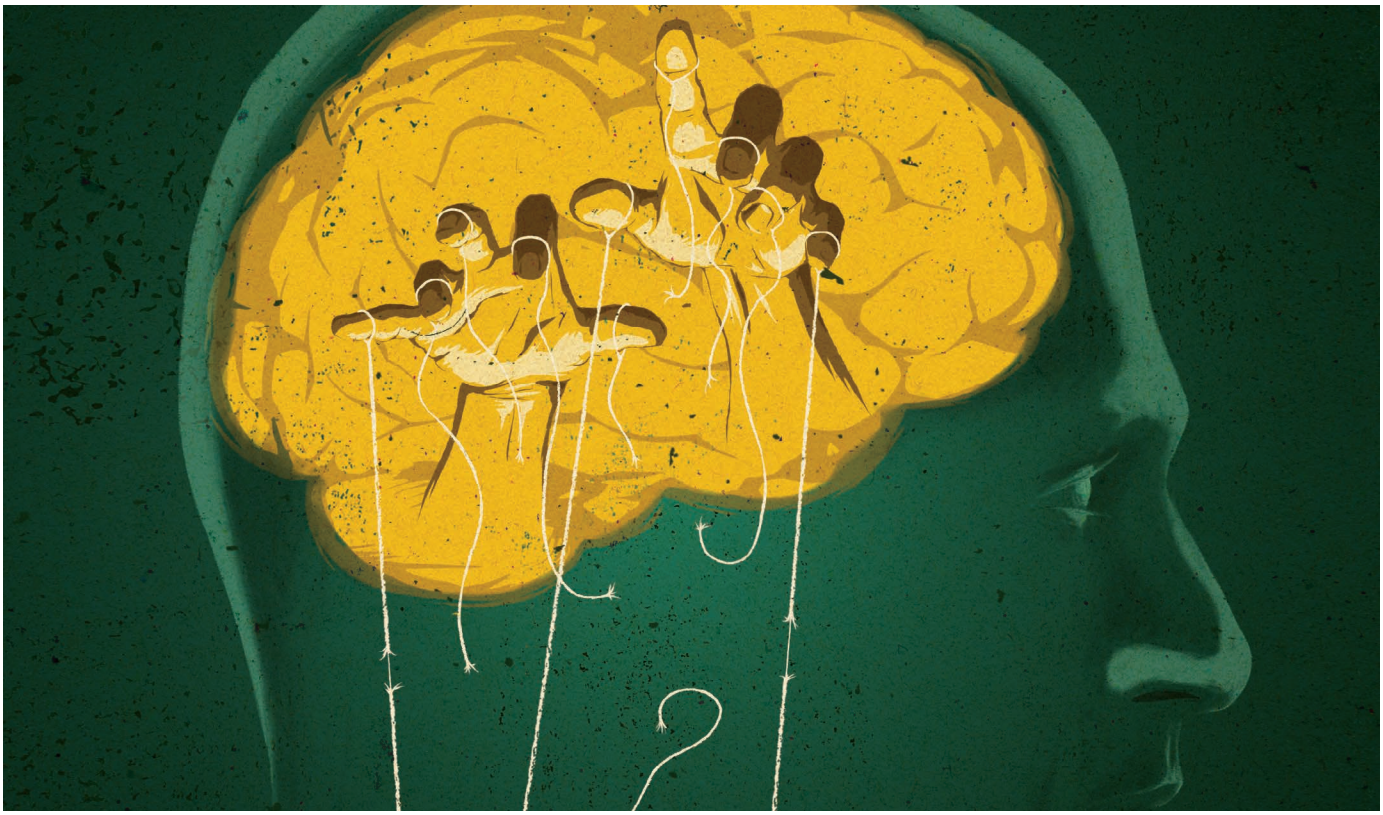
RESEARCH ROUND-UP

Highlights from clinical trials on amyotrophic lateral sclerosis



RESPIRATORY MEDICINE

Diaphragm pacing meets early end

Electrical stimulation of the diaphragm does not delay the need for ventilation support in people with amyotrophic lateral sclerosis (ALS), nor does it prolong survival.

The phrenic nerves, which stimulate the diaphragm muscle, undergo progressive degeneration in ALS. Muscle weakness ensues, and the patients eventually lose the ability to breathe independently. Those with late-stage ALS usually breathe through a mask attached to a ventilation machine.

Observations suggesting that muscle degeneration in ALS might be slowed down by diaphragm pacing — which attempts to mimic the role of the phrenic nerves — led the US Food and Drug Administration to approve this approach on humanitarian grounds. Jésus Gonzalez-Bermejo at the Pitié-Salpêtrière Hospital Group, Paris, and colleagues at 12 ALS centres in France tested this possibility in a randomized controlled trial involving 74 participants with a moderately decreased, but independent, ability to breathe.

The trial, called RespiStimALS (see go.nature.com/2xpqrbx), was under way in July 2015 when the results of a UK trial on the same topic, called DiPALS (see go.nature.com/2hnwghe), became known. DiPALS showed that patients with late-stage ALS receiving diaphragm pacing in addition to non-invasive ventilation had a higher risk of death than those receiving non-invasive ventilation only. An analysis of RespiStimALS data revealed that people in the diaphragm-pacing group had higher mortality and an earlier need for non-invasive ventilation than those receiving a sham procedure, and the trial was terminated.

The results of these two trials show that diaphragm pacing should not be used at any stage of ALS.

Lancet Neurol. 15, **1217–1227 (2016); *Lancet Neurol.*** 14, **883–892 (2015)**

NEUROTROPHIC FACTORS

Stem-cell delivery of factors is safe

Stem cells that secrete neurotrophic factors (NTFs) can be safely administered to people with ALS and might have clinical benefits.

NTFs are small proteins and peptides that help neurons to grow and survive. Studies in animal models of ALS have shown that NTFs can slow nerve degeneration and heal damaged motor neurons, and that different NTFs have a synergistic effect when combined. But direct administration of individual NTFs to people with ALS did not change disease progression or survival. Dimitrios Karussis at Hadassah-Hebrew University Medical Center, Jerusalem, and his colleagues investigated whether delivery of stem cells secreting multiple NTFs to affected tissues would be a better strategy.

Sponsored by BrainStorm Cell Therapeutics, based in Hackensack, New Jersey, the researchers conducted two consecutive trials involving a total of 26 patients with ALS of less than two years'

duration and varying severity (see go.nature.com/2wj9c09 and go.nature.com/2w9uhfq). Stem cells collected from the patients' bone marrow were stimulated to produce NTFs. Injection of the cells into the muscle or spinal cord proved safe, although most participants experienced mild temporary reactions such as headache, fever and leg and back pain.

A comparison between the rate of decline in the ALSFRS-R score (which quantifies the level of ALS-related disabilities in speech, salivation, swallowing, breathing, motor function and self-care) before and after treatment suggests that this type of intervention might slow the rate of disease progression. A follow-on trial is now under way to assess clinical benefits (see go.nature.com/2fkhwhy).

JAMA Neurol. 73, **337–344 (2016)**

ANTIOXIDANTS

Edaravone slows decline

The antioxidant drug edaravone has slowed the progress of ALS in a phase III clinical trial.

High levels of reactive oxygen species, a class of oxygen-containing chemicals that cause damage in cells, are associated with many diseases, including ALS. Edaravone is thought to act by scavenging these chemicals before they can harm neurons. The drug has been used in Japan since 2001 to treat patients with acute ischaemic stroke. A subgroup analysis of data from a 2014 trial suggested that it might also benefit some people who have ALS.

In the most recent trial (see go.nature.com/2xtrlje), Makoto Akimoto at Mitsubishi Tanabe Pharma, Tokyo, and his colleagues investigated whether edaravone was effective in individuals with early-stage ALS, good respiratory function and other well-defined disease indicators. The trial included 137 patients from 31 hospitals in Japan.

The ALSFRS-R score of functional ability declined significantly less in those who were treated with edaravone than in those receiving placebo over a six-month period.

In May 2017, the US Food and Drug Administration approved edaravone for ALS — only the second ALS therapy it has approved. The drug was approved for ALS in Japan in 2015.

Lancet Neurol. 16, **505–512 (2017)**

DRUG COMBINATIONS

Nuedexta ups quality of life

ALS is associated with progressive and severe deterioration in quality of life. Drugs are therefore needed that preserve the ability of people with the disease to function as well as possible. Most drugs used to control symptoms, however, have not been trialled specifically in this disease. In a phase II trial (see go.nature.com/2jnaw0b), Richard Smith at the Center for Neurologic Study, La Jolla, California, and his colleagues showed that a combination of dextromethorphan and quinidine (marketed as Nuedexta) improved speech, swallowing and control over salivation in people with ALS from seven medical centres.

The trial included 60 patients who had had ALS for less than two years. They received either the drug or a placebo for 28–30 days followed by 10–15 days without treatment, and then were switched to the opposite intervention for another 28–30 days. Patients self-reported their ability to speak, swallow and control the secretion of saliva during the trial, which revealed that Nuedexta therapy significantly improved symptoms in this patient population.

The researchers are planning a phase III trial to determine how long the treatment effects last and whether Nuedexta affects disease progression.

Neurotherapeutics 14, **762–772 (2017)**

MONOCLONAL ANTIBODIES

No future for ozanezumab

An antibody against Nogo-A — a protein that halts neuronal growth — has no benefit to patients with ALS.

Progressive muscle weakness is a hallmark of this disease. High levels of Nogo-A have been linked to a loss of contact between nerves and muscles, and poor muscle function in animal models and patients' tissue samples. In 2014, a first-in-humans trial showed that treatment with ozanezumab, an antibody against Nogo-A, was safe (see go.nature.com/2jl2jdv).

This prompted the drug firm GlaxoSmithKline in London, developers of the antibody, to conduct a phase II trial of its effect in ALS (see go.nature.com/2xkqclw). The trial involved 303 participants recruited from 34 centres in 11 countries. Patients received ozanezumab or a placebo every 2 weeks for 46 weeks, and were assessed 2 and 12 weeks after the intervention period.

"The results suggest the futility of further clinical testing of an anti-Nogo-A monoclonal antibody for the treatment of ALS."

Arseniy Lavrov at GlaxoSmithKline and an international team of colleagues found that ozanezumab did not improve a combined score of functional ability (measured using the ALSFRS-R scale) and survival. The rate of adverse events, including death, was slightly higher in the group that was given ozanezumab.

"The results suggest the futility of further clinical testing of an anti-Nogo-A monoclonal antibody for the treatment of ALS," the researchers conclude.

Lancet Neurol. 16, **208–216 (2017)**

DRUG REPURPOSING

Parasite drug cuts ALS marker levels

A drug used to treat parasitic diseases has been shown to lower the levels of a biomarker of ALS in patients.

Pyrimethamine is used to treat the parasitic diseases toxoplasmosis and isosporiasis. It was also widely used to treat malaria until resistance developed. In a previous pilot study, the drug lowered the levels of the antioxidant enzyme superoxide dismutase (SOD1) in white blood cells and in cerebrospinal fluid in people with ALS who carried mutations in the *SOD1* gene.

SOD1 mutations are thought to account for up to 20% of cases of familial ALS and up to 3% of all ALS cases. High levels of SOD1 protein have been linked to disease progression in animal models and in patients with ALS.

Dale Lange at the Hospital for Special Surgery in New York, in collaboration with an international team of researchers, conducted a larger, longer-term phase I/II trial (see go.nature.com/2hkpdor) involving 32 patients with ALS of varying levels of severity and with different *SOD1* mutations. Participants received pyrimethamine for nine months.

Treatment lowered the levels of SOD1 in the cerebrospinal fluid by more than 10%. The authors note that, although this is a statistically significant decrease, more research is needed to determine whether the drug can slow ALS progression.

Ann. Neurol. 81, **837–848 (2017)**

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