

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY • Adult Patient or • Parent, for Minor Patient	
TITLE:	NIMH	
STUDY NUMBER	91-M-194	PRINCIPAL INVESTIGATOR: Susan Molchan, M.D.
STUDY TITLE:	The Evaluation of Lithium Treatment in Dementia of the Alzheimer's Type, Major Depression, and Age-Matched Controls (Patients)	

## INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. If you have personal, religious or ethical beliefs which you think might limit the types of medical treatment (for example, blood transfusions) that you would agree to receive (or would want your child to receive), you should discuss them fully with your NIH physicians (or appropriate members of the research team) before entering this study. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

## NATURE OF THE STUDY

The purpose of this study is to evaluate the effects of the medication lithium in patients who have memory problems thought to be due to Alzheimer's disease, as well as in older patients with major depression. Lithium is a commonly used medicine, and is actually a naturally occurring salt, which has been used by millions of people for decades, primarily for the treatment of mood disorders (severe depressions or mania). Depressed mood and anxiety are common symptoms in patients with Alzheimer's disease. The medications currently used to treat these symptoms may have serious side effects, especially in older people. A medicine like lithium, if it was of benefit to some symptoms in Alzheimer's disease, may be safer and tolerated better by some patients. In addition, in comparing the effects of lithium on some physiological or chemical measures obtained from blood samples patients and normal volunteers, we hope to obtain information on changes in hormones and brain chemicals that occur in Alzheimer's disease and depression, as well as clues as to the mechanism of action of lithium.

Acetylcholine is a brain chemical that serves as a "messenger" (neurotransmitter). Acetylcholine appears to be involved in normal memory functioning, and patients with Alzheimer's disease are known to have deficits in the acetylcholine system.

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CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient  
NIH-2514-1 (8-93)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

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Lithium had been shown to increase acetylcholine in the brain, as well as other neurotransmitters that may be involved in memory function. Therefore, the effects of lithium on memory will also be tested.

Physostigmine is a medicine that slows the breakdown of acetylcholine, allowing higher levels of it to exist in the brain. Physostigmine has been shown in some studies to have modest positive effects on the memory performance of patients with Alzheimer's disease, so has been a much studied drug for this disease. It has also been shown to effect mood. We propose in this study to use physostigmine as a "drug probe", which means that after we administer a single dose of it, we will examine its acute effects on memory, mood, and on measures of hormones and neurotransmitters that will be obtained from blood samples collected. This may give us information on why physostigmine may be of benefit in some patients. Also, in comparing responses to physostigmine between patients with Alzheimer's disease and normal volunteers, we may learn something about what may be different in Alzheimer's disease and in depression.

#### Baseline Evaluation

A physical exam, blood tests, urinalysis, EKG, and EEG will be done prior to participation in the protocol to confirm your state of general health. Blood will be withdrawn for later measurement of certain hormones and other biological substances. Blood taken from you over the course of the protocol would never exceed the amount that an individual would donate to a blood bank. You will also be asked to save your urine for a 24 hr period, again for later measurement of hormones and other body chemicals.

#### Clinical Trial

After being off all medicines for at least 3 weeks, you will be administered pink capsules, two times a day, that contain either lithium or a placebo ("sugar pill") for a period of 6 weeks. This will allow us to compare the effects of lithium to that of the placebo, and neither you nor the staff (except for the physician prescribing the capsules) will know whether you are taking lithium or placebo at any specific time. This is called the "double-blind" procedure. Drug effects using this procedure are more accurately assessed, as it helps to keep assessments more objective. This is also

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why the lithium and the placebo will be given in identical-appearing capsules and why code numbers instead of drug names are used. A physician who is aware of what medication you are on will be available at all times through our inpatient unit.

During the period you are taking the capsules, you will be assessed periodically with memory tests and staff will record changes in the way you are feeling or behaving according to standardized assessment forms. Blood tests and urine collections will be done during both the lithium and placebo phases of the protocol. Additional small samples of blood will be removed to check blood levels of lithium and for other biochemical tests. For one of these tests, called the dexamethasone suppression test, a dose of a hormone will be given to you to take at bedtime, for one evening during each phase of the study. Blood will be withdrawn the next day at 8:00am and 4:00pm, for measurement of hormones in response to the hormone given the night prior. This test has been used for many years in medicine and psychiatry and no risks or side effects are associated with it.

#### Risks and Possible Side Effects

In some people lithium has been shown to cause temporary mild memory impairment. Someone who already has some memory impairment (as in Alzheimer's disease) may be especially susceptible to this side effect and to confusion after taking lithium. In addition, people with a history of a seizure disorder will be excluded from this study; one reason for this is that lithium when given in combination with physostigmine at high doses causes seizures in rats. Seizures have not been reported from lithium in addition to physostigmine in humans. The most common side effects reported with lithium are nausea, feeling slowed down, skin rash, decreased concentration, and mild tremor. If you experience any bothersome side effects, the dose can be adjusted to reduce them or the drug can be stopped entirely.

Any risk of stopping medication that you are on prior to the study will be explained. If this risk is more than minor, you will not be asked to stop the medication.

Two complications have been reported in a small minority of patients who have taken lithium for long periods of time (months to years). One is a reversible slowing of the thyroid gland. The other is damage to the kidney which in some cases has been permanent. Neither of these effects has been observed with lithium treatment for as brief as two weeks. Your thyroid and kidney function will be monitored during the study to assure their stability.

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## CEREBROSPINAL FLUID EXAMINATION

Purpose

A great deal of research has been conducted here at the National Institute of Health and elsewhere in the past decade on chemicals found in the cerebrospinal fluid (CSF) of neurologically and psychiatrically ill patients. These chemicals are thought to be important in the normal and abnormal functioning of the brain. Studies of these chemicals significantly advance our knowledge of psychiatric and neurologic illness and of the actions of the medications used to treat these illnesses. For example, our studies suggest associations between levels of some of these chemicals and response to treatment in depression. In the present study, we would expect that measurement of these chemicals might help us better understand how lithium and physostigmine might act to help you or others.

The technique of lumbar puncture (LP) provides a method to study the CSF to learn some of what is going on in the brain biochemically without danger to the patient. The CSF is produced in the brain and collects various brain chemicals. The CSF then flows down the spinal column and collects in a sac in the lower part of the spine, four to six inches below where the spinal cord ends. We have attached a diagram of the anatomy of this region to demonstrate that direct damage to the spinal cord by the needle used is impossible, since the cord ends above where the needle is inserted. We would like you to participate in this procedure once during each phase (so twice altogether) of the protocol.

Procedure

You will be asked to follow a low monoamine diet for 3 days prior to the procedure; instructions for this will be given to you before the procedure; inpatients on 6W will already be on this diet. The LP will be performed in the morning, after a night's bedrest. You will lie on your side, your lower back will be cleaned with antiseptic, and a local anesthetic such as novocaine will be injected in order to temporarily numb a small area of skin. We then place a needle into the spinal fluid sac and allow approximately an ounce of CSF to drip into collection tubes. The needle is then removed and you are asked to lie on your abdomen for three hours to reduce

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the likelihood that you might develop a headache after this procedure. The LP should take only several minutes for insertion of the needle plus 5-15 minutes to allow the fluid to flow out one drop at a time. Most subjects experience only the minor discomfort of the pin prick used to administer the novocaine and compare it with the discomfort of having blood drawn from the arm. Others experience mild to moderate pain for a few minutes, similar to that experienced when an injection is received. The 15 minutes or so required for the fluid to flow out slowly is without pain or discomfort.

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Risks and Discomforts

The LP is a routine neurological procedure that is a common diagnostic procedure in every hospital. The only common discomforts are headache and mild backache. If it occurs, the slight backache resolves over one to two days. With the special bedrest procedure, three-quarters of all LPs (even less than that in older people) produce no headache. If a headache occurs, it generally is relieved by lying down. Most headaches last one to four days, although on rare occasions headaches can last more than a week. The rare prolonged headaches are thought to result from the continued leakage of CSF from the area of the LP. If the headache should last longer than one week, it would be possible to perform a "blood-patch." This involves the injection of a small amount of your blood into the region of the supposed leak, in an attempt to seal it. The blood-patch is usually effective in relieving the headache.

The other discomfort that can occur is a brief pain or tingling sensation in either leg. This is caused by brief stimulation of a nerve, and ends quickly with no further complications. On extremely rare occasions, a temporary weakness of the eye muscle that moves the eye to the side may develop, producing double vision. In all cases, this complication has been temporary, and normal vision is completely restored. Neurological problems could arise in patients taking anticoagulants ("blood thinners"), in patients who have an illness that slows blood clotting, or in patients who have a brain tumor or brain abscess. You will be screened thoroughly prior to the LP to insure that you do not have any of these medical problems. Our own experience at the NIH involves over 6,000 LPs performed for research purposes; there have been no lasting complications.

----- I wish to participate in the cerebrospinal fluid examination.

----- I do not wish to participate in the cerebrospinal fluid exam.

\_\_\_\_\_  
 Signature

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## PHYSOSTIGMINE TEST

During both the lithium and placebo phases of the study, you will be asked to participate in the evaluation of the drug physostigmine, which has been used in many studies of memory, and is thought to work by inhibiting the breakdown of the neurotransmitter acetylcholine. In addition, on another day you will go through the same procedure but receive a placebo instead of physostigmine. Neither the staff doing the test with you or you will be aware of which day physostigmine and which day a placebo is administered, though this information will be available in the NIH pharmacy.

The purpose of this test is to evaluate changes that may occur in responses to after lithium treatment, as well as differences in responses between people with Alzheimer's disease or major depression and normal volunteers. Physostigmine affects acetylcholine, a brain chemical involved in memory processes, and possibly in the regulation of mood and the regulation of various hormones. The results of this study should tell us more about the chemical basis of certain behaviors and mood, and help us understand how lithium works.

Physostigmine Test

You will be asked not to eat or smoke for approximately 8 hours before each study day. During the test, you will sit either in a bed or a reclining chair for up to 4 hours during which time you will not be allowed to eat, drink, or smoke.

On the day of the test, a small plastic tube called a catheter will be placed in a vein in your arm. Prior to receiving physostigmine or a placebo, and at three points after, blood samples for hormone measurements will be obtained. You will receive a dose of glycopyrolate, a medicine used to counteract side effects of physostigmine, mainly nausea. After that you will receive a single small dose of physostigmine or of placebo (salt water) through the catheter in your arm. Three times during each study day, the examiner will ask you questions about how you are feeling. A short time after receiving either physostigmine or placebo, a staff member will do some memory tests with you. Your heart rhythm may be monitored during the procedure, using an EKG.

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Possible Risks and Side Effects:

The placement of a small plastic tube (catheter) in your arm vein is associated with some discomfort, as when a blood test is taken. There is also the slight risk of a small bruise forming in the area of the catheter or a superficial skin infection. The total amount of blood samples taken during all three test days will be less than 150 ml (five ounces), which is less than 1/3 that taken during a routine blood donation.

The administration of glycopyrolate may be associated with dry mouth and sometimes slightly blurred vision. Side effects of physostigmine include nausea, excess salivation, sweating, dizziness, increased or decreased heart rate and blood pressure, feeling slowed down, and occasionally vomiting. Seizures have been reported to occur in animals given high doses of lithium in addition to high doses of physostigmine. We do not anticipate seizures as a side effect, but we are prepared to stop any seizure activity immediately if signs of it occur. Side effects will be minimized by the use of a small dose of physostigmine, as well as by prior administration of glycopyrolate. Any side effects experienced would be brief.

I wish to participate in the physostigmine test.

I do not wish to participate in the physostigmine test.

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(Signature)

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part of your participation in this study, it will be necessary to test your blood for the presence of antibodies to the Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immunity Deficiency Syndrome (AIDS). In order to perform the test, a small amount of blood (approximately 2 spoons) will be withdrawn from one of your arms with a needle. You may experience some slight discomfort at the needle entry site and there may be some bruising. In addition, there is a very small chance of your fainting or of infection at the needle entry site. If your test results are found to be positive, or if you are otherwise diagnosed as having AIDS, you should be aware of the following Clinical Center HIV Testing Policy:

Your physician will notify you promptly of the HIV test results.

Your physician and/or the Clinical Center HIV counselor will offer you, and any current and/or ongoing sexual partner(s) (spouses are generally considered to be current or ongoing sexual partners) or needle-sharing partner(s) you identify, information on the meaning of the test results and how to prevent the spread of the infection.

Because the virus may be transmitted in several ways, it is important that you inform sexual and/or needle-sharing partner(s) that any, or all, of them may have been exposed to the HIV virus and encourage them to be tested. If you request it, staff at the Clinical Center will assist you in notifying your partner(s) and arrange counseling for them through an HIV counselor.

Your results of your HIV test and/or documentation of the diagnosis of AIDS will become a part of your Clinical Center medical record and, as such, will be protected from unauthorized disclosure by the Federal Privacy Act of 1974. In general, access to your medical record will be restricted to those health care professionals directly involved in your care or in the conduct of ongoing biomedical research, and information is not usually released to other third parties without your permission or that of your designated representative. However, there are some particular routine uses of such information of which you should be aware.

- a. If you are unwilling or unable to notify your partner(s), the Clinical Center is responsible for attempting to contact and inform them of their possible exposure to the virus. Reasonable attempts will be made to protect your identity including withholding your name when notifying any partner(s) of their possible exposure. Some notification or counseling of current and/or ongoing partners may be carried out through arrangements with, or referral to, local public health agencies.
- b. A summary of your care at the Clinical Center will be sent to the physician who referred you here for treatment.
- c. The Clinical Center may report certain communicable diseases, including AIDS, to appropriate State and Federal government agencies.

If you have any questions regarding the HIV testing or the information provided above, you are encouraged to discuss them with your physician and/or a Clinical Center HIV counselor (496-8955).

identification

INCLUSION OF HIV TESTING IN CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY  
NIH-2514-3 (2-89)

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**OTHER PERTINENT INFORMATION**

**Confidentiality.** When results of a study such as this are reported in medical journals, or at meetings, the identification of those taking part is withheld. Medical records of Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.

**Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.

**Payments.** If you are a patient, you are not paid for taking part in NIH studies. Exceptions for volunteers will be guided by Clinical Center policies.

**Problems or Questions.** Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the principal investigator, Dr. Susan Molchan, or these other staff members also involved in this study: Dr. Trey Sunderland; Dr. Hussein Manji \*; Dr. John Little; Room 3D41. Telephone: (301) 496-3421 OR (301) 496-2375.  
 National Institutes of Health  
 Bethesda, Maryland 20205  
 \*496-2456

**Consent Document.** It is suggested that you retain a copy of this document for your later reference and personal records.

**COMPLETE APPROPRIATE ITEM BELOW, A or B:**

**A. Adult Patient's Consent.**  
 I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

\_\_\_\_\_  
 Signature of Adult Patient & Date Signed

**B. Parent's Permission for Minor Patient.**  
 I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.  
 (Attach NIH 2514-2, Minor's Assent, if applicable.)

\_\_\_\_\_  
 Signature of Parent(s) & Date Signed

\_\_\_\_\_  
 (if other than parent, specify relationship)

\_\_\_\_\_  
 Signature of Investigator & Date Signed

\_\_\_\_\_  
 Signature of Witness & Date Signed

IDENTIFICATION

**CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY**  
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