WAKE FOREST
UNIVERSITY
HEALTH SCIENCES

Department/Section of Anesthesiology

# Three way interaction among gabapentin, duloxetine, and donepezil in patients with diabetic neuropathy

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## INTRODUCTION

You are being asked to read the following document as a part of the informed consent process. The informed consent process is to inform you of the risks and benefits involved in the study so you can make a free decision whether or not to participate. Informed consent includes having the study fully explained to you, an opportunity to ask questions, your questions answered to your satisfaction and a written informed consent to read and sign. Your participation is voluntary.

Research studies are designed to gain scientific knowledge that may help other people in the future. You may or may not receive any benefit from being part of the study. There may also be risks associated with being part of research studies.

You are being asked to participate in this research study to be performed by Dr. James C. Eisenach in the General Clinical Research Center (GCRC) at Wake Forest University Baptist Medical Center. There will be approximately sixty-six subjects involved in this research project. The length of participation will last approximately 16 weeks.

You are being asked to take part in this study because you have been diagnosed with diabetic neuropathic pain or you have had surgery on your back and you continue to have chronic lower back pain.

Diabetic nerve pain can happen when people with diabetes develop damage to the nerves throughout their body. This "nerve damage" or "neuropathy" can lead to numbness, pain and weakness in the hands, arms, feet, and legs. This same type of nerve pain can also develop after you have had back surgery.

## WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to test whether the combination of the following medicines, including donepezil (used for treatment of Alzheimer's disease), gabapentin (used to treat neuropathic pain), and duloxetine (used for the treatment of depression and diabetic neuropathic pain) will have a greater reduction in pain if taken together than if taken separately. Donepezil, gabapentin, and duloxetine are FDA approved drugs. What we learn in this study may lead to future research studies to try to find effective combinations of medicine therapy for pain management. In this study these drugs will be compared to placebo. In this study these drugs will be compared to placebo (placebo contains no active medication).

Placebos are used in research studies to see if the drugs being studied really do have an effect.

## HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

There will be about 66 people included at all sites across the country included in the study. Approximately 46 people will be enrolled at this site; Wake Forest University Baptist Medical Center. Subjects will be assigned to one of four groups. All four groups will be treated with gabapentin in addition to the assigned study drug for the last eight weeks of the study.

Group 1: Will receive donepezil 5mg.
Group 2: Will receive duloxetine 30 mg.
Group 3: Will receive a combination of donepezil 2.5 mg and duloxetine 30mg.
Group 4: Will receive placebo pills.

This is a double blind study which means that neither you nor your doctor will know which group you are assigned to during the study. This information is available in case of an emergency. Regardless of the group you are in, you will be instructed to take one study pill twice each day. All four groups will be treated with gabapentin in addition to the assigned study drug for the last eight weeks of the study.

## WHAT IS INVOLVED IN THE STUDY?

The study lasts 16 weeks. We ask that you do not add any new medications or receive injections to treat your pain during this 16 week study period. You will have five visits to the GCRC.

<u>First visit</u>:

- We will ask you questions about your pain. You will complete some questionnaires and computer tests that describe the type of pain you have as well as how you are feeling.
- You will receive a physical exam.
- If you are a woman who is able to become pregnant, you will give a urine sample for a pregnancy test. If you are pregnant, you cannot participate in this study.
- If you are taking any of the medications we are using in the study (i.e. donepezil, duloxetine, or gabapentin) or are taking a certain type of antidepressant (monoamine reuptake inhibitors), you will stop taking them.
- We will give you a Personal Digital Assistant (small, computer-like device that is held in your hand, commonly known as a PDA) to take home, and ask that you turn it on twice a day (every

morning and evening) to answer the questions. These questions are about your pain. This visit will take about four hours.

Second visit (two weeks later):
- We will connect your PDA to a computer and check if you have been answering the questions twice a day. We will do this at every visit.
- If you are still eligible for the study, you will be randomized into one of the four study groups described above. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have a one in four chance of being placed in any group. Neither you nor the study doctor will know which group you are in but we can find that out in case of emergency.
- You will start the study drug. You will take the blinded study drug as prescribed for the next six weeks.
- You will answer the questions using your PDA every morning and evening.
- This visit will take about two hours.

Third visit (six weeks later):
- You will bring your blinded drug and PDA so we can check to make sure you are taking the study drug properly and answering all your questions.
- We will add the drug gabapentin to the study drug you are already taking. We will start you out with 400mg of gabapentin three times a day. The study doctor or study nurse will call you twice a week to ask you a set of standard questions about your pain and any side effects you have. We will adjust your dose of gabapentin based on your answers. The highest gabapentin dose will be 3200 mg per day. This titration (adjusting of the dose) of the gabapentin will last about 3 weeks. Once we determine your maximum needed dose, you will maintain that dose for another 3 weeks.
- You will still take your other study drug during this time and continue using your PDA to answer the questions in the morning and evening.
- This visit will take about two hours.

Fourth visit (six weeks later):
- You will bring your blinded drug, gabapentin and PDA so we can check to make sure you are taking the study drug and gabapentin properly and answering all your questions.
- You will stop taking your assigned study drugs (placebo, donepezil, duloxetine, or donepezil/duloxetine combination) at this visit but you will keep taking the gabapentin for two more weeks.
- You will continue using your PDA to answer the questions in the morning and evening.
- This visit will take about two hours.

Fifth visit (two weeks later):
- You will bring your gabapentin and PDA so we can check to make sure you are taking the gabapentin properly and answering all your questions.
- You will return the PDA and study drugs provided during the study. At this last visit, you will stop all study drugs.
- This visit will take about two hours.

- You will be instructed to resume your prescribed medication schedule.

## HOW LONG WILL I BE IN THE STUDY?

You will have five study visits over a 16 week period. Your study participation will be complete after the fifth visit to the GCRC.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

## WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. The following risks exist, and side effects may happen. You should discuss these with your doctor. There also may be other side effects that we cannot predict.

The most common side effects of duloxetine observed in diabetic peripheral neuropathy patients include but are not limited to nausea, excessive drowsiness, dizziness, constipation, dry mouth, excessive sweating, decreased appetite and weakness.

The most common side effects of gabapentin are dizziness, excessive drowsiness, peripheral edema, nausea, dry mouth, constipation and ataxia. Other side effects include tiredness, flu syndrome, double or blurred vision, shakiness, and abnormal thinking.

Common side effects of donepezil include (but are not limited to) nausea, diarrhea, vomiting, weight loss. These symptoms usually subside within a few days. Adverse events that were also reported during clinical trials conducted with donepezil include: headache, pain in various locations, accident, fatigue, fainting, loss of appetite, bruising, muscle cramps, arthritis, insomnia, dizziness, depression, abnormal dreams, sleepiness, and frequent urination.

With donepezil, there are some known potential risks involving this class of drugs. If you are planning on having surgery, you would need to tell the doctor you are taking this medication. It could increase the effects of your anesthesia depending on the drugs they treat you with. There is a risk of fainting episodes, known as syncope, associated with this drug. If you have a history of ulcer disease or you are taking nonsteroidal anti-inflammatory drugs (like aspirin, Advil, Motrin, Aleve, and others), we will watch closely for any signs of ulcer disease and intestinal bleeding. Although not observed in clinical trials with donepezil, this class of drugs may cause difficulty urinating. This class of drugs is also believed to have some potential to cause seizures. If you have a history of asthma or coronary obstructive pulmonary disease (COPD), you should take caution in taking this medication.

As with all medications, side effects may include an allergic reaction. Allergic reactions may range from minor reactions, such as itching or rash, to major, life threatening reactions which can result in death.

Any drug has possible side effects. The drugs used in this study may cause some or none of the side effects listed. In addition there is always the risk of uncommon or previously unknown side

effects occurring. If you have any kind of unusual or unexpected symptoms, you should report them immediately to your study doctor.

Also, there is a risk of a temporary increase of chronic pain during the washout period (the first two weeks of the study) or if the study drugs do not work well for you.

Taking part in this research study may involve providing information that you may consider confidential or private. This may make you feel uncomfortable or embarrassed. There is always a risk this information may be accidentally released. The PDA you will use will contain no personal identification information about you. Efforts, such as coding research records and keeping them secure so that only study staff have access to them, will be made to keep your information safe, but we cannot guarantee absolute confidentiality and privacy.

**Reproductive risks:**
Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives (the pill), intrauterine device (IUD), DepoProvera, Norplant, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge**.** We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. If you are a sexually active woman of childbearing potential and have not been using a reliable method of birth control, two negative pregnancy tests performed 15 days apart are required to check for possible early pregnancy prior to starting treatment. During the study, you must use one of the reliable methods of birth control described above.

## ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
You may benefit from this study by getting better pain relief than with your regular pain medications. We also hope the information learned from this study will benefit other people in the future.

## WHAT OTHER CHOICES ARE THERE?
Your participation is voluntary. Your alternative is to continue with your treatment as prescribed by your physician and not participate in this study.

## WHAT ABOUT THE USE, DISCLOSURE AND CONFIDENTIALITY OF HEALTH INFORMATION?
By taking part in this research study, your personal health information, as well as information

that directly identifies you, may be used and disclosed. Information that identifies you includes, but is not limited to, such things as your name, address, telephone number, and date of birth.

Your personal health information includes all information about you which is collected or created during the study for research purposes. It also includes your personal health information that is related to this study and that is maintained in your medical records at this institution and at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, your family health history, how you respond to study activities or procedures, laboratory and other test results, medical images, photographs/videotapes/audiotapes and information from study visits, phone calls, surveys, and physical examinations.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

If this research study involves the treatment or diagnosis of a medical condition, then information collected or created as part of the study may be placed in your medical record and discussed with individuals caring for you who are not part of the study. This will help in providing you with appropriate medical care. In addition, all or part of your research related health information may be used or disclosed for treatment, payment, or healthcare operations purposes related to providing you with medical care.

When you sign this consent and authorization form you authorize or give permission for the use of your health information as described in the consent form. You can revoke or take away your authorization to use and disclose your health information at any time. You do this by sending a written notice to the investigator in charge of the study at the following address:

James C. Eisenach, MD
Wake Forest University School of Medicine
Department of Anesthesiology
Winston-Salem, NC 27157-1009

If you withdraw your authorization you will not be able to be in this study. If you withdraw your authorization, no new health information that identifies you will be gathered after that date. Your health information that has already been gathered may still be used and disclosed to others. This would be done if it were necessary for the research to be reliable. You will not have access to your health information that is included in the research study records until the end of the study.

Your participation is confidential and although the results of the study will be published in a scientific journal, no individuals, including yourself, will be identified. The records for this study will be kept private to the extent permitted by applicable law. Representatives of the study staff, the WFUSM Institutional Review Boards, may however, review your records for this study.

This authorization is valid for six years or five years after the completion of the study, whichever is longer.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

## WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All the study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

## WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $150.00 if you complete all the scheduled study visits. There is no payment given for the screening (first) visit. The remaining four visits are paid at $25.00 each and an additional $50.00 for answering the questions on the PDA for the full length of study and returning the equipment at the end of the study.

If you withdraw for any reason from the study before completion you will be paid according to the schedule above for visits you completed.

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

## WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the National Institutes of Health. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

## WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at (336) 716-3467.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. James C. Eisenach at (336) 716-4498.

## WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because, you had an unexpected reaction, or because the entire study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

## WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

You have the right to ask questions concerning this study at any time, and you are urged to do so. If you have any questions concerning this study or have questions concerning a research related

injury, please contact Dr. James C. Eisenach at (336) 716-4498 for further information about this study. After hours you may page the study coordinator, Regina Curry, RN at (336) 806-9496 and ask that she contact Dr. Eisenach to return your call.

You may also contact the Chairman of the Institutional Review Board at (336-716-4542) at Wake Forest University School of Medicine for any questions about your rights as research participant.

You will be given a signed copy of this consent form.

## SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

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| Subject Name (Printed) | Date/Time |
| Subject Signature | Date/Time |
| Person Obtaining Consent | Date/Time |