LETTER

Lithium may slow progression of amyotrophic lateral sclerosis, but further study is needed

To the Editor: In the February 12, 2008 edition of PNAS, Fornai *et al.* (1) suggest that lithium slows human ALS progression. We have several questions about their study.

Was this trial registered before enrollment, as required by the International Committee of Medical Journal Editors (2)? If not, why? How were participants selected? What were the inclusion/exclusion criteria? How many were screened to accrue 44 participants? Most ALS trials employ a 1:1 randomization ratio or one that places more patients in the treatment group. Why was this 16:28 ratio chosen? Was placebo administered in the nonlithium group? Were patients blinded to treatment assignment? If so, how was this blinding affected by adjusting the lithium dosage in the treatment group to maintain desired plasma levels? Why were these particular lithium levels targeted? Were there drop-outs? Was use of bilevel positive airway pressure (BiPAP), mechanical ventilation, and percutaneous endoscopic gastrostomy (PEG)—interventions that prolong ALS survival—similar in both treatment groups? What specific safety monitoring was done? Is there a listing of adverse events by treatment group?

Responses to these questions are critical in planning follow-up studies to confirm the possible benefits of lithium on ALS survival and to delineate potential detrimental effects. It is our sincere hope to learn from recent history, when physicians prescribed the drug minocycline off-label while it was under study only to find that the definitive trial showed that it increased ALS progression rate (3).

Richard S. Bedlack*†, Nicholas Maragakis‡, and Terry Heiman-Patterson§

**Duke University ALS Clinic, 932 Morreene Road, Durham, NC 27705; ‡The ALS Center at Johns Hopkins, 600 North Wolfe Street Baltimore, MD 21287; and §MDA/ALS Center of Hope, Drexel University College of Medicine, P.O. Box 40777, Philadelphia, PA 19107*

1. Fornai F, *et al.* (2008) Lithium delays progression of amyotrophic lateral sclerosis. *Proc Natl Acad Sci USA* 105.2052–2057.
2. International Committee of Medical Journal Editors (2004). Clinical trial registration: A statement from the international committee of medical journal editors. *Ann Int Med* 141:476–477.
3. Gordon PH, *et al.* (2007). Efficacy of minocycline in patients with amyotrophic lateral sclerosis: A phase III randomized trial. *Lancet Neurol* 6:1045–1053.

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†To whom correspondence should be addressed. E-mail: bedla001@mc.duke.edu.