The New Cholinesterase Inhibitors for Alzheimer's Disease, Part 1

Their Similarities Are Different

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Issue: *Soon there will be 3 new cholinesterase inhibitors for the treatment of Alzheimer's disease. Marketing of donepezil (Aricept) was followed recently by the introduction of rivastigmine (Exelon), and soon galantamine (Reminyl) will become available. Although all 3 drugs inhibit acetylcholinesterase, they can be distinguished from each other on the basis of secondary pharmacologic properties.*

Contemporary treatment of the memory disturbance in Alzheimer's disease is to boost declining cholinergic function, which is characteristic of this disease.[1,2] The best way to do this so far is to stop the breakdown of acetylcholine (ACh) by inhibiting the enzyme acetylcholinesterase (AChE). The first available agent to stop the breakdown, tacrine (Cognex), was limited by its short duration of action, narrow dosing range, drug interactions, and liver toxicity. Donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl) all remove these unfavorable actions. They also inhibit AChE. Are these 3 drugs therefore all the same? In considering the answer, let's think of baseball great Yogi Berra's response to a question about whether he and his son were alike: "Our similarities are different." All 3 cholinesterase inhibitors are similar in that they inhibit AChE, yet they are also different in terms of other pharmacologic properties (Table 1). These distinctions may help prescribers decide how to select one agent over another for different Alzheimer patients.

The Role of AChE Inhibition

AChE is a key inactivator of neuronally released ACh. It is now well known that inhibiting this enzyme can boost the action of ACh long enough to enhance cognition in Alzheimer patients,[1,2] which accounts not only for the mechanism of therapeutic action of donepezil,[3] rivastigmine,[4] and galantamine,[5,6] but also for their side effects. Centrally enhanced ACh improves cognition and probably also improves disruptive behavior in Alzheimer patients. Peripherally enhanced ACh causes the gastrointestinal (GI) side effects characteristic of these agents, especially at initiation of dosing, such as nausea and diarrhea, and in some cases vomiting and weight loss.[1–7] Although all 3 agents appear to inhibit central AChE more than peripheral AChE, rivastigmine may be uniquely more selective for the form of AChE present in hippocampal neurons (G1) where cognition is important than for the form of AChE present in neurons in other parts of the brain such as pons (G4), which are not important for cognitive functioning.[4]

Table 1. Pharmacologic Actions of Currently Available Drugs Used to Treat Alzheimer's Disease

Drug	AChE Inhibitor	BuChE Inhibitor	Nicotinic Receptor Modulator
Tacrine	✓	✓	
Donepezil	✓		
Rivastigmine	✓	✓	
Galantamine	✓		✓

The Role of BuChE Inhibition

A second enzyme called butyrylcholinesterase (BuChE; sometimes also known as "pseudo" cholinesterase) also breaks down ACh.[4,7] Normally, this enzyme seems to be more important in regulating ACh in peripheral tissues such as liver, plasma, and gut than in brain. How-

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Take-Home Points

- Donepezil is a selective acetylcholinesterase (AChE) inhibitor.
- Rivastigmine is a dual inhibitor of both AChE and butyrylcholinesterase.
- Galantamine is both an AChE inhibitor and a selective booster of nicotinic action.
- These properties are potentially important to clinicians who must decide when to treat Alzheimer's disease and with which cholinesterase inhibitor.

ever, as Alzheimer's disease progresses, especially in late stages, neuronal dropout is replaced by glia, which contain BuChE. Only one of the new agents inhibits this enzyme, namely rivastigmine. It may thus have theoretical advantages in later stages of Alzheimer's disease when less AChE and more BuChE may be present as neurons die and gliosis occurs. Whether rivastigmine in fact has greater benefits in late-stage Alzheimer's disease than agents that do not inhibit BuChE is not yet known. On the other hand, the higher incidence of GI side effects upon initiation of therapy with rivastigmine[4] may be explained in part by its property of inhibiting peripheral BuChE.

The Role of Allosteric Modulation of Nicotinic Receptors

Nicotinic cholinergic receptors may be especially important in regulating cognitive functions, such as attention, and in causing the release of more neurotransmitter from cholinergic neurons as well as from numerous other neurons that release dopamine, serotonin, γ-aminobutyric acid (GABA), glutamate, and norepinephrine.[8,9] Nicotinic receptors can be regulated both by ACh and by allosteric modulators that help ACh. In much the same way that benzodiazepines help GABA at $GABA_A$ receptors, galantamine helps nicotinic cholinergic receptors by allosterically modulating them.[10] This modulation produces more "bang" from each ACh molecule and causes even more ACh release.[8,9] Since nicotinic receptors are also located presynaptically on numerous other neurons that utilize various other neurotransmitters, this nicotinic modulating action of galantamine will lead to release of these other neurotransmitters throughout the brain.[8–10] The extent to which deficiencies of such neurotransmitters are restored could lead to improvement in functions mediated not only by ACh, but also by norepinephrine, dopamine, serotonin, glutamate, and GABA. Whether such theoretical actions will mean more improvement for cognition or for behaviors such as depression or anxiety associated with Alzheimer's disease is a provocative possibility that must await head-to-head trials of dual-action galantamine versus cholinesterase inhibitors that lack this property.

Summary

Three new cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, all inhibit the enzyme AChE. Rivastigmine also inhibits BuChE, which could lead to additional benefits in late-stage Alzheimer's disease, but also cause more GI side effects at initiation of therapy. Galantamine is also an allosteric modulator of nicotinic receptors, which could lead to additional efficacy for attention and for behaviors mediated by neurotransmitters other than ACh.

We are now entering an exciting era where the options for treating the devastating illness Alzheimer's disease are multiplying and creating a foundation upon which new therapies with new mechanisms of action can be built.

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Coming Next Issue

Part 2: Illustrating Their Mechanisms of Action