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Commentary

Commentary on William Summers Paper on Tacrine March 6, 2000

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Challenge with tacrine may diagnose AD

The cholinergic dysfunction in AD is not necessarily predominant (1,4,5) and responsivity to a cholinesterase inhibitor is not diagnostic for Alzheimer's disease. Normal young people have improved on psychometric measures in memory and attention after physostigmine challenge (3). Additionally, postmortem neurochemical measures of cholinergic function in AD patients do not correlate with ante mortem measures of cognitive dysfunction as measured with CDR (2) suggesting that patients who have responded to cholinesterase inhibitors in clinical trials (with mild to moderate AD) may have a limited cholinergic deficit. The argument of using acetylcholinesterase inhibitors as a diagnostic challenge in AD is tautological. AD patients may respond to cholinesterase inbibitors and there is a cholinergic deficit in AD. However, a response to cholinesterase inbibitors does not reliably diagnose AD.

Tacrine dosage should be individualized

It is possible that if higher doses of tacrine could be used that the dose could be individualized. However, the FDA approved dosages of tacrine are limited to 160 mg per day, and require a very long and slow titration period.

Cholinergic side effects indicate that the dosage of tacrine is too high

Although cholinergic deficits do occur at high doses, the interpretation that the dosage is too high does not acknowledge the effect of dose titration as a contributor to cholinergic side effects. Evidence from the clinical trial data of other cholinesterase inhibitors (rivastigmine and donepezil) supports the titration rate as a significant contributor to cholinergic side effects (6–10). When the rate of titration is slowed, tolerability improves, presumably because of tolerance to the cholinergic side effects, and allows patients to achieve higher doses.

Optimal dose should be confirmed by serum tacrine levels, because of the narrow therapeutic window

The data does not support this contention. Tacrine has multiple active metabolites and the clinical significance of the levels of any of these molecules remains unclear. Furthermore, the serum measures may not accurately reflect brain concentrations of the compound. Moreover, the *in vitro* effects of tacrine on cerebral blood flow and amyloid-beta processing cannot be generalized to AD patients when given tacrine under current clinical situations. The *in vivo* concentrations of tacrine have not been shown to be the same concentrations in the *in vitro* work described in the Summers article.

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Lecithin should be used to diminish the risk of hepatic effects

There is no carefully controlled evidence to support this conclusion.

Tacrine can be useful in all stages of AD

We agree that cholinesterase inhibitors have a theoretical role through the continuum of AD stages. In fact, intriguing neuropathological and neurochemical data suggest that the cholinergic deficit occur later in the stage of AD (2). The instrument used by Summers to measure change through the stages of AD was neither validated nor tested for reliability. Clinical trial data to test the hypothesis that cholinesterase inhibitors may be useful in all AD stages is urgently needed and will require reliable and valid instruments to measure changes later in the course of the disease.

Although tacrine's clinical utility is limited, there is evidence suggesting that newer agents such as donepezil, rivastigmine and galantamine do not require blood monitoring or four times a day dosing. Hence they are easier for clinicians to use. Tacrine's actual value in AD therapeutics may have been to help raise public and professional awareness that a pharmacological intervention may exist for this devastating disease and instill some needed hope for patients and their caregivers.

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