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ON THE COVER

Uncertainty, by Martin Ma

Although the deteriorating effects of AD are centred around the affected individual, the impact of AD is much more widespread and can often have a profound effect on friends and family. This is particularly true for the children of individuals afflicted with AD, who must face the uncertainty of the disease’s hereditary component.

In this painting, I attempt to explore the impact of AD on an afflicted individual’s children. Here, a physician tells a concerned son that his father’s strange behavior in recent months is the result of AD. The son listens and hears the physician’s words of explanation. However, as the explanation continues, the doctor’s words are interrupted and quickly dominated by the son’s own thoughts and worries, as he attempts to grasp the meaning of what the doctor has said. In the end, the son is left with the uncertainty that his father’s AD diagnosis brings to his own future.
T his issue of the Canadian Alzheimer Disease Review appears in timely fashion. Many readers have taken notice of the “backlash” against the use of cholinesterase inhibitors (ChEIs) for Alzheimer’s disease (AD). I allude to the well-known article in the New York Times which questioned whether “naming 11 animals in a minute instead of 10” was worth the expense of this class of medications. A further “cold shower” has been the report in the June 25 edition of the Lancet, which describes the results of courses of treatment with donepezil in 565 community-dwelling residents with mild to moderate AD. These subjects taking donepezil fared only slightly better on cognition and function and did not experience delays in institutionalization or progression of disability. The authors raised the sober question of the drug’s cost-effectiveness. Although the methodology of this study initially appears sound, by the trial’s completion, it becomes apparent that it is flawed. Only a small percentage of the target enrollment sample is reached, a large drop-out of subjects transpires, and the serial washouts of donepezil (six-week and four-week) do not parallel the model of good clinical practice. Readers should not suddenly discount the numerous clinical trials that have demonstrated improvements in cognition, function, and behavior with these agents in placebo-controlled trials.

Furthermore, Dr. Rockwood’s article (page 13) points out that the outcome measures in clinical trials are simply not applicable to clinical practice. Do statistically significant differences manifested in these studies translate into truly positive results recognized by AD patients and caregivers in the real world? To answer this question, Rockwood designed a trial using Goal Attainment Scaling (GAS), a formal method by which patients, caregivers and the treating physician would set their own goals and expectations of treatment. Rather than using outcome measures designed by an individual geographically and culturally remote from any individual patient, GAS puts this process in the hands of the patient, the caregiver and the primary care physician. The results indicated that the priorities of patients and caregivers were indeed distinct from those of the treating clinician. Their goals were more numerous and more oriented to leisure and social interactions than those of the family physician. Their evaluation of the treatment effect was more optimistic than the physician’s. The results clearly showed the viewpoint of patients and caregivers differed considerably from the standard outcomes of Phase III trials; it also serves as a rebuttal to the backlash mentioned above.

Drs. Loy-English and Feldman complete their article from last month, focusing on parkinsonian dementias (page 9). Akin to its predecessor, this article has a clinical focus and deals with the practical approach to problem-solving within this group of diseases. Accordingly, the differing characteristics of these perplexing conditions are elucidated. The clinical indications for ChEIs and atypical neuroleptics is documented.

In their article, Drs. Rapoport et al clarify the muddy waters surrounding the connection between traumatic brain injury and dementia (page 4). Physicians understand that cognitive impairment and dementia put the senior driver at risk for car crashes, as well as the known relationship between traumatic head injury and subsequent dementia. This article covers the driving issue in useful detail. The literature is reviewed to illustrate how dementia is a risk factor for traumatic encephalopathy and how dementia is one of the cognitive sequelae of head injury. Evidence reviewed indicates that the association between the two has not been found consistently in the various studies.

Roberta Bedard describes with sensitivity the experience of interacting with her husband, declining further into the tangled web of advancing AD (page 20). Relating to the Reisberg theory of retrogenesis, she describes her own adjustments that facilitate continuing personal interaction with her failing spouse.

A contribution from the Alzheimer Society of Canada describes the process of establishing the First Link program, which has spread throughout the country (page 22). The value of an experienced AD caregiver offering guidance and moral support is emphasized. The spin-off is increased linkages between physicians, community support providers and their organizations.
Traumatic Brain Injury and Dementia

As Canada’s population ages, the incidence of traumatic brain injury (TBI) and the prevalence of dementia will certainly increase. Dementia is a significant risk factor for the two most common causes of brain injury, namely falls and motor vehicle accidents. TBI is associated with a variety of cognitive deficits and may lead to the development of dementia. There is now compelling data to suggest that TBI causes AD.

by Mark Rapoport, MD, FRCPC, Nicolaas Paul L.G. Verhoeff, MD, PhD, FRCPC and Robert van Reekum, MD, FRCPC

While traumatic brain injury (TBI) is most commonly seen in adolescents and young adults, there is a bimodal distribution with a second peak in incidence after the age of 65 years. In Canada, unintentional injuries were the sixth-leading cause of death (22.8 deaths per 100,000 population) among adults aged 65 years and older in 1996/1997. Among the causes of these injuries, falls and motor vehicle collisions were the most common causes of death and hospitalization. TBI is the third-most common injury leading to hospitalization in older adults.

In Canada, an estimated 8% of the population has dementia and a further 16.8% have cognitive impairment without dementia. Alzheimer’s Disease (AD) is the most common cause of dementia in older adults. As of 1992, 364,000 Canadians over the age of 65 years had AD and related dementias, and it has been estimated that, by 2021, this figure will reach 592,000. As persons over the age of 65 years represent the fastest-growing segment of the Canadian population, and are expected to comprise 25% of the total population by the year 2030, it will become increasingly important to prevent TBI and AD whenever possible.

For the purposes of this paper, we will first explore dementia as a risk factor for TBI and then discuss evidence that suggests that TBI may cause dementia. This paper will discuss the relationship between TBI and dementia, using Sir Bradford Hill’s criteria for the establishment of an argument of causation. As reviewed by Dr. van Reekum, the most important of these criteria require that: a) the causal agent and the purported outcome be associated; b) the causal agent should come first; and c) it should be biologically plausible that the putative causative agent might cause the purported outcome.

Dementia as a Risk Factor for TBI

The two most common causes of TBI in the elderly are motor vehicle accidents and falls. Dementia is an important risk factor for both of these.

Driving. An estimated 4% of male drivers aged 75 years and older have dementia, although in an older study of a retirement community, 18% of drivers aged 60 years and older were found to have “senility.” While incident dementia is a common reason for driving cessation, between 22% and 68% of dementia patients continue to drive, and about one third of patients with dementia have at least one motor vehicle collision before ceasing to
Crash rates in dementia are increased two to eight times relative to age-matched controls. Research generally supports the notion that patients with dementia have higher crash rates and perform more poorly during on-road or simulator assessments, but there are many exceptions. Cognition itself, however, only captures some elements of driving risk. Cognitive screening tests, such as the Mini-Mental Status Examination (MMSE), have limited utility in predicting driving performance in mild dementia. Furthermore, more detailed neuropsychological tests, which are not readily available in the community, predict only 19% of the variance of collisions. Other factors, such as comorbid health problems and medication use, may play a significant role.

Falls. In a cross-sectional survey of emergency-room patients presenting with falls, dementia was seen as a strong risk factor for falls in the previous 12 months with an odds ratio of 3.80. Similarly, a recent prospective cohort study in a chronic-care setting found dementia to be a strong predictor of the risk of falls. The risk of falling is double for those with dementia compared to those without. Analogous results were found in a cross-sectional analysis of patients discharged from medical inpatient services.

The studies above describe an association between a causative agent (i.e., dementia) and an outcome (i.e., falls or motor vehicle collisions) in which the causative agent comes first. Decline in attention, visuospatial skills, and psychomotor speed associated with dementia provide a feasible biological mechanism that puts such patients at risk of injury. While clearly not all falls or collisions lead to TBI, they are the most common causes of TBI and represent a means by which TBI may be prevented in the dementia population. Clearer institutional and governmental policies are needed to provide guidance on which patients with dementia should not be allowed to drive and measures must be put in place to prevent falls in chronic-care or ambulatory patients with dementia.

TBI is the third-most common injury leading to hospitalization in older adults. In Canada, an estimated 8% of the population has dementia and a further 16.8% have cognitive impairment without dementia.

TBI as a Cause of Dementia

Cognitive sequelae of TBI. Cognitive sequelae are among the most disabling of post-concussion symptoms following TBI and typically contribute more to persisting disability than physical impairment. Following TBI, deficits are consistently demonstrated in the domains of attention, memory and executive functioning. To date, there are few studies of cognitive outcome following TBI in the elderly, and these have generally had small sample sizes or have lacked a control group. A recent report indicated that patients with mild TBI were similar in terms of cognition to matched controls in the first months after injury, and that only patients with moderate TBI demonstrated deficits. Another study showed no difference in cognition six weeks post-injury between older patients with TBI and orthopedic controls. Longer-term studies with larger sample sizes are needed to further elucidate the effects of TBI on cognition in the elderly.

Dementia. Results of a recent meta-analysis of 15 of the available and methodologically rigorous case-control studies show that TBI is associated with AD, at least in males (odds ratio of 2.3 for males, and of 0.9 for females). The absence of an association in females may relate to protective effects of estrogen, or to other differences in female vs. male neuroanatomy/physiology, or may relate to differences in the nature of the accidents which cause TBI in males vs. females, or perhaps to other factors not yet understood. As reviewed by Dr. Rapoport, the association between TBI and AD has not been found consistently between studies, with, for example, a relative risk of 4.1 found in one prospective cohort study and an absence of increased relative risk found in another. An historical cohort study found an association between TBI and AD, not in terms of increased frequency of AD but rather in terms of earlier onset of AD (median 10 years
from the date of the TBI vs. an expected 18 years based on age of onset distributions). Finally, evidence of an association between AD and TBI exists at the pathological level as well.\textsuperscript{38} Of 58 consecutive autopsies performed on individuals (mean age 77.0 years), who had suffered a severe TBI, 22.4\% had definite or probable AD based on Braak staging of Alzheimer’s pathology vs. 14\% in the general population older than age 70 years. Note that there is evidence that even mild TBI (or concussions) may be associated with AD.\textsuperscript{34,39,40}

**Common pathologies.** The temporal sequence frequently appears to be correct\textsuperscript{31,34,35,37,38} in that both the case-control and cohort studies examined cases in which the TBI preceded the dementing illness. As discussed above, it is clear that the temporal sequence will sometimes occur in the opposite direction (with some individuals with AD having a TBI). In terms of biologic plausibility, TBI has been found to:

i) affect hippocampal synaptic plasticity\textsuperscript{41} in a number of animal studies;

ii) cause accumulation of amyloid precursor protein in injured axons\textsuperscript{42} with subsequent cleavage to A\textsubscript{\textbeta} peptide in rats;

iii) cause persistent increase in cerebrospinal A\textsubscript{\textbeta}-peptide levels in humans who have suffered a severe TBI;\textsuperscript{43}

iv) cause mild atrophy of the hippocampus\textsuperscript{40} in mice who have had a single mild TBI (the atrophy is severe in apo-E-deficient mice, suggesting an interaction with apo-E); and

v) cause glial protein immunoreactivity\textsuperscript{40} in these same mice (which is also worse in apo-E-deficient mice).

Another theory is that TBI does not cause AD but rather that, by destroying neurons, TBI reduces the critical reserve of neurons and hence hastens the onset of AD.\textsuperscript{44} Finally, a review\textsuperscript{45} of limited data has suggested that major depression is common following TBI,\textsuperscript{48-50} it may interact with the TBI itself to perpetuate the cognitive disturbance.

ii) The epsilon 4 allele of apolipoprotein E (apoE-\textepsilon\textsubscript{4}) has been established as a genetic risk factor for AD, but may also predict poor functional\textsuperscript{51,52} outcome following TBI. While one short-term study found that the presence of apoE-\textepsilon\textsubscript{4} was associated with memory deficits post TBI,\textsuperscript{53} a recent study with long-term neuropsychological data failed to demonstrate a relationship between apoE-\textepsilon\textsubscript{4} and cognition.\textsuperscript{54} Nonetheless, apoE-\textepsilon\textsubscript{4} appears to interact with the TBI in predicting the development of AD.\textsuperscript{31} In about 30\% of severe TBI patients, beta-amyloid protein deposits were observed post-mortem in one or more brain areas.\textsuperscript{55} The beta-amyloid protein deposition post-TBI is strongly, and probably synergistically, enhanced by the presence of the apoE-\textepsilon\textsubscript{4} allele.\textsuperscript{56-59} The beta-amyloid protein is, at least initially, mainly deposited as diffuse rather than dense core plaques.\textsuperscript{55,60-62}

iii) The elderly are commonly affected by an array of medical illnesses and medications, which can affect their cognition. Following a TBI itself, particularly when associated with orthopedic trauma, elderly patients are commonly treated with a number of medications which can lead not only to cognitive impairment, but also to acute delirium.

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**Between 22\% and 68\% of dementia patients continue to drive, and about one third of patients with dementia have at least one motor vehicle collision before ceasing to drive. Crash rates in dementia are increased two to eight times relative to age-matched controls.**
Conclusions
With the aging of the population, the incidence of TBI and the prevalence of dementia will certainly increase in the years to come. Dementia is a significant risk factor for the two most common causes of brain injury, namely falls and motor vehicle accidents. TBI itself is associated with a variety of cognitive deficits and, over time, may lead to the development of dementia. There is now compelling data to suggest that TBI causes AD, as TBI is associated with an increased risk of developing AD, the temporal sequence is generally correct (with understandable exceptions) and finally because TBI causes changes in the brain that are typical of the pathological changes of AD.

There is now increasing evidence that AD may be prevented, or at least its onset delayed. Clearly, individuals at greater risk are more likely to consider AD prevention and the risks/costs inherent in some of the possible preventive strategies. The TBI population deserves to be made aware of the increase in their level of risk and to be made aware of some of the possible prevention strategies available to them. While further research is required to establish their role, such strategies may include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), vitamin E (and perhaps other antioxidants), control of other risk factors (such as blood pressure and cholesterol/triglycerides) and prevention of further insult to the brain. Maintaining cognitive activities, especially new learning, may also play a preventive role. In the future, there may well be other, perhaps riskier/costlier, strategies. Public health efforts aimed at preventing collisions in younger adults have thus far targeted alcohol, drunk driving, seatbelts and helmets in their campaigns, while research and policy has lagged behind in investigating health conditions and medications that put older adults at high risk of collision. Falls in older people are multi-factorial and yet a multidisciplinary assessment and treatment program involving exercise and, potentially, home modifications can often prevent these quite effectively. In the decades to come, it will be increasingly critical to prevent falls and motor vehicle collisions in older adults (and their younger counterparts) as TBI represents a common and preventable cause of cognitive deficits and dementia.

References
21. Guse CE, Porinsky R. Risk factors associated with hospitalization for uniten-
Dementia with Lewy Bodies

The treatment of DLB can be challenging. The mainstays of pharmacologic treatment include the acetylcholinesterase inhibitors (AChEIs) and judicious use of the atypical neuroleptics and levodopa (l-dopa).

*AChEIs* have recently been shown to have efficacy in the treatment of DLB. Given the profound cholinergic deficit of DLB, which is greater than that in AD, these medications are pharmaceutically rational therapy.

Rivastigmine has been reported to have both efficacy and safety in the treatment of DLB. A double-blind, randomized, placebo-controlled trial (RCT) demonstrated improvements in neuropsychiatric symptoms, including hallucinations and delusions. As well, there were benefits on cognitive outcomes, including a series of computerized attentional tests. There was a striking loss of clinical benefit with short withdrawal of the medication.

Donepezil has also been reported to show efficacy in the treatment of DLB, however there are not yet any RCTs with this agent. The available observational studies have reported that donepezil also has an effect on cognition (increasing or stabilizing scores on tests of cognition) and on neuropsychiatric symptoms, including hallucinations and delusions.

There are no published reports on the use of galantamine in the treatment of DLB.

Atypical neuroleptics.

Neuroleptics are used in the treatment of DLB because of the frequency and severity of neuropsychiatric symptoms. While many of these symptoms can often be ameliorated by the use of AChEIs, they often still require adjunct treatment. This is especially true if the patient requires dopaminergic agents for his or her parkinsonian symptoms. DLB patients have an exceptional sensitivity to neuroleptics, especially the older, atypical neuroleptics. This supersensitivity can result not only in a worsening of their parkinsonian features, but also in sedation, falls, neuroleptic malignant syndrome and death.

Because of this sensitivity, treatment of hallucinations and other psychotic symptoms with neuroleptics is generally limited to situations where such symptoms are interfering...
with the care or well-being of the patient. Even then, treatment is approached cautiously. The current preferred atypical neuroleptic for this situation is quetiapine, though hard evidence for this preference is still limited. Fernandez et al. studied 11 patients with DLB using a retrospective chart review. Quetiapine was well tolerated, with a 90% response rate for psychosis. Motor decline was noted in 27% of subjects.

There have been two studies evaluating olanzapine in the treatment of DLB, with conflicting results. Walker et al. found that the majority of their patients were either unable to tolerate even minimal doses of olanzapine, or experienced no benefit with the medication. Cummings et al., with a slightly larger study group in a placebo-controlled study, found benefit for olanzapine. The best dose was found to be 5 mg/day.

Risperidone has also had mixed results in the treatment of DLB. While some investigators have found it useful in controlling psychotic and behavioral symptoms, others have found that the adverse effects outweigh the benefits. L-Dopa. There have been no formal studies evaluating the effects of l-dopa in patients with DLB, however it is used clinically to treat the parkinsonian symptoms of this disease. Caution must be exercised in its use to not exacerbate psychotic symptoms. However, in many instances, it can be safely instituted with the target symptoms being motor parkinsonism and not the associated dementia.

Combination therapy. There have been a few case reports detailing successes with combination therapy in DLB. The combinations include risperidone and donepezil, and l-dopa and other agents.

AChEIs have recently been shown to have efficacy in the treatment of DLB. Given the profound cholinergic deficit of DLB, which is greater than that in AD, these medications are pharmacologically rational therapy.

There are a number of RCTs with placebo control being performed.

Atypical neuroleptics. There are no large-scale, blinded, placebo-controlled studies using atypical neuroleptics in PDD. Again, as in DLB, caution must be exercised when using these agents, as PDD patients are extremely sensitive to the extrapyramidal side effects of these medications.

Alzheimer’s Disease with Parkinsonism.

There are currently no reports in the literature looking at the pharmacologic treatment of parkinsonism in Alzheimer’s disease, however recent study reports have indicated that AchEIs are safe and well tolerated in more advanced AD including in patients with motor parkinsonism.

Conclusions

The Parkinsonian dementias are a challenging therapeutic problem, however recent research findings have informed clinicians of new treatment options. DLB has deep cholinergic deficits for which symptomatic benefits can be obtained with acetylcholinesterase inhibitors. The utility of AchEIs for PDD is not yet determined but preliminary reports are encouraging. For more advanced AD where Parkinsonian features are encountered AchEIs can still be efficacious therapy and are generally well tolerated without increasing motor Parkinsonism. The use of neuroleptics in the Parkinsonian dementias must be very judicious.
References
The ACADIE Study: Does Donepezil Meet the Expectations of Treatment?

The Atlantic Canada Alzheimer Disease Investigation of Expectations (ACADIE) study was a 12-month phase IV trial, in which patients with mild to moderate Alzheimer’s disease (AD), their primary caregivers and treating physicians set treatment goals, divided into five domains: cognition, function, behavior, leisure activities and social interactions. Patients and caregivers described consistent goal attainment, whereas physicians observed variable effects, such as decline in cognition, but improved social interaction and behavior.

by Kenneth Rockwood, MD, FRCPC

Knowing whether or not Alzheimer’s disease (AD) has been successfully treated remains difficult, due in part to a lack of understanding of how to translate the results of pivotal studies into clinical practice. As many of the measures employed in these pivotal trials are rarely used in practice, and because the course of treatment is long, there is uncertainty about what treatment effects to look for, how long to look for them, or whether a given benefit is worthwhile. For example, a recent article in the New York Times raised the question of whether “naming 11 animals in one minute instead of 10” was worth it. That frustration can perhaps be better summarized like this: are treatment results clinically important?

At present, while we have no standard criteria for understanding whether a given effect is likely to be clinically important, some features make it more likely. For example, the strategy of cholinesterase inhibition appears to be biologically plausible. An overview of the cholinesterase inhibitor trials shows a reproducible dose response effect and that the outcome measures converge. As reviewed elsewhere, clinically detectable patterns seem to hold in interviews using the Clinician’s Interview-based Impression of Change (CIBIC). Still, the essential question of whether all these statistically significant differences translate into clinically evident treatment success recognized by non-experts remains a troubling one. This is what the Atlantic Canada Alzheimer’s Disease Investigation of Expectations (ACADIE) study sought to address.

ACADIE: The Objectives

The results of ACADIE have been published elsewhere. ACADIE sought to add to the existing body of information about cholinesterase inhibition in general, and donepezil in particular, in two ways. First, we sought to understand whether treatment met the expectations of patients, caregivers and their physicians. Next, we wanted to know whether the treatment effects observed in highly selected clinical trial patients might also be seen in patients who more closely conformed to those seen in usual clinical practice. The latter we attempted to achieve by situating the study in Atlantic Canada, by using sites (with the exception of Halifax and Saint John) that had not been part of earlier trials, and by using liberal enrolment criteria. That we enrolled 108 patients, brought 100 to their baseline visit, and had 88 complete all 12 months of the trial suggests that this objective was achieved.

The objective of understanding whether treatment met expectations was tested using Goal Attainment Scaling (GAS). GAS is a formal method of setting individualized treatment goals, and was reviewed in The Canadian Alzheimer Disease Review.
Using GAS, goals are defined prior to the initiation of treatment. Over the course of the ACADIE trial, they were monitored every three months. Although the goals are individualized, so they vary between one patient and the next, the extent to which goals are achieved can be standardized. We used a formula which takes into account the number of goals set, the importance of one goal compared to the others for a given patient, the proportion of goals attained, and the extent, over a nine-point scale of “much worse than expected” to “much better than expected,” to which goals were met. Because their perspectives differ, and because each has important insights into expectations and their attainment, we elicited goals separately from patients, from their caregivers and from treating physicians. In addition, because our intent was to understand how these patient-centred accounts might help us interpret the usual clinical trials accounts from standard clinical trials measures, several of the latter were also incorporated in the ACADIE study as secondary measures. These secondary measures included the Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-cog),14 and the Clinician’s Interview-based Impression of Change, Plus Caregiver Interview (CIBIC-Plus).9

**ACADIE: The Methods**

ACADIE was conducted like many phase IV trials, in that all patients were treated with 5 mg/day donepezil for the first 12 weeks, after which they could either receive 10 mg/day (this was done in 82%) or stay with 5 mg/day. At baseline and at each of the quarterly follow-up interviews, patients and caregivers underwent a battery of standard clinical assessments. In contrast to other phase IV trials, they participated in an open-ended, home-based interview conducted by trained field researchers. Clinicians’ findings were blinded from those of the field researchers and vice versa.

Having used GAS in an early dementia drug study,15 we required that inquiries about goal areas be made in at least four general domains: cognition, function, behavior and leisure. Within each of these domains, patients/caregivers and physicians could choose to set as many goals or as few (including none) as they wished. As we reviewed these goal areas, as part of our planned qualitative research program, each of the goals that had been recorded was classified in one of these domains. However, it quickly became apparent, particularly for the patient/caregiver goals set in their own homes, that a fifth domain (social interaction) was needed and was added.

Sometimes, a single goal could be classified into more than one domain. For example, consider the goal of being able to use the telephone. This could be classified as an aspect of function, under the subdomain of instrumental activities of daily living (IADLs). In some cases, it might also reflect cognition, as improved telephone use might be...
an instance of better language abilities. In other cases, it might reflect better visuospatial function. Better use of the telephone might reflect recovery of lost initiative, or reflect improved socialization or be key to less caregiver stress. The point is that, in the absence of knowing what successful treatment means, our strategy was to listen closely to what patients, caregivers and physicians observed, and then to evaluate which patterns emerged.

In addition to GAS, the ADAS-Cog and the CIBIC-Plus, we also studied treatment response regarding performance on the Mini-Mental State Examination (MMSE) and measures of function and depression, including caregiver depression.

**ACADIE: The Results**

Most ACADIE patients (71%) were elderly women (mean age 76 years) and most had mild AD. Eighty-two patients had treatment increased from 5 mg/day to 10 mg/day for at least one dose. Most caregivers were women (66%), spouses (48%) and younger than the patients (mean age 61 years). We were interested to observe that patients and caregivers set more goals (855; or 9 ± 3 per patient) than did clinicians (342; or 3 ± 1 per patient). While patients/caregivers and clinicians set cognition goals in the great majority of cases (83% and 85%, respectively) and behavior goals (58% and 57%) there were intriguing differences in other domains. For example, patients/caregivers set function goals most often (86%, compared to 68% of cases for physician goals).

The biggest differences were in the domains of leisure and social interactions. In 76% of cases, patients and caregivers set leisure goals, compared to only 20% of cases for clinician goals. Similarly, social interaction goals were set in twice as many cases by patients/caregivers (49%) as by clinicians (24%).

In general, patient/caregiver goal attainment scores gave a more optimistic account of the extent to which treatment met expectations than did physician accounts. Statistically significant improvements in the total patient/caregiver GAS scores were seen to week 36 (mean change = 3.19, p = 0.03; treatment effect size = 0.28). However, by week 52, there was no significant difference from baseline (mean change = 1.62, p = 0.74; treatment effect size = 0.15).

The total GAS score for clinician-identified goals improved significantly from baseline to week 24 (mean change = 2.39, p = 0.04; treatment effect size = 0.26), but was not significantly different from baseline thereafter (week 52 mean change = 0.43, p = 1.00; treatment effect size = 0.03).

Clearly, the perspective of patients and caregivers, whether elicited from detailed interviews in their own homes or by clinician-driven inquiries in physicians’ offices, offer a different perspective on disease treatment success than do the standard measures. For example, despite improved overall performance, including improved cognition (see Figures 1 and 2), the standard cognitive measures showed significant improvements only at week 12 (MMSE mean change = 0.86 and ADAS-Cog mean change = -1.17). Decline from baseline was observed for both measures thereafter (e.g., week 52: mean change = -1.04 and mean change = 3.07, respectively). Similarly, the functional assessments showed patterns of initial maintenance of functional performance, followed by later decline, chiefly in IADLs. In general, the correlations between GAS total scores, GAS domain scores and the standard measures were low, save for moderate correlations between clinician-assessed GAS cognition.
goals and the MMSE ($r = 0.51$) and the ADAS-cog ($r = -0.43$) at week 52, each of which reflected worsening. However, there was no significant worsening from baseline in the patient/caregiver cognition goals (Figure 1).

However, there were interesting differences between patient/caregiver goal areas and clinician goals. Briefly, patients and caregivers generally observed improvement and each domain tended to go with the others, and with the global were reported in 16 patients, one of whom died as the result of myocardial infarction. No serious adverse events occurred more than once and none had a clear relation to the study drug. Ten patients were obliged to discontinue due to adverse events, which included anxiety ($n = 2$), weight loss ($n = 2$), diarrhea ($n = 1$), pacing ($n = 1$), transient ischemic attack ($n = 1$), agitation ($n = 1$), and foot pain ($n = 1$).

The ACADIE study found that, for at least the first six months of treatment, a patient-centred account gave an optimistic profile of expectations being met, whether judged by patients/caregivers or by physicians.

GAS score (Figure 1). The largest treatment effects were observed in behavior. The physician profiles of patient goal attainment are less readily summarized. Of note, similar to the standard cognitive measures, clinician-identified cognition and function goals had been met at week 12, but these initial gains were not maintained. Few leisure goals were set, resulting in particularly wide confidence intervals. Clinicians recorded behavior and social-interaction goals above baseline at each time-point (Figure 2) but in contrast to the patient/caregiver goals, goal attainment was not consistent across domains.

Almost all patients (104/108) experienced at least one adverse event, usually pain ($n = 46$, including 19 with headache) or various gastrointestinal problems, such as diarrhea ($n = 24$), nausea ($n = 23$) and dyspepsia ($n = 15$). Twenty-two serious adverse events

**ACADIE:**

**Points for Discussion**

The ACADIE study found that, for at least the first six months of treatment, a patient-centred account gave an optimistic profile of expectations being met, whether judged by patients/caregivers or by physicians. After six months, the picture became murkier, with patients/caregivers continuing to see overall goal attainment for another three months but in contrast to the patient/caregiver goals, goal attainment was not consistent across domains.

Like any study, ACADIE is subject to important caveats. Note that it is not a controlled trial, so we cannot answer the question (nor did we seek to) about whether donepezil is more effective than placebo. The reason we did not test this question is that it appears to have been satisfactorily answered in placebo-controlled double-blind conditions.22-26 Our question was whether treatment of AD meets a priori expectations. This is an important question because the debate has now moved to whether the treatment effects demonstrated in earlier studies are clinically meaningful. As detailed in the main report,11 the ACADIE patients appear to be comparable to those in double-blind studies, and have ADAS-Cog responses comparable to other published reports.

Perhaps the most striking feature of the ACADIE study is the wide range of expectations patients and caregivers bring to the table when it comes to dementia treatment. Reflecting our training and conceptualization of the disease, physicians tend to focus on cognition, behavior and, to a lesser extent, function. But our patients have a broader range of concerns. We can learn from this not just clinically, in terms of what we talk to our patients about, but also scientifically. In as many ways as they can, patients and caregivers are telling us that impaired executive function is an essential aspect of dementia. Yet, in comparison with memory impairment, it has received scant formal attention. Although some relatively brief (in the sense of several minutes) tests exist,27-29 this lack of attention reflects that executive function is an area that is less standardized than other aspects of cognitive testing—there is nothing about it on the MMSE, for example. In addition, many of the standard items that purport to test executive function seem quite removed from knowing how someone’s judgment will actually hold up in practice.
Clinical Consequences
What should we look for in patient interviews? The experience of studying formal goal setting and attainment in patients with dementia has changed my practice in this way: I now routinely inquire about so-called target symptoms as part of my clinical interview. I do so because I know from ACADIE that, despite their broad range of expectations, patients and caregivers largely set goals that reflect a realistic understanding of what might be possible. In ACADIE, only about 1% of goals were judged to be unrealistic. It is also important to recognize that sometimes maintenance is explicitly understood as the desired goal: “we’ll be fine if things stay as they are.” That realization, and the observation that setting goals can be problematic for some patients and caregivers, has led me to focus on particular symptoms. These target symptoms, like goals, need to be observable and measurable, but they do not require people to anticipate how they will react to a future change. For example, a common target symptom is repetitive questioning and it often responds to treatment. Another commonly reported symptom is misplacing objects, which responds far less frequently, so I find it to be of little value as a target. The same is true for forgetting names. Other responsive symptoms include getting lost in familiar neighborhood environments, irritability, lack of initiative (especially for social events), not answering the telephone, and needing assistance with tasks that require sequencing, such as housework and meal preparation.

In my clinical practice, I also recognize that, even in successfully treated patients, not everything will be improved. More often, especially after nine to 12 months, patients are more likely to exhibit new combinations of symptoms and signs, as some that were present at baseline improve, while others worsen, and still others stay the same.1,8

ACADIE’s Legacy
The ACADIE study has allowed us to learn how to listen to patients with dementia. GAS is now being used in another anti-dementia drug study. In Nova Scotia and New Brunswick, the experience with GAS has informed the way in which the provincial formularies approve and monitor anti-dementia drugs: instead of specified changes on the MMSE, the standard is that target symptoms be set and monitored. The ACADIE data have also shown that we must develop better ways to measure executive dysfunction if we are to understand clinical meaningfulness in dementia. They also produced results compatible with the proposal for a prefrontal compensatory network in AD and one that might be enhanced by cholinesterase inhibition. In addition, they have inspired us to also consider cholinesterase-inhibitor studies as unique ways in which we can understand human cholinergic neurotransmission. Given that so much of what we uniquely value as a species depends on our abilities of abstract reasoning, this perspective gives us a means of communicating the vital importance of cholinesterase inhibition as both a clinical and scientific stratagem.

References:
75:677-85.


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Personal Revelations, Experiences and Reflections of an AD Caregiver

Roberta Bedard is a caregiver for her husband who has Alzheimer’s disease (AD). She has written many humorous and touching vignettes about her personal experiences in dealing with the development of the disease, and has graciously agreed to feature these vignettes as a series in the *Canadian Alzheimer Disease Review*. Roberta’s writings enable readers to share in her journey with AD caregiving, provide valuable insight on the human aspect of disease and stimulate contemplation on the deeper meanings of life and love.

**In this feature...**
In “New Stage,” Roberta talks about how the Reisberg theory is a source of comfort and confidence as she and her husband must accept that, as she puts it, “he is slipping.”

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**CHAPTER 5**

*by Roberta Bedard*

**New Stage**

“Looking at you right now, I’m not quite sure who you are.”

This addressed to me by the quiet, gentle man who is my husband, as he sits up in bed.

He has just explained to me seriously that, “… we have to make sure that the windows are open, because Roberta needs her fresh air.”

“I’m Roberta. I’m your wife and I love you more than anything.”

“Okay, good.”

This confirms what I have been suspecting for a few months now. The Alzheimer’s symptoms are becoming worse. This after four years of a moratorium on symptoms imposed by donepezil.

Lately, even an overnight stay at a hotel has left him disoriented for about a week afterward. I have awakened to find him packing because, “It’s really too bad that we have to move every month. There should be a way that we can stay in the same place for longer than that. Oh, we have purchased this home? We can stay? That’s good,” he says as he snuggles under the covers and drifts off. He’s also been asking me where Juliette, his long-dead sister, is. I have to accept the reality. He is slipping.

Oddly, I am not terribly upset by this. I have had four years to
prepare for this time, and the knowledge I have gained, especially understanding the Reisberg theory, has given me the confidence that I will know what to do.

My biggest fear when I undertook this journey was that I would not be able to cope; that Ray would not have good care from me.

But now I have a road map. What I must establish is where Ray is now in terms of AD and then correlate this to a developmental stage in a child. I am already, without much thought, relating to him at a different level.

I was right that joy can still be found. We are having many hilarious moments. This is because I am also free to express my inner childishness. Ray is the one person with whom I can be as silly and childish as I want, and it’s alright with him. So we share stupid jokes at which no one but us would laugh. I can dance around making monkey noises and the fact that I am in my mid-sixties, and a large woman, does not appear to him to be incongruous. He just thinks it’s funny and we laugh together.

At this point, his moments of disorientation are few. Most of the time, he is himself. He can still think and has invaluable insights that I am not willing to overlook just because he doesn’t always know exactly what’s going on at any particular moment.

The man I married still lives. Because we have been honest and clear with each other from the start of this illness, we can discuss what is going on and the changes we need to make.

He doesn’t have to pretend he does not get confused. He can acknowledge that I have to hide the medications. If I don’t hide them, he does, which leads to panic on my part when I can’t find them. He accepts that driving is not a good idea and that he should not have the ignition key to the car. This wonderful man looked me straight in the eye and said, “We have to do what we have to do. My ego’s not involved here.”

I have never lied to him. Never pretended that things were different than they are. And he knows at the core of his being that all he has to do to be loved by me is to breathe.

I have never lied to him. Never pretended that things were different than they are. And he knows at the core of his being that all he has to do to be loved by me is to breathe.

AD patients like children.” They feel that AD patients are adults and should be treated like adults. My feeling is that it is the height of disrespect to the individual to refuse to respond to who they are, and rather insist on responding to them as we wish they were.

Treating a person with dignity involves being truthful. I believe the AD patient knows in the core of his/her heart that something is wrong. How frustrating must it be to have that inner truth denied by those who are supposed to be loving them and caring for them.

As my husband changes, I plan to continue to relate to him as he is at that moment. As an adult when he is an adult and as my beloved child when that is where he is.

It’s working so far.

Please look for Chapter 6: I am Loved in the next issue of the Canadian Alzheimer Disease Review.
First Link: Your Link to a Community of Learning, Services and Support

“The first steps in the Alzheimer journey are just like the steps we would take when beginning any other voyage: we need to plan early, anticipate any problems we may encounter along the way, talk to others who have already been there, learn about where we are going and how best to get there, and make sure we have a faithful companion with whom to travel. First Link can help with those first steps and make your journey a little bit smoother.”

These words, from the First Link brochure, describe a pilot project led by the Alzheimer Society of Ottawa, in collaboration with the Dementia Network of Ottawa (www.alzheimerott.org/network/network1.htm). First Link is a direct referral system that links newly diagnosed individuals with dementia and their families to a continuum of care through a community of learning, services and support.

Once an individual has been diagnosed, their physician offers to refer the patient and their family to the First Link Coordinator. With the family’s consent, their physician contacts the First Link Coordinator with the information. This referral connects the family directly to the Alzheimer Society of Ottawa and the Dementia Network of Ottawa programs.

Within three to four weeks of the referral, families receive a phone call from the First Link Coordinator. This initial call builds a connection with the family and the First Link program. Families are given the opportunity:

• to ask questions about the new diagnosis;
• to receive written information about the disease;
• to learn of community supports as needed; and
• to participate in First Link learning series, the peer support program and other appropriate supports provided by Dementia Network of Ottawa organizations.

“The idea for First Link was developed when we recognized that there were many unmet needs in the areas of service delivery, education and research related to dementia,” said Marg Eisner—Director, Family Support and Education, Alzheimer Society of Ottawa. “First Link ensures support services are in place for families affected by dementia from onset to end-stage.”

The peer support component of First Link involves an experienced Alzheimer caregiver offering guidance, a listening ear, understanding, encouragement and moral support to a new caregiver. The peer volunteer acts as a mentor to the caregiver, by providing support over the phone, through in-person meetings, or by e-mail.

The First Link learning series covers every step of the Alzheimer journey. These sessions are progressive, building upon each other to provide participants with a complete overview of dementia, information, skills and resources. Sessions are taught by staff within the Dementia Network of Ottawa, including geriatricians, social workers, nurses and occupational therapists. Learning series are offered in the spring, fall and winter, during the day and evening.

The learning series include:

• First Steps: focusing on the early stages of the disease;
• Care Essentials: centering on the best ways to provide care;
• Options for Care: concentrating on the increasing care needs and long-term options; and
• Quality of Life at the End of Life: focusing on the later stages.

Funding for the First Link pilot program was provided by the Ontario Trillium Foundation from April 2002 to March 2004. Initially created as a pilot project, First Link will continue to be offered by the Alzheimer Society of Ottawa, and is being expanded to include the satellite regions of Renfrew County.

An evaluation report of First Link was completed in May 2004 demonstrating that the program is a success. More than 690 referrals were received by the First Link Coordinator from family physicians, community service providers and community service organizations. Linkages between physicians, community service providers and the Alzheimer Society of Ottawa were strengthened, as all partners worked collaboratively to develop a referral system, to design and implement learning series, and to develop evaluation methodologies. More than 250 different families participated in the First Link learning series since the project’s inception, improving their understanding of Alzheimer disease, dementia and coping skills.

“We know that after a diagnosis, families are feeling overwhelmed,” said Inika Anderson, First Link Coordinator. “It can be extremely difficult for them to pick up the phone and ask for help. With First Link, we can reach out to families instead of waiting for them to call us. Families truly appreciate knowing that there is someone they can call when they need to.”

Evaluation results indicate that First Link has helped people with dementia and their family members in several ways, including learning about the disease, linking families to community services, increasing caregivers’ confidence in caring for their family member, and helping caregivers to more effectively manage crises.

First Link also has benefits for community agency staff and family physicians. Health care professionals reported that their patients greatly benefited from First Link.

The program has worked so well that, in addition to First Link programs in Ottawa and Renfrew County, other provincial societies including British Columbia, Alberta, Saskatchewan and Nova Scotia are exploring adapting the First Link program.

In addition, local Ontario Alzheimer Society chapters in Halton-Wentworth, Lanark County, London Middlesex, and Kitchener-Waterloo have all discussed the program with their respective dementia networks. The Alzheimer Society of Brant is moving ahead with a version of the program and Perth County is reproducing the First Link referral materials and actively working with local physicians while Toronto has implemented the program on a limited basis and is working with one or two partners to receive referrals.

The Alzheimer Society of Ottawa has developed a First Link Toolkit as a how-to guide that discusses how the program was implemented there and makes suggestions as to how it can be adapted to suit other communities. They are assisting other Alzheimer Societies by providing resource materials, answering questions and offering consultation services.

For more information on First Link, or to obtain the Toolkit, please visit the Alzheimer Society of Ottawa’s web site at www.alzheimerottawa.org/first_link or contact Inika Anderson, First Link Coordinator by phone at 613-523-4004 or by e-mail at ianderson@alzheimerott.org.

The Alzheimer Society of Canada is a not-for-profit health organization dedicated to helping people affected by Alzheimer Disease. The Society provides support and educational programs for people with Alzheimer Disease and their caregivers. The Society also funds research into finding the causes and cure of the disease, and into improved methods of caregiving. The Society consists of a national office, 10 provincial organizations and more than 140 local groups across the country.

For more information on Alzheimer Disease and related dementias, Alzheimer Society programs and services, and how you can help, contact your local Alzheimer Society or visit the Society’s website at www.alzheimer.ca or call 1-800-616-8816.