GUEST EDITORIAL

Could cholinesterase inhibitors be harmful over the long term?

Long-term studies of cholinesterase inhibitors

Given the rather modest clinical effects of cholinesterase inhibitors, an important question is: For how long should they be prescribed? The clinical trials that supported marketing of the drugs were only 3–6 months in duration. A couple of 12-month, placebo-controlled donepezil trials showed some advantage for Mini-Mental State Examination (MMSE) scores and maintaining a level of activities of daily living (ADL) function during that interval (Mohs *et al.*, 2001; Winblad *et al.*, 2001). The controversial AD2000 trial in the UK tended to show MMSE and ADL efficacy over at least two years (Courtney *et al.*, 2004), but the authors questioned whether treatment was worthwhile or cost-effective.

Despite donepezil having been marketed since 1996 and rivastigmine and galantamine since 2000 and 2001, respectively, prospective, randomized, long-term trials for Alzheimer's disease (AD) have not been performed. There have been several randomized, placebo-controlled trials for mild cognitive impairment lasting one to four years (Petersen *et al.*, 2005; Feldman *et al.*, 2007; Winblad *et al.*, 2008; Doody *et al.*, 2009). None showed cholinesterase inhibitors to be efficacious compared to placebo (Raschetti *et al.*, 2007). In one trial, however, donepezil was associated with small effects on some secondary outcomes, including memory and language subscales, and MMSE at 12–24 months but the effects were not sustained.

Several observational studies have tracked cholinesterase inhibitor-treated patients over longer periods and all reported benefits for patients continuing with the medications in terms of less cognitive decline, less decline in ADL, or delay of institutionalization. These were studies of patients whose treatments had been extended after completing the three- and six-month pharmaceutical company-sponsored registration trials (Doody *et al.*, 2001; Geldmacher *et al.*, 2003; Pirttilä *et al.*, 2004; Raskind *et al.*, 2004; Small *et al.*, 2005; Burns *et al.*, 2007; Feldman *et al.*, 2009; Kavanagh *et al.*, in press), and of patients tracked in academic and research clinics (Gillette-Guyonnet *et al.*, 2006; Atri *et al.*, 2008; Lopez *et al.*, 2009; Rountree *et al.*, 2009). In these studies, patients continuing medications were compared to patients who had never been treated, used the drugs only briefly, or had dropped out of the randomized trials for one reason or another; some of the studies also used "projected" data from placebo patients, or historical data.

The observations of benefit, however, are confounded in that the various sources of bias cannot be controlled for. Mainly, the analyses of the observational datasets are of very different or incomparable cohorts creating in effect extreme comparisons (Schneider and Qizilbash, 2004). For example, the open-label extensions of randomized, placebo-controlled trials compare patients continuing on drugs, tolerating them well and – not surprisingly – not declining, with patients who are intolerant of the medication, discontinue it for various reasons, drop out of the study, or are declining rapidly. The academic clinics tend to compare a cohort of patients prescribed cholinesterase inhibitors after their advent in the late-1990s with an earlier cohort of patients not taking cholinesterase inhibitors, because the drugs had not been marketed yet. The more recent cohorts also tend to have higher cognitive scores at their inception than the cohorts not taking the drugs. Moreover, the observational studies do not take into account the patients who refused medication in the first place, started medications and stopped because of adverse events or personal preference, or those who stopped precisely because they were deteriorating rapidly. Demographic and clinical differences between the cohorts at inception cannot simply be "corrected" by statistical modeling. Indeed, the chronological date when patients entered the clinics predicted drug use, and this fact underlines the need to be able to compare contemporaneously constructed cohorts, and the need for randomized trials.

Results from these studies, the way they are reported, and their redundancy create a strong impression that the drugs continue to show efficacy over the long term, over at least two to five years, and patients are better off taking them than not. This impression of sustained clinical benefit in turn leads to prevalent recommendations from experts that cholinesterase inhibitors (and from some analyses, memantine) should be taken for indefinitely long periods. Intuitively, we tend to think a drug that is beneficial over the short term and appears to be tolerated will be beneficial over a longer, indefinite period. This hypothesis might well be true but there is sparse evidence for it.

AIBL, ADNI, and cholinesterase inhibitors

While examining differences between rapid decliners and normal decliners in a cohort of 211 participants with AD, investigators from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing report in this issue of *International Psychogeriatrics* (Sona *et al.*, 2012) the remarkable and counter-intuitive finding that a subgroup of rapid decliners was more likely to have been treated with cholinesterase inhibitors at the time of entering AIBL and continuing through the study than a slower declining subgroup. The observation is remarkable because the association of cholinesterase inhibitor use and worse clinical course has not been widely reported; it is counter-intuitive in that earlier analyses of clinical trials' open-label extension data and research clinic cohorts produced the opposite effects discussed above. As in other studies, however, cognitive impairment at entry into AIBL predicted more rapid MMSE decline as well. The size of the cohort was about the same as most of the other studies; and the univariate and multivariate odds ratios of 3.4 and 4.3, respectively, are moderately strong for the association of cholinesterase inhibitor use with rapid decline.

Earlier, my colleagues and I reported that patients with "mild cognitive impairment due to Alzheimer's disease" – essentially the same as prodromal AD – who entered the Alzheimer's Disease Neuroimaging Initiative (ADNI) on cholinesterase inhibitors were slightly more cognitively impaired, showed greater decline in clinical scores, and progressed to dementia sooner than patients who did not receive the drugs (Schneider *et al.*, 2011). Moreover, the mild AD disease patients, i.e. having MMSE scores from 21 to 26, who received both cholinesterase inhibitors and memantine were more functionally impaired, and showed greater decline on the MMSE and Clinical Dementia Rating scale (but not on the ADAS-Cog) than those who received cholinesterase inhibitors only. Patients had been using the drugs for about 12 to 15 months before entry into ADNI, and we noted that from a pragmatic perspective the decline associated with medications was as large as the effect sizes expected for the experimental drugs currently in clinical trials but in the opposite, counter-therapeutic direction. We concluded that their use might affect both the outcomes and interpretations of clinical trials and biomarkers studies.

The rate of cholinesterase inhibitor use in AIBL was 68% for AD patients (Ellis *et al.*, 2009) and comparable to the rate of 84.6% for mild AD patients among the mostly academic ADNI centers (Schneider *et al.*, 2011). This is similar to rates in recent mild to moderate AD clinical trials conducted from 2003 through 2009 that ranged from about 53% to nearly 100% (Schneider and Sano, 2009), and to a recent tarenflurbil trial in mild AD, in which 75.0% of the patients were taking cholinesterase inhibitors.

In randomized clinical trials that do not exclude patients who are on cholinesterase inhibitors, something similar to what was found in AIBL and ADNI can be observed. Examination of the placebo groups supports the basic observation that patients entering research studies already on cholinesterase inhibitors decline faster (Schneider and Sano, 2009). For example, in the randomized, placebo-controlled trial of the allosteric modulator of γ-secretase and tarenflurbil (Green *et al.*, 2009) involving 1,684 patients, those randomized to placebo who were taking cholinesterase inhibitors (with or without memantine) at enrollment worsened more than twice as much on cognitive and other outcomes over 18 months than the patients who were not taking cholinesterase inhibitors (unpublished data).

Why do these outcomes differ from previous studies?

As with the studies suggesting benefits for cholinesterase inhibitors, those suggesting disadvantages have similar confounds and potential sources of bias that cannot be wholly controlled for. One similarity between them is that the group with the better cognitive scores at the inception of the cohort tended to decline less, although not always. In the case of the earlier studies, these were the groups on cholinesterase inhibitors. In the later AIBL, ADNI, and clinical trials cohorts, however, they were the groups not on the drugs. To be sure, the parsimonious explanation that cognitive severity at the inception of the cohorts predicts outcomes could explain the differences. If so, however, it would imply that the cholinesterase inhibitors, overall, are neither beneficial nor harmful over the longer term.

Yet, an important characteristic of the AIBL, ADNI, and clinical trials data is that the cohorts were contemporaneously defined, i.e. patients were recruited during the same period and without regard to whether or not they were taking cholinesterase inhibitors, and there is little opportunity for a survivor bias (Sona *et al.*, 2012). By comparison, there were several years between the cohorts being compared in the earlier clinic-based studies; and the open-label extension studies effectively required all patients to be on drugs. Thus, one important feature of the AIBL, ADNI, and clinical trials cohorts

is that residual confounding due to different time periods, treatment requirements, and follow-up of the cohorts is minimized.

Important limitations to making inferences are that these are not randomized clinical trials in which medication was assigned randomly and that minimize biased outcomes. As with all observational studies, known and unknown potential biases cannot be fully corrected for by statistical analysis.

Physicians at the two AIBL centers and the many ADNI clinical sites could have made preferential treatment decisions based on a number of factors including greater clinical severity, neuropsychological test performance, and perceived deteriorating clinical course, and done so before the patient was considered for AIBL or ADNI. Patients entering clinical trials may be motivated by experiencing more rapid worsening despite their use of cholinesterase inhibitors.

What should we expect?

In a milieu of uncertainty, what should we expect from cholinesterase inhibitors? Is it reasonable to be sanguine that they work over the longer term or indefinitely? Or could the drugs possibly worsen cognition or be harmful over the long-run, perhaps by depleting neurotransmitter substrate, altering tone of surviving neurons, or just having no effect or pooping out as compensatory biological mechanisms such as increased acetylcholinesterase evolve? Analyses of healthcare databases Canadian and US veterans suggest that cholinesterase inhibitors are associated with increased rates of bradycardia, syncope, pacemaker insertion, and hip fracture (Gill *et al.*, 2009; Hernandez *et al.*, 2009).

Contradictory outcomes of observational studies contribute to the uncertainty about long-term treatment, and allow the possibility that such treatment could do harm rather than good, that there might be a certain effective treatment duration after which it is better to discontinue the drugs, or that some patients might be harmed from longer treatment even though others may benefit. Thus, any longer-term benefit or lack of benefit must be weighed against emerging long-term risks.

Related to this is the question of what we want to believe from *post hoc* and exploratory analyses of imperfect databases. The null condition for all these analyses is that the drugs have no particularly meaningful average effect at all and apparent results are influenced by the structure of the databases, bias, statistical models, and play of chance.

As these drugs become cheaper, more widely available from generics manufacturers, and as higher doses of brand name donepezil (and memantine) are marketed with associated greater rates of adverse effects (Farlow *et al.*, 2010), serious attention needs to be paid to the long-term effects of anti-dementia medications. Randomized controlled trials over the long term are not likely to happen unless prosecuted by government healthcare agencies. Better designed effectiveness research and epidemiology, and better modeling, will be needed to address these questions. In the meantime, physicians and patients might at least consider the possibility that over the long term cholinesterase inhibitors may not be all good for all patients. Nevertheless, there can be substantial variation in the effectiveness of the drugs for individual patients, and what works for one person may not work for another. Consequently, treatments must be individualized – not an easy task with this illness and these drugs.

Conflict of interest

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