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Can Lithium or Valproate Untie Tangles in Alzheimer's Disease?

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The article in this issue by Hampel et al[1] offers a glimpse of an interesting chapter in the history of Alzheimer's disease (AD) treatment research. An understanding of the significance of this report, which touches on issues ranging from the identification of novel targets for treatment to widely differing approaches to trial design, provides an appreciation of the rapid pace of treatment development in the field and allows one to gain some insight into an interesting historical sidebar.

Alzheimer's disease is now the fourth leading cause of death in people over age 65 years in the United States and the only major cause of death that is *increasing* over time. The Alzheimer's Association estimates that there are 5.3 million Americans affected by AD, a number expected to increase to 11 to 16 million by 2050.[2] It is imperative that we find a way to put this illness behind us. But where does lithium fit in?

As Hampel et al concisely summarize, the major neuropathological hallmarks of AD include amyloid-containing plaques and neurofibrillary tangles. There are numerous therapeutics in development targeting the amyloid pathway, chiefly because of the finding that several autosomal-dominant genetic mutations leading to early onset AD all involve dysregulation of amyloid processing. This finding has led to the development of animal models of this aspect of AD pathobiology and, in turn, numerous opportunities to ameliorate this process. We are much further behind in our efforts to target tangles, yet they are an important part of the picture since tangle burden correlates with clinical severity of dementia more clearly than does amyloid burden.[3] Tangles, located within neurons, are believed to develop in part because of aberrant phosphorylation of tau proteins, essential structural features normally functioning as stabilizers of microtubules. Phosphorylation of tau leads to microtubular destabilization and ultimately cell death. Several kinase enzymes appear to be involved in this process, including glycogen synthase kinase-3 (GSK-3).

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Developing kinase inhibitors has proven to be daunting, although there have been at least some encouraging initial developments.[4] At the same time, novel techniques to understand the biologic effects of clinically proven psychoactive agents have revealed quite surprising mechanisms of action affecting functions as disparate as cell cycle regulation, synaptogenesis, and aspects of cellular resilience. For instance, both lithium and valproate, agents well known to psychiatrists for their utility in the treatment of mania, have been shown to inhibit GSK-3, thereby affording the hope of increasing microtubule stability, reducing tangle burden, and hopefully conferring clinical benefit to patients with AD. Actually, both agents also have other laudatory effects relevant to the pathobiology of AD, including upregulation of the powerful anti-apoptotic factor Bcl2, induction of nerve growth factors, and even normalization of amyloid processing. The surprising reality is that well-worn lithium and valproate may be the most accessible agents for attenuating the progression of AD by targeting tangles. But will these medications "work"? And what are the best ways to test them?

The National Institutes of Health (NIH)–funded Alzheimer's Disease Cooperative Study (ADCS) began weighing this question in 2000 as it considered whether to pursue development of 1 agent or the other or both. The ADCS concluded that, while both agents were of interest, a trial of valproate would be undertaken initially, primarily because of concerns about lithium toxicity in older people with AD and the absence of valid biomarkers to establish proof of mechanism. The same lack of availability of biomarkers led to the decision to conduct a full-scale clinical trial of valproate to establish whether it could alter the clinical progression of AD. There had also been inconsistent reports of possible relief of agitation in patients with AD, lending further weight to the decision to choose valproate at that time, although a later ADCS symptomatic trial was negative.[5]

A unique "secondary prevention" design was created in which patients with AD who lacked psychopathology were randomly assigned to treatment with valproate or placebo for 26 months, with the primary outcome being survival until incident psychopathology and the key secondary outcome being rate of decline of cognitive and clinical assessment scores.[6] The trial, which we had the privilege to lead

along with numerous ADCS colleagues, also incorporated exploratory biomarkers and changes in brain volumes on repeated magnetic resonance imaging scans. Over 300 participants were enrolled in the study beginning in late 2003, the last participant finished in March 2009, and results will be reported later this year.

Over time, the ability to track the biologic effects of treatments has improved, and the urgency to find effective treatments for AD has increased as well. In 2004, the ADCS re-examined the possibility of a lithium trial and in 2005 obtained NIH funding to conduct a study beginning in 2009. At that juncture, it had been established that it was possible to measure biochemical manifestations of AD pathobiology in the cerebrospinal fluid (CSF), notably tau, phospho-tau, and amyloid species. Therefore, it might be possible to administer lithium over a relatively brief period and use biomarkers to address whether AD biology was impacted. This study design was indeed proposed. Further, measures of target engagement had been (and still are) in development, meaning that proof of mechanism might be possible as well. That is, it might be possible to show that lithium given to patients with AD might inhibit GSK-3. Showing this target engagement would be important not necessarily to bring lithium forward as a treatment for AD, but as a valuable stepping stone for the development of other GSK-3 inhibitors. The ADCS thus adopted an entirely different design for its lithium trial: a short-term CSF biomarker study. One of the authors of this commentary (P.N.T.) also served as the project director for this effort.

In parallel, scientists at AstraZeneca and academic collaborators, having come to the same conclusions, designed and executed a nearly identical study. One might wonder why a large pharmaceutical company would be interested in funding a lithium trial. The answer is almost certainly that such a trial might shed light on how the company might best develop its own GSK-3 inhibitor(s).

In brief, the trial of Hampel et al[1] accomplished most of our shared aims, although there are still questions. The authors state that the results do not support the hypothesis that lithium has significant effects on core biologic outcomes. Perhaps this is overstated; that is, it is entirely possible that lithium *at sufficiently high concentrations* might show the anticipated effects on CSF biomarkers. Hampel et al deployed clinically reasonable, and possibly optimal, doses of lithium, achieving mean plasma levels of about 0.8 mM. That dose might have been close to the lower end of the range needed to affect the target of greatest interest, GSK-3. Tolerability was acceptable: there were expected side effects, but they were mild. However, the mean CSF lithium concentration was about 0.3 mM, well below the range needed to adequately test lithium's engagement with the target and therefore its effect on AD biology as well. Put differently, the study showed that lithium at tolerable doses and CSF levels insufficient to engage GSK-3 does not affect the "core biologic outcomes." But are these the maximally tolerated doses in this population?

Hampel et al and AstraZeneca shared their prepublication results with the ADCS, an example of industry/academic collaboration and generosity. The ADCS took this opportunity to reassess its planned lithium study. The 2 trial designs were so close that the rationale for conducting the ADCS trial as planned now seemed insufficient. The ADCS steering committee debated trial design modifications, such as longer duration of treatment, higher lithium doses, or selection of different biomarkers. The prevailing view, after some months of deliberation, was that the core issue was the ability to achieve higher lithium levels than those in the Hampel et al study. The decision that the ADCS recently made, not without dissent, was to abandon its plans to pursue lithium because of uncertainty regarding the feasibility of safely achieving significantly higher doses in this vulnerable group of patients.

The lithium story may not necessarily end here, although it could. It is highly likely that more novel measures of GSK-3 inhibition and/or disease progression will be found, leading to renewed interest in studying lithium at clinically acceptable doses. It is possible that the results from the ADCS valproate trial will shed new light and stimulate further interest in lithium. Our greatest hope, however, lies with discovery teams working to identify viable tau kinase inhibitors, microtubule stabilizers, tau antiaggregation agents, or even biologics to attack and untie tangles.

In the meantime, this commentary affords a means to gratefully acknowledge the courage and humanity of the patients who participated in the lithium trial reported here, as well as their families, and indeed of all patients and families who volunteer for studies such as this. And to acknowledge the combined efforts of AstraZeneca and their academic collaborators that allowed their US colleagues to *not* expose additional research volunteers in vain, nor misuse scarce public funds.

Drug name: lithium (Eskalith, Lithobid, and others).

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