

LETTER

## The role of lithium in ALS remains unknown

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Dear Sir

In a recent issue of *The Lancet Neurology*, Aggarwal et al. (1) reported a multicentric, randomized, double-blind, clinical trial comparing lithium carbonate plus riluzole with riluzole plus placebo in sporadic amyotrophic lateral sclerosis (ALS) with a time-to-event design in order to study lithium safety and efficacy. The study was early finished because of a pre-specified futility endpoint suggesting that lithium did not alter ALS progression.

Since 1994, when the first evidence of an effective treatment for ALS was published (2), many other clinical trials with different drugs and strategies were developed; none but riluzole produced significant clinical improvements. A systematic review of riluzole treatment in ALS reported a small benefit in favour of this medication on survival with a small effect on both bulbar and limb functions (3).

In 2008, Fornai et al. (4) published the first randomized clinical trial investigating lithium effects in ALS. This trial was developed after the demonstration of lithium efficacy in a transgenic mouse model of motor neuron disease. Patients treated with lithium plus riluzole showed an increased survival and decreased disease progression rate measured by functional scores compared to patients treated only with riluzole. Although a small sample pilot study, this trial brought hope for ALS treatment together with concerns over the off-label use of lithium due to its availability and low cost.

By conducting a larger, randomized, controlled clinical trial, Aggarwal et al. aimed to answer the question raised by Fornai et al. about lithium efficacy in ALS; however, this study also presented important limitations. After two months of treatment

only 18/38 (47%) patients achieved the target lithium level and the study mean follow-up was 5.4 months. Thus, therapeutic lithium levels were not evaluated for the minimum six months period established by the authors for primary endpoint. Secondly, there were three deaths in the placebo and one in the lithium group. Even if lithium therapeutic levels were maintained for six months this is not enough time for showing survival differences in ALS. According to previous studies evaluating lithium (2) and riluzole (3,4), differences in survival were only detected after a minimum follow-up of 12 months.

Therefore, considering that lithium is a cheap and safe drug with limited side-effects, further studies are still justified in order to clarify the real efficacy of this drug in progression and survival rates of ALS patients.

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### References

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