Disease-modifying therapies for amyotrophic lateral sclerosis (ALS) remain elusive, but early data on some agents suggest neuroprotective and progression-delaying effects. Following is a closer look at some promising therapies currently under investigation.

**Creatine for ALS**

Although studies have found mixed results for the use of creatine in ALS, no significant safety concerns have been associated with the agent. A recent publication suggests that, while supplementation did not affect disease progression, it can improve survival.

A phase III, multi-center, double-blind, placebo-controlled, randomized study of creatine monohydrate in ALS is still ongoing (ClinicalTrials.gov identifier NCT00069186). The promising multicenter, double-blind study randomized 107 patients with probable or definite ALS (less than five years duration from symptom onset) to either treatment with daily creatine monohydrate 5g/day or placebo. Patients were followed for nine months. While treatment did not significantly improve motor, respiratory, or functional capacity, there was a trend toward improved survival in patients taking daily creatine monohydrate.

Of note, although anecdotal patient reports suggested improvement of fatigue associated with treatment, measurement of fatigue during isometric contraction revealed no significant improvement.

While previous research supported the safety of creatine 10g/day in ALS, it failed to demonstrate a statistically significant impact on survival or disease progression.

**Pramipexole**

The reactive oxygen and nitrogen species (RONS) scavenger pramipexole demonstrated safety and tolerability in early trials that were reported last year. Reported data came from small dose-escalation and futility-design studies. In the futility study, among 30 patients with early suspected ALS measures using the revised ALS Functional Rating Scale (ALS-FRS-R) and forced vital capacity (FVC) were non-significantly reduced. Measures were taken monthly for three months during lead-in, followed by open-label dosing at 30mg/day for the next six months.

In the dose-escalation study, 10 subjects with early ALS received pramipexole doses from 10mg to 100mg three times daily over seven weeks then were switched in open-label extension analysis to 30mg/day for at least six months before switching to 60mg/day. ALFRS-R and FVC measures were either unchanged or improved. Changing from 30 to 60mg/day caused a 17 percent reduction in slope of decline of ALSFRS-R, but this was non-significant.

**Memantine**

Memantine, which has demonstrated neuroprotective effects in a murine model of ALS is now under investigation in combination with riluzole in human subjects (ClinicalTrials.gov identifier: NCT00353665).

Despite evidence that both direct and indirect glutamate toxicity contribute to the pathogenesis of motor neuron degeneration, researchers note that the therapeutic effect of various glutamate receptor antagonists has not been clearly demonstrated. So researchers examined the therapeutic efficacy of memantine in an ALS mouse model carrying a high copy number of SOD1(G93A).

Treatment significantly delayed the disease progression and increased the lifespan of mice, from 121.4 +/- 5.5 to 129.7 +/- 4.5 days (P = 0.032). Researchers report that they detected NMDA receptor subunits in the spinal cord of SOD1(G93A) mice at levels similar to those in the wild-type littermate control.

**Pioglitazone**

Pioglitazone is an anti-inflammatory peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist of interest
for possible use to quell inflammation and cell death in ALS. A study currently recruiting human subjects will assess the benefits of pioglitazone 45mg plus riluzle 100mg in 220 subjects over 18 months of treatment (ClinicalTrials.gov identifier: NCT00690118).

Data suggests that peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists may block a pathway to neuropathological damage caused by inflammation in ALS and other neurodegenerative diseases, including perhaps Huntington’s. Murine trials suggest a potential benefit. The study involved mice carrying a transgene for G93A mutant human superoxide dismutase-1 (SOD1) (ALS mice) and non-transgenic littermates as controls. Immunohisto-chemical and immunoblot analyses of PPAR-γ, active form of phosphorylated p38 mitogen-activated protein kinase (p-p38) and inhibitor of nuclear factor-κβ (NF-κβ) in the spinal cords in each population verified changes in the population of neurons, astrocytes, and microglia in the ventral horns of spinal cord lumbar segments for the pioglitazone-treated mice. Image analysis revealed significantly lower optical density of NeuN-immunoreactive neurons in the non-treated groups of presymptomatic and advanced ALS mice than in the non-treated groups of age-matched controls. Levels in diseased mice recovered with pioglitazone treatment.

Optical densities of GFAP-immunoreactive astrocytes and Iba1-immunoreactive microglia were significantly higher in the non-treated group of advanced ALS mice than in the non-treated group of control mice. These levels also recovered with pioglitazone treatment.