Title:

Treatment for post-concussive headache: A randomized, placebo-controlled, double blinded trial

Document Date:

November 14, 2023

NCT Number:

NCT04226365

ICF:

Athlete 18 + Consent for participation in a research study

Athlete 18 + Consent for participation in a research study

I. **Study title:** Persistent post-concussive headache: a randomized, double-blind, placebo-controlled trial

II. **Primary Investigator: Laura DiPaolo, MD**

LGHP Sports Medicine
51 Peters Road, Suite 200
Lititz, PA 17543
(717) 627-7675

III. **Sub-Investigators: Patrick Moreno, MD**

IV. **Introduction:** Doctors may ask patients to take part in a research trial of a drug. Before a patient agrees, the doctor or research staff must give the patient information about the risks and benefits of the study. The form you are about to read gives such detailed information. Once you understand the study, you can decide if you want to take part in it. If you do, you will need to sign this consent form. You will get a copy of the form that you sign.

The purpose of the study is to learn whether the drug nortriptyline is useful in treating individuals aged 13-21 who have a headache that has lasted 4 weeks or longer after a concussion. Doctors often prescribe medications in these cases, but we do not know how well they work or which ones work best. The study drug is already widely used to treat headaches from concussion in children, but there are no research studies with data about this use. In this study, we will compare nortriptyline to a placebo pill (e.g. sugar pill). This will help us learn about any benefits, as well as the risks. (This form discusses below the possible benefits and risks that we might expect.) We will use a random process (much like flipping a coin) to decide who gets the study drug and who gets placebo. Subjects in the study drug group will take 10 mg nortriptyline once a day, while subjects in the control group will take the placebo once a day. Treatment will last for 4 weeks. The subjects will answer questions about their symptoms, and a study doctor will follow their progress. After these 4 weeks, for subjects who still have a headache, the subject, parents, and doctors can decide what treatment to try next. For all subjects, we will continue to collect information at 6 weeks, 3 months, and 6 months.

V. **Purpose:** This study aims to find out if adding nortriptyline to the standard post-concussion treatment improves symptoms and helps get subjects back to physical activities and school faster.

VI. **Number of Subjects:** A total of 100 subjects will participate in the study.

VII. **Study Involvement:** The study will be enrolling subjects for 24 months. Each subject's involvement lasts for 6 months.

Follow-up schedule:

Enrollment	• Consent (in-office visit)
Week 1	• Phone call with research coordinator (Survey)
Week 2	• Office visit with Sports Medicine →Provider assessment →Conduct surveys →Provider visit
Week 3	• Phone call with research coordinator (Survey)
Week 4	• Office visit with Sports Medicine →Provider tells subject which group they were in (study drug versus placebo) →Provider assessment →Conduct surveys →Provider visit
Week 6	• Phone call with research coordinator • Office visit with Sports Medicine
Week 12	• Phone call with research coordinator • Office visit with Sports Medicine
Week 24	• Phone call with research coordinator • Office visit with Sports Medicine

Someone from the study team will call you the business day before your Sports Medicine appointments to remind you to bring the study drug with you to the appointment.

VIII. Risks and Benefits: The risks of taking nortriptyline include any adverse reactions to the medication itself. There are no known interactions between nortriptyline and standard of care, over-the-counter headache medications (i.e. ibuprofen, acetaminophen).

Risks of nortriptyline include:

- Constipation
- Sleepiness (take at bedtime)
- Cardiovascular side effects (rare, may be increased in subjects with preexisting cardiac disease): dysrhythmia, heart block, prolonged QT interval, acute MI, arrhythmia (in subjects with hyperthyroidism or who take thyroid medications)
- Hepatic (liver) side effects: abnormal liver functions tests, jaundice
- Seizures, especially in subjects with history of seizures
- Serotonin syndrome, when used with other serotonergic medications
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Increased thoughts of self-harm and/or suicide. This is rare, but the risk is greater in subjects who had symptoms of depression before their concussion. The study doctor and study coordinator will closely monitor every subject.
- It is possible there are some risks from the study drug that are not yet known.

The potential benefits of the study are that your symptoms may improve faster, allowing you to return to physical activities and school sooner. Your mood also could improve as a result of returning to your activities sooner and as a result of taking nortriptyline.

IX. **Pregnancy:** You should not take this drug if you are pregnant. If you become pregnant during the study, notify the study doctor immediately.

X. **Alternatives to participation:** If you do not want to participate in the study, you will still be treated for your concussion, which may include nortriptyline.

XI. **Payment and Costs:** Study costs will be funded by a grant from the von Hess Foundation. There will be no cost to you to take part in this study. There is no payment for participation in this research study.

If you are injured because of taking part in this study, you could need medical treatment for your injuries. You or your insurance company would be responsible for the costs of that treatment. Lancaster General Hospital does not have a program to pay for medical expenses, lost wages, lost time or discomfort for such injuries.

You do not waive any legal rights to seek compensation by signing this consent form.

XII. **Voluntary Participation:** Your participation in this study is voluntary. This means it is your choice whether to take part or not. You may refuse to take part in this study, or you may withdraw from this study at any time. You will not lose benefits you would otherwise receive or suffer any penalty if you do so. You also will not jeopardize the medical care you receive from your doctor. If we learn of important new information during the study that may affect your decision to participate, we will provide this information as soon as possible to you and your doctor. You then can review and discuss it together. If you sign below but later change your mind, please tell your study doctor right away in person, or by calling the office at the number provided above. You will then be removed from the study, but any data already collected will be retained.

XIII. **Termination of Participation:** The study doctor may end your involvement in the study if they determine it is unsafe for you to continue or if the study is stopped for any reason.

XIV. **Further information/questions:** If you have any questions about this research or if you believe you have been injured as a result of participating in this research study, you can contact Dr. DiPaolo or Dr. Moreno. (See Section I for complete list of investigators and sub-investigators.)

XV. **Confidentiality:** All answers will be stored in a secure password-protected database only accessed by the study team. Health information will include name, age, medical history, current symptoms, history of injury, and treatments tried. If we share or publish data from the study, we will not identify you in any way.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

XVI. Subject's rights: The Human Research Protection Program (HRPP) provides oversight of all research activities involving human subjects at Lancaster General Health. If you have any questions about your rights as a research participant, or if you have any complaints or concerns, you may send an e-mail to the HRPP (SM-HRPP@lghealth.org). You may also call the chair of the Institutional Review Board at Lancaster General Hospital at 717-544-5091.

XVII. Statement of Consent:

I have read the above information, or have had it read to me. I understand the purpose of the study, as well as the possible benefits and risks of taking part in the study. I have had the chance to ask questions, and all of my questions have been answered. I am at least 18 years of age, and I freely give my informed consent to take part in this study.

By acknowledging and signing this consent form, we have permission to contact you at the number provided below to conduct the study surveys.

Subject Name (printed)	Subject Signature	Date & Time
Phone Number (for surveys and reminders)	This phone number belongs to: ◯ Parent ◯ Child	
Witness Name (printed)	Witness Signature	Date & Time
Physician Name (printed)	Physician Signature	Date & Time

XVIII. HIPAA AUTHORIZATION

To conduct clinical research studies, we need to use and disclose subjects' health information in several ways. The Federal law known as the Health Insurance Portability and Accountability Act ("HIPAA") requires that we get you to authorize the ways we use and disclose your health information.

A. We will obtain information about your concussion, current treatments, relevant medical history, and tests. During the study we will obtain information about how you are doing and any problems that you experience.

B. The researchers and the study team are the only people who will access and use your health information for study purposes.

C. We will use the data to help us learn if nortriptyline, in addition to standard headache treatments, reduces post-concussion headaches.

D. We will not disclose your health information to anyone outside the study unless we de-identify it (remove all information that could identify you or anyone else). People whose job it is to make sure that research is being conducted properly (such as the Institutional Review Board) might see your data.

E. Your permission for us to access and use your health information for the study does not expire.

F. You may refuse to authorize us to access and use your health information. If you refuse, you cannot be in the study.

G. You have the right to revoke your permission to access and use your health information for the study. You must notify us in person or via phone if you want to do so. You cannot withdraw permission for us to use any data that we have already collected about you. If you withdraw permission, you will no longer be in the study.

I authorize my health information to be accessed, used, and disclosed as described above.

_____
Subject Name (printed)

_____
Subject Signature

_____
Date & Time

Title:

Treatment for post-concussive headache: A randomized, placebo-controlled, double blinded trial

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Child Athlete Assent for Participation in a Research Study

Penn Medicine
Lancaster General Health

Child Athlete Assent for Participation in a Research Study

I. **Study title:** Persistent post-concussive headache: a randomized, double-blind, placebo-controlled trial

II. **Overview:** We are asking you to join a research study. It is for children who have had a headache for at least 4 weeks after a concussion. Doctors often prescribe medicine to these children, but we do not know how well they work or which ones work best. We want to study the drug nortriptyline. It is already widely used to treat headaches from concussion in children. However, there are no research studies with data about this use. In this study, we will compare nortriptyline to a placebo pill (e.g. sugar pill). This will help us learn about any benefits, as well as the risks. We will use a random process (much like flipping a coin) to decide who gets the study drug and who gets placebo. Subjects in the study drug group will take 10 mg nortriptyline once a day, while subjects in the control group will take the placebo once a day. Treatment will last for 4 weeks. The children in the study will answer questions about their symptoms. A study doctor will follow their progress. After the 4 weeks of treatment, if any children still have a headache, they, their parents, and doctors can decide what treatment to try next. For all children in the study, we will continue to collect information at 6 weeks, 3 months, and 6 months.

III. **Benefits and Risks:** We study medicines because we think they may help treat a problem. However, all drugs have possible side effects too. The study doctor can explain the possible benefits and risks of nortriptyline. This drug is usually used to treat depression.

If you receive nortriptyline, it is possible that your symptoms may improve faster and allow you to return to physical activities and school sooner. You might also find that your mood is better. However, we do not know if this will occur. Also, some children can have thoughts of self-harm or suicide. This is very rare, but the risk is greater when children had some symptoms of depression before their concussion. We will closely watch the children in the study. If you join the study, we want you to report any changes in your mood.

IV. Please talk this over with your parent or guardian. It is your choice whether to join the study. You may refuse; it will not affect the care you receive at Sports Medicine. You could still receive nortriptyline outside of the study. If you join the study, you will need to sign this assent form. Your parent or guardian will sign a parental consent form. You both will receive copies for your records. If you have any questions, please ask Dr. DiPaolo or Dr. Moreno.

Signing your name below means that you agree to be in this study.

Subject Name (printed)	Subject Signature	Date & Time
Witness Name (printed)	Witness Signature	Date & Time
Name of person obtaining consent (printed)	Signature of person obtaining consent	Date & Time

Title:

Treatment for post-concussive headache: A randomized, placebo-controlled, double blinded trial

Document Date:

November 14, 2023

NCT Number:

NCT04226365

ICF:

Parental Consent for participation in a research study

Penn Medicine
Lancaster General Health

Parental Consent for participation in a research study

I. **Study title:** Persistent post-concussive headache: a randomized, double-blind, placebo-controlled trial

II. **Primary Investigator: Laura DiPaolo, MD**

LGHP Sports Medicine
51 Peters Road, Suite 200
Lititz, PA 17543
(717) 627-7675

III. **Sub-Investigators: Patrick Moreno, MD**

IV. **Introduction:** Doctors may ask parents and their children to take part in a research trial of a drug. Before a parent (or guardian) and child agree, the doctor or research staff must give them information about the study and its risks and benefits. The form you are about to read gives such detailed information for parents or guardians. Your child will get a simpler form with information about the study as well. Once you both understand the study, you and your child can decide if your child will join the study. Children will only be enrolled if both they and a parent or guardian agree to the study and sign the needed forms. You will need to sign this parental consent form. Your child will need to sign the assent form. You both will get copies of the forms that you sign.

The purpose of the study is to learn whether the drug nortriptyline is useful in treating individuals aged 13-21 who have a headache that has lasted 4 weeks or longer after a concussion. Doctors often prescribe medications in these cases, but we do not know how well they work or which ones work best. The study drug is already widely used to treat headaches from concussion in children, but there are no research studies with data about this use. In this study, we will compare nortriptyline to a placebo pill (e.g. sugar pill). This will help us learn about any benefits, as well as the risks. (This form discusses below the possible benefits and risks that we might expect.) We will use a random process (much like flipping a coin) to decide who gets the study drug and who gets placebo. Subjects in the study drug group will take 10 mg nortriptyline once a day, while subjects in the control group will take the placebo once a day. Treatment will last for 4 weeks. The subjects will answer questions about their symptoms, and a study doctor will follow their progress. After these 4 weeks, for subjects who still have a headache, the subjects, parents, and doctors can decide what treatment to try next. For all subjects, we will continue to collect information at 6 weeks, 3 months, and 6 months.

V. **Purpose:** This study aims to find out if adding nortriptyline to the standard post-concussion treatment improves symptoms and helps get subjects back to physical activities and school faster.

VI. Number of Subjects: A total of 100 subjects will participate in the study.

VII. Study Involvement: The study will be enrolling subjects for 24 months. Each subject's involvement lasts for 6 months.

Follow-up schedule:

Enrollment	• Consent (in-office visit)
Week 1	• Phone call with research coordinator (Survey)
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Week 4	• Office visit with Sports Medicine →Provider tells subject which group they were in (study drug versus placebo) →Provider assessment →Conduct surveys →Provider visit
Week 6	• Phone call with research coordinator • Office visit with Sports Medicine
Week 12	• Phone call with research coordinator • Office visit with Sports Medicine
Week 24	• Phone call with research coordinator • Office visit with Sports Medicine

Someone from the study team will call you the business day before your Sports Medicine appointments to remind you to bring the study drug with you to the appointment.

VIII. Risks and Benefits: The risks of taking nortriptyline include any adverse reactions to the medication itself. There are no known interactions between nortriptyline and standard of care, over-the-counter headache medications (i.e. ibuprofen, acetaminophen).

Risks of nortriptyline include:

- Constipation
- Sleepiness (take at bedtime)
- Cardiovascular side effects (rare, may be increased in subjects with preexisting cardiac disease): dysrhythmia, heart block, prolonged QT interval, acute MI, arrhythmia (in subjects with hyperthyroidism or who take thyroid medications)
- Hepatic (liver) side effects: abnormal liver functions tests, jaundice
- Seizures, especially in subjects with history of seizures
- Serotonin syndrome, when used with other serotonergic medications

- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Increased thoughts of self-harm and/or suicide. This is rare, but the risk is greater in subjects who had symptoms of depression before their concussion. The study doctor and study coordinator will closely monitor every subject.
- It is possible there are some risks from the study drug that are not yet known.

The potential benefits of the study are that your child's symptoms may improve faster, allowing your child to return to physical activities and school sooner. Your child's mood also could improve as a result of returning to activities sooner and as a result of taking nortriptyline. However, we do not know if your child will have these benefits.

IX. **Pregnancy:** You should not take this drug if you are pregnant. If your child becomes pregnant during the study, notify the study doctor immediately.

X. **Alternatives to participation:** If you do not want your child to participate in the study, they will still be treated for their concussion. Your child could receive nortriptyline outside the study.

XI. **Payment and Costs:** Study costs will be funded by a grant from the von Hess Foundation. There will be no cost to you or your child to take part in this study. There is no payment for participation in this research study.

If your child is injured because of taking part in this study, they could need medical treatment for their injuries. You or your insurance company would be responsible for the costs of that treatment. Lancaster General Hospital does not have a program to pay for medical expenses, lost wages, lost time or discomfort for such injuries.

You do not waive any legal rights to seek compensation by signing this consent form.

XII. **Voluntary Participation:** Your child's participation in this study is voluntary. This means it is your choice and their choice whether to take part or not. You or your child may refuse to take part in this study, or you or your child may withdraw from this study at any time. Your child will not lose benefits they would otherwise receive or suffer any penalty if they do so. You also will not jeopardize the medical care they receive from their doctor. If we learn of important new information during the study that may affect your or your child's decision to participate, we will provide this information as soon as possible to you, your child, and your doctor. You then can review and discuss it together. If you sign below but later change your mind, please tell your study doctor right away in person, or by calling the office at the number provided above. Your child will then be removed from the study, but any data already collected will be retained.

XIII. **Termination of Participation:** The study doctor may end your child's involvement in the study if they determine it is unsafe for them to continue or if the study is stopped for any reason.

XIV. **Further information/questions:** If you have any questions about this research or if you believe your child has been injured as a result of participating in this research study, you can contact Dr. DiPaolo or Dr. Moreno. (See Section I for complete list of investigators and sub-investigators.)

XV. **Subject's rights**: The Human Research Protection Program (HRPP) provides oversight of all research activities involving human subjects at Lancaster General Health. If you have any questions about your or your child's rights, you may send an e-mail to SM-HRPP@lghealth.org). You may also call the chair of the institutional Review Board at Lancaster General Hospital at 717-544-5091.

XVI. **Confidentiality:** All answers will be stored in a secure password-protected database only accessed by the study team. Health information will include subject name, age, medical history, current symptoms, history of injury, and treatments tried. If we share or publish data from the study, we will not identify your child in any way.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

XVII. Statement of Consent:

I have read the above information, or have had it read to me. I understand the purpose of the study and the possible benefits and risks of taking part in it. I have had the chance to ask questions, and all of my questions have been answered to my satisfaction. I freely give my informed consent for my child to take part in this study.

By acknowledging and signing this consent form, we have permission to contact you or your child at the number provided below to conduct the study surveys.

Subject Name (printed)		
Parent/Guardian Name (printed)	Parent/Guardian Signature	Date & Time
Phone Number (for surveys and reminders)	This phone number belongs to: ◯ Parent ◯ Child	
Witness Name (printed)	Witness Signature	Date & Time
Physician Name (printed)	Physician Signature	Date & Time

XVIII. HIPAA AUTHORIZATION

To conduct clinical research studies, we need to use and disclose subjects' health information in several ways. The Federal law known as the Health Insurance Portability and Accountability Act ("HIPAA") requires that we get you to authorize the ways we use and disclose your child's health information.

A. We will obtain information about your child's concussion, current treatments, relevant medical history, and tests. During the study we will obtain information about how your child is doing and any problems that they experience.

B. The researchers and the study team are the only people who will access and use your child's health information for study purposes.

C. We will use the data to help us learn if nortriptyline, in addition to standard headache treatments, reduces post-concussion headaches.

D. We will not disclose your child's health information to anyone outside the study unless we de-identify it (remove all information that could identify your child or anyone else). People whose job it is to make sure that research is being conducted properly (such as the Institutional Review Board) might see your child's data.

E. Your permission for us to access and use your child's health information for the study does not expire.

F. You may refuse to authorize us to access and use your child's health information. If you refuse, your child cannot be in the study.

G. You have the right to revoke your permission to access and use your child's health information for the study. You must notify us in person or via phone if you want to do so. You cannot withdraw permission for us to use any data that we have already collected about your child. If you withdraw permission, your child will no longer be in the study.

I authorize my child's health information to be accessed, used, and disclosed as described above.

_____
Parent Name (printed)

_____
Parent Signature

_____
Date & Time