



Dementia Drugs Demystified

What to expect—and not to expect—from Alzheimer’s medications

BY DAN HURLEY

Ask specialists about the medications available for treating Alzheimer’s disease, and you’re likely to wish you had more than just two hands.

On the one hand, they’ll tell you, none of the drugs approved to treat the progressive mind-robbing disease is likely to make a big improvement in a patient’s condition.

On the other hand, they’ll quickly add, all of the approved drugs have been shown to slightly slow a patient’s decline, giving an extra three to nine months of retained mental clarity, on average.

But on the *other* hand, that “average” benefit doesn’t mean the drugs will work for everyone, and figuring out whether to keep taking them when the benefits are so hard to detect can be tricky.

That’s three hands—and counting. Luckily, though, most of these apparent contradictions and fine distinctions end up mattering little for families’ real-life practice. The bottom line is that the vast majority of people with Alzheimer’s will give one or two of the drugs a shot, and see what happens.

“They’re not very powerful, and certainly no one’s satisfied with the response typically,” says John H. Growdon, M.D., director of the Alzheimer’s Disease Research Center’s memory disorders unit at Massachusetts General Hospital in Boston. “But they’re the only game in town. And I have rarely seen anyone come into my office and say, ‘I want to stop taking this medicine.’”

A similarly balanced view comes from David Knopman, M.D., a neurologist at the Mayo Clinic Alzheimer’s Disease Research Center in Rochester,

Minn. “I am in general an advocate of using one of the medications, because the data shows that they slow down the progression of symptoms,” he says. “I think that’s worthwhile. But I’m always quick to point out to patients that these drugs don’t stop the disease, nor do they generally bring about improvement.”

The lack of spectacular results is not



for lack of trying. The search for a drug treatment began in earnest in the 1970s, when scientists noticed that patients had very low levels of certain natural chemicals that shuttle messages between brain cells. One of these neurotransmitters is called acetylcholine. Scientists tried slowing down the brain’s process of getting rid of acetylcholine by interfering with the protein that normally breaks it down. They finally succeeded in blocking this protein, cholinesterase, with a drug called tacrine (Cognex), which in 1993 became the first medication approved by the Food and Drug Administration for mild to moderate Alzheimer’s symptoms. Unfortunately, tacrine often caused vomiting

and sometimes even liver failure, leaving patients and their families wishing they could get the same benefits (mild though they were) without the toxic side effects.

Their wish came true in 1996 when the FDA approved another cholinesterase blocker, donepezil (Aricept). Almost overnight, sales of tacrine stopped cold. To this day, donepezil remains the most widely sold Alzheimer’s drug in the U.S., accounting for just over half of the nearly 16 million prescriptions dispensed to treat the disease last year (according to IMS Health). And although two other cholinesterase inhibitors have since come on the market, donepezil’s side-effect profile remains the mildest of the bunch.

One of those other cholinesterase inhibitors, rivastigmine (Exelon), was approved by the FDA in 2000. Its claim to fame is that it blocks a different enzyme that breaks down acetylcholine. But unfortunately, it causes nausea, vomiting, and diarrhea far more often than does donepezil.

The third cholinesterase blocker, galantamine (Razadyne), was approved in 2001. Its side effects are generally milder than rivastigmine but not quite as mild as donepezil. On the other hand, it also stimulates the release of acetylcholine and other neurotransmitters.

But in fact, the distinctions between the three drugs are much ado about nothing much. “They all have the same basic effects,” Dr. Growdon says. “They vary a bit in dosing schedule, duration of action, and a little bit in side effects. But we use them almost interchangeably.”

Even so, the milder side effects associated with donepezil and galantamine are usually enough to tilt doctors toward one of them at the beginning of treatment,

Drugs offer Alzheimer's patients comfort, if only modest benefits.

says David A. Drachman, M.D., professor of neurology at the University of Massachusetts.

One key shortcoming of all three cholinesterase inhibitors, however, is that they are approved to treat only mild to moderate Alzheimer's.

Then, in late 2003, the FDA approved the first drug shown to be effective for moderate to severe disease: memantine (Namenda). The new drug blocks a different neurotransmitter than do cholinesterase inhibitors—glutamate, which can kill brain cells. After less than three years on the market, memantine already accounts for nearly a third of prescriptions written for Alzheimer's drugs.

Although it's not approved for mild to moderate Alzheimer's, some doctors prescribe memantine for that stage of the disease because it has such a good side-effect profile. However, Dr. Knopman says he's "quite skeptical of adding [memantine] when you have a mild Alzheimer's patient who is already on a cholinesterase inhibitor—the scientific data don't really support it."

Studies have shown, though, that once the disease has progressed, taking memantine along with a cholinesterase blocker is better than taking just a cholinesterase blocker alone.

But hold on a minute. If the benefits of all these drugs, including memantine, are so mild that you might not be able to tell any difference, why keep on taking them?

Because, Dr. Knopman and others point out, patients usually decline quicker without them—an effect that can often be seen if a patient stops taking them. And one study of donepezil found that even among patients who showed no benefit after three months of taking it, 70 percent showed a benefit after six months compared to those who were

taking a placebo.

"When I have told family members of patients with advanced Alzheimer's, 'Oh, I don't think the medication is doing anything, let's go

ahead and stop it,' I have actually seen people get worse before my eyes," Dr. Knopman says. "I am generally cautious now about withdrawing it. Sometimes it is entirely justified. But at other times, when the living situation is hanging in the balance, withdrawal of the medication may precipitate deterioration and lead to a crisis."

But if a family is convinced that a drug is not benefiting a patient, Dr. Drachman believes that withdrawing it under a doctor's supervision is reasonable—at least as a test to see what happens. "I wouldn't

abruptly stop the drug," he says. "I taper it and then see if there's any difference. If the family is not able to notice any difference on or off the drug, then it's probably not making a difference. Remember, none of the drugs modify the course of the disease—as much as we wish they would. They modify only the symptoms. So if those symptoms are not noticeably different, there's no point in continuing."

As long as families have realistic expectations given such limitations, then the approved drugs for Alzheimer's offer at least the comfort of a treatment with a known, if modest, effect. NN

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