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.[1] 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.[2] 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.[3] For example, the strategy of cholinesterase inhibition appears to be biologically plausible.[4-6] An overview of the cholinesterase inhibitor trials shows a reproducible dose response effect and that the outcome measures converge.[7] As reviewed elsewhere, clinically detectable patterns seem to hold in interviews[8] using the Clinician's Interview-based Impression of Change (CIBIC).[9] 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.[10] This is what the Atlantic Canada Alzheimer's Disease Investigation of Expectations (ACADIE) study sought to address.

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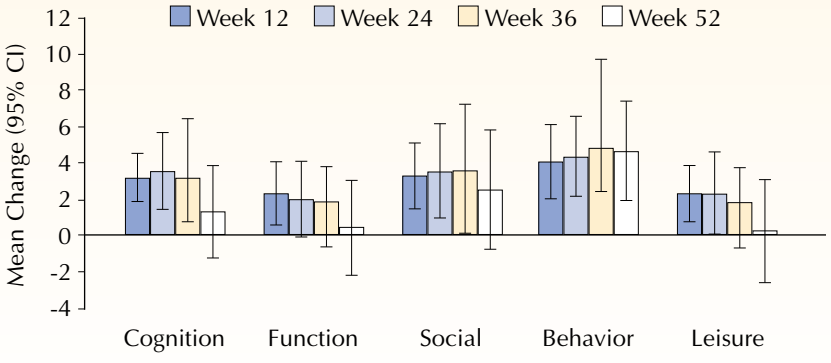
ACADIE: The Objectives

The results of ACADIE have been published elsewhere.[11] 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).[11] GAS is a formal method of setting individualized treatment goals, and was reviewed in *The Canadian Alzheimer Disease*

Figure 1

Mean Change From Baseline by Domain for Patient/Caregiver GAS



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Review last year.[13] 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]

We wanted to know whether the treatment effects observed in highly selected clinical trials patients might also be seen in patients who more closely conformed to those seen in usual clinical practice.

ACADIE: The Methods

ACADIE was conducted like many phase IV trials, in that all patients were evaluated for participation and gave written, informed consent. 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.

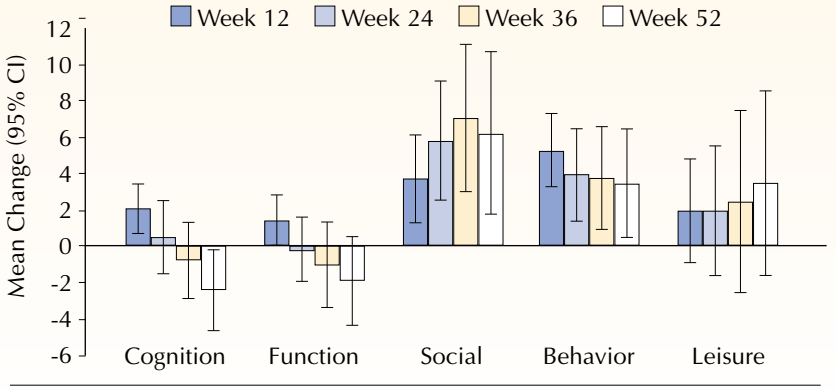
In addition to GAS, the ADAS-Cog and the CIBIC-Plus, we also studied treatment response regarding performance on the Mini-Mental State Examination (MMSE)[16] and measures of function[17,18] and depression,[19] including caregiver depression.[20,21]

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).

Figure 2

Mean Change From Baseline by Domain for Clinician GAS



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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 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 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 ($n = 1$), confusion ($n = 1$), agitated depression ($n = 1$) 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.

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 and persistently beneficial effects in behavior throughout the study. While physician-set goals were also met in behavior and in social interactions, their account showed decline in some areas by 12 months.

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, lacking 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.

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