



VIEWPOINT

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# ALS and Unproven Treatments: What Should Patients and Physicians Do?

BY JEREMY M. SHEFNER, MD, PHD,  
AND MERIT CUDKOWICZ, MD

**A**LS is a relentlessly progressive and ultimately fatal neurodegenerative disease for which there is no effective treatment. In the last 10 years, progress has been made in understanding the likely pathophysiology of amyotrophic lateral sclerosis (ALS), and at least 10 therapies are in the clinical trial pipeline. However, most people with ALS do not have access to clinical trials or, at most, may have access to one of many that are enrolling at any time.



DR. JEREMY M. SHEFNER



DR. MERIT CUDKOWICZ

The mismatch between patient needs and available trials arises for two reasons. First, most trials selectively enroll newly diagnosed patients who are still functioning well, excluding those more severely disabled. Second, trials in North America are concentrated at large clinical centers, making them inaccessible to many patients who do not live nearby. Even for eligible patients cared for at a large center, study design necessities, including a placebo group, may cause some candidates to opt out.

**ALS DRUGS IN THE PIPELINE**

When experimental drugs are available only through a clinical trial, the decision for an eligible patient is whether or not to participate. However, drugs of possible value in ALS may be prescribed off label by physicians, or bought by patients over the counter.

In the last few years, large studies of gabapentin, minocycline, topiramate, creatine, and co-enzyme Q have been

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What are your 'Good Samaritan' rights?

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## Viewpoint

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performed; currently studied drugs include ceftriaxone and lithium. All of these drugs are readily available. For the agents already tested, there is no longer conflict; all of them have been found ineffective in ALS, and some have had deleterious effects. However, while these studies were enrolling participants, some patients were prescribed or purchasing these agents outside of the clinical trial.

Current data support an optimistic view of both ceftriaxone and lithium for ALS. Ceftriaxone was initially identified as positively affecting multiple important pathways in neurodegenerative diseases; especially important for ALS, it increases production of a vital glutamate transport protein, according to a 2007 report in *Nature* by Jeffrey Rothstein, MD, PhD, and colleagues. Lithium has been studied in a small number of patients with ALS with similarly encouraging results, as reported in a 2008 study in the *Proceedings of the National Academy of Sciences*.

### THE CONCEPT OF EQUIPOSE

We believe that no single answer applies to all patients or all situations but some considerations are worth discussing. One important concept is that of equipoise, which was applied to clinical research in 1987 as the “state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial.” Equipoise requires that a clinical study be performed ethically, and considers the state of knowledge of the medical community rather than the feeling of a single physician. Thus, clinical trials of readily available compounds in ALS are ethical if true uncertainty exists about the value of the treatment. It is therefore reasonable to ask patients to accept a randomly selected and undisclosed assignment to a treatment group that may be an active agent or a placebo.

### A CLINICAL TRIAL VERSUS OFF-LABEL USE

What does this say about patients not in clinical trials? Ethically, if it is justifiable to put a patient in a placebo group in a clinical trial, it must be justifiable to not prescribe an available drug with an untested efficacy or safety in that disease population. The justification for administering an available drug is more complex, however.

In a clinical trial, safety measures are in place that are not routinely present in a single clinical encounter. Adverse events are collected from the entire trial, and a safety monitoring board will monitor the data for evidence of toxicity. Individually and collectively, subjects in trials are surveyed more carefully than in routine clinical care.

It can be argued that a physician may watch a patient on an experimental medication more carefully than usual, even if

**‘Ethically, if it is justifiable to put a patient in a placebo group in a clinical trial, it must be justifiable to not prescribe an available drug with an untested efficacy or safety in that disease population.’**

the patient is not participating in a trial. However, information showing poor outcomes for treated patients in the minocycline and topiramate trials became apparent only after grouped data were studied. Patients treated off label with these medications were not noted to have faster progression as a result.

Using an off-label medication during the conduct of a clinical trial also can impede or slow enrolment in a trial, which has the effect of increasing risk to subjects in the trial. For example, enrollment in

the ongoing trial of ceftriaxone in ALS has been slow in part because of the presence of well-identified clinics that have been willing to prescribe this medication off-label. In addition, patients are often excluded from clinical trials because they do not meet entry criteria, implying an extra disease burden that further increases their risk. Recognition of all of these factors is critical to providing appropriate advice and care. For some patients, the extra risk may be worth taking, because of rapid disease progression or a need to feel that

they are treating their disease as aggressively as possible. For most patients, however, we have found that appropriate dissemination of information leads to patients deciding against off-label use of unproven medications.

Many patients also want to take either drugs, or nutraceutical agents of other treatments for which there is no significant preclinical supporting data. Possible therapies may range from nutritional supplements with benign safety profiles to therapies such as chelation, dental

amalgam removal, or administration of unknown substances said to be stem cells. For these types of therapy, it is important for physicians to provide supportive but clear guidance. It could be suggested that these treatments might benefit patients as a placebo effect. However, data do not suggest that placebos have measurable benefits in ALS. In fact, in a 2007 report in *Neurology*, investigators reported results from a clinical trial that showed an acceleration of disease progression when patients moved from

a clearly defined lead-in phase to a period of active treatment.

ALS is a life-threatening disease, but clearly some treatments can reduce quality or length of life. It is critical for patients to be given the information they need to avoid interventions that generate danger. •

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