When our patients are faced with less-than-optimal treatment modalities, as they are for Alzheimer’s disease (AD), the physician is expected to guide the patient and family to the “right approach.” The decision is not a simple one, nor is there a “one size fits all” solution to the dilemma involving medications currently available. A recent conference at Johns Hopkins on the future of therapies in AD highlighted the dilemmas we face at the present time, when pharmaceutical options are far less helpful than we hope will be the case in the future. As is often the case in such situations, there is little disagreement about the basic facts. The controversy is over how to weigh those facts in the case of each individual.

Currently, 5 drugs have been approved by the Food and Drug Administration (FDA) for use in patients with AD. Four of these (donepezil, tacrine, rivastigmine, and galantamine) belong to a class of drugs called anticholinesterases. Thought to have approximately the same mode of action, these medications block the breakdown of acetylcholine, thereby boosting the levels of this neurotransmitter in the brain. The fifth drug, memantine, is thought to work by a different mechanism, blocking the action of glutamate, a neurotransmitter thought to be overactive in AD.

Double-blind, placebo-controlled studies of thousands of subjects have collectively shown that, on the average, anticholinesterase treatment can stabilize performance on formal test measures for at least a year, compared to the general deterioration that usually occurs in AD. Perhaps even more importantly, families and physicians report stabilization on global subjective rating scales, as well. There also is some evidence that treatment with anticholinergics can reduce the frequency of neuropsychiatric symptoms, such as aggression or apathy. Several studies have suggested that treatment with anticholinesterases can delay admission to nursing homes by approximately 17 to 21 months, on the average, thus providing both economic and human benefit to patients and their families.

It has generally been felt that the anticholinesterases do not alter the underlying neuropathology, and therefore do not alter the intrinsic deterioration in AD; they only modify its expression. However, there is some slight evidence that they may indeed do more. Researchers at Duke University reported that there was less reduction in hippocampal volume as well as improvement on cognitive scores for subjects receiving a cholinesterase inhibitor as compared to subjects receiving placebo. Memantine has been approved, in the past year, for use in moderate-to-severe AD. Double-blind, placebo-controlled clinical trials have shown that it is effective by itself. Memantine in combination with donepezil also has been shown to have greater effects than donepezil alone, at least in one Phase III study, presumably because it works through a different mechanism. There are also hopes, but not yet proof, that because of its presumed mechanism of action, memantine will be truly neuroprotective in AD.

No one thinks of these drugs as cures. No one thinks that, on an absolute scale, these drugs effect major improvements. No one believes that they permanently alter the course of the disease (although there is some evidence and hope that they might). Despite the fact that they are far from the wonder drug one might hope for, we must remember that only 11 years ago, there were no FDA-approved drugs that had any efficacy at all against AD.

What are the risks involved if the decision is to offer medication? Nausea, vomiting, nightmares, and leg cramps occur in some patients. There is the potential inconvenience of adding to a patient’s regimen a drug that needs to be taken anywhere from once (donepezil), twice (rivastigmine,
galantamine, or memantine) or four times a day (tacrine). And cost is an important consideration. At list prices, each of these medications costs approximately $120 per month ($4.00 per day). There is no difference in the cost of different-sized dosages, so patients all pay the same daily amount no matter what the dose.

Given these basic facts, it is no surprise that some physicians, patients, and families can reach differing conclusions than others about whether drug treatment is the right course. In an absolute sense, these drugs do not cause a dramatic change in the patient. Some physicians and some patients therefore choose not to take them, because in their judgment, these drugs are worth neither the risk nor the expense. Others have decided that even with their limitations these therapies have proven effective for many patients, and therefore might be effective for them, too. They feel doing something, no matter how imperfect, is better than doing nothing. Moreover, as medical care providers we should never underestimate the value of making patients active participants in the fight against their illness. So long as patients and their families have a fair understanding of what is possible, what is known, and the extent of our ignorance about the actions and effects of these drugs, then both positive and negative decisions can be justified.

Ultimately it is essential that patients and caregivers be well-informed about the limitations and reasonable expectations of these drug therapies in order to proceed. In the final analysis, the physician’s role is to lay out treatment options and to clarify the decision making process. In AD, “no decline” can actually be considered a “success,” given the limitations of currently available pharmaceutical treatments. We can hope that a more optimistic future is close, but in the here and now, this is the choice we and our patients face.

Reference