In Anna Karenina, Tolstoy proposed that, “Happy families are all alike; every unhappy family is unhappy in its own way.” Consider any family (happy, unhappy, or both) when one of its members—usually a senior member—develops Alzheimer’s disease (AD). For some, the family fabric, resources, understanding, and commitment are adequate to meet the needs of the individual. For many, as the individual deteriorates, requirements for care may expand and challenge the family’s ability to provide. The balancing of demand with capacity, and the consideration of nursing home placement, are as unique as each individual family.

By clinical definition the disease is insidious in onset and gradual in progression; few milestones are given. As with the dramatic growth that takes place during adolescence, 365 individual days may seem without apparent change, but can make a tremendous difference when added together. These slow accretions of cognitive short-fall, at first unnoticed by companions, eventually demand acknowledgment. Later, day-to-day care needs are likewise gradually acknowledged, their significance interpreted, and responsibility accepted—in piecemeal fashion and with as much variability as in the relationships among spouses and children.

These many stories of heroism, heartbreak, and occasional villainy can also be medicalized. AD is an organ failure—of the brain rather than the heart, kidney, or respiratory system. Minimizing the work of any failing organ, by modifying behaviors and environment, is essential. Medications may modify the organ’s performance, and the medication’s value should be judged based on outcomes that are meaningful.

Management strategies are 2-pronged. Education and support for caregivers are valuable. I believe it is often helpful to recommend readings to reassure caregivers that they are neither unique nor alone in shouldering this unimaginable burden. Acknowledging a small institutional conflict of interest, I recommend “The 36-hour Day,” by Nancy Mace and Peter Rabins, as a classic that has benefited many of my patients and their caregivers in important ways. If a caregiver acts with artistry, endurance, and compassion, I believe a physician can help by simply reflecting this to the caregiver and expressing admiration.

Strategies targeted at the patient are easily conceptualized. For a patient with renal failure nearing dialysis, the work required of the kidney should be minimized. Sodium, potassium, and nitrogen intake should be monitored so as not to overwhelm the kidneys’ ability to excrete. Loop diuretics may maximize excretion of salt and water. Administering exogenous erythropoietin may replace the kidneys’ failing production of this messenger. Nephrotoxins should be avoided.

For a failing brain, optimal sensory input (by attending to hearing and sight), familiar routines, and a recognizable environment can reduce demand on the organ. Polypharmacy is a clear and present danger and efforts at medicinal debridement should be a persistent reflex.

The role of medication to treat AD is much less clear. On one hand, there is no doubt that the currently marketed acetylcholinesterase inhibitors (AChEIs) have a detectable effect on cognitive performance; groups of patients receiving these treatments score significantly differently from groups receiving placebo in randomized, clinical trials. These findings have been widely ballyhooed, and sales of these medications exceed a billion dollars annually. A few authors have written that because these medications are so effective, placebo-controlled trials are no longer ethical. These authors are industry-supported.

On the other hand, publications that are not supported by drug companies view the situation differently. The American Academy of Neurology, in its “Practice Parameter: Management of Dementia (an Evidence-based Review),” provides the following guideline: “Cholinesterase inhibitors (ChEIs) should be considered in patients with AD (standard), although studies suggest a small average degree of benefit.” Some articles assert that treatment with ChEIs is a standard of care and cite this guideline as support. Such referencing is a misrepresentation that tends to promote the use of medication. Several other important sources writing without conflict of interest note that many patients have no response, and for many others the response has no clinical significance. This difference in rhetoric arises despite a well-developed corpus of good randomized clinical trials. A comprehensive review of ChEIs with sensible recom-
mendations, published by the British National Health Service's National Institute for Clinical Excellence, may be found at www.nice.org.uk/article.asp?a=14487. This exemplifies a data review in the absence of industry support.

Claims about “stabilization of disease” and “delaying time to nursing home placement (NHP)” are based on trials of much weaker design. The Food and Drug Administration does not allow these drugs to be labeled for such indications. There is no reason to believe that any of the ChEIs is better than another, although the review by Dr. Geldmacher names donepezil 14 times compared to twice for rivastigmine and once for galantamine. What do the data about delays to NHP look like? In the largest trial to date, the records of 671 patients enrolled in 1 of 3 prior randomized controlled trials of a ChEI were reviewed. The authors showed that patients who took the medication faithfully (more than 80% of the time) and for longer periods of time had a substantial delay in time to NHP compared to patients who took the drug less faithfully or for shorter periods of time. The authors write that use of the drug “resulted” in a longer time to NHP.

But let us revisit these hundreds of patients and their caregivers. They signed up to be in a clinical trial and some were randomly assigned to receive the active drug. At the end of the trials, some patients assigned to placebo crossed over and began taking active drug. Of those receiving active drug, some patients took their medications faithfully for long periods of time. Others were unable or unwilling to do so. Patients and caregivers who remained enrolled and compliant were compared to those who did not. Is it possible that the group with long-term good adherence was different in important ways from the group composed of drop-outs and poor adherers? I believe the answer is yes. Caregivers who can assure a patient will take his or her medicine regularly and stay in the drug study long-term are simply different from caregivers who will not or cannot accomplish this. For the group with the drop-outs and poor adherers, the balancing of demand and capacity was likely unfavorable—exactly the imbalance that might accelerate NHP. Although available to the authors, a great deal of baseline data about patients and caregivers were not presented in the paper.

The critical importance of adherence with respect to outcome has been demonstrated repeatedly, beginning at least as far back as the 1980 Coronary Drug Project. In that large randomized trial, the authors looked carefully at patients assigned to placebo. They found that among patients who were assigned to the placebo group, those who took the lactose placebo 80% of the time or more had half the death rate of those who did not take the placebo faithfully. These authors did not claim that faithful use of the placebo “resulted” in a 50% reduction in mortality. They noted that adherent patients differ in important ways from nonadherent patients.5

When behavioral disturbances arise, maintaining patients with AD at home will often require the purely empirical use of psychoactive medication, generally haloperidol or a short-acting benzodiazepine, and others when these fail. As with the ChEIs, the beneficial effect of a drug, if any, must be balanced against the cost, risks, and adverse effects. As with ChEIs, these drugs should be stopped if there is no beneficial effect.

What can we say about ChEIs, then, to a family who is supporting a loved one with moderate or severe worsening dementia?

- Expect a “small average degree of benefit”
- For many patients and caregivers, there is no benefit at all. A few patients will experience a meaningful change.
- No good scientific evidence shows that these drugs slow down the running clock. On average, they turn hands back about 6 months.
- There is no meaningful scientific evidence that these drugs delay nursing home placement.
- If after 8 or 12 weeks you do not see enough benefit to justify the cost, stop the drug.

Caring at home for a patient with AD can be relentless hard work on behalf of someone who never says “thank you.” Part of the hard work is watching helplessly as a partner or parent of many decades deteriorates slowly and without remedy. Ethical conundrums abound. Good primary care doctoring can probably help many patients, and perhaps even more, help their caregivers. Prescribing a pill or 2 a day of a ChEI will have no meaningful benefit to most patients.

I believe that in 10 years we will be embarrassed that we used these expensive, marginally useful drugs so profligately; that we allowed the drug companies’ promotional strategies to link to the desperate hopes of caregivers; and that we diverted billions of dollars away from these families with such profound care needs.

Addendum—A randomized trial of donepezil with nursing home placement as an endpoint will be published soon in Lancet.

References