

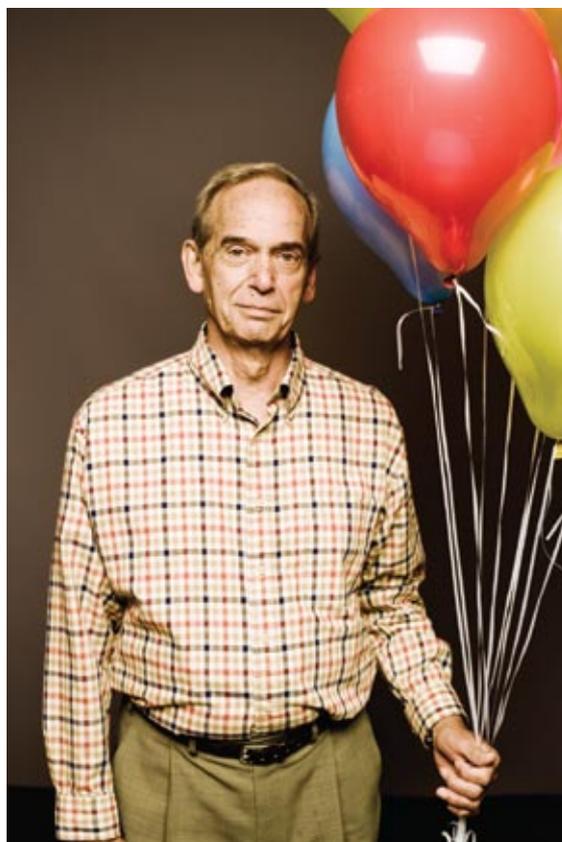
# Hype or Hope?

## Does lithium hold promise for the treatment of ALS?

BY CATHERINE WOLF

**T**here is no cure or effective treatment for ALS. The only FDA-approved drug for the disease, riluzole, extends life by a paltry three months, with no improvement in muscle strength. Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, relentlessly attacks the motor neurons, nerve cells located in the central nervous system that have long fibers (axons) extending outside that system. Motor neurons directly or indirectly control muscles. Within two to five years, most people with ALS lose the ability to walk, use their arms, talk, swallow, and breathe. Death usually comes by respiratory failure, unless one opts to go on a ventilator, as I did more than seven years ago.

That's why patients were abuzz with excitement when the results of a small Italian study appeared in the February 2008 issue of the *Proceedings of the National Academy of Sciences*. The 15-month study found that lithium plus riluzole slowed the progression of ALS compared to riluzole alone. Lithium is used in higher doses to treat bipolar disorder (manic depression). Sixteen patients received lithium plus riluzole and 24 patients received riluzole only. The authors reported no statistically significant decline in the lithium group over the course of the study on the ALS Functional Rating Scale-Revised (ALS-FRS-R). This widely used measure of physical functioning consists of questions about activities of daily living. And while 29 percent of the riluzole-only patients died during the duration of the study, none of the lithium-plus-riluzole patients died.



### PROBLEMS WITH THE STUDY

The findings spread like wildfire across the ALS community. Patients from all over the world began clamoring for lithium almost immediately. (See map, page 33, with balloons indicating patients currently taking lithium.)

Is lithium the Holy Grail of ALS? I'm skeptical. In my 11 years of living with this disease, I have seen many promising drugs come and go: brain-derived neurotrophic factor, topiramate, minocycline, indinavir, celecoxib, and more. Initially they all seemed promising, but later they were found to be ineffective or had adverse effects.

A mouse study conducted earlier by the same authors suggested that lithium might have neuroprotective effects. They

gave lithium to mice genetically engineered to have the SOD1 gene mutation, common in approximately 20 percent of familial cases of human ALS (familial cases comprise about 5-10 percent of the total cases of ALS), and found they lived 36 percent longer than control mice. The onset of disease was delayed as well. And in motor neurons cultured with lithium, the researchers observed positive effects on the mitochondria, which are vital for cell energy: The mitochondria of the lithium-treated motor neurons were able to digest abnormal proteins, and there was an increase in the number of healthy mitochondria. However, the findings have yet to be replicated.

The beneficial effects in the human study may have been the result of an interaction between lithium and riluzole. But the study did not have equal numbers in each group, and the number of patients receiving lithium was very small. Both of these factors make it difficult to generalize about the outcome.

Moreover, patients knew which group they were in, notes Merit Cudkovicz, M.D., M.Sc., associate professor of neurology at Harvard Medical School and director of the ALS Clinic and Clinical Research at Massachusetts General Hospital. Clinical trials ideally are conducted by a double-blind procedure in which neither patients nor researchers know whether they have received the active drug or a placebo. There was no placebo group in the Italian study that took riluzole plus a harmless substitute for lithium, such as a sugar pill, and so the response could be due to the placebo effect. This occurs when a patient's

symptoms are altered in some way by a treatment due to the individual expecting or believing that it will work.

### LARGER STUDIES PLANNED

Nevertheless, Hiroshi Mitsumoto, M.D., professor of neurology at the Columbia University Medical Center and director of the Eleanor and Lou Gehrig ALS Center, both in New York, NY, says that the study is “very interesting. If this is true, it is very important. We need a large confirmatory study.”

Based primarily on the survival data from the Italian research, controlled trials are being planned by the Northeast ALS Consortium, the Western ALS Study Group, and the Canadian ALS Consortium. The Northeast Consortium anticipates a fall start to their trial, which will be a randomized, placebo-controlled study comparing the safety and efficacy of lithium plus riluzole versus riluzole alone. The Western ALS Study Group is taking a different approach: All participants will receive lithium, and the placebo group will be the historic placebo group from the minocycline trial. The Italian group also plans larger human trials.

Meanwhile, some ALS patients are taking lithium “off label,” which means outside of the scope of the drug’s approved indications. Currently, lithium is approved only for treatment of bipolar disorder. Dr. Mitsumoto and Dr. Cudkowicz both warn of the potential problems of taking lithium for people with ALS. For one, blood levels must be carefully monitored. “Lithium can be toxic to the thyroid, kidneys, brain, and other organs,” Dr. Mitsumoto says. When patients take a drug off label, there is no system-

atic collection of data about effectiveness or side effects.

### PATIENTS WON’T WAIT

Despite these warnings, some people with ALS are determined not to wait for the results of a clinical trial. An online community of people living with ALS at [PatientsLikeMe.com](http://PatientsLikeMe.com) is providing members with tools to chart their progress and compare themselves to others through a set of data filters, such as years since diagnosis and gender. The site also contains a list of lithium’s side effects and the number of members who are experiencing these effects, a world map showing the location of patients taking lithium, and forum topics so that people can share their experiences with the drug. However, since lithium can be toxic, people with ALS should have a thorough discussion with their doctors about the po-

“If this is true, it is very important. We need a large confirmatory study.”  
—Dr. Mitsumoto

tential benefits and risks of taking the drug in their case.

Users can also

generate interactive graphs. The site includes longitudinal data from a self-administered version of the ALSFRS-R. (Longitudinal data are observations collected over a period of time.) One can plot ALSFRS-R score for a selected group of patients before and after starting lithium. And because lithium may have varying effects at different stages of disease progression, the site allows users to compare the effects of the drug on patients with different scores using data filters. One could plot all patients with a score of more than 36 (out of 48) compared to those with a score of less than 18. Says James Heywood, co-founder of PatientsLikeMe, “Not enough time has passed for any clear conclusions to be drawn. But for the first time, patients might answer a scientific question about a new treatment before the research process will.”

Although PatientsLikeMe has more than 200 patients tracking their progress, questions about the process linger. Will the expectations of patients taking lithium bias their self-reported scores? Since there is no way to ensure that measurement is done at regular intervals, as in a controlled study, how will progression be measured?

Despite such flaws, the findings may give the first hint to the question: Does lithium slow progression of ALS? For now, the answer is a question mark. NN

*Catherine G. Wolf has been living with amyotrophic lateral sclerosis since 1997 and is a frequent contributor to Neurology Now.*



### Lithium Map

This map, provided by [PatientsLikeMe.com](http://PatientsLikeMe.com), shows the geographical distribution of ALS patients currently taking lithium. The site also contains a list of lithium’s side effects, the number of members who are experiencing these effects, and forum topics so that people can share their experiences with the drug.