By David S. Geldmacher, MD

Setting Treatment Goals: A Modest Proposal

Unrealistic expectations set up patients and physicians alike for disappointment. Here's a better approach.

Pharmacotherapy for dementia is a controversial topic. Although the FDA has approved several drugs for treatment of the cognitive symptoms of dementia, there is lingering doubt in the medical community that these agents really "do" anything. There is a disconnect between the results of multiple double-blind, placebo-controlled, clinical trials that show statistical efficacy of these agents and the impression of many clinicians, commentators and pundits that those results don't translate to clinically meaningful benefit for their patients.

Everyone has biases; I should reveal mine at this point. I believe that drug therapy with acetylcholinesterase inhibitors is an important part of a comprehensive plan of care for patients with dementia. I base this belief on multiple studies (of varying sponsorship), evidence-based practice guidelines and clinical experience. There is support, though less comprehensive and diverse, for the use of the one currently approved NMDA receptor antagonist as well.

I recognize that there are intrinsic flaws in the literature on this topic, including prominent sponsor bias and insidious publication bias. The reader should also know that I have served as an investigator and consultant for the companies that manufacture and market the approved agents, as well as several others that did not receive marketing licenses, and still more that are currently under study. I have also served as an advisor to patient and caregiver advocacy groups, like the Alzheimer's Association that strongly support pharmacotherapeutics. Apart from my roles as a payer of taxes and health insurance premiums, I have not been a part of the payment side of the dementia treatment equation. I am a clinician too, and don't like seeing my patients doing poorly. I acknowledge, as we all should, that my biases contribute to my opinion about pharmacotherapy in Alzheimer's disease.

Sources of Negative Bias

So, what are the biases that might lead some of us to think that symptomatic treatment of the cognitive and functional domains in dementia is not worthwhile? One evolves from the pervasive use of the word "modest" to describe the level of benefit of the cholinesterase inhibitors. For instance, the American Academy of Neurology's Practice Parameter on the Management of Dementia states the "average 'effect size' is modest."[1]

Read almost any critique of the use of cholinesterase inhibitors and you'll find the word "modest" in the commentary. The problem with modest is that it has no medical, quantitative or statistical definition. I looked in my beloved (and admittedly out of date) Stedman's Medical Dictionary and modest just wasn't there. I turned to the American Heritage Dictionary of the English Language, Fourth Edition and found something very interesting. Modest can mean "moderate or limited in size, quantity, or range; not extreme," which is how I think it is usually intended in the context of treatment response. It can also mean (more commonly in everyday usage) "free from showiness or ostentation; unpretentious."

Certainly, elements of both definitions apply to the case of cholinesterase inhibitors.

The clinical trial results are clear. Most patients will not experience an extreme, restorative response to cholinesterase inhibitor therapy. However, the same trials suggest that a majority of patients will have a response that is neither showy nor ostentatious, but that they do respond.

In medicine, we should be used to treatments without ostentatious results by now. Antihypertensives, lipid-lowering agents and treatments for osteoporosis are all accepted to have consistent beneficial and important results without altering symptoms at all. If not for our ability to measure biological intermediaries like blood pressure, blood lipids and bone density, we wouldn't know that these treatments were working at all until years after treatment was begun.

Looking at antiplatelet agents, which are the stock and trade of both neurologists and cardiovascular specialists, there are no routinely monitored biological intermediaries, usually no symptomatic responses and typically years before any impact on the outcome is likely to be expressed. And what is that outcome? Nothing. We know that antiplatelet agents work when nothing bad happens. Despite the observation that number needed-to-treat analyses suggest the cholinesterase inhibitors are an order of magnitude more effective at meeting their intended outcomes than these other classes of agents,[2] we don't hear much about those other drugs' "modest" efficacy.

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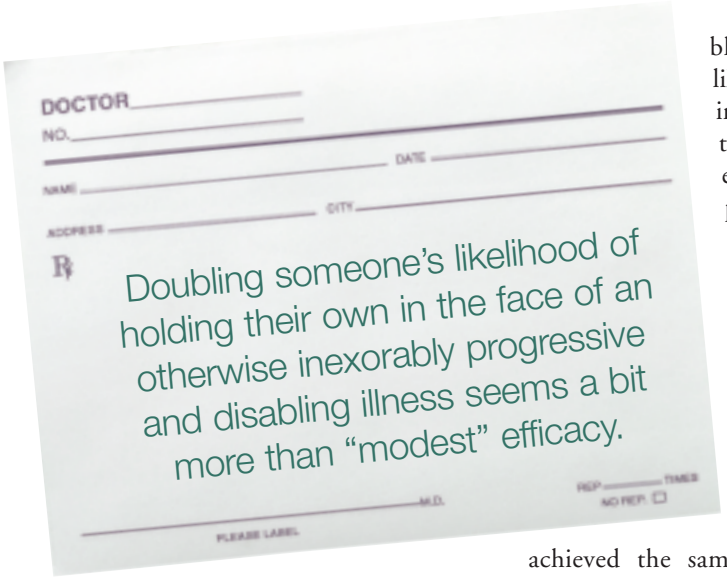

Another potential contributor to the bias against cholinesterase inhibitors stems from the enthusiasm following the earliest reports of their benefits. There were some rather immodest claims about the efficacy of tacrine in a sample of 14 patients who completed a double-blind cross-over study, and the long term open-label follow-up of 12 from that group.[3] The authors of that preliminary report stated that, with treatment, the "degree of improvement has often been dramatic." They highlighted participants who resumed homemaking, part-time employment, daily golf, and self-feeding. There was great hope, echoed in an accompanying editorial, that tacrine would offer sustained improvement in abilities over the long term. When the subsequent, much larger, double-blind, placebo controlled trials of tacrine came out, they provided a denominator to those original claims. Sure, some patients showed dramatic improvements, but most improved only a little over three or six months and some got worse. In contrast to Summers and colleagues' pilot trial, this was pretty disappointing.

What got lost in the disappointment was the result that nearly twice as many patients (approximately 70 percent) had no progression on cognitive test scores over six months of maximal tacrine therapy compared to placebo. To me, doubling someone's likelihood of holding their own in the face of an otherwise inexorably progressive and disabling illness seems a bit more than "modest" efficacy. Admittedly, neither lower doses of tacrine nor clinically supported doses of its successors have achieved the same magnitude of effect. However, looking at those difficult-to-interpret triple-S curves in the newer AChEI package inserts reveals that being on treatment consistently shifts the odds of improvement or stabilization in the patient's favor.

Don't Expect a "Hollywood Ending"

Still, the question lingers: are we doing anything meaningful with these agents? Colleagues far more expert than me think so. A consensus panel was convened at the World Alzheimer Congress/International Conference on Alzheimer's Disease in Washington, DC in 2000. Their intent was to review the state of knowledge on outcomes of cholinesterase inhibitor therapy and inform regulatory agencies, the pharmaceutical industry and clinical researchers on how to assess the effectiveness of treatment. Their consensus statement emphasizes that looking only for improvement, especially improvement in cognition, is an inadequate way to determine therapeutic success and may deprive patients and caregivers of important treatment benefits.[2]

Interestingly, even physicians acknowledge that the standard clinical assessment methods, like brief mental status tests, do not capture important and clinically meaningful outcomes of dementia therapy.[4] Recent research also supports the idea that patients and families feel that treatment provides important benefits[5] beyond those things routinely assessed in the doctor's office, and that they believe that the outcomes achieved are worth more than the cost of the drug.[6]

So, with all due apologies to Jonathan Swift for misappropriating the title of his satiric 1729 essay, I offer a modest proposal: Let's ban "modest" from our descriptions and our way of thinking about cholinesterase inhibitor therapy for dementia. These medications are "modestly" effective only in the context of unrealistic expectations, and provide meaningful benefits to many of our patients that can't be measured as improvements on a 30-point scale.

Yes, you're right; they don't work in everyone. But, then again, neither do antiplatelet agents, anticoagulants, antimigraine drugs, analgesics and a host of other medication classes we routinely use in neurological practice. When they do work, it *is* modest—but in the sense of not being showy, not in the sense of being inadequate.

I'd love to have my patients respond with something showy, like the stories in *Awakenings* (but remember, that didn't have a happy ending either). Our job, as I see it, is not to give our patients a shot at a Hollywood ending, but rather to give them the best chance at doing better in the face of some terrible diseases. There is far more than modest support for the cholinesterase inhibitors as a way to offer that chance for our patients with Alzheimer's disease. **PN**

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