Section 2
Medication and Drug Research
ALS Medications and Drug Research

Medications

Currently, there are no drugs available to cure or reverse ALS, due to the complexity of the disease. However, there are several interventions and drug therapies that treat symptoms and can make living with ALS easier.

The three types of medications most commonly used in the treatment of ALS are:

- prescription drugs developed specifically to treat ALS,
- prescription drugs used to relieve the symptoms of ALS,
- over-the-counter medications.

A physician must be involved in the decision to take prescription drugs, but is not required for over-the-counter medications. However, over-the-counter medications can interact with each other and with prescription drugs. Therefore, before using over-the-counter medications, people with ALS (PALS) are advised to discuss the medications being considered and the dosage with their neurologist. The neurologist should also be aware of all the prescription drugs someone is taking.

Prescription Drugs Developed Specifically to Treat ALS

At present, there are two drugs approved by the U.S. Food and Drug Administration (FDA): Rilutek (riluzole) and Radicava (edaravone).

Rilutek: according to the clinical drug trial that led to approval of Rilutek by the FDA in 1995, taking 100 milligrams of Rilutek each day is modestly effective in prolonging survival for patients with ALS. However, no increase in muscle strength or in bulbar function was noted. Rilutek is available in generic form as riluzole.

Radicava: the clinical trial using Radicava was conducted in Japan and approved by the FDA in May 2017. The data showed a 33 percent slowing of loss of function in participants as rated on the ALS Functional Rating Scale; survival was not studied. Radicava is an intravenous drug - it is given daily over 60 minutes for a 60 mg dose (two 30 mg IV bags) for 14 consecutive days in month one, then 14 days off. Monthly follow up treatments are given 10 days over a two weeks period; then two weeks off and repeated each month thereafter. Length of treatment should be discussed with your clinician.

Prescription Drugs Used to Relieve Symptoms of ALS

Several prescription drugs are used to relieve symptoms of ALS. In some people, prescription drugs are helpful in controlling such symptoms as excess saliva, muscle stiffness, emotional lability (excessive response to a laughing or crying situation), insomnia, muscle cramps,
constipation, gastric reflux, depression, and pain. The following is a partial list of prescription drugs used to help relieve symptoms of ALS:

- Lioresal (baclofen) or Valium (diazepam) may be prescribed for muscle stiffness
- Elavil (amitriptyline) may be prescribed for excess saliva and for emotional lability.
- Nuedexta, approved by the FDA in 2011, is used to treat pseudobulbar affect, which is characterized by inappropriate laughing or crying.

All of the medications have side effects, which must be taken into account when deciding whether to use them.

### Over-the-Counter Medications

Chemicals called free radicals have been shown to cause damage to cells throughout the body. Scientists think that the free radicals may be one cause of damage of the motor neurons of people with ALS. Certain other chemicals, called antioxidants, may help to counteract the cell damage caused by free radicals. A number of nutrients, including certain vitamins, minerals, and herbs are antioxidants. The most commonly used antioxidants are vitamin E, vitamin C and beta-carotene, which is the precursor of vitamin A. Coenzyme Q-10 and melatonin are also antioxidants. Be aware that taking excessive amounts of these vitamins may be counterproductive. As with any over the counter medication, ask the neurologist what dosage you should take and how frequently the vitamins should be taken.

There are few hard and fast rules for determining which over-the-counter medications to take and at what dosage. This decision depends upon a person’s onset of disease, current symptoms, age, weight, and other health supplements. Many outrageous, unproven claims are made for nutritional supplements. This is done by people who take advantage of people who may be vulnerable and willing to try almost anything. Their methods can border on quackery. It is best to discuss these issues with the neurologist before taking such medications.

Another good resource for claims of ALS cure or treatments is ALS Untangled at [http://www.alsuntangled.com](http://www.alsuntangled.com)

### Clinical Drug and Therapy Trials

Everyone with ALS seek a cure for their disease. Short of a cure, an effective treatment to halt the progression of the disease would be acceptable. Pharmaceutical companies spend millions of dollars conducting clinical drug trials trying to find effective treatments. The Food and Drug Administration (FDA) approves only drugs that have been found to be safe, well-tolerated and significantly effective. The process by which drugs are approved in the US is outlined below. Drugs are tested by a series of clinical trials, also called drug studies.

### How Can I Find Out About Drug Studies?

The best source of information about drug studies for which you might be qualified is your neurologist. Major ALS drug and research studies are regularly conducted at the [Lois Insolia ALS Clinic at the Les Turner ALS Research and Patient Center at Northwestern Medicine](http://www.lesturnerals.org). You may or may not qualify for any or all of the studies, but your doctor can assist in helping
you evaluate them. Other sources of applicable ALS drug studies are listed below, especially the National Institutes of Health (NIH) Clinical Trials.gov website, the Northeast ALS Consortium (NEALS) and the National ALS Registry conducted by the Centers for Disease Control (CDC). People with ALS who have enrolled in the National ALS Registry are eligible to receive notifications of applicable clinical trials from researchers or pharmaceutical companies.

**Resources for Current Drug Trial Information**

www.clinicaltrials.gov

https://www.neals.org/lesturnerals.org


**Who Can Enroll in a Drug Study?**

Strict guidelines for participation in clinical drug studies are an important factor in achieving acceptable results. To be eligible for an ALS drug study, a person with ALS must have a diagnosis of ALS made by a qualified neurologist who follows internationally accepted criteria. These criteria eliminate the chance of misdiagnosis.

Other considerations might also be required for clinical trial participation, such as:

- **Age**—a particular age range might be required for inclusion
- **Gender**—the study might include only males, only females, or both males and females
- **Past medical history**—certain health conditions might be disqualifying, such as other muscle and nerve diseases or heart, lung, endocrine or kidney diseases
- **Present condition**—might affect the study results or a person with ALS’s ability to follow the study procedures. For example, alcoholism, mental disorder, or hypertension might be disqualifying factors
- **Current medications**—might interact with the study drug, cause harm or confuse the study results

The ability to travel to the testing center for regularly scheduled visits is also an important requirement.

Factors that might confuse the analysis of the information collected would also require exclusion from a clinical trial. These factors might not be related to the study drug, but could distort information about its effectiveness. For example, persons with ALS using permanent ventilation usually are not eligible for ALS drug studies because judging the drug’s effectiveness is based on survival, improved or stabilized breathing capacity, muscle strength, functional abilities and quality of life.
Why Do ALS Drug Studies Use Placebos?

Placebo-controlled drug studies help prove the effectiveness of the study drug. Persons enrolled in any drug study may believe that they feel better because they are actively involved in the drug study process, rather than because of the effectiveness of the drug. Comparison with a group taking a placebo, or inactive substance, can determine how much better the study drug is working over and above the “placebo effect.” FDA approval requires that there be no doubt that the study drug is effective. The placebo group in the study is the standard against which the drug groups are measured.

Safety is just as important as efficacy. Side effects related to a given treatment cannot be identified without using a control group that does not get the treatment under study. For example, if during a clinical trial the investigator asks about nausea or headaches or muscle cramps, these conditions could be falsely attributed to the drug being studied since many people will experience these over the course of a year. Without a placebo group, it cannot be determined if these conditions are treatment related.

Why Should I Participate in a Drug Study?

All persons enrolled in drug studies receive increased attention to their condition and have the best current medical care. Study participants are not only actively trying to help themselves; they also are participating for the benefit of current and future persons with ALS or various other medical conditions. Even studies that do not have positive results add important information about the underlying process of the disease.

What Happens in the Drug Approval Process?

A pharmaceutical company targets a need for treatment of a specific condition. Researchers develop a drug that they think will improve, slow the progress of, or cure the disease. A written protocol describing the methods to be used in the study is submitted to the FDA for approval. Once it has been approved, the company selects medical centers with specific patient populations to participate in the research. The protocol is submitted to the each university medical school’s Institutional Review Board (IRB) in the Office of Protection of Research Subjects. The IRB ensures that patient safety is properly adhered to.

Another possibility is that investigators will suspect that a treatment already approved for other diseases might work for ALS. They may apply to the NIH or non-governmental organizations for financial support and safety oversight to conduct experiments.

Pre-Clinical Studies are done in animals. Investigation of safety and effectiveness begins here.

Clinical Trial Phases

Phase I: Phase I studies are done with normal volunteers to evaluate whether the drug is safe for human consumption. Once the drug is known to be safe, the correct dose must be determined.

Phase II: Phase II studies measure safety, tolerability and “dose ranging.” Often people with ALS take doses of study drugs for only a short period of time to determine how much can be
taken before the amount is toxic. Then, persons with the disease are enrolled in the study to determine the correct doses, as well as to get some measures of the drug’s effect. In Phase II studies, some subjects will get no drug, others will get a small amount of drug, while still others may get a larger dose. The goal is to find the one or two most effective dosages to use in a larger Phase III study. The safety of all doses is carefully monitored; large doses are not necessarily better. Phase II studies also allow researchers to select the tests or measurements that have the best chance of recognizing aspects of success in the Phase III study. Side effects are considered at all times. An accurate record of all side effects, as well as of other medications a person may be taking, is needed to determine the safety and effectiveness of the study drug.

**Phase III:** A Phase III study is a large trial, usually done at several medical centers. This study determines the effect of the drug on a large number of individuals over a longer period of time. ALS studies are typically done for 12 to 18 months to determine long-term safety and effects. Phase III studies include the greatest number of patients. The number depends on the length of the study and what size effect or “statistical significance” is expected. The selection of doses and tests is based on the Phase II study results. The duration of the study or length of time each subject takes the drug or placebo is no trivial matter. Some studies require 12-month participation, while others need 18 months. It takes a certain amount of time to enroll several hundred participants and answer about the effect of the drug can be available until all subjects have completed their 12 or 18 months. If many people will participate in a 12-month study, it might take more than 6 months to enroll everyone. Fewer subjects could be enrolled in an 18-month study in a shorter period of time and produce the same “significance” or effect. A prolonged enrollment period also limits the number of drugs that can be tested at many centers because the number of persons with ALS who meet all the study criteria is limited.

**Compassionate Use/Open Label**

Subjects who have participated in a Phase II or Phase III study are given the opportunity to take the study drug after they have completed their 12 or 18 months. People with ALS who were taking the “active” study drug may continue to take it. The control or placebo group can begin taking the study drug. These patients can continue to take the study drug while other subjects complete 12 or 18 months and while the study data is being analyzed and presented to the FDA. The patients may continue to receive the drug for another year or more while data is analyzed and a request for marketing is completed. This is often an incentive for people to participate in a Phase III study even if there is a high chance they will be receiving a placebo.

**Expanded Access**

When Phase III studies are complete, the pharmaceutical company may make a promising drug available, while awaiting FDA approval, to patients who did not participate in the studies. Some people with ALS who have not participated in the studies ask if they can take a drug before completion of a Phase III study. The answer is no for two reasons. Drug studies investigate the safety and efficacy of drugs. While the drugs are being investigated, there are no clear-cut efficacies or safety profiles. If a patient who has not been screened for medications or other medical conditions takes a drug and becomes ill, researchers will not know if it was the drug or other factors that caused the effect. The patient is at risk for serious side effects. Also, if a study
drug is made available before the study is completed, some participants, especially those who feel they are in the placebo group, might drop out and get on the drug being studied. Unfortunately, this could jeopardize the study conclusions and make it impossible to obtain FDA approval, which impacts the entire ALS community. Drug companies cannot provide a drug forever at no cost, and they cannot charge for it without FDA approval for marketing.

**Will I Ever Know What I Was Taking?**

The pharmaceutical company may decide to inform participants what dose of the drug or placebo they were taking. This information can only be released after all participants have completed the course of the trial, all data has been collected from all centers, and all the information has been verified. This is called “locking the database.” After this occurs, there is no risk that information might be changed or that researchers recording the data could be influenced by knowing whether a certain subject was taking the drug.

**Stem Cell Treatment**

As of this writing, there have been a small number of international and North American stem cell trials conducted in individuals with ALS. These studies are on-going and definitely showing some progress, but more work has to be done. Currently treatment strategies could be grouped along several methods. One method aims to replace damaged glia at the cellular level and hopefully halt the disease. Another method could possibly replace damaged motor neurons and repair damage that has already occurred. It might also be possible to use stem cells to coax the axons of damaged upper motor neurons to remake their connections with the lower motor neurons and increase coordination. While these avenues of research look hopeful, more work needs to be done in this very complex area of potential ALS treatment.

**Laboratory-Based Research**

Most research that aims to find effective treatments for ALS starts in the laboratory. This kind of research is known as basic research, or bench research.

**Cultures**

Some experiments take place in cultures, or small flat dishes that contain a substance in which different types of cells can grow outside the body. Various chemicals or drugs can be added to the dishes to see if any changes occur in the growth process or if there are any positive or negative effects on the cells. The information gained from this type of research is published for other scientists, who may take it into consideration as they do future investigations.

**Gene Studies**

The DNA in cells is usually studied by examining the genes in white blood cells found in blood taken from people with ALS and their relatives. The DNA from the cells is spread on a special gel sheet, so that the genes in different samples can be compared. Similarities and differences among the samples help trace family traits. Matching the characteristics of the samples against the family history of disease helps determine whether the gene contributes to the disease.
family history can show a disease occurring in several ways. It may be sporadic, with only one individual in a family having the disease. It may be familial, occurring in more than one individual in the family. It may be genetic, indicating that a specific gene is passed from one family member to another.

Scientists need to study large numbers of families to learn about a specific gene and its mutations, or changes. Information from a single sample does not give a definite result, the way a test for blood sugar or cholesterol does. Only after a gene has been identified as one that contributes to a disease process can a specific test be developed that gives a “lab result.” However, even a definite result means little until scientists understand how the gene works. Each gene causes body cells to produce one or more proteins, complex chemicals that cause certain actions and reactions in the body. No test result is meaningful until all of these actions and reactions are known and understood for each gene.

Since the co-discovery of the first gene for ALS, SOD-1, by Teepu Siddique, MD, at the Les Tuner ALS Research and Patient Center at Northwestern Medicine in 1993, over 30 genes for ALS have now been identified and the chromosomal addresses are now known. Having one of these genes does not predict whether a person will actually develop the disease, at what age it might begin, or what course it might take.

**Animal Research**

Using animals in research helps scientists understand the normal mechanisms and pathological processes in the body and enables them to test possible treatments. An investigator may test a certain substance in a laboratory animal to find out if a living animal can tolerate the substance and to observe any changes in the animal’s alertness, muscle strength, and coordination. Only animals that show the same disease symptoms as humans do are useful for testing these substances. By altering the DNA of mice and other animals, scientists can produce animal models that are useful for testing substances that might successfully treat diseases in humans. Animals with altered DNA are called transgenic animals.

The transgenic SOD-1 mouse was developed to show the same disease symptoms as people with ALS. Other transgenic mice have been developed for other conditions. Many important clinical research studies have been developed based on information gained from these animal studies. All animal projects done at the Les Turner ALS Research and Patient Center at Northwestern Medicine are reviewed by the Northwestern University Animal Care Committee. The Animal Care Committee of the IRB oversees animal research.

**Resources for FDA Drug Approval Process**


*Disclaimer: All care has been taken in preparing this document. This information is of a general nature and should be used as a guide only. Always consult your health care team before starting any treatments.*