Section 2
MEDICATIONS AND DRUG RESEARCH

MEDICATIONS

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, patients 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 a patient is taking.

Prescription Drugs Developed Specifically to Treat ALS

At present, Rilutek (riluzole) is the only drug approved by the U.S. Food and Drug Administration (FDA). According to the clinical drug trial that led to approval by the FDA, 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.

Prescription Drugs Used to Relieve Symptoms of ALS

Several prescription drugs are used to relieve symptoms of ALS. In some patients, 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. For example, Lioresal (baclofen) or Valium (diazapam) may be prescribed for muscle stiffness. Elavil (amitriptyline) may be prescribed for excess saliva and for emotional lability. 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 ALS patients. Certain other chemicals, called antioxidants, may help to counteract the cell damage free radicals cause. 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. The steroid hormone, DHEA (dehydroepiandrosterone), is another antioxidant some patients are using. Taking excessive amounts of these vitamins may be counterproductive. 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 patient'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 the patients who are vulnerable and willing to try almost anything. Their methods often border on quackery. It is best to discuss these issues with the neurologist before taking such medications.

CLINICAL DRUG TRIALS

All patients 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. It would be irrational and unscientific to offer a treatment that has not been shown to be safe, well-tolerated, and effective and to expect people, or their insurance companies, to pay for it.

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, an ALS patient must have a diagnosis of ALS made by a qualified

neurologist who follows internationally accepted criteria. These criteria eliminate the chance that the patient could have conditions that mimic ALS.

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

- **age**—only patients in a particular age range might be included.
- **gender**—the study might include only males, only females, or both males and females.
- **past medical history**—certain health conditions might disqualify a patient, such as other muscle and nerve diseases or heart, lung, endocrine, or kidney diseases.
- **present condition**—might affect the study results or a patient's ability to follow the study procedures. For example, alcoholism, mental disorder, or hypertension might disqualify a patient.
- **medications**—might interact with the study drug and harm the patient or confuse the study results.

The ability of the patient and the family 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 a patient's exclusion. These factors might not be related to the study drug, but could distort information about its effectiveness. For example, patients using permanent ventilation usually are not eligible for ALS drug studies because judging the drug's effectiveness is based on a patient's survival and 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 many people will get one or more such things over the course of a year. One can see that the study treatment might get blamed for the headache yet if the headaches occur no more frequently in one group or the other then it is not 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. They are not only actively trying to help themselves, they also are participating for the benefit of fellow ALS patients and of future patients with various 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 University Medical School Institutional Review Board (IRB) in the Office of Protection of Research Subjects. The Board ensures that patient safety is properly adhered to. The Animal Care Committee of the IRB oversees animal research.

Another possibility is that University or other investigators will suspect that a treatment already approved for other causes might work for ALS. They may then band together and apply to the NIH or non-governmental organizations for financial support and safety oversight to conduct their experiments. This has become a more commonplace occurrence in the last few years with trials underway for Minocycline and Co-Q 10 as well as interest in nutritional support and breathing assistance.

PreClinical Studies are done in animals. Investigation of safety and effectiveness begins here.

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 ALS patients 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 patients 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 patient 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 patients. No answer about the effect of the drug can be available until all patients have completed their 12 or 18 months. If many patients will participate in a 12-month study, it might take more than 6 months to enroll everyone. Fewer patients 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. Patients who were taking the "active" 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 patients 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 efficacy 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 patients, especially those who feel they are in the placebo group, might "drop out" and "get on drug." This would jeopardize the study conclusions and make it impossible to obtain FDA approval. 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 patients 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 patient was taking the drug.

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 ALS patients 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. The 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.

Two genes for ALS have been identified and the chromosomal addresses of several more are now known. Having one of these genes does not predict whether a person will actually develop the disease, at what age it will begin, or what course it will 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 patients do are useful for testing these substances. By altering the DNA of mice and other animals, scientists can produce individuals that are useful for testing substances that might successfully treat diseases in humans. Animals with altered DNA are called transgenic animals.

The transgenic SOD1 mouse was developed to show the same disease symptoms as ALS patients. 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 are reviewed by the Northwestern University Animal Care Committee.

STEM CELLS

As of this writing (May 2005) there are no European or North American stem cell trials going on in humans with ALS. However, it is an exciting area. Currently treatment strategies are speculative but could be grouped as follows. One could aim to replace damaged glia and hopefully halt the disease. It may also be possible to replace damaged neurons and repair damage that has already occurred but that is likely to happen further in the future. 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.

Resources for Current Drug Trial Information

www.alsa.org
www.als.mdausa.org
www.lesturnerals.org
www.neurogenetics.northwestern.edu