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New ALS drug slips through telling 'phase II' clinical trials

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A drug already used to treat symptoms of epilepsy has potential to slow the muscle weakening that comes with amyotrophic lateral sclerosis (ALS), scientists report after completing a Phase II clinical trial—an early, small-scale test to show if the drug works and continues to be safe.

A report online December 4 in the journal Amyotrophic Lateral Sclerosis says the drug talampanel showed some ability to slow the loss of major daily life activities such as speaking, walking and dressing that typically slip away as the disease progresses. The drug is a member of the benzodiazepine family — anti-anxiety and muscle-relaxing agents that work in the brain and spinal cord.

The study, by a scientific team from Johns Hopkins and Indiana University, reveals there's enough benefit from this new use of talampanel to propel it into larger trials that will definitively tell its worth.

The trial in 59 volunteers with ALS — also called Lou Gehrig's disease — showed that talampanel can be safe for patients with the disease and that any recorded side effects are tolerable, says Johns Hopkins neurologist Jeffrey D. Rothstein, senior scientist on the new study. Rothstein heads the Robert Packard Center for ALS Research at Johns Hopkins.

Phase II trials are designed to show on a small scale if a drug is safe and if it works. So the present trial included ways to measure the drug's

benefits, which came across as clear, if not statistically significant. "The research demonstrates that talampanel appears able to slow the progression of disabling ALS symptoms," Rothstein says. "The effect isn't overwhelming at the dosage of medicine used in this early, very small trial," he adds. "Still, having promising human data is reason enough to keep it in the drug pipeline where we can really find out where it stands for patients."

Rothstein says the promise of talampanel is especially important in ALS because the always-fatal neurodegenerative disease has foiled therapy for years.

With the exception of riluzole, the single FDA-approved drug for the disease, there's no other treatment to slow or stop it. "Riluzole can extend life only modestly and hasn't been shown to slow ALS symptoms," says Rothstein, "so the need for better therapy is real. Barring a cure, we'd still be glad for agents strong enough — either singly or in combination — to put ALS in the chronic disease category."

In the study, ALS patients in the talampanel-receiving group (40 of the 59) at both Johns Hopkins and Indiana University took a month to ease into the trial-desired dose of the drug. Most stayed there for the remaining eight months of the study.

Periodically, clinicians rated the 40 who got talampanel and 19 control subjects (those who took a placebo) on a measure of isometric arm muscle strength. Testing also included the rate of decline in breathing and the ALS Functional Rating Scale (ALSFRS) — a standard measure of abilities that include speech, swallowing, handwriting, breathing, walking and food-cutting.

To see if the drug was safe for ALS patients, subjects received a variety of laboratory blood tests, an electrocardiogram, a neurological exam and

other measures.

In most of them, talampanel slowed progression of ALS. Results stood out, especially, in the ALSFRS, where patients' decline in abilities slowed 30 percent.

Several facts about talampanel make it especially attractive to try as a possible therapy, Rothstein says. The drug's talent is its ability to block specific receptors on ALS-vulnerable nerve cells that are docking sites for the neurotransmitter glutamate.

An excess of glutamate trips excitotoxicity — a process that can kill the motor neurons that enable movement. Earlier studies by Rothstein and others on cell and animal models of ALS consistently confirm excitotoxicity as a source of damage in the models and ALS patients. Levels of glutamate are elevated in spinal fluid and in the brain in as many as 40 percent of ALS patients whose disease appears to arise spontaneously.

Talampanel and other molecules that whisk glutamate out of harm's way prolong life in animal models of ALS while also preserving motor neuron life and muscle strength.

Also attractive, Rothstein adds, is that talampanel is a small molecule that can penetrate into the brain and spinal cord where it's needed.

Currently, a large international trial of talampanel is under way, due to end in 2010.

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