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

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Investigators: James C. Eisenach, M.D.; James C. Crews, M.D.; Tim Houle, Ph.D., James B. Caress, M.D., Regina Curry, R.N.

Hypothesis: Based on laboratory studies and our understanding of their mechanism of action, there will be a profound positive interaction between two oral drugs approved for the treatment of neuropathic pain (gabapentin and duloxetine) and an oral drug approved for treatment of dementia (donepezil) to treat patients with chronic pain.

Background: We have recently demonstrated that peripheral nerve injury in rats, which results in hypersensitivity to mechanical stimuli and presumably chronic pain, also results in increased capacity for analgesia. Specifically, nerve injury induces sprouting of noradrenergic fibers in the dorsal horn of the spinal cord, accompanied by changes in α2-adrenoceptor function and development of a spinal α2-adrenoceptor - cholinergic circuit. These changes likely underlie the increased potency and efficacy of intrathecal clonidine observed in animals and humans with chronic compared to acute pain, but may have considerably wider therapeutic implications. For example, commonly used, oral drugs for the treatment of neuropathic pain, gabapentin and antidepressants, may depend in part on this noradrenergic plasticity for their efficacy. A summary of the hypothesized sites and mechanisms of action of drugs to be studied in this application is shown in the adjacent figure.

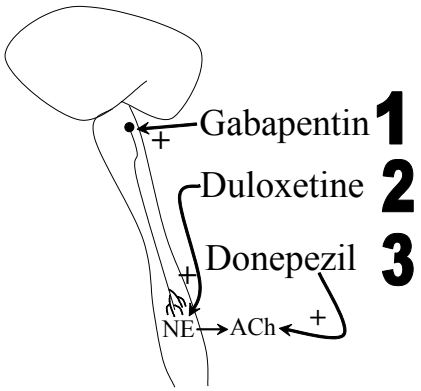

Figure : This study will test whether **1.** Gabapentin produces analgesia after nerve injury by a spinal noradrenergic mechanism, and its effects are enhanced by **2.** the norepinephrine transporter inhibitor, duloxetine, and **3.** the cholinesterase inhibitor, donepezil

We are currently examining in the laboratory the mechanisms which lead to sprouting of noradrenergic fibers in the spinal cord in models of chronic pain as well as the mechanisms that lead to a novel noradrenergic – cholinergic circuit in the spinal cord. In addition to examining the circumstances which generate this increased capacity for analgesia and the mechanisms by which they occur, we will test in this protocol whether approved and experimental treatments for neuropathic pain exploit this increased capacity.

This study is in patients with neuropathic pain, and will culminate in a quantitative description of interactions between activators of descending noradrenergic activity, norepinephrine transporter inhibitors, and cholinesterase inhibitors to exploit this unique plasticity of analgesia in chronic pain states. We focus not only on mechanistic hypotheses in the laboratory studies, but also on practical applications, using clinically approved drugs, including gabapentin (Neurontin®) to activate noradrenergic activity, duloxetine (Cymbalta®) to inhibit the norepinephrine transporter, and donepezil (Aricept®), approved for the treatment of Alzheimer's dementia, but not previously tested to treat neuropathic pain, to inhibit cholinesterase. Each of these drugs may act by mechanisms in addition to those involved in descending noradrenergic inhibition, but we hypothesize that the therapeutic strength of their combination relies heavily on this cascade engendered by noradrenergic sprouting and altered α2-adrenoceptor function. The proposed studies will provide critical tests of this hypothesis and critical information to guide more effective clinical therapy of neuropathic pain.

Protocol

Inclusion Criteria:

A total of sixty-six patients with diabetic neuropathic pain will be recruited from the Department of Neurology at Wake Forest University School of Medicine, surrounding Piedmont Triad community and we will also have a second site at the Cleveland Clinic Foundation in Cleveland Ohio. Patients with predominant neuropathic pain following back surgery will also be enrolled. Approximately 46

subjects will be enrolled at WFUHS and 20 will be enrolled from the Pain Clinic at the Cleveland Clinic. Wake Forest University Health Sciences will be the coordinating center. Jianguo Cheng, MD, will be the PI for the Cleveland Clinic site. Subjects from the Cleveland Clinic will follow the same protocol as the WFUHS subjects.

1. Diagnosis of diabetic neuropathy
2. Age 18-80
3. Willing to temporarily discontinue gabapentin or monoamine reuptake inhibitors upon entry into the study

Subjects will be able to continue their other prescribed medications maintaining a stable dose.

4. Diagnosis of failed back syndrome.

Exclusion Criteria:

1. Pregnant women or women of child-bearing potential not willing to practice a reliable form of birth control as specified in the informed consent
2. Allergy to duloxetine, gabapentin, donepezil or other piperidine derivatives (including fentanyl, alfentanil, sulfentanil, remifentanyl, demerol, tramadol, loperamide, diphenoxylate, betaprodine, alphaprodine, ethoprodine, anileridine, diminodine, MPTP, loradine, fexofenadine
3. Unstable medical conditions including cardiac, pulmonary, renal or hepatic diseases that, in the opinion of the investigator, would preclude patients from finishing the trial
4. Any person with pending litigation
5. A history of major psychosis requiring hospitalization within the last three years
6. Non-English speaking, illiterate, unable to comprehend consent
7. Lack of contact information
8. Known hypersensitivity to duloxetine or any of the inactive ingredients

9. Treatment with a monoamine oxidase inhibitor (MAOI) within 14 days of randomization or potential need to use an MAOI during the study or within 5 days of discontinuation of study drug
10. Uncontrolled narrow-angle glaucoma
11. Currently being treatment with thioridazine *(Mellaril)*
12. Patients taking opioids will be excluded if they are taking a dosage that exceeds an equivalent of 30 mg of morphine per day
13. Patients taking more than one regular (not rescue) medication for pain
14. Patients taking donepezil for dementia
15. Patients with a baseline pain score less than 2 (0-10 scale) or greater than 8 (0-10) will be excluded

Drug Administration (basis of randomization):

Following a two week baseline period, patients will be seen in The General Clinical Research Center (GCRC) at Wake Forest University Baptist Medical Center and data from the PDA device downloaded and checked for compliance. Patients will be randomized, using a balanced and double blind design, to receive either duloxetine, 30 mg bid, donepezil, 5 mg qd, both duloxetine 30 mg and donepezil 2.5 mg qd, or placebo for the next 12 weeks. All randomizations will include study medication to be taken twice a day to maintain the blinding for all groups. Placebo pills will be provided in addition to the study medications for group 1 and group 4 will take two placebo pills. At the end of 6 weeks, patients will return to The General Clinical Research Center and data from the PDA downloaded and checked for compliance. All patients will then receive gabapentin, 400 mg three times daily, titrated twice a week by telephone interview with the research nurse or investigator for three weeks up to a maximum of 3200 mg per day. Titration up or down will be determined by presence and severity of side effects and efficacy of analgesic treatment, using a standardized interview. Subjects will then be maintained on this gabapentin dose for 3 more weeks. At the end of this 6 week period of gabapentin administration, patients will return to The General Clinical Research Center and data from the PDA downloaded and checked for compliance. Their experimental treatment (placebo, duloxetine, donepezil, or combination) will then be

stopped for two weeks, with daily PDA entry and titration of gabapentin twice weekly by standardized telephone interview.

Experimental Design:

The study will be conducted over a period of 16 weeks; consisting of 2 weeks baseline (no study drug), weeks 3-8 randomized drug assignment, weeks 9-14 of open label gabapentin added to randomized drug assignment (gabapentin to be titrated twice weekly up to a maximum dose of 3200mg for three weeks), weeks 15-16 randomized drug assignment is discontinued while maintaining gabapentin. During this time patients will make 5 visits to the GCRC (screening visit with a 2, 8, 14 week and 16 week study termination visit with a +1/-1 day window). The first visit will entail a brief patient history and a physical exam. In addition, patients will complete primary and secondary measurements, including: McGill short form pain questionnaire (primary) and Profile of Mood States-Short Form (POMS-SF). The McGill short form pain questionnaire will be administered twice daily via PDA (personal digital assistant) and POMS will be used for patients to record total mood disturbance and pain. Study subjects will be trained to use their PDA at their initial visit.

Following the two week baseline period, subjects will be seen in the GCRC and data will be downloaded and checked for compliance. Patients will be randomized, using a balanced double blind design, to receive either duloxetine, 30mg bid, donepezil, 5 mg qd, both duloxetine 30mg and donepezil 2.5 mg qd, or placebo for the next 12 weeks.

At the end of week 8, subjects will return to the General Clinical Research Center and data from the PDA downloaded and checked for compliance. All subjects will then receive gabapentin, 400 mg three times daily, titrated twice a week by telephone interview with the research nurse or investigator for three weeks up to a maximum of 3200 mg per day. Titration up or down will be determined by presence and severity of side effects and efficacy of analgesic treatment, using a standardized interview. Subjects will then be maintained on the Gabapentin dose for 3 more weeks.

At the end of week 14, patients will return to the General Clinical Research Center and data from the PDA downloaded and checked for compliance. Their

experimental treatment (placebo, duloxetine, donepezil, and combination) will then be stopped for two weeks, with daily PDA entry and titration of gabapentin twice weekly by standardized telephone interview.

	Screening	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16
	Visit 1		Visit 2						Visit 3						Visit 4		Visit 5
Informed Consent	X																
Urine Pregnancy Test	X																
Pain Questionnaires	X																
Physical Exam	X																
PDA Instructions	X																
PDA Download			X						X						X		X
Randomization			X														
Blinded Study Med			X	X	X	X	X	X	X	X	X	X	X	X	X		
Gabapentin									X	X	X	X	X	X	X	X	X

Primary Outcome Measures:

Pain intensity measurements will be recorded twice daily, in the a.m. and p.m. using McGill short form pain questionnaire displayed on the personal digital assistant (PDA). The SF-MPQ is comprised of 15 descriptors (11 sensory; 4 affective) with an intensity scale from 0-3 (3 being the most severe), present pain intensity (PPI), and Visual Analog Pain Scale (VAS). The VAS will serve as the study's primary outcome measure.

Statistical Analyses:

All data will be analyzed using the most recent version of SPSS (SPSS Inc., Chicago, IL). Prior to performing analyses related to the aims and hypotheses, descriptive statistics will be computed to examine if assumptions needed for parametric analysis are met. Our previous studies of daily pain reports from neuropathic pain

patients (1) have indicated that such reports can be expected to be approximately normally distributed. If parametric assumptions are not met, standard transformations will be used to make the data more normal. An intent-to-treat analysis will be undertaken for all participants that receive at least one study dose (with last observation carried forward for drop-outs) with no attempts being made to impute missing data. A two-tailed probability value of .05 will be used for statistical significance criterion in all analyses.

To examine differences in the primary outcome of twice-daily pain reports as a function of "medication group" and "study phase", a Linear Mixed Model will be used. Subjects will be treated as a random variable, with the average of the daily pain reports nested within subject. A first-order autoregressive error term will be used to account for the repeated measures within subjects. Although all observations will be used to specify the model, only the observations from the last week (the optimal therapeutic dose) of each study phase ("baseline", "study med", and "gabapentin") will be used to evaluate the hypothesis. In essence, this allows changes in the dependent variable of pain reports to be modeled by two ANCOVAs (controlling for baseline). Group (placebo, duloxetine, donepezil, and duloxetine + donepezil) differences in pain reports will be evaluated separately at end of treatment alone and at end of treatment with gabapentin portions of the study. A significant group effect will indicate that mean self-reported pain scores differed significantly by treatment arm assignment during that phase of the study. If a main effect is found, post hoc analyses will be conducted to indicate the location of the differences and to index the degree of change exhibited by study group.

In addition to the primary analyses, we will examine pre-post changes in disability measures and psychometric measures, global assessments of change, and medication use. Each of these outcomes will be examined using General Linear Models (GLM), examining for differences in group either at one time period or as a function of study phase, as appropriate. Further, because the study design will result in a time-series of pain reports for each subject, we will fully utilize the available data by creating individualized interrupted time-series analysis models for each subject. Within each phase, increases in dose will be modeled as a gradual, permanent intervention. We will utilize ARIMA models (2) to account for the unique data structure that our design results

(i.e., diurnal variation in AM and PM reports). These analyses will better elucidate the nature of individual differences in the medication responses and identify the dose-response function for each medication condition.

Statistical Power Considerations:

For the proposed study all power calculations are based on the primary analysis of the primary outcome measure (daily pain reports). ANCOVA analyses were chosen to evaluate the primary outcome as they have repeatedly been shown to be the most powerful technique for these comparisons (3). Our previous diary studies examining novel agents on neuropathic pain (1) have demonstrated that high levels of visual analog pain reporting are common, M = 60.5, and that substantial variation is often observed, even within day-to-day reporting, SD = 14. Nevertheless, first-order autocorrelation among observations is often observed, r = .20. For the present study, we are preparing for a considerable placebo effect of 20%. Because of the novel nature of the agents being studied, we would like to detect differences as small as 5% between the active treatment and placebo groups (i.e., a 25% reduction in pain from baseline). Using Cohen's formulation for ANCOVA (6) (f = .25, r =.50 between phases) with adjustment (4) for the calculation of our repeated assessment of each study phase (7 observations contributed by each subject at each phase, first-order autocorrelation = .20), we estimate that an n = 15 for each medication group (15 x 4 = N = 60) will provide power = .80. It is of note that the proposed sample size indicates the number of participants that take at least one dose of the study drugs (i.e., recruitment will end when N = 60 participants have taken at least one dose of study medication). Further, the 16 week trial, with two observations per day provides a sufficient number of observations (n ~ 224 observations/subject) to incorporate the interrupted time-series analysis strategy for the secondary analyses (5).

Adverse Events/Side Effects:

The most common side effects of duloxetine observed in diabetic peripheral neuropathy groups 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, if experienced 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.

Additional warnings per package insert of donepezil are:

Anesthesia: ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT®.

Gastrointestinal Conditions: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®.

Genitourinary: Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions: Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease.

Pulmonary Conditions: Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

Risks:

Risks of the medications are described above. There is an overlap in side effects between gabapentin and duloxetine regarding sedation. As such, one could see enhanced sedation with this mixture. This should be minimized in the current study, since gabapentin is being titrated according to side effects. Additionally, there is a risk of temporary exacerbation of chronic pain during the washout period or if drugs are ineffective. Please note that we are studying patients who are failing current analgesic therapy, and this study may benefit these patients by providing a novel combination of medications otherwise not used. Data will be stored in a secure location. Additionally, the personal digital assistants (PDA) will hold no personal identification information.

Data Safety Monitoring Plan

Data will be continually monitored by the study coordinator and reported to the principal investigator who will review the data and all adverse events after each subject is studied. Serious and unexpected adverse events will be reported to the IRB within 24 hours of discovery.

References:

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