

**CONSENT TO PARTICIPATE IN A RESEARCH STUDY
Chronic Migraine Treatment Trial**

Being in a study is different from being a patient. As a patient, the doctor's focus is on you. As a subject, the investigator must, in addition, follow the rules of the study. Those rules and your individual needs may come into conflict. In the event of a conflict, the study doctor's first responsibility is for your safety and welfare.

This consent form describes the research study and your role as a participant. Please read this form carefully. Think about what participation might mean to you and what your motivations and fears are. Do not hesitate to ask anything about the information provided; it should stimulate your questions. The doctor or nurse will describe the study and answer your questions.

You may be eligible for participation in this clinical trial because you have a diagnosis of chronic migraine headaches. This research study will assess drug treatments for this problem.

INFORMATION YOU NEED TO KNOW ABOUT THIS STUDY

A. BACKGROUND AND PURPOSE

Topiramate, a drug previously used for epilepsy, has recently received Food and Drug Administration (FDA) approval to be used to help prevent migraines. In previous studies of chronic migraine, the number of headache days was decreased by 10-20%.

The National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health in Bethesda, Maryland will test if taking a second drug along with topiramate can further decrease the number of days with severe headache. The second drug used in this study is propranolol. Propranolol is also FDA-approved for prevention of migraine headaches and is widely used for this purpose, but it's effectiveness for chronic migraine and its effectiveness when combined with topiramate is not known.

In order to learn if this combination is better than topiramate alone, half of the 250 volunteers will receive propranolol and half will receive a placebo which is, in effect, an inactive pill designed to look and taste like

propranolol. Assignment will be by chance (a process called randomization), and neither you nor your doctor will know whether you will be receiving propranolol or inactive placebo until the end of the study.

B. PROCEDURES


There are two or three periods in this study, depending on whether you are currently using topiramate and are as follows:

1. Eligibility Period

- During this time we will see if you are eligible to participate in the study and you will begin to take topiramate. If you are currently taking topiramate, you will remain on your current dose or you will increase your dose.

2. Baseline Period

- A 4-week period to measure your number of headache days while taking topiramate alone. After these 4 weeks, if you are eligible and want to continue you will be randomized.

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3. Study Period

- A 6-month period after you are randomized, there is an additional 4-week follow-up to wean you off of the study pills.

1. Eligibility Period

Individuals with some conditions should not participate in this study. There will be an evaluation of your medical, medication and headache history and several short questionnaires. If you have a history of a heart problem, you may not be able to participate. An EKG performed within the last year is required. If you have not had an EKG within the past year, then an EKG will be performed to check for heart problems. Women who are pregnant or breastfeeding, or planning to become pregnant should not participate in this study. If you are a woman who is able to bear children you will have a urine pregnancy test before you begin the study. You must use an effective birth control method while you are participating in the study. If you do become pregnant during the course of the study, you should notify the study doctor immediately.

If you meet the study eligibility requirements then you will begin topiramate, continue on your current dose of topiramate if you have been taking it less than 3 months and you can not increase your dose, or increase your dose of topiramate up to 100 mg daily if you can tolerate more. If you are taking topiramate at a dose of 100 mg daily or as much as you can tolerate for more than 3 months, you will enter the one-month baseline period.

Begin Topiramate

If you are **not** taking topiramate currently the first step is to start you on 25 mg a day of topiramate, which you will take for a week. Each week, for the next 3 weeks, another 25 mg will be added for a total up to 100 mg daily or the highest dose that you can tolerate.

After you have finished this four-week period you will begin the baseline period.

If you are taking topiramate at a dose less than 100 mg daily and can tolerate more, you will add 25 mg a day of topiramate, which you will take for a week, until you are taking the highest dose you can tolerate up to 100 mg daily. After you have reached and maintained the highest dose you can tolerate (up to 100 mg daily) for one week and have completed at least 28 days of topiramate following your eligibility period, you will begin the baseline period.

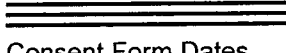
If you have been taking topiramate for less than 3 months and can not increase your dose because you are taking 100 mg or because you are taking the maximum tolerated dose, then you will continue to take this dose for 4 weeks before beginning the baseline period.

2. Baseline Period

During this period you will be asked to keep a headache diary each day for 28 days that asks: how long your headaches last, how severe your headache is, what types of symptoms you are having when you have a headache and what medications you take when you have a headache. The study will use this diary information to see if you qualify for randomization and to compare the frequency of your headaches at the baseline period to the frequency of headaches at the end of six months.

Randomization

At the end of this last 28-day baseline period, there will be a further discussion of this study to see if you qualify to continue in the study. If you qualify and wish to continue, you will be randomized. This means a computer will be deciding what study pills the next person gets. Each person will continue on their dose of topiramate but in addition will be taking up to another 4 study pills. Those pills will be

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either propranolol or the propranolol look-alike that is fake (placebo). Neither you nor the study team will know what pill you are getting. You will begin by taking one study pill a day for a week. Each week, for the next 3 weeks, another study pill will be added for a total up to 4 study pills/day or the highest dose you can tolerate.

You will be asked to come for your follow-up visits regardless of whether or not you are able to continue to take the study medications.

3. Study Period

Once you have been randomized, you will be seen in the clinic at 1 month and 3 months and 6 months or more often if you need to return. You will be called or contacted every 2 weeks for the first 2 months, at 3 months and every month thereafter by a person at this clinic or a person at the study center. You will be asked to complete a daily headache diary for 28 days via telephone or computer beginning on days 57, 113, and 141 after you are randomized.

It is possible that you will continue to have bad headaches. You and your neurologist can decide how to treat these. When you are keeping a headache diary, any medication taken should be recorded in your headache diary.

You will be taken off the study pills 6 months after randomization. You will take one less study pill every week until you are no longer taking study pills. When the last person has completed 6 months the study will be over. You can be told what was in the pills you took (propranolol or placebo).

C. POSSIBLE RISKS OR DISCOMFORTS

Both of these drugs (topiramate and propranolol) are available and could be prescribed to you by your own physician. Each of them has known side effects.

Being in this study will not alter the possibility of side effects from either drug. What is not known is whether combining them could contribute to more problems.


Topiramate: In a small study of topiramate, tingling or prickling of the skin was experienced in 53% (about half) of subjects, nausea in 9% (about one person in 11), and 6% (about one person in 16) had dizziness, fatigue, and weight loss (average weight loss was about 4 pounds). In a larger study tingling or prickling of the skin was reported by 29% of subjects assigned topiramate and the average weight loss was about 5 pounds.

Clinical trials in patients with epilepsy (a disorder of the nervous system) in which higher doses (200-400mg daily) were used, the most frequently reported side effects were:

- Dizziness – 4-32%
- Clumsiness – 6-16%
- Drowsiness – 15-29%
- Fatigue – 9-30%
- Weight loss – 8-13%
- Tingling or prickling of the skin – 1-19% (higher in migraine trials)

Kidney stones are reported in 1.5% of patients taking topiramate chronically for epilepsy (about 2-4 times the frequency in participants not taking topiramate). This risk may be reduced by increasing fluid intake. A decrease in appetite (anorexia), blurred vision and decreased effectiveness of oral contraceptives have also been reported in clinical trials.

Propranolol: Tiredness, depression, short-term memory loss, impotence and trouble thinking are recognized side effects of beta-blockers; how often this happens cannot be accurately estimated from older studies, but they are believed to be rare in the migraine patient population in these dosages. The

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combined use of propranolol with some drugs that you may use to treat a headache (like ergots and triptans) may cause you to have too low a blood pressure.

Combination: In one study of patients taking topiramate plus propranolol, side effects included: trouble thinking (9%, or one person out of 11), tingling or prickling of the skin (5%, or one person out of 20), depression (5%), and exaggerated weight loss (2%). Taking both propranolol and topiramate may increase your risk of depression. Throughout the study you will be screened for the symptoms of depression. If you exhibit symptoms of severe depression you will be referred to a mental health care professional for evaluation. The study doctor will inform your Primary Care Provider (PCP) of the referral.

The use of certain medications may increase the side effects of propranolol. These medications include: bupropion (Wellbutrin, Zyban), fluoxetine (Prozac), paroxetine (Paxil), fluvoxamine (Luvox), quinidine (Quinidex), fluconazole (Diflucan), gemfibrozil (Lopid, Gemcor) and ciprofloxacin (Cipro). The use of a dietary supplement to treat depression may decrease the effectiveness of propranolol. It is very important that you inform your study doctor of all medications and dietary supplements that you are taking while participating in this study.

If you think that you are experiencing any of these side effects, you should report them to the study doctor. We will be taking many safety measures to minimize the potential side effects of the medications.

In addition to this consent form, we will provide you with a list of symptoms to look for and who to call or where to go if you

experience side effects. We encourage you to share the list with family members.

If you are having side effects your investigator can reduce or stop either the study pills or topiramate. If this is done you would be invited to remain in the study for continued data collection until the study ends.

Confidentiality: Because this is a study, information about each subject will be collected and shared. The information sent to the study center will be identified by number only. The study sponsor (NINDS), the NINDS Clinical Research Collaboration (CRC) Operations Center, the FDA, and the Institutional Review Board (IRB) all have limited rights to see identified information. An Institutional Review Board is an independent committee that aims to protect research subjects. More information about how information is used is on the separate HIPAA Authorization form.

D. POSSIBLE BENEFITS

There is not likely to be any direct benefit to you. The primary benefit is the knowledge from this study that could assist in the treatment of future patients or could help in the design of future studies.

E. FINANCIAL CONSIDERATIONS

Costs: If you require any medical treatment your insurance carrier will be billed, even if you think the medical treatment is a result of being part of this study. You may be required to pay a co-pay for these visits or treatments depending on your insurance plan. By agreeing to this, you do not waive any of your legal rights. You will not be responsible for the costs of the study visits. Both drugs used in this study are currently used to treat your condition. The costs of the pills will be covered by the study.

Compensation: You will be paid \$25 for every completed 28-day diary as a gift card

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after you are randomized and have completed your 6-month follow-up visit.

Injury: The cost for treating any research-related injury will be billed to your insurance carrier.

Potential Conflicts of Interest: The NINDS wants you to be aware of some financial relationships that relate to this study. You should consider them when making your decision about whether to participate in this study.

The study investigators are being paid for their time by NINDS. OrthoMcNeil Pharmaceuticals has agreed to donate the topiramate that will be used in the study.

A member of the Steering Committee has a research contract with OrthoMcNeil to study

the natural history of chronic migraine. One member of the Data and Safety Monitoring Board (DSMB) serves as an advisor to OrthoMcNeil and is paid for his time. Another DSMB member holds a patent and earns some money for an (experimental) intravenous form of topiramate which is a different form of the drug from that used in this study.

No members of the study team or the DSMB will receive any type of compensation related to the use of topiramate in this study nor will they benefit financially from the outcome of this clinical study.

F. ALTERNATIVES

Instead of participating you could be treated with one or both of these drugs or with a variety of other drugs.

G. QUESTIONS

Subjects should know where to get answers or help. The first person to ask should be the investigator.

Type of question	Role	Person	Contact
About the study, procedures, risks, benefits, alternatives and rights	Investigator	Norman Gordon, MD	800-707-6013
About changing the appointment or parking or further discussion	Coordinator	Patricia Epple, RN, BS, CCRC	401-996-4400
About long term effects	Sponsor NINDS CRC Operations Center	CMTT Study Coordinator	Phone 1-800-305-7811
About questions or concerns you don't think you can discuss with the investigator.	Institutional Review Board	IRC	1-800-472-3241 subject@irb-irc.com

H. RIGHTS

Both subjects and investigators have some rights.

Subject rights:

- Participation should be voluntary. You should not feel compelled to agree.
- You should be told about the study and your questions should be answered to your satisfaction. You should have all the information you wish. Keep asking questions.
- If you refuse, there should be no penalty.

- If you agree and later wish to withdraw, you may do so without penalty. You should tell the investigator in case there are any safety issues. In California, a Bill of Rights should be attached.
- A HIPAA Authorization is attached.

Investigator rights:

- It is the investigator's right to accept or not accept participants.
- Occasionally studies must be stopped or individuals dropped from a study. Investigators can do this.

I. Agreement

	<u>SUBJECT</u>	<u>INVESTIGATOR OR DELEGEE</u>
Agreement	I agree to participate. My current questions have been answered. I will be given a copy of this form to keep and to refer to as needed.	<i>As the person delivering and explaining the information, I have answered all of this person's questions. I take responsibility for enrolling this person into this study.</i>
Signature	_____	_____
Printed Name	_____	_____
Date and Time	_____	_____