761) to placebo in 327 healthy subjects with AD or multi-infarct dementia. Only 50% of the ginkgo group and 38% of the placebo group completed the entire study. Of the 309 subjects in the ITT analysis, and 202 who provided evaluable data at 52 weeks, the ginkgo group showed modest but statistically significant improvement in cognition and in daily living and social behaviour as measured by the Geriatric Evaluation by Relatives Rating Instrument, a cumulative measure of daily living and social behaviour. No difference was noted in the CGIC. Adverse events related to the study drug were enumerated but poorly defined. The lack of standardized ginkgo preparations in North America and the high dropout rate are limitations of this study.

**Recommendation:** Ginkgo biloba slightly improves the scores on certain cognitive tests and on some assessment instruments but not others. Therefore, uncertainty remains as to its practical value in the treatment of dementia. *Level I, Class C.*

6. Propentofylline

In a multinational RCT, 260 patients with mild to moderate AD or vascular dementia (VaD) received 300 mg propentofylline or placebo. After 12 months, the total patient population showed statistically significant treatment differences in favour of...
propentofylline on global and some cognitive measures and on an ADL scale but no significant treatment differences were found with rating scales performed by the patients. Although all treatment differences for AD patients were in favour of propentofylline, they only reached statistical significance on one scale.

**Recommendation:** The results in this single trial are conflicting and propentofylline is not at present considered appropriate for prescription in the treatment of AD. *Level 1, Class C.*

### 7. Hydergine

Hydergine, a metabolic enhancer, may affect cerebral glucose metabolism and multiple neurotransmitters. Schneider and Olin conducted a detailed review limited to placebo-controlled, double-blind, parallel group RCTs in patients with symptoms consistent with dementia. Overall and for the subgroup with VaD, significant benefit was identified across all outcome measures but subjects with probable AD showed only a small effect on the neuropsychological outcomes. The original studies have several limitations. For example, 71% of the studies (all before 1980) used simpler statistical techniques and reported selective outcomes; definitions of dementia were not uniform and descriptions of the clinical course were poor. The total number of subjects was small (297) and the categorization between VaD and AD was not always clearly defined. It is concluded that, at best, there is modest evidence of benefit from hydergine, affecting behaviour more than cognitive functions and more in subjects with VaD than in those with possible AD.

**Recommendation:** Overview analyses of hydergine indicate a significant, but clinically modest, effect of hydergine in patients with dementia, especially VaD. The benefits only achieved statistical significance on cognitive-neuropsychological measures. While hydergine appears to be relatively safe, it is not recommended for the management of dementia. *Level 1, Class C.*

### 8. Other therapies

Numerous other drugs proposed for the treatment of dementia have been subjected to study. None of the agents listed in Table 2 can be recommended (Level 1, Classes C or D) on the basis of the information published to date because of inadequate study design, lack of efficacy or effectiveness, lack of replication or the occurrence of unacceptable side effects.

**DISCUSSION**

We have reviewed seven drugs with regard to their use in the symptomatic treatment of dementia. Regarding clinical trial design and outcome measures used in studies of medications for AD, we note that many studies have used outcome measures that are foreign to usual clinical practice, including the ADAS, although this was designed to assess the cognitive and behavioural dysfunctions characteristic of AD. This compound measure consists of a cognitive subscale (ADAS-Cog), often used as the primary outcome measure, and a noncognitive subscale (ADAS-Noncog). Its 11 items test memory, orientation, language and praxis. The maximum score is 70 points, and a higher score indicates a worse performance. It is a reliable tool and a sensitive indicator of dementia progression. A longitudinal study of 111 AD patients estimated that the change in score on the ADAS-Cog was approximately 9–11 points per year. However, the clinical relevance of a change for the better by one, two or three points is uncertain and likely to be minimal.

In 1990, in an attempt to make outcome measures for RCTs more relevant, the U.S. Food and Drug Administration (FDA) mandated that all clinical trials of drugs for the treatment of AD must include a clinician’s global assessment as a primary outcome measure. Various such scales have been developed, varying in their administration and in the information used to determine change but all using a baseline interview as a reference for future assessments of change. The CIBIC was a specific CGIC measure including a worksheet delineating the domains to be assessed (concentration, orientation, memory, language, behaviour, initiative, and ADL). As it may be inappropriate to preclude interviewing caregivers at follow-up, the CIBIC-Plus was created, in which both the patient and caregiver are interviewed before a rating is made. Although these scales are now required by the FDA, usually as a primary outcome measure, their validity and reliability remain uncertain. We suggest alternative goals for therapy, but are aware that few of them are directly assessed by neuropsychological tests, although some are assessed by rating scales.

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**Table 2:** Other therapies not recommended for the symptomatic treatment of dementia

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<tr>
<th>Agents Not Recommended for Clinical Use</th>
<th>Standards of Evidence*</th>
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<tr>
<td>Acetyl L-carnitine (ALCAR)</td>
<td>Level 1, Class C</td>
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<td>Lecithin</td>
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<td>Arecholine</td>
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<td>Nimodipine</td>
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<td>Velacrine</td>
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<td>Physostigmine</td>
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<td>Memantine</td>
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<td>4 Aminopyridine (4AP)</td>
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<td>Milacemide</td>
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<td>Idenbenone</td>
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<td>Thyrotropin</td>
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* As outlined in Table 1
We suggest that the following are reasonable goals for anti-dementia therapy:
1. Slowing of the course of the disease (measured against the course in appropriate comparison groups) with respect to cognitive and functional decline or leading to institutionalization.
2. Improvement in memory and other cognitive functions.
3. Improvement or maintenance of functional abilities.
4. Improvement in behavioural abnormalities.
5. Improvement in mood/contentedness and quality of life of the patient and/or caregiver.

None of the drug therapies reviewed satisfy all these criteria, although the results in some cases do suggest future strategies for the treatment of this disease. In the donepezil studies, a minority of patients seem to improve in a clinically meaningful manner.

The clinical trials reviewed here have numerous shortcomings in common. Most have focused on statistically significant changes in outcome measures that do not easily translate into meaningful clinical changes. They thus fail to determine whether patients had clinically important changes in function, behaviour, quality of life, need for institutionalization, caregiver burden or health care resource utilization. In the absence of data pertaining to these important clinical outcomes, it is difficult to interpret the results of most of the clinical trials in AD that have been reported. The duration of many was comparatively short – sometimes less than three months. While this may be sufficient to demonstrate positive effects on a highly sensitive cognitive scale, it is not sufficient to allow for an evaluation of the impact on important clinical outcomes such as function and institutionalization, or on slowing of the disease process. The use of open-label marketing studies for longer term follow-up can provide important information about side effects, but is a weak design for studying effectiveness because it necessitates comparisons with historical controls. This is particularly troublesome given the strength of the placebo effects that have been demonstrated in the clinical trials.

**CONCLUSION**

Over the last fifteen years, many agents have been tested for their effects in assuaging the burden of dementia, either empirically or based upon various rationales. Few have been found to be efficacious but the fact that occasional improvement in cognitive functioning has been shown indicates that the search for relief from a huge personal, social, economic and societal burden may, at last, be appropriately directed. The goals of anti-dementia therapy suggested above have not yet been attained, but the occasional successes reported to date suggest that they may be attainable.

Although the treatment of dementia is still in its early stages, at least one form of therapy is now approved, albeit with limited effect. This nevertheless represents an important step forward, for the prevalence of Alzheimer’s disease is likely to increase in the next few decades. There remains a need for consensus agreement on the goals of therapy and on the most appropriate means for assessment of those new agents subjected to clinical trial. The ability of any drug to influence the quality of life of the patient and of the caregiver for the better should be the most important factor determining its usefulness.

**REFERENCES**
