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Guest Editorial

Treating Alzheimer's Disease With Cholinesterase Inhibitors: What Have We Learned So Far?

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For almost 90 years following the original description of Alois Alzheimer's patient and the identification of Alzheimer's disease (AD) (Alzheimer, 1907), physicians faced the bleak prospect of observing the inexorable and relentless decline in cognition, function, and behavior with little or no opportunity for therapeutic intervention. In the last 5 years clinicians have finally been provided with a class of medications, the cholinesterase (ChE) inhibitors, which have passed the test of efficacy and safety in the symptomatic management of AD and related dementias. With the arrival of donepezil, rivastigmine, and galantamine as the second generation of ChE inhibitors, a renewed and sustained interest in the diagnosis and care of AD patients might have been anticipated. However, there remains residual therapeutic nihilism and skepticism over the utility of these treatments in some quarters of the medical community and among some paying authorities. In moving forward and addressing these concerns, we must reflect carefully on the question, "What have we learned about the ChE inhibitors so far?"

The development process of ChE inhibitors inadvertently fostered some of this reserve in the community and among funding authorities. The pivotal studies and indeed regulatory approval of the ChE inhibitors were directed towards their indication and use as cognitive enhancers. A variety of well validated psychometric scales including the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) (Rosen, 1984) were developed for use as primary outcome measures in clinical trials. However, their use remained outside usual care and unfamiliar to practitioners trying to understand the significance of ADAS-Cog rates of decline. The trials were short, generally lasting 12-30 weeks within a disease timeline that runs for 8-10 years. This initially left clinicians without a readily available translation of treatment effects from clinical trials to their clinical practice, as well as leaving uncertainty over the longer-term

cognitive effects of these medications. In some quarters, the absence of longer-term data was taken as being indicative of the absence of long-term benefit, creating a short-term therapy mindset. The Mini-Mental State Examination (MMSE), more widely used in clinical practice, lacks sensitivity in evaluating aspects of cholinomimetic response, including executive functioning, and is not well suited to identify treatment response along short timelines of weeks to months, when clinicians see their patients in follow-up.

In this supplement of the journal, Dr. Corey-Bloom comprehensively reviews the ADAS-Cog and MMSE across the studies of donepezil, galantamine, and rivastigmine. She emphasizes that cognitive benefits extend for longer periods of disease than has been formerly appreciated and that delay of treatment initiation by 6 months with rivastigmine and galantamine is associated with less cognitive benefit at 1 year than is found in those receiving such treatment from the outset. Rather than having an expectation of cognitive improvement over longer periods of treatment, the expectation of slowing the rate of cognitive decline with ChE inhibitors is the more likely attainable goal.

In the early studies with the ChE inhibitors, noncognitive outcomes were not emphasized, leading to serious criticism in some quarters that the more meaningful symptoms of AD were not being addressed (Mohr, 1995). This reflected on the limited AD-specific instruments that were available for measuring behavioral and psychological symptoms of AD at the time and the lack of recognition of the potential impact of the ChE inhibitors on both behavior and function. In this supplement, Dr. George Grossberg provides a comprehensive review of the clinical trials data and other studies that have investigated behavioral symptoms with ChE inhibitors. He emphasizes the important clinical pathologic correlations that can be made between behavioral symptoms (such as psychosis, agitation, and aberrant motor activity) and neurofibrillary tangles in the orbitofrontal, anterior cingulate, and neocortex. He also remarks on the cholinergic deafferentation of limbic and paralimbic regions from basal forebrain degeneration and the impaired cholinergic thalamic activity that are likely to underlie other behavioral symptoms. He points out that levels of butyrylcholinesterase (BuChE) in the limbic system in AD increase with disease severity, offering some evidence from clinical trials that ChE inhibitors with BuChE inhibitory properties such as rivastigmine may have added benefit for some AD behavioral symptoms.

Dr. Steven Potkin reviews the most recent clinical trials data of ChE inhibitors, with attention given to their impact on functional disability. He underscores the stabilization of function that emerges as the more realistic and achievable functional benefit of ChE inhibitors. He presents evidence from the large pooled data set of rivastigmine studies that demonstrate improvement or stabilization in mild to moderately severe AD and significant attenuation in the rates of functional decline in the more advanced stages.

With the approval and widespread use of three ChE inhibitors since 1997, there are the inevitable questions as to which is the drug of choice for which patients. The basis of such decision making hinges on a number of considerations including their mechanisms of action,

pharmacology, and ultimately, the clinical evidence. In his article in the supplement, Dr. Nigel Greig elaborates the clear distinctions between the drugs in their binding domains, selectivity for AChE and BuChE, their pharmacokinetics, and their noncholinergic actions. He builds the case that BuChE has an important role in the pathogenesis of AD and that its inhibition is an important additional therapeutic target in AD. Animal studies support the role of BuChE inhibition improving cognition in rats and increasing extracellular acetylcholine. The advantage of rivastigmine as a dual BuChE and AChE inhibitor is underscored with the anticipation that there will be a forthcoming generation of selective BuChE inhibitors for testing in AD. In reviewing some of the comparative pharmacology, Dr. Martin Farlow considers whether underlying pharmacologic differences between ChE inhibitors translate into different outcomes in clinical practice. He notes that, in addition to differential inhibition of AChE and BuChE, the ChE inhibitors may differ in their selectivity for the molecular isoforms of ChEs. Selective inhibition of the G1 AChE isoform, as provided by rivastigmine, may target inhibition to areas of the brain affected in AD, such as the cortex and hippocampus, and may have an impact on the efficacy with which this agent alters disease progression. His review draws the working conclusion that at the present time there have not yet been any randomized controlled head-to-head studies of ChE inhibitors, so that comparisons are inferential and not conclusive. Pharmacologic differences and mechanisms of action may well presage specific advantages in more definitive long-term studies that are planned and in process.

Finally, in considering the treatment of AD, we must return to the more qualitative dimension of treatment response. In the clinic, the responsiveness or apathy of the patients and the engagement of patients and their ability to form intention can all be considered as markers of response. These will not necessarily be picked up on quantitative cognitive, functional, or behavioral scales but can provide for both patient and physician satisfaction in treating AD.

Thankfully, the era of treatable AD has begun. Armed with our first efficacious treatment for AD, we have the challenge of exploring a heretofore-uncharted disease treatment pathway. We should enjoy this unique opportunity to be the first generation of clinicians to participate in characterizing the phenotype of ChE inhibitor-treated AD.

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SUGGESTED READING

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