RATIONAL DESIGN OF NEW ACETYLCOLINESTERASE INHIBITORS

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INTRODUCTION

Six different classes of drugs, theoretically, could be useful for the treatment of the cholinergic deficit which characterizes Alzheimer's Disease (AD):

- Cholinesterase inhibitors (ChEI), which increase the synaptic levels of acetylcholine (ACh) by retarding its hydrolysis.
- ACh precursors, such as phosphatidylcholine, which might enhance the availability of choline.
- ACh releasers, which should facilitate the release of ACh from presynaptic end terminals, thereby activating the second messenger PIP$_2$ hydrolysis.
- M$_1$ and M$_3$ receptor agonists, which mimic ACh on the postsynaptic end terminal receptors.
- M$_2$ receptor antagonists (M$_2$ generally are presynaptics and play a role in controlling ACh release via negative feedback).
- Nicotinic agonists or substances having nicotinic like effects, which should also favor the release of ACh.

So far the ChEIs are the only agents which have been shown to produce statistically significant improvements in large multicenter, double-blind, placebo controlled trials on both psychometric measures of cognitive performance and quality of life indices in Alzheimer patients.

Tacrine, whose proprietary name is Cognex®, was the first acetylcholinesterase inhibitor (AChEI) to be registered and is presently used for palliative treatment of AD in the USA and in some European countries.
SECOND AND THIRD GENERATION OF AChE INHIBITORS

The structural formulas of ChEI in clinical and preclinical study are shown in Figure 1. The references for these compounds are collected under "additional references."

Several tacrine analogues are under pre-clinical or clinical evaluation, including amiridine, SM-10888, and 7-methoxytacrine. These AChEIs act at a site close to the catalytic triad of the enzyme. The X-ray crystal structure of

* Launched in 1993

FIGURE 1. Acetylcholinesterase inhibitors in clinical and preclinical study.