

**COMMENTARY**

**Lithium therapy in ALS**

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In a recent issue of PNAS, Fornai et al. reported that lithium has neuroprotective effects in a mouse model of motor neuron disease. They also reported that lithium seemed to slow disease course in a small number of people with ALS.

Sixteen people were treated with lithium and compared with 28 who were not. Most striking was the observation that eight of 28 patients on riluzole died during the 15 months of treatment, while none of the 16 patients taking the combination of riluzole and lithium died over that time.

The magnitude of these effects has generated great excitement in the ALS community; however, the very small number of treated patients and a number of aspects of the trial design should be signals to treat this finding with caution as well as enthusiasm. For some patients, however, the hope that has been generated by this pilot study is translated into a desire for immediate treatment with lithium. An international effort is already underway to initiate a larger, randomized trial to verify whether these pilot data are correct.

It is critical to remember that this study was designed to be a pilot study. The report leaves several questions unanswered. One critical question is how patients were chosen for treatment. The duration of subject accrual was not stated, and it is not clear that consecutive patients were enrolled. If this is not the case, it is important to know what criteria were employed to decide which patients were offered inclusion. The rationale for the larger placebo group than treatment group is not given; this is an unusual ratio as most studies have either

1:1 or greater active treatment to placebo ratios. The number of patients who completed the study on drug is also not stated. Although the percentage of bulbar patients in both groups, the initial ALSFRS score, and initial forced vital capacity are all similar for the two groups, the lithium treated patients seemed younger and had earlier onset of symptoms. Both the number of survivors at month 12 (and 15) and the survival curve of the placebo group are rather unusual compared with other ALS trials and need to be clarified by a better understanding of the causes of death.

This was also not a blinded study, which, although appropriate for a pilot trial, limits the degree to which results can be generalized. Given the lack of blinding, it would be important to know that both groups were treated equivalently, especially with regard to potentially life-prolonging interventions. The percentage of patients in the two groups receiving BIPAP or PEG tubes is not stated and is critically important in this regard. Also appropriate for a pilot study is the broad inclusion criteria allowing patients to enter the study with symptom duration less than five years. However, for a more definitive trial, a shorter symptom duration is important to reduce the number of slowly progressing patients.

It is clear that the next step forward is a larger, randomized, controlled study of lithium to quickly determine whether these findings are truly a new treatment for ALS or the result of chance and small sample size.

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