CHIEF EDITOR DR. SYED MUBIN AKHTAR

KARACHI PSYCHIATRIC HOSPITAL

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Dr. Syed Mubin Akhtar speaking about "Addiction" on the occasion of monthly CME program organized by Karachi Psychiatric Hospital.

Dr. Syed Mubin Akhtar being interviewed about Mental Health Problems, Prevention and Management, by GEO and ARY channels' teams.

Dr. Syed Mubin Akhtar speaking on the occasion of 192th monthly meeting of "بزم سائنسی ادب"

Dr. Syed Mubin Akhtar, Prof. Ghafoor Ahmed and author Zia-ur-Rehman on the occasion of inauguration of his book comprising short stories for children entitled "سحر ہونے تک"

Mrs. Mahrukh speaking on the occasion of monthly Public Awareness Programme organized by Karachi Psychiatric Hospital.

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(Psychiatric Research Articles)

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تم میں کچھ لوگ تو ایسے ضرور ہی ہونے چاہیں جو نیکی کی طرف بولائیں، بھلائی کا حکم دیں، اور برائیوں سے روکتے رہیں۔ جو لوگ یہ کام کریں گے وہی فلاح پائیں گے۔

(آل عمران:۱۰۴)

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SPECIAL ISSUE ON DEMENTIA

DONEPEZIL, GALANTAMINE, RIVASTIGMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Adopted from an article in the National institute for health and clinical excellence

I Guidance

This guidance applies to donepezil, galantamine, rivastigmine and memantine within the marketing authorisations held for each drug at the time of this appraisal; that is:

- donepezil, galantamine, rivastigmine for mild to moderately severe Alzheimer's disease
- memantine for moderately severe to severe Alzheimer's disease.

The benefits of these drugs for patients with other forms of dementia (for example, vascular dementia or dementia with Lewy bodies) have not been assessed in this guidance.

The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer's disease of moderate severity only (that is, subject to section 1.2 below, those with a Mini Mental State Examination [MMSE] score of between 10 and 20 points), and under the following conditions:

- Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers' views on the patient's condition at follow-up should be sought. The drug should only be continued while the patient's MMSE score remains at or above 10 points (subject to section 1.2 below) and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect.

In determining whether a patient has Alzheimer's disease of moderate severity for the purposes of section 1.1 above, healthcare professionals should not rely, or rely solely, upon the patient's MMSE score in circumstances where it would be inappropriate to do so. These are:

- where the MMSE is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties or
- where it is not possible to apply the

MMSE in a language in which the patient is sufficiently fluent for it to be an appropriate tool for assessing the severity of dementia, or there are similarly exceptional reasons why use of the MMSE, or use of the MMSE by itself, would be an inappropriate tool for assessing the severity of dementia in that individual patient's case.

In such cases healthcare professionals should determine whether the patient has Alzheimer's disease of moderate severity by making use of another appropriate method of assessment. For the avoidance of any doubt, the acetylcholinesterase inhibitors are recommended as options in the management of people assessed on this basis as having Alzheimer's disease of moderate severity.

The same approach should apply in determining for the purposes of section 1.1 above, and in the context of a decision whether to continue the use of the drug, whether the severity of the patient's dementia has increased to a level which in the general population of Alzheimer's disease patients would be marked by an MMSE score below 10 points.

When the decision has been made to prescribe an acetylcholinesterase inhibitor, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative acetylcholinesterase inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical comorbidity, possibility of drug interactions and dosing profiles.

Memantine is not recommended as a treatment option for patients with moderately severe to severe Alzheimer's disease except as part of well-designed clinical studies.

Patients with mild Alzheimer's disease who are currently receiving donepezil, galantamine or rivastigmine, and patients with moderately severe to severe Alzheimer's disease currently receiving memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including after the conclusion of a clinical trial) until they, their carers and/or specialist consider it appropriate to stop.

II Clinical need and practice

Dementia is a chronic progressive mental disorder that adversely affects higher cortical functions including memory, thinking and orientation. Alzheimer's disease is the most common form of dementia. It is a degenerative cerebral disease with characteristic neuropathological and neurochemical features.

Alzheimer's disease is usually insidious in onset and develops slowly but steadily over a period of several years. It affects predominantly the elderly. Progression is characterised by deterioration in cognition (thinking, conceiving, reasoning) and functional ability (activities of daily living) and a disturbance in behaviour and mood.

Changes in one or more of these domains and their effects on the person provide the basis for diagnosis and they are used to assess the severity and progression of the condition. Evidence suggests that Alzheimer's disease progression is dependent on age, and the time from diagnosis to death is about 5-20 years (median 5 years in people aged 75-80 years).

People with Alzheimer's disease lose the ability to carry out routine daily activities like dressing, toileting, travelling and handling money and, as a result, many of them require a high level of care. Behavioural changes in the person, such as aggression, are particularly disturbing for carers.

Non-cognitive symptoms in dementia include agitation, behavioural disturbances (for example, wandering or aggression), depression, delusions and hallucinations.

Several different methods are used to assess the severity of Alzheimer's disease. These include: the Clinician's Interview-based Impression of Change (CIBIC) and CIBIC-plus for global outcomes; the Progressive Deterioration Scale (PDS) for functional/quality-of life scales; and the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog - 70 points) or the MMSE (30 points) for cognitive outcomes. MMSE score, for example, denotes the severity of cognitive impairment as follows:

- mild Alzheimer's disease: MMSE 21-26
- moderate Alzheimer's disease: MMSE 10-20
- moderately severe Alzheimer's disease: MMSE 10-14
- severe Alzheimer's disease: MMSE less than 10.

Population data (2002) for England and Wales show an estimated prevalence of 290,000 people with Alzheimer's disease. On the basis of these figures a primary care trust (PCT) with a population of 200,000 might expect to have approximately 1100 cases of Alzheimer's disease. The incidence rate for Alzheimer's disease in people over the age of 65 years has been estimated at 4.9 per 1000 person-years in the UK. The incidence rate appears to have been stable over the past two decades and is found to be related to age (rising with increasing age) and gender (women have a higher risk than men). In people with Alzheimer's disease, 50-64% are estimated to have mild to moderately severe disease, and approximately 50% have moderately severe to severe Alzheimer's disease.

People with mild dementia are sometimes able to cope without assistance, but as the disease progresses, all eventually require the aid of carers, and about half need residential care. The total cost of care for people with dementia is estimated by the Audit Commission to be £6 billion per year in England, with half of this amount attributed to health and social services.

2.8 People with dementia usually present to their general practitioner with memory problems, and an estimated 39% present to specialist clinics.

III The technologies

Acetylcholinesterase inhibitors: donepezil, galantamine, rivastigmine

Acetylcholinesterase (AChE) inhibitors increase the concentration of acetylcholine at sites of neurotransmission.

Donepezil (Donecept) is a specific and reversible inhibitor of AChE, licensed in the UK at a dosage of 5 mg/day and 10 mg/day. It is licensed for the symptomatic treatment of people with mild to moderately severe Alzheimer's dementia.

Galantamine (Reminyl, Shire Pharmaceuticals) is a selective, competitive and reversible inhibitor of AChE, licensed in the UK. It is licensed for the symptomatic treatment of people with mild to moderately severe dementia of the Alzheimer type.

Rivastigmine (Exelon, Novartis Pharmaceuticals UK) is an AChE and butyrylcholinesterase inhibitor, licensed in the UK. It is licensed for symptomatic treatment of people with mild to moderately severe Alzheimer's dementia. The usual maintenance dosage is 3-6 mg twice daily.

Typical side effects of donepezil, galantamine and rivastigmine are related to the gastrointestinal tract (including nausea and vomiting). These side effects are dose related and although they are usually short term they can lead to non-adherence.

Memantine

Memantine (Synaptol) is a voltage-dependent, moderate affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. It is used in the treatment of people with moderate to severe Alzheimer's disease. The recommended maintenance dosage is 10 mg twice daily.

In clinical trials in mild to severe dementia, involving patients treated with memantine and patients treated with placebo, the most frequently occurring adverse events with a higher incidence in the memantine group than in the placebo group were dizziness, headache, constipation and somnolence. These adverse events were usually of mild to moderate severity. For full details of side effects and contraindications, see the summary of product characteristics.

IV Evidence and interpretation

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease, having considered evidence on the nature of the condition and the value placed on the benefits of donepezil, galantamine, rivastigmine and memantine by people with Alzheimer's disease, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

Mild to moderately severe Alzheimer's disease

The quality of the reporting and

methods of the included published randomised controlled trials (RCTs) of the AChE inhibitors (donepezil, galantamine and rivastigmine) was mixed.

Donepezil

Thirteen published RCTs (aggregate number of people randomized 4200), one unpublished RCT and two systematic reviews met the inclusion criteria set by the Assessment Group for the systematic review of clinical effectiveness of donepezil. (The original guidance included five RCTs, four studies from manufacturers and three systematic reviews.) Three of the new trials followed up participants for longer than 6 months.

Six RCTs reviewed by the Assessment Group showed a statistically significant improvement in cognition following treatment with donepezil compared with placebo, as assessed using the ADAS-cog scale. Higher doses of donepezil were associated with increasing benefit. Three RCTs with a duration of 12-24 weeks contained data in a form that could be combined by the Assessment Group in a meta-analysis. A weighted mean difference of -2.51 (95% confidence interval [C I]-3.26 to 1.76) in terms of a change from baseline on the ADAS-cog was found for the 5 mg daily dose (aggregate number of people randomised 850) and a weighted mean difference of 13.01 (95% C I -3.91 to 2.10) was found for the 10 mg daily dose when compared with placebo (aggregate number of people randomised 608). An analysis based on the trial of 24 weeks' duration produced a mean difference in ADAS-cog change from baseline at 24 weeks of -2.88 (95% C I 0.5 to 1.2, $p < 0.0001$)

Eight RCTs showed trends towards improved MMSE scores following treatment with donepezil compared with placebo. Results of a meta-analysis performed by the Assessment Group on two of these RCTs (aggregate number of people randomised 610) showed a change from baseline in MMSE score of 1.30 (95% CI 0.78 to 1.82) for 10 mg donepezil when compared with placebo. One UK study (486 people randomised), excluded from the metaanalysis by the Assessment Group, used MMSE as a secondary outcome and showed that, over the first 2-year study period, the MMSE scores of the donepezil group were an average of 0.8 points higher than those of the placebo group (95% CI 0.5 to 1.2, $p < 0.0001$).

Seven RCTs (aggregate number of people randomised 2460) assessed the effect of donepezil compared with placebo on global outcomes, using the clinical global impression of change (CGIC) or CIBIC-plus. There was a statistically significant greater change from baseline (improvement) in CGIC or CIBIC-plus scores following treatment with donepezil compared with placebo.

Studies reporting on the effects of donepezil on functional outcomes in people with Alzheimer's disease (using a variety of measures of activities of daily living) generally found better, or less deterioration in, functional ability than for placebo, although these findings were not

statistically significant in all of the trials. These trials generally measured changes in functional outcomes over treatment periods of 24 or 52 weeks. One UK study (486 people randomised) that measured rates of institutionalisation as a primary outcome for as long as 3 years found some differences between donepezil and placebo at 1 year (9% donepezil versus 14% placebo), although this difference was not statistically significant (p = 0.15) and not sustained at 3 years (42% donepezil versus 44% placebo, respectively, p = 0.4). Results for the other primary outcome - progression of disability - showed little difference at 1 year and no benefit at 3 years (13% donepezil versus 19% placebo at 1 year; 55% versus 53%, respectively, at 3 years); again these differences were not statistically significant.

Quality-of-life estimates for people with Alzheimer's disease associated with the use of donepezil showed varied results, and only three studies reported on this outcome. Over the three studies, the impact of donepezil on this set of health measurements is unclear. One study showed improvement in quality of life, another showed no change and the third showed worsening of quality of life. The effect of the dose of donepezil used was unclear in all three studies.

Behavioural symptoms were measured using the neuropsychiatric inventory (NPI) in four RCTs of donepezil. The results varied but generally a small and statistically significant effect was found for donepezil compared with placebo on improving or limiting further deterioration on the NPI scale in the short term.

Adverse events were recorded more frequently in participants treated with donepezil compared with those receiving placebo, and numbers of adverse events increased with higher doses of donepezil. Similar numbers of participants in the low-dose donepezil groups and the placebo groups withdrew from the studies because of adverse events. However, higher numbers of participants in the higher dose group withdrew because of adverse events.

The manufacturer's submission included a 24-week RCT that evaluated the safety and efficacy of donepezil treatment compared with placebo in people with moderately severe Alzheimer's disease (baseline MMSE score 5-17). People receiving donepezil scored statistically significantly better on global, cognitive, functional and behavioural outcomes. A number of open-label and observational studies were also included in the manufacturer's submission. The effect size of donepezil on cognitive and global outcomes in these studies was similar to those recorded in the RCTs. The use of donepezil also appeared to show a benefit on outcomes such as 'delayed time to nursing home placement' and improvements in social behaviour (assessed by the carer).

The manufacturer's submission and the assessment report included a study that aimed to establish the effect of continuation of treatment with donepezil (5 or 10 mg/day) for 153 people who had not

shown a response ('no apparent clinical benefit') after 24 weeks of open-label donepezil treatment. Double-blind treatment was continued for 12 weeks and there was a statistically significantly greater mean improvement in MMSE score (1.62 versus 0.49) and

NPI scale (-2.40 versus 0.76) following treatment with donepezil (10 mg/day) versus placebo, respectively.

In further analyses using the manufacturer's intention to treat - last observation carried forward (ITT-LOCF) data from five RCTs of at least 24 weeks (aggregate number of people randomised 1425) and applying the responder definition presented in NICE technology appraisal guidance 19, the MRC Biostatistics Unit reported in their review that 39% (95% CI 23% to 56%) of people on donepezil would have been a responder compared with 22% (95% CI 11% to 34%) on placebo. The magnitude of response of these responders on donepezil, expressed as the change from baseline on ADAS-cog versus the change from baseline on ADAScog of all on placebo, was -6.26 (95% C I -7.80 to -4.72). The corresponding group of responders on placebo showed a magnitude of response of - 5.27 (95% -6.90 t0 -3.64), while the non-responders on donepezil showed a magnitude of response of -1.21 (95% C I -2.11 t0o -0.30) and on placebo 0.99 (95% CI 0.04 to 1.94). When using an alternative definition of response (no change or improvement on ADAS-cog) the manufacturer reported a response rate of 63% for those people on donepezil and 41% for those on placebo. The magnitude of change from baseline compared with all placebo reported by the manufacturer was -5.82.

Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITTLOCF data from the trials of at least 24 weeks, reported for donepezil a magnitude of change from baseline on ADAS-cog of -2.03 (99 C I -3.36 to -0.71) for people with mild Alzeimer's disease (MMSE of 21 or more; aggregate number of people randomised 546), of with moderate Alzheimer's disease (MMSE 15-20; aggregate number of people randomised 396) and of -3.63 (99% C I -7.98 to 0.72) for people with moderately severe Alzheimer's disease (MMSE 10-14; aggregate number of people randomised 253) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. When ADAS-cog was used for the definition of severity, the magnitude of change from baseline reported for people with mild cognitive impairment (ADAS-cog 4-28) was -3.24 (99% CI-7.10 to 0.62) and -3.91 99% C I -8.64 to 0.64) for people with moderate cognitive impairment (ADAS-cog 29-61). Comparable proportions of people were mild, moderate and moderately severe at baseline in the donepezil and placebo groups.

Responder analyses for each of the three subgroups stratified according to cognitive impairment (based on MMSE) and using the responder definition of NICE

technology appraisal guidance 19 resulted in 34% of the people using donepezil in the mild cohort, 31% in the moderate cohort and 10% in the moderately severe cohort retrospectively being designated a responder. The magnitude of response (analysis of observed cases) reported for these three subgroups was -5.12 (95% C I -6.82 to -3.43), -10.14 (95% C I -13.55 to -6.73) and - 6.32 (95% C I -13.11 to 0.47) for mild, moderate and moderately severe, respectively.

In summary, evidence from studies using cognitive and global outcome measurement scales suggests that donepezil is beneficial in treating Alzheimer's disease. The effect of donepezil on quality of life and behavioural symptoms in Alzheimer's disease is less clear. Short-term benefits are seen on scales that measure functional outcomes but these were not always statistically significant and do not seem to be sustained in the long term. Retrospective responder analyses using NICE technology appraisal guidance 19 and subgroup analyses based on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the Institute and suggest some differential advantage for more severely cognitively impaired subgroups.

Galantamine

Seven published RCTs, one unpublished RCT (aggregate number of people randomised 4300) and one systematic review met the inclusion criteria set by the Assessment Group for the systematic review of clinical effectiveness of galantamine. (NICE technology appraisal guidance 19 was based on one systematic review, three RCTs and three unpublished studies from the manufacturer.) All comparisons were versus placebo, with trials reporting dosages of 8-36 mg/day and durations of 3-6 months.

All six published RCTs and the unpublished RCT assessed the clinical effectiveness of galantamine compared with placebo using the ADAS-cog scale. In all studies, galantamine conferred a statistically significant benefit to participants when compared with placebo. The benefit varied depending on the dose of galantamine.

Four RCTs that assessed treatment with galantamine at a dose of 24 mg were combined by the Assessment Group in a metaanalysis. The fixed-effects model showed a weighted mean difference of -3.28 (95% C I -3.89 to -2.67) statistically significant improvement following treatment with galantamine versus placebo.

Six RCTs assessed the effect of galantamine compared with placebo on the CIBIC-plus scale. They showed that, in individual studies, more participants on galantamine improved than on placebo (0-6.5 percentage points more), whereas more participants on placebo than on galantamine deteriorated (4-18 percentage points more). When the studies were pooled by the Assessment Group (aggregate number of people randomized

2294) no statistical significance was noted between treatment groups and placebo.

The results of five RCTs showed that participants receiving galantamine at dosages of 16-32 mg/day had statistically significantly less deterioration than those receiving placebo, as assessed using scales that measure activities of daily living.

In one RCT, higher dosages of galantamine (16 mg/day or over) were associated with a statistically significant slowing in the deterioration of participants' behavioural condition compared with placebo, as assessed using the NPI scale. In two trials, the slowing of deterioration was not statistically significantly different between galantamine and placebo groups.

Across RCTs, between 2 and 27 percentage points more participants on galantamine experienced an adverse event compared with those on placebo. Between 6% and 44% of participants receiving galantamine withdrew from the studies because of adverse events, and this number increased with higher doses of galantamine.

A number of open-label studies included in the manufacturer's submission suggested a slightly reduced long-term decline in the cognition of people treated with galantamine.

In 6-week follow-on studies of two RCTs (aggregate number of people randomised 570), included in the manufacturer's submission, people who were switched from galantamine to placebo experienced a greater decline in measures of cognition than those who remained on galantamine. This difference reached statistical significance only in the study where the decision to stop treatment was not randomised (number of participants 500).

In further analyses using the manufacturer's ITT-LOCF data fromfive RCTs of at least 24 weeks (aggregate number of people randomised 2682) and applying the responder definition presented in NICE technology appraisal guidance 19, the MRC Biostatistics Unit reported that 41% (95% CI 31% to 51%) of people on galantamine would have been a responder compared with 27% (95% CI 20% to 35%) on placebo. The magnitude of response of these responders on galantamine, expressed as the change from baseline on ADAS-cog versus the change from baseline on ADAScog of all on placebo, was -6.40 (95% C I - 7.15 to -5.65). The corresponding group of responders on placebo showed a magnitude of response of -5.28 (95% C I - 5.93 to -4.63), while the non-responders on galantamine showed a magnitude of response of -0.44 (95% C I - 1.83 to 094) and placebo, 2.05 (95% CI 1.35 to 2.74). When using alternative definitions of response (no change or improvement on ADAS-cog and on global measures; no change, no improvement, or deterioration no more than 4 points on the ADAS-cog) a response rate of 57% and 87%, respectively, for those people on galantamine and 20% and 17%, respectively, for those on placebo was reported. The magnitude of change from baseline compared with all those on

placebo by the manufacturer was -6.26 (95% C I - 6.87 to -5.66) and -4.33 (95% C I - 4.89 to -3.77) for the first and second alternative definitions of responders respectively.

Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITTLOCF data from the trials of at least 24 weeks, reported for galantamine a magnitude of change from baseline on ADAS-cog of -2.40 (99% C I - 3.33 to -1.47) for people with mild Alzheimer's disease (MMSE of 21 or more; aggregate number of people randomised 938), of -4.1 (99% C I - 5.03 to - 3.17) for people with moderate Alzheimer's disease (MMSE 10-20; aggregate number of people randomised 1215; includes the moderately severe) and of -6.1 (99% C I - 7.93 to -4.27) for people with moderate Alzheimer's disease (MMSE 10-14; aggregate number of people randomised 340) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. Comparable proportions of people were mild, moderate and moderately severe at baseline in the galantamine and placebo groups.

In summary, evidence from studies using cognitive and functional outcome measurement scales suggests that galantamine is beneficial in Alzheimer's disease. Improved benefits in cognition tended to be related to higher doses. Improvements in measurements of function were also demonstrated at higher doses. On global outcome measures, individual studies showed that higher proportions of participants improved with galantamine, but this was not reflected in the meta-analysis. In some studies, considerably more participants than those on placebo withdrew because of adverse events. Retrospective responder analyses using the NICE technology appraisal guidance 19 and subgroup analyses on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the Institute and suggest some differential advantage for more severely cognitively impaired subgroups.

Rivastigmine

Four published RCTs (aggregate number of people randomized 1940), two unpublished RCTs (aggregate number of people randomised 1380) and three systematic reviews met the inclusion criteria set by the Assessment Group for the systematic review of the clinical effectiveness of rivastigmine. (NICE technology appraisal guidance 19 was based on three systematic reviews, five RCTs and two unpublished studies from the manufacturer.) All published comparisons were versus placebo, and trials reported dosages of between 1mg/day and 12 mg/day with durations of 26 weeks or less.

Four RCTs reviewed by the Assessment Group showed that rivastigmine within its licensed maintenance dose (6-12 mg/day, mean dosage approximately 10 mg/day) conferred a statistically significant

benefit to participants when compared with placebo, as measured using the ADAS-cog scale. One RCT found no significant differences. No statistically significant effects were seen in the low-dose treatment groups in these studies. A meta-analysis, using a fixed-effects model, of two RCTs both with a duration of 26 weeks, was associated with a weighted mean difference of -3.08 (95% C I - 3.78 to - 2.38) for rivastigmine 6-12 mg/day when compared with placebo. Statistically significant heterogeneity was found when pooling the two studies for meta-analysis, which led the Assessment Group to conclude that the statistically significant treatment effect seen for rivastigmine in the fixed-effects model should be treated with caution.

Four RCTs showed statistically significantly higher MMSE scores in the groups treated with rivastigmine within its licensed maintenance dose regime (6-12 mg/day) compared with placebo.

Four RCTs assessed the effect of rivastigmine compared with placebo on the CIBIC-plus scale. In the two published RCTs, statistically significant mean improvements were recorded following treatment with rivastigmine in the high-dose - licensed - regimen only, compared with placebo. The percentage of improvers or responders on the CIBIC-plus scale was also calculated in these two published studies. Clinical improvement was defined as a score of 1, 2 or 3 on the CIBIC-plus scale. For the two trials, 16-20% of participants treated with placebo were judged to have responded versus 30-57% of those treated with rivastigmine. **A statistically significant difference was found for the high-dose regimen only.**

Generally, participants treated with rivastigmine 6-12 mg/day demonstrated statistically significantly better functional outcomes than those who received placebo. One of the four studies using the PDS showed that there was no statistically significant difference for either the low- or high-dose regimen when compared with placebo.

The Nurses Observation Scale for Geriatric Participants (NOSGER) was used in two rivastigmine RCTs. Statistically significant benefits were seen on the subscale that measures impact on memory but no statistically significant benefits were demonstrated on measures of mood and behaviour in the groups treated with rivastigmine compared with the placebo groups.

The percentage of participants reporting adverse events, namely nausea and vomiting, resulting from treatment with rivastigmine was particularly high in those treated at a higher dose. The number of participants who withdrew because of adverse events was reported in all studies. **Estimates of the percentage of participants who withdrew varied considerably between studies; 7-28.6% for participants receiving treatment and 4-7.2% for participants receiving placebo.**

The manufacturer's submission included a number of open-label and observational studies. The duration of

these trials was between 26 weeks and 5 years. The effect size of rivastigmine on cognitive and behavioural outcomes was similar to that seen in the RCTs. Other open-label and observational studies, and experience with rivastigmine in a 'real-world' setting, appeared to show some benefit in outcomes such as 'delayed time to nursing home placement' and carer burden.

The manufacturer's submission included a prospective, open-label study that evaluated the efficacy, safety and tolerability of rivastigmine in people who had failed to benefit from treatment with donepezil (because of a lack of efficacy [80%] or tolerability [11%], or both [9%]). After 26 weeks, 56% of the 382 participants had responded to rivastigmine (defined as improvement or stabilization of symptoms using the CGIC).

In further analyses using the manufacturer's ITT-LOCF data from four RCTs of at least 24 weeks (aggregate number of people randomised 1670) and applying the responder definition presented in NICE technology appraisal guidance 19, the MRC Biostatistics Unit reported that 37% (95% CI 30% to 44%) of people on rivastigmine would have been a responder compared with 24% (95% CI 18% to 30%) on placebo. The magnitude of response of these responders on rivastigmine, expressed as the change from baseline on ADAS-cog versus the change from baseline on ADAScog of all on placebo, was -6.83 (95% C I - 8.25 to -5.40) corresponding group of responders on placebo showed a magnitude of response of -5.57 (95% C I - 6.49 to - 4.65) while the non-responders on rivastigmine showed a magnitude of response of -4.0 (95% C I - 1.94 to - 1.13) and on placebo, 1.81 (95% C I - 1.07 to 2.55).

Further analyses by the MRC Biostatistics Unit on subgroups by severity of cognitive impairment, using the manufacturer's ITTLOCF data from the trials of at least 24 weeks, reported for rivastigmine a magnitude of change from baseline on ADAS-cog of -1.20 (99% C I -2.10 to - 0.30) for people with mild Alzheimer's disease (MMSE of 21 or more; aggregate number of people randomised 734), -3.7 (99% C I - 5.13 to - 2.27) for people with moderate Alzheimer's disease (MMSE 10-20; aggregate number of people randomised 557) and of -5 (99% C I - 7.40 to - 2.6) for people with moderately severe Alzheimer's disease (MMSE 10-14; aggregate number of people randomised 232) versus the change from baseline on ADAS-cog of those on placebo with corresponding cognitive impairment. When ADAS-cog was used for the definition of severity, the magnitude of change from baseline reported for people within a number of strata for cognitive impairment was -0.4 (99% C I - 1.37 to 0.57) (ADAS-cog was 0-12), -1.7 (99% C I - 2.85 to 0.55) (ADAS-cog was 13-20), -2.6 (99% C I - 4.22 to -0.95) (ADAS -cog 21-28), -4.9 (99% C I - 7.28 to 2.52) (ADAS-cog 29-36), -5.9 (99% C I - 8.86 to -2.94) (ADAS -cog 37- 44) and -3.9 (99% C I - 7.38 to -0.42) (ADAS -cog 45 plus).

Comparable proportions of people were mild, moderate and moderately severe at baseline in the rivastigmine and placebo groups.

In summary, a range of fixed and flexible dosing regimens of rivastigmine was investigated across studies, which makes interpretation of the evidence more difficult. **Evidence from studies using cognitive and global outcome measurement scales suggests that rivastigmine is beneficial in Alzheimer's disease at higher doses (6-12 mg). Evidence for an effect on functional outcomes was less conclusive and no statistically significant benefit of rivastigmine on measures of behaviour and mood was reported.** Higher doses of rivastigmine were associated with considerable adverse effects and these effects caused withdrawals from studies. The results of the meta-analysis on cognition should be treated with caution because of statistically significant heterogeneity between individual trial results. Retrospective responder analyses using the NICE technology appraisal guidance 19 and subgroup analyses on severity of cognitive impairment were reported in extra analyses performed by the manufacturer on the request of the Institute and suggest some differential advantage for more severely cognitively impaired subgroups.

Head-to-head comparisons

Three RCTs met the inclusion criteria for the systematic review by the Assessment Group. Two compared donepezil with rivastigmine (aggregate number of people randomised 139) and one compared donepezil with galantamine (people randomised 120). The Assessment Group regarded the quality of the studies as generally poor. The manufacturer's submission for galantamine included a study comparing galantamine with donepezil, but this study was excluded by the Assessment Group because the study population was not described as patients with mild to moderately severe Alzheimer's disease by any definition and the MMSE scores fell outside the range of 10-26.

For the two RCTs that compared donepezil with rivastigmine, the difference in change from baseline, in measures of cognition or function, was small and not statistically significant. The number of adverse events tended to be higher in participants in the rivastigmine groups.

In the RCT that compared galantamine and donepezil, which was sponsored by the manufacturer of donepezil, participants on galantamine showed improvement on measures of cognition and function but the improvement in participants on donepezil was greater. However, in the comparison that was funded by the manufacturer of galantamine this effect seemed to be reversed and it appeared that galantamine exerted a more sustained effect than donepezil.

Moderately severe to severe Alzheimer's disease

Memantine

Two RCTs (aggregate number of people randomised 650) met the inclusion criteria set by the Assessment Group for the systematic review of the clinical effectiveness of memantine. (NICE technology appraisal guidance 19 did not consider memantine.) Both studies reported on participants with moderately severe to severe Alzheimer's disease, as measured by the MMSE, and treated with memantine 20 mg/day. One study compared memantine alone with placebo over a period of 28 weeks, and the other compared memantine plus donepezil with donepezil alone over 24 weeks. In the second study, participants were included on the basis that they had already been receiving donepezil for more than 6 months before entering the trial, and they had been at a stable dosage (5-10 mg/day) for at least 3 months. These participants were maintained on stable donepezil for the duration of the study. The quality of reporting and methods of the two trials was generally good.

In the RCT of memantine versus placebo, less deterioration of cognitive function was recorded following treatment with memantine compared with placebo, as measured by the Severe Impairment Battery (SIB) (mean change from baseline at end point LOCF analysis for memantine and placebo was !C#@&4,/&!%@#%J& respectively, p < 0.001), the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) (mean changes from baseline at end point LOCF analysis: !:#%&4,/&!$#"J&G = 0.02) and the Functional Assessment Staging scale (FAST) (mean changes from baseline at end point LOCF analysis: 0.2 and 0.6, p = 0.02). No statistically significant differences were recorded using CIBIC, MMSE and NPI when changes from baseline to end point were analysed using LOCF.

In the RCT in which participants received memantine and donepezil in combination, less deterioration in cognitive function was recorded in participants receiving combined treatment compared with donepezil alone.

The manufacturer of memantine also provided summary results from a number of pooled analyses. In one analysis, data for all three RCTs showed less deterioration in cognitive function for patients receiving memantine.

Similar pooled analyses were undertaken for patients who were subclassified as 'behaviourally disturbed', defined as a score > 0 on any of the NPI sub-item scores for three specific items: agitation/aggression; delusions and hallucinations. Patients had to score > 0 on any of the three items at baseline to qualify. For the analyses containing all three RCTs, less deterioration in cognitive function for patients receiving memantine.

Memantine's manufacturer also supplied a 'responder analysis', which itself was restricted to further consideration of

only the 'behaviourally disturbed' subgroup, where a responder was defined as an improvement or no worsening of CIBIC-plus scores at 6 months using data from all three RCTs.

A fourth RCT was also referenced by the manufacturer of memantine. This compared memantine with placebo, and a proportion (n = 79, 48%) of participants had moderately severe to severe Alzheimer's disease. Although different outcome instruments were used in this trial, the results were broadly in line with findings from the other three RCTs.

The frequency of overall adverse effects was similar for both the memantine and control groups in all RCTs.

Mild to moderately severe Alzheimer's disease

Donepezil

Eleven economic evaluations for donepezil were found. Three related to the UK. One of the 11 studies was of treatment for people with mild Alzheimer's disease; the other 10 were of treatment of people with mild to moderate Alzheimer's disease. **In 5 (of 11) studies donepezil was found to be cost saving.**

In a UK study associated with the manufacturer, the cost of gaining an additional year in a non-severe state was measured. The estimated cost ranged from £1200 to £7000, depending on dose and starting point (mild or moderate Alzheimer's disease).

In a recent economic analysis alongside a clinical trial, the authors concluded that the drug was not cost effective, mainly because there were no apparent benefits of the drug in delaying progression of disability or entry to institutional - that is, residential - nursing or NHS continuing care. The manufacturer's model used a transition state modeling approach in which disease progression was modeled across different levels of Alzheimer's disease severity to estimate the incremental cost effectiveness of donepezil compared with placebo. Transition probabilities were derived from trial data, with the drug efficacy rate persisting for the initial 12-month cycle of the model. For the remainder of the 5-year model, the transition probabilities for the treated group were proportional to those of the placebo group. Cost estimates were taken from the literature in which they were calculated for different severity levels of Alzheimer's disease by MMSE score. The submission reported that, for the base case of people with an MMSE score of 13-26, treatment with donepezil 10 mg/day was associated with an estimated cost of £1200 to keep a person outside of the severe Alzheimer's disease state for a year. Inclusion of people with an MMSE score of 10-12 increased this to £4000 per year outside of the severe state. The manufacturer's model allowed for estimates of CQG to be calculated but did not report utility estimates or results in terms of CQG either in the base case analysis or in the sensitivity analyses.

Galantamine

Five economic evaluations for

galantamine were found. One related to the UK. All published economic evaluations on galantamine used the same method for modelling disease progression - the Assessment of Health Economics in Alzheimer's Disease (AHEAD) model.

All studies estimated that galantamine was cost saving for moderate Alzheimer's disease. For mild Alzheimer's disease, four studies showed galantamine to be cost saving, and the fifth, a UK study, was associated with a CQG for galantamine of £9000.

Rivastigmine

Five economic evaluations for rivastigmine were found, one of them in abstract form only. Two related to the UK. All were of people with mild to moderate Alzheimer's disease. Four, including all three industry-associated studies, were found to be cost saving.

In a study supported by the manufacturer, for people using the drug compared with not using it, estimated cost savings (but not including the cost of rivastigmine) after 2 years were £1300 for people with mild Alzheimer's disease and £800 for those with moderate Alzheimer's disease.

An augmented base case for the Assessment Group model was formulated that included alternative cost estimates and all extra health benefits mentioned in section 4.2.6.1, as well as the increase in utility for pre-full-time care. When the cost component of the augmented base case was compared with the cost estimates of the Assessment Group base case there was no substantial difference between the two. Estimates of CQG presented here for the augmented base case use the assumption that 70% of costs of institutional care are being met by the NHS/PSS (Personal Social Service). The complete augmented base case was associated with an estimated CQG of £54,000, £46,000 and £39,000 for donepezil, galantamine and rivastigmine, respectively (including a correction for the coefficient 'age at onset' used in the risk-equation for 'fulltime care', a price adjustment for donepezil and an adjustment in the results of the meta-analysis of effectiveness for galantamine). This equates to a respective average QALY gain of 0.058, 0.062 and 0.060.

There is very little quantitative evidence related to carer utilities and the evidence that exists suggests that utility scores for the carers were insensitive to people's Alzheimer's disease stage and setting. When an assumed 0.01 of carer utility was included in a sensitivity analysis on the augmented base case, either as a direct benefit or as part of the total increment between the two health states of the Assessment Group's model, this was associated with marginally lower estimates of the CQG: £50,000, £44,000 and £36,000 for donepezil, galantamine and rivastigmine, respectively.

In the one-way sensitivity analysis on mortality on the augmented base case, a change in annual mortality rate only marginally affected CQG estimates. A

range of estimates of the prevalence of neuropsychiatric or behavioural symptoms was used to assess the impact on the CQG estimates. On its own, changing the estimates of effects of therapy on neuropsychiatric or behavioural symptoms.

Decision Support Unit report

The Decision Support Unit (DSU) evaluated the issues identified by consultees and considered that four issues were related to the economic model's technical reliability and required amending in the model. These were:

- implementing the hazard for transition to full-time care
- separating the characteristics of uncertainty and variability in the model
- implementing discounting
- implementing the augmented benefit

Each of these issues was corrected in the model. In addition their cumulative impact was examined.

Hazard for transition to full-time care

The DSU considered that an instantaneous hazard rate for the transition to full-time care had been treated as a probability. For mild disease, correcting this changed the ICER from £63,749 to £63,164 per QALY gained (donepezil) and from £59,108 to £59,500 per QALY gained (galantamine). For moderate disease correcting this changed the ICER from £31,550 to £31,556 per QALY gained (donepezil).

Sampling of patient characteristics

The probabilistic sensitivity analysis included both variables that were intrinsically unknown for any patient and variables that were known but subject to variation. The DSU set all patient characteristics to their mean value, and created subgroups by ADAS-cog score and age at starting treatment. For mild disease treated with donepezil, the base-case ICER was £63,749 per QALY gained. Three age subgroups were created (64, 70 and 74 years) and the ICERs for each of these subgroups were £84,659, £73,804 and £55,779 per QALY gained, respectively. For mild disease treated with galantamine, the base-case ICER was £59,108 per QALY gained.

Memantine (Synaptol)

Five economic evaluations were found for memantine in people with moderately severe to severe Alzheimer's disease; three were in abstract or poster form, and the other two were in press. One of the five evaluations related to the UK. **All suggested that memantine was more effective and less costly compared with no treatment.**

The manufacturer submitted a second economic evaluation, which compared the use of memantine in combination with donepezil against donepezil monotherapy. Most of the methods, results and accompanying discussion were marked commercial-in-confidence.

The model suggests that memantine plus donepezil is more effective and less costly compared with donepezil alone.

Acetylcholinesterase inhibitors: donepezil, galantamine and rivastigmine

The Committee heard that since NICE technology appraisal guidance 19 was issued in 2001, the evidence base relating to the use of the AChE inhibitors has matured and continues to demonstrate that, compared with placebo, the AChE inhibitors provide small but consistent gains in scores on cognitive and global scales for people with mild to moderately severe Alzheimer's disease. The Committee noted, however, that the evidence available on the long-term effectiveness of the AChE inhibitors on outcomes, such as quality of life and delayed time to nursing home placement, was limited and largely inconclusive.

The Committee considered the acquisition costs, the range of clinical effectiveness estimates, the different side-effect profiles and the results from direct comparisons between the AChE inhibitors. It concluded that it would not be appropriate to differentiate between the drugs on the basis of their effectiveness, but in the light of its responsibility to take account of the effective use of NHS resources, the Committee considered that it was appropriate to indicate that prescribers should take into account the acquisition costs of each AChE inhibitor when considering which of the AChE inhibitors to prescribe as well as other factors pertinent to the choice of an individual AChE inhibitor such as adverse event profile, expectations around concordance, medical co-morbidity, possibility of drug interactions, and dosing profiles.

Having considered all the evidence and the comments of consultees, the Committee concluded that the resulting estimates of cost effectiveness could be considered sufficiently acceptable to suggest that the prescribing of AChE inhibitors for people with Alzheimer's disease and moderate cognitive impairment (MMSE scores between 10 and 20) is cost effective.

Handling of variables in the economic model

The Committee accepted comments from consultees that note that the model calculates the transition to full-time care as a hazard but subsequently applies this as if it was a probability. The Committee noted the DSU's correction of this and accepted that this resulted in minimal changes to the ICERs for the population of people with mild Alzheimer's disease.

The Committee accepted the methodological comment from consultees that the model conflates heterogeneity in the patient population with uncertainty by including in the probabilistic sensitivity analysis values which are intrinsically known for each patient, but subject to variation (for example, age). The Committee noted both the consultees' and the DSU's explorations of this issue in subdividing the patient population by age and cognition and concluded that the

consultee and DSU age stratification (but see 4.3.26) of people with mild Alzheimer's disease did not result in the generation of ICERs within the normally accepted range, without making further changes to parameter estimates. The Committee further heard from the DSU that other exploratory analyses of the model using alternative approaches to separating variability from parameter uncertainty (for example, using a weighted average of the costs and QALYs for the different age groups or separating out the sampling of patient characteristics from the sampling of parameter uncertainty) had led to similar estimates of the ICER as those in the augmented base case. Overall, the Committee was not persuaded that the sampling of patient characteristics had led to an overestimation of the ICERs. In addition, the Committee considered that there was no evidence of differential effectiveness of the AChE.

Memantine

For moderately severe to severe Alzheimer's disease, the Committee considered evidence from three trials of memantine (including evidence from one trial that was submitted after the assessment report was completed). The results from pooled analyses of these data were also considered, as were the results from a fourth RCT in which a subgroup comprised patients with moderately severe to severe Alzheimer's disease. The Committee also took into account the submitted economic evidence.

The Committee noted that for the two memantine monotherapy trials (in which the majority of patients had Alzheimer's disease) the results were inconsistent, with the late submission of a trial having statistically non-significant results on all scales. Although data from the pooled analysis of these two memantine monotherapy RCTs and a pooled analysis of the three RCTs versus placebo showed statistically significant advantages (at the 95% level) on a number of outcomes, the absolute magnitude of difference on all outcomes was modest.

Overall, considering the published and unpublished evidence, the Committee concluded that the evidence to determine the clinical effectiveness of memantine in either the whole population of moderately severe to severe Alzheimer's disease or the subgroup of people with behavioural symptoms was currently insufficient. Nevertheless, irrespective of this conclusion, the Committee sought to consider the cost-effectiveness calculations that might be derived from these limited data.

However, in this scenario an average of 22% and 45% of patients who received memantine and no treatment, respectively, progressed from moderately severe to severe disease at the end of one (Markov) cycle.

The Committee therefore concluded that on the basis of current evidence on clinical effectiveness memantine could not reasonably be considered a cost-effective therapy for moderately severe to severe Alzheimer's disease.

MANAGEMENT OF ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

National Guidelines clearing House

Guidelines Being Compared:

1. **American College of Physicians/American Academy of Family Physicians (ACP/AAFP).**
2. **American Psychiatric Association (APA).**
3. **National Institute for Health and Clinical Excellence (NICE).**
4. **Singapore Ministry of Health (SMOH). Dementia. Singapore: Singapore**

Areas of Agreement and Difference

A direct comparison of recommendations presented in the above guidelines for the management of Alzheimer's disease (AD) and related dementias is provided below.

Areas of Agreement

Pharmacological Management of Dementia

Three groups-APA, NICE, and SMOH-provide explicit recommendations regarding appropriate medications for a certain type and/or severity of dementia. **The guideline developers agree that the three cholinesterase inhibitors donepezil, rivastigmine and galantamine are the primary medications used in the management of AD, and should be considered for the management of patients with mild to moderate disease.**

With regard to the use of cholinesterase inhibitors for types of dementia other than AD, APA and SMOH agree that they can be considered for patients with dementia with Lewy bodies and dementia associated with Parkinson's disease.

There is consensus that the NMDA antagonist **memantine** can be considered for the management of moderate and severe AD (NICE specifies that use in people with moderate disease should be reserved for those who are intolerant of or have a contraindication to cholinesterase inhibitors).

"The evidence is insufficient to compare the effectiveness of different pharmacologic agents for the treatment of dementia."

NICE specifies that pharmacological treatment be initiated only by specialists in the care of patients with dementia; that patients who continue treatment should be reviewed regularly using cognitive, global, functional, and behavioral assessment; and that carers' views on the patient's condition should be sought at baseline and at follow-up. NICE also cites circumstances in which it is inappropriate to rely solely on the patient's cognition scores when assessing the severity of AD and the need for treatment. In such cases, they recommend healthcare professionals use another appropriate method of

assessment.

Other Pharmacologic Agents

APA and SMOH agree that other classes of medication may be appropriate for the treatment of dementia-related symptoms including depression, psychosis, and anxiety. **The groups agree that antidepressants may be used for the treatment of comorbid depression, provided their use has been evaluated carefully for each patient, and that the antidepressant trazodone may be appropriate for patients with dementia-associated agitation. The guidelines agree that, if necessary, antipsychotics may be recommended with caution, given their side effect profile, to treat the neuropsychiatric symptoms of dementia.**

APA and SMOH further agree that the available effectiveness and safety data for other agents, including vitamin E, Ginkgo biloba, hydroxychloroquine, prednisolone, statin medications, selegiline, estrogen and NSAIDs, do not support recommendations for the treatment of core or associated symptoms in people with AD at this time. There is also agreement that anticonvulsants (e.g., sodium valproate) and mood stabilizers (e.g., lithium) are not indicated for routine use in the management of AD and its associated symptoms.

Patient and Caregiver Education

APA emphasizes the importance of communicating with the patient (as appropriate) and caregivers regarding the patient's status, treatment plan, and approaches to behavioral management.

Areas of Difference

Cholinesterase Inhibitors for the Management of Severe AD

While NICE recommends cholinesterase inhibitors as options for managing AD of mild to moderate severity only, SMOH states that they can be considered for the management of moderate to severe AD. APA similarly states that cholinesterase inhibitors may be helpful for patients with severe AD.

Memantine for the Management of Mild AD

NICE recommends memantine as an option only for managing moderate AD (in people who are intolerant of or have a contraindication to cholinesterase inhibitors) and severe AD. SMOH, in contrast, deems it an option for the management of mild to moderate AD if cholinesterase inhibitor therapy is contraindicated, not tolerated, or if there is disease progression despite an adequate trial of a cholinesterase inhibitor. APA notes that there is some evidence of memantine's benefit in mild AD, but the developer does not make an explicit recommendation for its use for this level of severity.

Cholinesterase Inhibitors for the Management of Vascular Dementia

The cholinesterase inhibitors have been shown to be of clinical benefit and may be considered for use in the management of

mild to moderate vascular dementia.

Memantine for the Management of Vascular Dementia

The NMDA antagonists have been shown to be of clinical benefit and may be considered for use in the management of mild to moderate vascular dementia. ACP/AAFP notes that patients with mild vascular dementia have shown mild benefit from memantine. They add, however, that memantine use in mild AD has not been well studied.

General Treatment Principles and Alternatives (APA)

Psychiatric Management

The treatment of patients with dementia should be based on a thorough psychiatric, neurological, and general medical evaluation of the nature and cause of the cognitive deficits and associated noncognitive symptoms, in the context of a solid alliance with the patient and family. It is particularly critical to identify and treat general medical conditions, most notably delirium, that may be responsible for or contribute to the dementia or associated neuropsychiatric symptoms.

Ongoing assessment includes periodic monitoring of the development and evolution of cognitive and noncognitive psychiatric symptoms and their response to intervention. In order to offer prompt treatment, enhance safety, and provide timely advice to the patient and family, it is generally necessary to see patients in routine follow-up at least every 3 to 6 months. More frequent visits (e.g., up to once or twice a week) or even psychiatric hospitalization may be required for patients with acute, complex, or potentially dangerous symptoms or for the administration of specific therapies. Recommended assessments include evaluation of suicidality, dangerousness to self and others, and the potential for aggression, as well as evaluation of living conditions, safety of the environment, adequacy of supervision, and evidence of neglect or abuse.

All patients and families should be informed that even mild dementia increases the risk of vehicular accidents. Mildly impaired patients should be advised to limit their driving to safer situations or to stop driving, and moderately impaired patients should be instructed not to drive.

No recommendations offered.

- **SMOH (2007)**
- **APA (2007)**

Specific Psychotherapies and Other Psychosocial Treatments

In addition to the general psychosocial interventions subsumed under psychiatric management, a number of specific interventions are appropriate for some patients. Few of these treatments have been subjected to double-blind randomized evaluation, but some research, along with clinical practice, supports their effectiveness. Behavior-oriented treatments are used to identify the antecedents and

consequences of problem behaviors and attempt to reduce the frequency of behaviors by directing changes in the environment that alter these antecedents and consequences. Behavioral approaches have not been subjected to large randomized clinical trials but are supported by small trials and case studies and are in widespread clinical use. Stimulation-oriented treatments, such as recreational activity, art therapy, music therapy, and pet therapy, along with other formal and informal means of maximizing pleasurable activities for patients, have modest support from clinical trials for improving behavior, mood, and, to a lesser extent, function, and common sense supports their use as part of the humane care of patients. Among the emotion-oriented treatments, supportive psychotherapy can be employed to address issues of loss in the early stages of dementia. Reminiscence therapy has some modest research support for improvement of mood and behavior; validation therapy and sensory integration have less research support; none of these modalities has been subjected to rigorous testing. Cognition-oriented treatments, such as reality orientation, cognitive retraining, and skills training focused on specific cognitive deficits, are unlikely to have a persistent benefit and have been associated with frustration in some patients.

Treatment of Psychosis and Agitation

Psychosis, aggression, and agitation are common in patients with dementia and may respond to similar therapies. When deciding if treatment is indicated, it is critical to consider the safety of the patient and those around him or her. A careful evaluation for general medical, psychiatric, environmental, or psychosocial problems that may underlie the disturbance should be undertaken. If possible and safe, such underlying causes should be treated first. If this does not resolve the symptoms, and if they do not cause significant danger or distress to the patient or others, such symptoms are best treated with environmental measures, including reassurance and redirection. For agitation, some of the behavioral measures discussed above may also be helpful. If these measures are unsuccessful or the behaviors are particularly dangerous or distressing, then the symptoms may be treated judiciously with one of the agents discussed in the following paragraphs. The use of such agents should be reevaluated and their benefit documented on an ongoing basis.

Treatment of Depression

Depression is common in patients with dementia. Patients with depression should be evaluated for suicide risk. Depressed mood may respond to improvements in the patient's living situation or to stimulation-oriented treatments.

Treatment of Sleep Disturbances

Sleep disturbances are common in patients with dementia. Interventions

include maintaining daytime activities and giving careful attention to sleep hygiene. Pharmacological intervention could be considered when other approaches have failed.

Special Issues for Long-Term Care

Many patients eventually require long-term-care placement; approximately two-thirds of nursing home patients have dementia. Care should be organized to meet the needs of patients, including those with behavioral problems. Employing staff with knowledge and experience concerning dementia and the management of difficult behavior is important.

Appropriate use of antipsychotic medications can relieve symptoms and reduce distress and can increase safety for patients, other residents, and staff. However, their use may be associated with worsening cognitive impairment, oversedation, falls, tardive dyskinesia, and neuroleptic malignant syndrome, as well as with hyperlipidemia, weight gain, diabetes mellitus, cerebrovascular accidents, and death. Thus, good clinical practice requires careful consideration and documentation of the indications and available alternatives, both initially and on a regular ongoing basis. A dose decrease or discontinuation should be considered periodically for all patients who receive antipsychotic medications.

Physical restraints are rarely indicated and should be used only for patients who pose an imminent risk of physical harm to themselves or others. Reasons for the use of physical restraints should be carefully documented. The need for restraints can be decreased by environmental changes that decrease the risk of falls or wandering and by careful assessment and treatment of possible causes of agitation.

Pharmacologic Interventions

- **ACP/AAFP (2008)**

☆ **Recommendation 1:** Clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or memantine on individualized assessment.

The decision to initiate therapy should be based on evaluation of benefits and risks associated with an individual patient. In particular, in more advanced dementia, family or other decision makers may not view stabilization or slowing of decline as a desirable goal if quality of life is judged to be poor. All of the drugs have known adverse events, and the decision to manage patients with dementia should balance harms against modest or even no benefit. Although the evidence shows statistically significant benefits of treatment with some cholinesterase inhibitors and memantine for all kinds of dementia, these benefits, on average, are not clinically significant for cognition and are modest for global assessments. However, limited evidence suggests, but does not demonstrate conclusively, that a subgroup of patients achieves clinically important improvements. These findings should be interpreted cautiously because many trials

did not report the proportion of patients who achieved clinically important improvements, and for trials that did, these outcomes were often not the primary end point of the trial. In addition, many trials that did report the proportion of patients who achieved clinically important improvements did not report the statistical significance of these findings. Currently, we have no way to predict which patients might have a clinically important response. **Therefore, the evidence does not support prescribing these medications for every patient with dementia.**

Evidence is insufficient to determine the optimal duration of therapy. A beneficial effect, if any, would generally be observed within 3 months on the basis of duration of trials. This effect could be an improvement or stabilization. In addition, no evidence demonstrates when it is appropriate to stop the treatment if the patient becomes unresponsive or shows decline in various domains of dementia. However, if slowing decline is no longer a goal, treatment with memantine or a cholinesterase inhibitor is no longer appropriate.

☆ **Recommendation 2:** Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. **Because few trials compare one drug with another, evidence about effectiveness is insufficient to support the choice of specific drugs for the treatment of dementia.**

Therefore, tolerability, adverse effect profile, ease of use, and cost of medication are reasonable criteria to help select a treatment.

Cholinesterase inhibitors discussed in this guideline are approved for treatment of mild to moderate dementia, and memantine is approved by the FDA for the treatment of moderate to severe AD. Patients with mild vascular dementia have shown mild benefit from memantine. **Major contraindications of cholinesterase inhibitors and memantine include, but are not limited to, uncontrolled asthma, angle-closure glaucoma, the sick sinus syndrome, and left bundle-branch block.**

- **APA (2007)**

Special Concerns Regarding Somatic Treatments for Elderly Patients and Patients with Dementia

Medications are effective in the management of some symptoms associated with dementia, but they must be used with caution in this patient population. Because age may alter the absorption, distribution, metabolism, and elimination of many medications, elderly individuals may be more sensitive to their effects. General medical conditions and use of more than one medication may further affect the pharmacokinetics of many medications. In addition, patients with dementia may be more likely to experience certain medication adverse effects, including anticholinergic effects, orthostasis, sedation, and parkinsonism.

Finally, symptoms of dementia may alter medication adherence in ways that are unsafe. Consequently, when using pharmacotherapy in patients with dementia, low starting doses, small increases in dose, and long intervals between dose increments may be needed, in addition to ensuring that a system is in place that can enhance proper medication adherence.

Treatment of Cognitive Symptoms

Three cholinesterase inhibitors-donepezil, rivastigmine, and galantamine-are approved by the U.S. FDA for treatment of mild to moderate AD, and donepezil has been approved by the FDA for severe AD.

Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease. Only rivastigmine has been approved by the FDA for this indication, but there is no reason to believe the benefit is specific to this cholinesterase inhibitor.

Cholinesterase inhibitors can be considered for patients with dementia with Lewy bodies.

The constructs of mild cognitive impairment and vascular dementia are evolving and have ambiguous boundaries with AD. The efficacy and safety of cholinesterase inhibitors for patients with these disorders are uncertain; therefore, no specific recommendation can be made at this time, although individual patients may benefit from these agents.

Treatment of Psychosis and Agitation

On the basis of good evidence, antipsychotic medications are recommended for the treatment of psychosis in patients with dementia and for the treatment of agitation. These medications have also been shown to provide modest improvement in behavioral symptoms in general. Antipsychotic medications as a group are associated with a number of severe adverse events, including increased risks for death, cerebrovascular accidents, tardive dyskinesia, neuroleptic malignant syndrome, hyperlipidemia, weight gain, diabetes mellitus, sedation, parkinsonism, and worsening of cognition. Thus, they must be used with caution and at the lowest effective dosage, after considering the risks of not treating the psychiatric symptoms.

Data demonstrating benefit from benzodiazepines are modest, but benzodiazepines occasionally have a role in treating patients with prominent anxiety or on an as-needed basis for patients with infrequent episodes of agitation or for those who require sedation for a procedure such as a tooth extraction or a diagnostic examination. Adverse effects of benzodiazepines include sedation, worsening cognition, delirium, increased risk of falls, and worsening of breathing disorders. **Lorazepam and oxazepam, which have no active metabolites, are preferable to agents with a longer**

half-life such as diazepam or clonazepam.

Treatment of Depression

Depression is common in patients with dementia. Patients with depression should be evaluated for suicide risk. Depressed mood may respond to improvements in the patient's living situation or to stimulation-oriented treatments.

SSRIs may be preferred because they appear to be better tolerated than other antidepressants. Bupropion, venlafaxine, and mirtazapine may also be effective. Agents with substantial anticholinergic effects (e.g., amitriptyline, imipramine) should be avoided. Despite the lack of research data, clinical experience suggests that unilateral electroconvulsive therapy (ECT) may be effective for patients who do not respond to pharmacological agents.

Treatments for apathy are not well supported, but psychostimulants, bupropion, bromocriptine, and amantadine may be helpful. Psychostimulants are also sometimes useful in the treatment of depression in patients with significant general medical illness.

Treatment of Sleep Disturbances

Pharmacological intervention could be considered when other approaches have failed. If a patient also requires medication for another psychiatric condition, an agent with sedating properties, given at bedtime, could be selected. For primarily treating the sleep disturbance, medications with possible effectiveness include trazodone, zolpidem, or zaleplon, but there are few data on the efficacy of specific agents. Benzodiazepines are not recommended for other than brief use because of risks of daytime sedation, tolerance, rebound insomnia, worsening cognition, falls, disinhibition, and delirium.

When using assessment scales to determine the severity of AD, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the results and make any adjustments they consider appropriate.

- SMOH (2007)
- **APA (2007)**

☆ Psychiatric Management

Important aspects of psychiatric management include educating patients and families about the illness, its treatment, and sources of additional care and support (e.g., support groups, respite care, nursing homes, and other long-term-care facilities) and advising patients and their families of the need for financial and legal planning due to the patient's eventual incapacity (e.g., power of attorney for medical and financial decisions, an up-to-date will, and the cost of long-term care).

☆ Adverse Effects of Medications

- Donepezil: Withdrawal rates because of adverse events associated with donepezil ranged from 0% to 57% in

the treatment groups (0% to 20% in placebo groups). No study showed a statistically significant difference between the treatment and placebo groups for serious adverse events except for the expected side effects of cholinesterase inhibitors (diarrhea, nausea, and vomiting). Six studies reported a dose-response effect with increasing frequency of adverse events as dosage increased.

- Galantamine: Withdrawal for adverse events for galantamine ranged from 8% to 54% in the treatment group (4% to 17% in the placebo group). Four studies showed a dose-response relationship for adverse events during titration. Although most trials did not report statistical analysis of adverse effects, 2 studies reported statistically significant weight loss in the treatment group. Commonly reported adverse effects included gastrointestinal symptoms (nausea, vomiting, and diarrhea), eating disorders/weight loss, and dizziness.
- Rivastigmine: Withdrawal rates related to adverse events ranged from 12% to 29% in the treatment group (0% to 11% in the placebo group). The frequency of adverse events between treatment and control groups did not differ. However, 2 studies showed a dose-response relationship for adverse events. The types of adverse events were consistent with those related to cholinesterase inhibitor use and included dizziness, nausea, vomiting, eating disorder/weight loss, and headache.
- Memantine: The withdrawal rates related to adverse effects varied from 9% to 12% in the treatment group (7% to 13% in the placebo group), including nausea, dizziness, diarrhea, and agitation.
- Compared with AchEI, gastrointestinal-related side effects are uncommon with memantine use. Common adverse events of memantine include dizziness, headache, fatigue, hallucinations and confusion, but these tend to be transient. Memantine should be used with caution in patients with epilepsy and renal impairment, and the clinician should be aware of interactions involving commonly prescribed medications such as dextromethorphan and L-dopa.
- Doses of vitamin E in excess of 400 IU a day should be avoided for the treatment of AD until there is further data on its safety, especially in patients with cardiovascular disease.
- Conventional antipsychotics are associated with extrapyramidal side effects and somnolence.
- Atypical antipsychotics are associated with somnolence and gait disturbance. These adverse effects are 7.5 to 11 times more common in olanzapine-treated group compared to placebo. Serious adverse events occurred in 16.8% of risperidone versus 8.8% of placebo group, including 5 strokes and 1 transient ischaemic attack, all in risperidone group.

Meta-analysis of adverse events performed showed 3-fold statistically increased risk of cerebrovascular adverse events with risperidone and olanzapine (no statistically significant increase in mortality) while another meta-analysis comparing risk of death with atypical antipsychotics (aripiprazole, olanzapine, risperidone and quetiapine) with placebo showed increased risk of death. Other serious adverse events reported included somnolence and metabolic complications of hyperglycemia and weight gain.

- A recent retrospective cohort study had shown increased mortality among subjects using conventional antipsychotics compared to atypical antipsychotics. Antipsychotic medication should be used cautiously in patients suspected to have dementia with Lewy Body as these patients have marked sensitivity to neuroleptic agents, including life-threatening neuroleptic malignant syndrome.

Contraindications

☆ **ACP/AAFP (2008)**
☆ **APA (2007)**

- Side effects occur infrequently with cholinesterase inhibitors, but bradycardia should be considered a relative contraindication to their use.
- The main contraindication to use of cholinesterase inhibitors is hypersensitivity to the individual drugs.
- Sleep apnea is a relative contraindication to the use of benzodiazepines or other agents that suppress respiratory drive.
- Selegiline use is considered contraindicated in combination with meperidine, SSRIs, or tricyclic antidepressants.

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http://guideline.gov/syntheses
/printview.aspx?id=36778

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EFFECT OF PURPOSE IN LIFE ON THE RELATION BETWEEN ALZHEIMER DISEASE PATHOLOGIC CHANGES ON COGNITIVE FUNCTION IN ADVANCED AGE

Boyle PA et al - Arch Gen Psychiatry 2012

An active mind has been found to have protective effects on the brain. A new study has now examined the interaction of "purpose in life" with cognition and with postmortem neuropathology of Alzheimer disease.

Purpose in life was defined as an ability to derive meaning from experience and to behave with intentionality and goal directedness. The 246 nondemented elderly participants had yearly cognitive testing until death (mean age at death, 88), and their purpose in life was measured at a mean of 3.9 years before death.

Analyses controlled for depression, APOE4 alleles, medical illness, and other relevant confounding factors. Amyloid, neurofibrillary tangles, and their combination were associated with reduced cognition. Cognitive function declined progressively with increased neuropathology of Alzheimer disease, and every unit of increase in purpose of life proportionately reduced neuropathologically driven cognitive decline. The slowing of cognitive decline associated with greater purpose in life was most marked in subjects with more neuropathology, particularly tangles.

Comment: With aging, nearly everyone accumulates the neuropathology of Alzheimer disease, but not everyone's cognition deteriorates accordingly. It appears that without preventing actual pathology, having a robust purpose in life strengthens cognitive reserve, health behaviors, and the psychological, biological, and social resiliency to compensate for adverse biology. Hopefully, those without a strong sense of purpose in life can be helped to find more meaning and protect themselves from illness.

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http://psychiatry.jwatch.org/cgi/ontent/full/2012/604

CALORIC INTAKE, AGING, AND MILD COGNITIVE IMPAIRMENT: A POPULATION-BASED STUDY

Geda Y, et al "" AAN 2012

Overeating is associated with an increased risk of mild cognitive impairment (MCI) in people 70 or older.

In a population-based, case-control study, people who consumed more than 2,142, kilocalories a day had nearly twice the risk of MCI as those eating fewer than 1,526 kilocalories a day, according to Yonas Geda, MD and colleagues.

The researchers also observed a dose-response pattern. The higher the amount of calories consumed each day, the higher the risk of MCI.

Geda and colleagues noted that dietary intake has been associated previously with MCI, but the role of daily energy consumption has not been clear. Indeed, the study is "noteworthy" in that regard.

The findings might have clinical implications, as doctors and patients discuss "the links between common healthy living practices [and] overall cognitive function."

The findings might also help the research agenda by highlighting possible mechanisms for the onset of mental decline.

People with MCI are not regarded as having dementia, but they have cognitive deficits that appear to precede the development of such diseases as Alzheimer's.

To understand the links between caloric intake and MCI, Geda and colleagues turned to the Mayo Clinic Study of Aging, a continuing population-based cohort study in Olmsted County, Minn.

They asked a random sample of 1,233 non-demented study participants, ages 70 through 89, to fill out a food frequency questionnaire for the year preceding an interview.

The volunteers included 1,070 cognitively normal people and 163 with MCI, as determined by an expert consensus panel on the basis of published criteria.

The volunteers were divided into three groups, based on the caloric intake derived from their questionnaire answers.

The reference group for subsequent analysis was participants who ate between 600 and 1,526 kilocalories a day. The middle group ate from 1,526 to 2,142.5 kilocalories a day, while the third group ate 2,142.5 to 6,000 kilocalories a day.

Geda and colleagues conducted multivariable logistic regression analyses, adjusting for age, sex, education, depression, apolipoprotein E (APOE) genotype, history of stroke, coronary artery disease, diabetes, and body mass index.

Compared with the reference group, those in the middle group had an elevated risk of MCI, but it did not reach statistical

significance (odds ratio 1.05, 95% CI 0.63 to 1.77).

On the other hand, daily energy consumption in the third group was associated with a greater chance of having MCI (OR 2.41, 95% CI 1.51 to 3.86).

There was also a significant trend ($P<0.001$) for increasing caloric consumption to increase the risk of MCI.

One implication of the study might be that cutting calories and eating foods that make up a healthy diet may be a simpler way to prevent memory loss as we age.

The study includes a large number of non-demented people from the general community in the U.S., which might make the results relatively widely applicable.

However, some questions remain including:

- What sort of questionnaire was used and how it was administered and interpreted?
- Was there an effect of male or female sex or race and ethnicity?
- Did the researchers distinguish between amnestic MCI, in which memory is affected, and MCI in which other cognitive domains, such as orientation, language, and executive function, are impaired?

The study was supported by the NIH, the Robert Wood Johnson Foundation, and the Robert H. and Clarice Smith and Abigail van Buren Alzheimer's Disease Research Program.

http://www.medpagetoday.com
/Geriatrics/GeneralGeriatrics/31139?

GOOD NEWS FOR DEMENTIA CARE: CAREGIVER INTERVENTIONS REDUCE BEHAVIORAL SYMPTOMS IN PEOPLE WITH DEMENTIA AND FAMILY DISTRESS

Laura N. Gitlin, Ph.D. - Am J Psychiatry 2012

These interventions should be central to the clinical management of behavioral symptoms.

Dementia has devastating social, economic, and emotional consequences not only for patients but also for their family caregivers. It is a critical public health concern for which the global burden by the year 2050 is expected to exceed 115.4 million people worldwide and 16 million in the United States. The near future is poised to yield new diagnostic criteria, assessments for early detection, and treatments postponing disease progression, resulting in an even greater number of people who will be diagnosed and living longer with the disease than current estimates indicate.

Most patients with dementia are cared for at home by family members living with or near them. In the United States, this represents 15 million informal family members who provide protracted care to people with dementia extending over the course of the disease until the end of life. One of the most demanding and difficult aspects of care is managing multiple troublesome behaviors associated with the disease. Behaviors such as wandering, repetitive questioning, shadowing, aggressiveness, apathy, sleep disorders, hoarding, and resistance to help with daily activities are often more challenging for families to prevent, reduce, or manage than the cognitive decline of the disease.

These behavioral symptoms are nearly universal and occur at any disease stage, with multiple behaviors often occurring simultaneously. For patients, the consequences are profound; if untreated, behavioral symptoms are associated with more rapid disease progression, greater disability, higher health care utilization and costs, poor quality of life, and nursing home placement. Equally disturbing are the effects on families. Behaviors are associated with increased caregiver upset, burden, depression, time in daily oversight, and care costs.

Given the numbers of patients and family members affected by dementia, the pervasiveness of behavioral symptoms, and their poor prognosis, behavioral management should be a clinical priority. Nevertheless, there is no systematic, coordinated, uniform, or agreed-upon approach to clinically managing behavioral symptoms. Typically, when behaviors are presented in a medical setting, an antipsychotic prescription-specifically the off-label use of an atypical antipsychotic-is provided. Although use of antipsychotics for dementia has declined, there is still an overreliance on these medications and other pharmacologic treatments. Their use occurs despite known risks (e.g.,

cerebrovascular events, mortality) outweighing the benefits and a Food and Drug Administration boxed warning. Importantly, no pharmacologic treatments exist for the behaviors that families identify as the most troublesome.

Clinical guidelines from numerous medical organizations for managing behavioral symptoms recommend nonpharmacologic approaches, including caregiver supportive interventions, as first-line treatment. Interventions for caregivers may include skills training, education, actisvity planning, environmental redesign, and social and emotional support, tested either singly or in combination. However, nonpharmacologic approaches are not widely implemented, largely because of lack of provider knowledge concerning their efficacy and limitations imposed by reimbursement mechanisms.

Given the crisis in dementia care, the study by Brodaty and Arasaratnam is significant and welcome news. A robust corpus of research demonstrating the efficacy of psychosocial and environmental interventions directed toward family caregivers has emerged over the past two decades. Yet, this body of strong evidence has been largely ignored by the medical community. Furthermore, it has been unclear whether interventions targeting family caregivers yield patient benefits. Brodaty and Arasaratnam conducted a meta-analysis of 23 high-quality caregiver intervention studies to evaluate their combined effects on behavioral symptoms and caregiver distress. Of these, 16 (69.6%) met criteria for a randomized clinical trial and seven, although using random allocation, were considered pseudorandomized because of unclear explication of methods. Collectively, these studies involved 3,279 family caregivers of community dwelling individuals with dementia.

Significant treatment effects were demonstrated for reductions in behavioral symptoms (effect size=0.34, 95% confidence interval [CI]=0.20-0.48; z=4.87, p<0.01) and caregiver negative reactions (effect size=0.15, 95% CI=0.04-0.26; z=2.76, p=0.006). Although effect sizes were small to medium, improvements compared more than favorably with pharmacologic trials and are clinically meaningful. Even small changes in behaviors can help families keep a relative with dementia living at home longer with improved quality of life. Notably, these gains were achieved with no adverse events or known risks. Characteristics of the most successful interventions included tailoring to specific behaviors, needs, and contexts, providing an average of nine to 12 sessions, and assessing needs from which to link intervention strategies. Of three studies (13%) reporting neutral outcomes, other positive outcomes for caregivers were demonstrated; one of these studies included behavioral management training in both the intervention and comparison arms, with both groups improving. Only one study, a cognitive-behavioral intervention, reported negative outcomes, with both the intervention and comparison groups declining similarly over time.

Two key conclusions can be drawn from this study. First, the meta-analysis provides the strongest evidence to date that caregiver interventions have a twofold

advantage: they reduce distress in caregivers, and they reduce behavioral symptoms in individuals with dementia. This quantitative synthesis of high-quality studies provides confirmation that helping families is an important vehicle for helping patients. As such, these interventions should be central to the clinical management of behavioral symptoms. The primary challenge remains how to widely implement and financially sustain delivery of these interventions to address the urgent need of families.The second key point is that in order to optimize clinical potency, relevance of interventions, and the implementation potential of interventions, much more research is required. For example, cost analyses for almost all of the included interventions are woefully missing, yet an economic perspective could guide implementation considerations. Additionally, as Brodaty and Arasaratnam indicate, "fine-grained questions" concerning dosing, start and stop rules, and which interventions and their components are most effective for improving which behavioral symptoms need greater clarification. It is difficult to discern whether any one intervention is more effective than another and which intervention works best for which service setting, specific behavior, disease stage, or caregiver and patient profile. How is a clinician to choose which intervention to invest in and learn to use? At this stage of the evidence and until clarity, decision rules, and more precision are achieved, it may be preferable to consider all of these interventions as part of a tool kit for addressing behavioral symptoms. Clinicians may want to pick and choose the interventions showcased in the meta-analysis based on the specific family needs they encounter and their context of care delivery, such as the available professional and financial resources for delivering any one intervention.

This article is timely in view of the 2012 World Health Organization report urging countries to develop dementia plans that balance searching for a cure with advancing evidence-based quality care. Current health care reform initiatives in the United States to reduce nursing home placements and overreliance on psychotropic medications and the 2011 National Alzheimer's Project Act, suggest cautious optimism that policy change may move caregiver interventions into real-world settings.

In an editorial concerning the main outcomes of the National Institutes of Health multisite Resources for Enhancing Alzheimer's Caregiver Health initiative, one of the 23 trials included in the meta-analysis, Covinsky and Johnston concluded that "if these interventions were drugs, it is hard to believe that they would not be on the fast track to approval. The magnitude of benefit and quality of evidence supporting these interventions considerably exceed those of currently approved pharmacologic therapies (for dementia)." This statement, 6 years later, applies. It raises the question, If not now, then when will these proven programs be made available to families who continue to receive suboptimal care or no treatment at all for behavioral symptoms? Brodaty and Arasaratnam's meta-analysis provides strong evidence that helping families is good news for dementia care.

PERFORMANCE-BASED MEASURES OF EVERYDAY FUNCTION IN MILD COGNITIVE IMPAIRMENT

Terry E. Goldberg, Ph.D & Colleagues-Am J Psychiatry 2010- Abstract

Objective The view that everyday function is preserved in mild cognitive impairment may be problematic. The objectives of this study were to determine the magnitude of impairment in everyday function in patients with mild cognitive impairment and Alzheimer's disease using a novel sensitive performance-based measure (the UCSD Performance-Based Skills Assessment; UPSA), contrast it with use of an informant-based measure (the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; ADCS-ADL), and model the relationship between cognitive measures and the performance-based measure.

Method Fifty cognitively normal elders, 26 patients who met criteria for amnestic mild cognitive impairment, and 22 patients who suffered from mild to moderate Alzheimer's disease were assessed on the UPSA, the ADCS-ADL, and a battery of neurocognitive tests.

Results Patients with mild cognitive impairment had significant impairments on the UPSA but not on the ADCS-ADL. The magnitude of the effect size between the cognitively healthy and the mild cognitive impairment group for the UPSA was large (d=0.86). A strong and significant relationship was observed between cognitive performances in speed (R2=0.37), episodic memory (R2=0.10), and semantic processing (R2=0.03) and UPSA score using multiple regression models. The psychometric properties of the UPSA were acceptable, as were its sensitivity and specificity in contrasts between cognitively normal elders and patients with mild cognitive impairment and between the latter group and patients with Alzheimer's disease.

NUTRIENT BIOMARKER PATTERNS, COGNITIVE FUNCTION, AND MRI MEASURES OF BRAIN AGING

Bowman GL et al.. Neurology

Many studies have suggested that dietary factors, including specific nutrients, the Mediterranean diet, and obesity, are important in cognition. However, the data obtained are usually from questionnaires that rely on recall of food intake. These investigators examined plasma nutrient biomarkers of diet in 104 participants in a brain aging study (mean age, 87; 62% women).

The investigators constructed several nutrient biomarker patterns (NBPs) and assessed the relationships of NBPs to findings from neuropsychological tests and volumetric magnetic resonance imaging (in 42 patients). Of the group, 10% were carriers of theAPOE4 gene, 21% had depression, and 44% had hypertension.

Several NBPs were associated with outcomes. **A profile high in plasma vitamins B (B1, B2, B6, folate, and B12), C, D, and E was associated with better global cognitive function, especially executive and visuospatial functions and attention. A profile high in plasma trans fat was associated with worse cognitive function.** A profile high in plasma marine omega-3 fatty acids was associated with better executive function. Total cerebral brain volume was greater in participants with the plasma vitamin NBP and smaller in those with the trans fat NBP. The omega-3 NBP was associated with significantly fewer white-matter hyperintensities, but only in individuals without depression.

Comment: This study confirms what we have previously gleaned from dietary studies: Plasma vitamins found in green, leafy vegetables and fatty acids found in some fish are good for your brain; trans fats found in bakery items, fried foods, etc., are not. We should not interpret these findings, however, as recommending vitamin supplements. Taking supplemental vitamins is not the same as obtaining nutrients through real food.

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http://psychisatry.jwatch.org/cgi/content/full/2012/206/2?q=etoc_jwneuro&eaf

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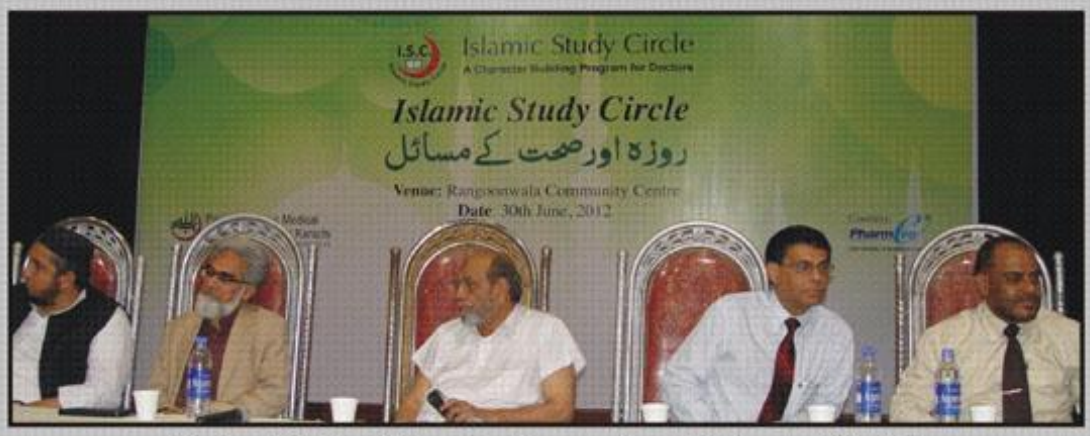

Dr. Syed Mubin Akhtar attending a seminar "Fasting and Health"
organized by Islamic Study Circle

Dr. Syed Mubin Akhtar addressing a press conference on the occasion of Anti Narcotics Day

Ms. Mehjabeen Akhtar speaking on the occasion of Independence Day Programme
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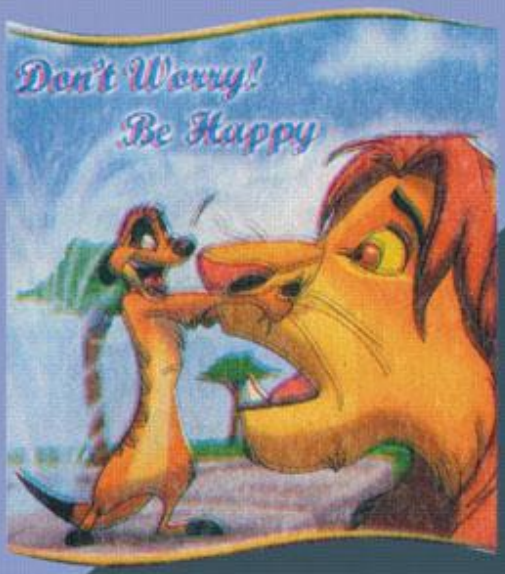

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