

- 915 Effect of a Serotonin Reuptake Inhibitor on Irritability, Apathy, and Psychotic Symptoms in Patients With Alzheimer's Disease.
- 919 Can Lithium or Valproate Untie Tangles in Alzheimer's Disease?
- 922 Lithium Trial in Alzheimer's Disease: A Randomized, Single-Blind, Placebo-Controlled, Multicenter 10-Week Study.

Untangling the Roles of Antidepressants and Mood Stabilizers in the Treatment of Alzheimer's Disease

Two articles and a commentary in this issue underscore the need to clarify the roles of antidepressants and mood stabilizers in the treatment of Alzheimer's disease (AD). Siddique and colleagues investigate the effects of the selective serotonin reuptake inhibitor (SSRI) citalopram on the treatment of irritability and apathy in AD. Hampel and colleagues use a biomarker strategy to investigate the potential of lithium to modify tau phosphorylation, a cardinal feature of AD pathology. In an invited commentary, Tariot and Aisen note the need for investigational tau-modifying treatments, the role that research studies of lithium and valproic acid could have in this endeavor, and the impact of the biomarker study by Hampel et al on their own work and the field.

Antidepressants in the Treatment of Irritability and Apathy

Siddique et al performed a retrospective analysis of data from the Clinical Antipsychotic Trials of Intervention Effectiveness in AD, a large naturalistic multicenter trial of 3 atypical antipsychotics and the SSRI citalopram in patients with AD and the associated features of aggression or psychosis. Their analysis was restricted to 34 patients who were initially randomly assigned to placebo and subsequently randomly assigned to citalopram when the patients' medication was changed at the discretion of the treating physician. The authors report a large decrease in irritability in these mostly non-depressed patients, a concomitant decrease in apathy, and a significant association between medication dose and length of treatment. On the basis of their findings, the authors suggest that an SSRI might be a reasonable first-line treatment for irritability in patients with AD and underscore the need for a larger randomized clinical trial to clarify the efficacy and tolerability of SSRIs for the treatment of irritability in patients with AD.

Readers may find some of the conclusions not that uplifting or conclusive. As the authors note, the reductions in irritability were not statistically significant, the sample was small, and the original trial was designed to assess a different endpoint: the length of treatment before the medication was discontinued for any reason. The authors are to be commended for highlighting the need for a larger randomized clinical trial to help clarify the efficacy and safety of citalopram and other antidepressants in treating the irritability commonly associated with AD.

Until then, what is the clinician to do for these patients? Recommendations previously published in the *Journal* are restated here.¹ First, identify and try to address the possible contribution of environmental factors, delirium, other medical illnesses, or unrecognized pain to the patient's symptoms. Second, if a cholinesterase inhibitor or memantine is already prescribed for a patient's cognitive symptoms, empirically determine its beneficial effects, if any, on the patient's noncognitive symptoms. Third, if a suggested but not well-established medication is prescribed for the time-limited treatment of an AD patient's psychiatric symptoms, monitor the patient's response and adjust the medication accordingly. The medication may help some patients but not others, harm some patients but not others, or produce a combination of beneficial or adverse effects that need to be monitored and managed accordingly.

Mood Stabilizers in the Modification of Underlying AD Pathology

Alzheimer's disease is characterized neuropathologically by neuritic plaques, the major constituent of which is an aggregated form of certain amyloid- β (A β) peptides,

tangles, the major constituent of which is an aggregated and hyperphosphorylated form of the microtubule-associated protein tau, and the loss of synapses and neurons. While many investigational A β -modifying treatments are being studied in clinical trials, treatments targeting other elements of the disease pathway may be needed, alone or in combination with A β modifiers, to have the greatest therapeutic effect. For this and other reasons, researchers are eager to study sufficiently safe and well-tolerated treatments that inhibit tau hyperphosphorylation, inhibit tau aggregation, or stabilize microtubules.

Interestingly, lithium and, in some but not all studies, valproic acid have been shown to inhibit the activity of glycogen synthase kinase-3 β (GSK-3 β), a key mediator of tau hyperphosphorylation, to inhibit tau hyperphosphorylation in cells, and to reduce neurofibrillary pathology and degeneration in transgenic mice. Moreover, each of these treatments has been shown to inhibit GSK-3 α , which interacts with γ -secretase in the production of A β , and to inhibit A β production, neuritic plaque formation, and behavioral deficits in mouse models of AD.

In an elegant and important proof-of-concept biomarker study, Hampel and colleagues evaluated the effects of short-term lithium treatment on lymphocytic measurements of GSK-3 activity and cerebrospinal fluid (CSF) measurements of phosphorylated tau in patients with AD. While lithium was reasonably well tolerated at the targeted serum levels, the trial did not detect significant effects of short-term lithium treatment on GSK-3 activity or tau phosphorylation.

While the findings are disappointing, several important questions remain to be addressed. Could lithium reduce tau-phosphorylation and clinical progression at higher serum levels (closer to those in the study of transgenic mice), over longer treatment durations, at an early stage of AD (before the development of extensive neurofibrillary pathology), or in combination with a potent A β -modifying treatment? Do lymphocytic measurements provide an accurate representation of GSK-3 activity in CSF or the brain? How long does

a treatment need to be continued in order to reduce phosphorylated tau in neurons before an effect can be measured in CSF? What about the effects of valproic acid? Most importantly, when will we be able to start evaluating a few sufficiently potent, safe, and well-tolerated tau-modifying or microtubule-stabilizing treatments in clinical trials?

In their commentary, Tariot and Aisen note the importance of the biomarker study while providing an inside look at how study decisions are made. It turns out that these investigators and their colleagues in the National Institutes of Health (NIH)-funded AD Cooperative Study (ADCS) shared an interest in the role of lithium (and valproic acid) for the very same reasons. The researchers had NIH approval to conduct a biomarker study of lithium very similar to the one conducted by Hampel's team in an industry-sponsored study. After Hampel and colleagues generously shared their findings with the investigators prior to publication, the ADCS came to the reluctant decision not to move forward with their own biomarker study of lithium despite the interest in trying higher serum levels, due to lingering concerns about the safety of higher levels in this vulnerable population.

Still, the questions remain. Could lithium be helpful in the earlier clinical and presymptomatic stages of AD, alone or in combination with A β -modifying treatments? When will researchers have the chance to study more potent tangle-busting treatments over longer durations, in the presymptomatic, early clinical, and late clinical stages of AD, alone or in combination with A β -modifying treatments? We hope the answers are not too far away.

REFERENCE

1. Reiman EM. Clinical trials and tribulations. *J Clin Psychiatry*. 2007;68(3):428-429.

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