

Corticostriatal plasticity in the transition to chronic pain: Effect of Levodopa

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Participants (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

ADL	Activities Of Daily Living
AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BDI	Beck Depression Inventory
BID	Twice Daily
BP	Blood Pressure
BSE	Bovine Spongiform Encephalopathy
BUN	Blood Urine Nitrogen
CBC	Complete Blood Count
CBP	Chronic Back Pain
CFR	Code Of Federal Regulations
CNS	Central Nervous System
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
DHHS	Department Of Health And Human Services
DTI	Diffusion Tensor Imaging
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FDA	Food And Drug Administration
FFR	Federal Financial Report
FL	Fluid
fMRI	Functional Magnetic Resonance Imaging
g/dL	Gram Per Deciliter
GI	Gastrointestinal
HCT	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Insurance Portability And Accountability Act
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
ICMJE	International Committee Of Medical Journal Editors
IND	Investigational New Drug Application

IP	Investigational Product
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IUD	Intrauterine Device
K/uL	Thousands Per Cubic Milliliter
m/uL	Thousands Per Cubic Milliliter
MAOI	Monoamine Oxidase Inhibitor
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
mEq/L	Milliequivalents Of Solute Per Litre Of Solvent
Mg	Milligram
mg/dL	Milligram Per Deciliter
mL	Milliliter
MMRM	Mixed Model Repeated Measure
mPFC	Medial Prefrontal Cortex
MPQ	Mcgill Pain Questionnaire
MRI	Magnetic Resonance Imaging
N	Number (Typically Refers To Participants)
NAc	Nucleus Accumbens
NIDCR	National Institute Of Dental And Craniofacial Research, Nih, Dhhs
NIH	National Institutes Of Health
NMFF	Northwestern Medical Faculty Foundation
NMH	Northwestern Memorial Hospital
NMPG	Northwestern Memorial Physicians Group
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
NU	Northwestern University
NUCATS	Northwestern University Clinical And Translational Science
OHRP	Office For Human Research Protections
PANAS	Positive And Negative Affect Schedule
PASS	Pain Anxiety Symptoms Scale
PCS	Pain Catastrophizing Scale
PDI	Pain Disability Index

PFc	Prefrontal Cortex
pg	Picogram
PHH	Personal Health History
PHI	Protected Health Information
PI	Principal Investigator
PRO	Patient Reported Outcome
PSQ	Pain Sensitivity Questionnaire
QA	Quality Assurance
QC	Quality Control
QD	Once Daily
RDW	Red Cell Distribution Width
RN	Registered Nurse
SAE	Serious Adverse Event/Serious Adverse Experience
SBP	Subacute Back Pain
SBPp	Subacute Back Pain – Persisting Phenotype
SBPr	Subacute Back Pain – Recovering Phenotype
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
TID	Thrice Daily
Unit/L	Unit Per Liter
UP	Unanticipated Problem
US	United States
WOCBP	Women Of Childbearing Potential

PROTOCOL SUMMARY

- Title:** *Corticostriatal plasticity in the transition to chronic pain: Effect of Levodopa*
- Summary:** This study is a 28-week, double-blind, randomized, placebo-controlled two-arm, flexible dose-escalation, parallel-group trial of a pharmacological treatment (**Carbidopa/Levodopa and Naproxen**), selected based on positive results from previous preclinical studies, for the treatment of **subacute back pain (SBP)**. After a 2-week screening period, individuals deemed at high risk of developing **chronic back pain (CBP)** will be randomized to receive either 12 weeks of Carbidopa/Levodopa plus Naproxen or placebo plus Naproxen and then followed for an additional 12 weeks to evaluate persistence of benefit at study endpoint, 24 weeks after randomization. During the 12-week treatment period, participants will undergo evaluation at Baseline and at clinic visits on weeks 1, 4, 8, and 12 after randomization to assess pain, proper treatment use and side effects. During the subsequent 12-week follow-up period, pain and safety will continue to be assessed monthly by phone calls. All patients will also be assessed daily by a smartphone app regarding pain and mood. T1-MRI, resting state, fMRI, and DTI-MRI will be performed at Baseline and at the end of 24 weeks for individuals completing MRI, except for a subset of individuals not receiving MRI, who will be directly put on treatment. Individuals identified as **recovering subacute back pain (SBPr)**, will not be treated. However, they have the choice to participate in an optional substudy where their pain and mood will be assessed daily for 24 weeks using the smartphone app.
- Objectives:**
- Primary: To determine if treatment with Carbidopa/Levodopa and Naproxen in individuals with subacute back pain (SBP), who are at high-risk for developing chronic pain, will diminish their rate of transition to chronic back pain (CBP) compared to individuals with SBP treated with Naproxen alone.
- Secondary: To determine whether treatment efficacy is gender dependent.
- Secondary: To determine the brain reorganization with treatment response
- Population:** Sample size: 126

Gender: Male and Female
 Age: 18 years and older
 Demographic group: No racial/ethnic restrictions
 General health status: History of low back pain for a minimum of 4 weeks and a maximum of 12 weeks; no other source of pain and good general health.

Phase: 2

Number of Sites: One
 Northwestern University
 Chicago, IL 60611

Description of Intervention: A flexible dose-titration designed intervention based on dose-response: Initially, Carbidopa/Levodopa (12.5mg/50mg), or matching placebo, administered orally as capsules, will be titrated up to TID over one week and then continued at that level for 4 weeks. If at the end of this initial 4 week period the participant has “responded” (had a reduction in pain from baseline of $\geq 20\%$), the participant will be maintained on that dose for the duration of the treatment period (12 weeks total). If there has not been a response, the dose will be increased to Carbidopa/Levodopa (25mg/100mg) TID for the following 4 weeks at which time the pain status will be re-evaluated. Again, if a response has occurred, that dose will be maintained in a blinded manner for the following 4 weeks of treatment; if not, further dose-titration will occur to Carbidopa/Levodopa (50mg/200mg) TID for the final 4 weeks. If a participant experiences an AE at higher doses, then the participant will be given the next lower dose that s/he was able to tolerate and then be maintained on that dose for the remainder of the 12 week dosing period.

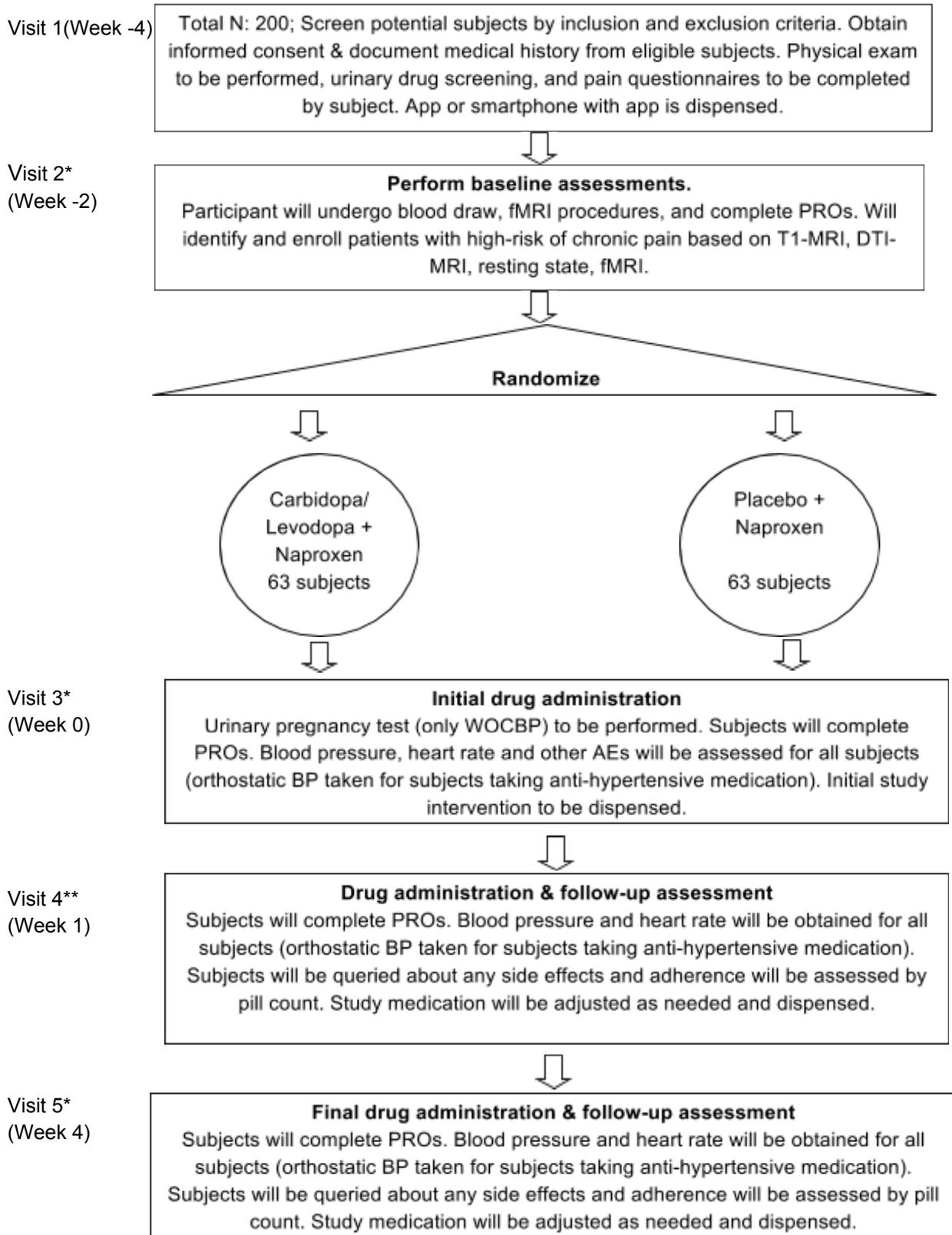
Naproxen (250mg) capsules will be administered orally, one capsule TID, throughout the 12 week treatment period.

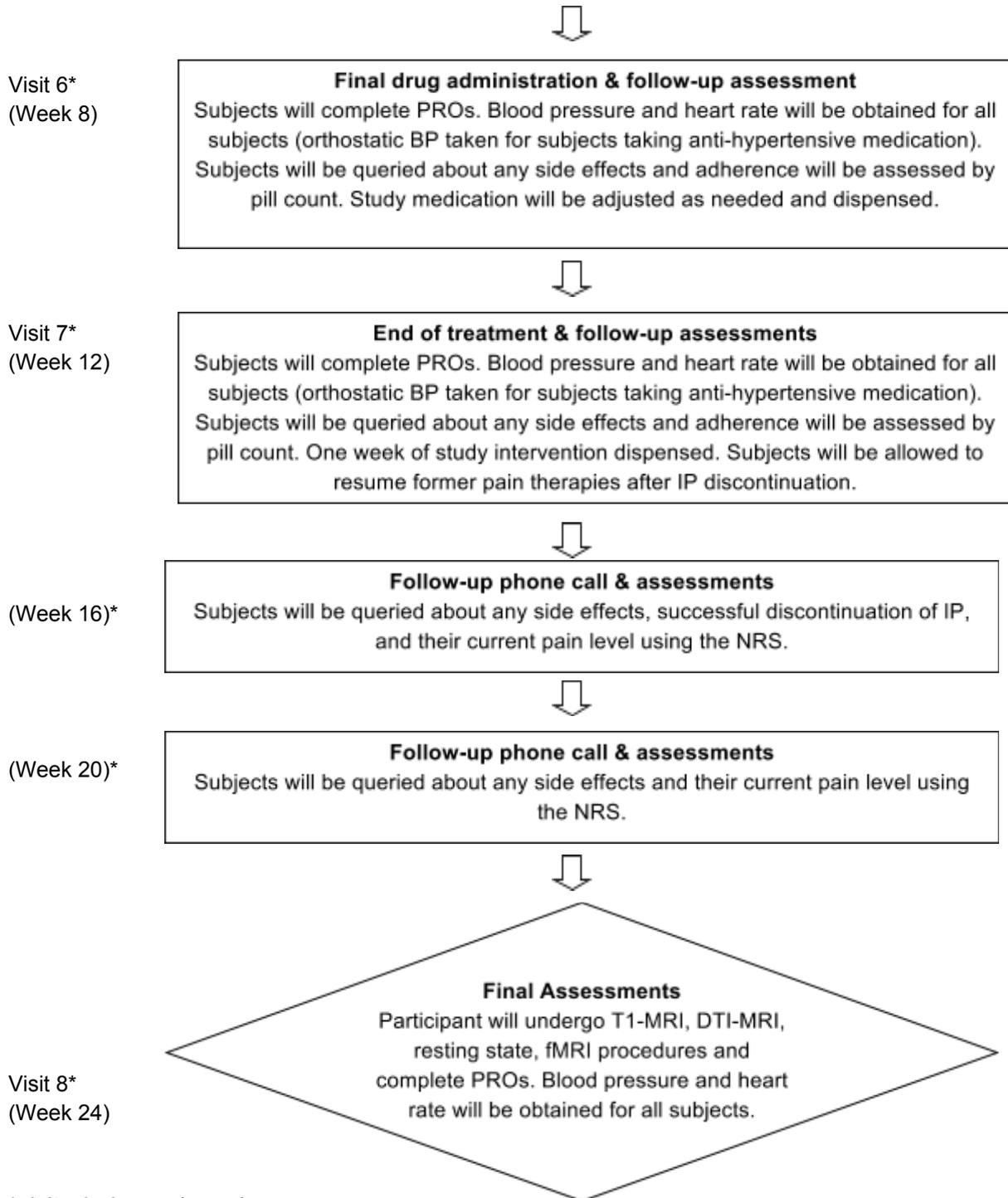
Study Duration: 36 months

Participant Participation Duration: 28 weeks

Estimated Time to Complete Enrollment: 24 months

SCHEMATIC OF STUDY DESIGN:





*visit window = 1 week

**visit window = 3 days

(See [Appendix A](#) for a detailed schedule of events table)

1. KEY ROLES AND CONTACT INFORMATION

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 *Health problem*

When pain becomes chronic, it dramatically decreases quality of life and imparts a huge healthcare cost (more than \$500 billion annually in the USA). Its prevalence is on the increase worldwide (back pain has become the number one leading cause in the USA, and number six cause worldwide, for days lost to disability). Even though there is extensive evidence for a long list of peripheral and central adaptations that are observed in humans' pain conditions, and in animal models for neuropathic or inflammatory pain, there is minimal understanding of critical mechanisms that control the transition from an acute injury to persistent/chronic pain. Perhaps more importantly, there are no scientifically validated clinical intervention strategies to abrogate the transition from acute to chronic pain. The present clinical trial will test a potential strategy for this.

Acute back pain is highly prevalent, and about 85% of the population suffers from back pain throughout life. The large majority of such participants properly recover from the condition within a few weeks and lead a healthy life. Although only approximately 5-10% of people with acute back pain progress to develop chronic back pain, this number is large given the almost universal incidence of back pain, and it has enormous economic consequences. Furthermore, the current treatments for low back pain are largely ineffective, providing at best modest pain relief, and often with unacceptable and even dangerous side effects (e.g., opioids are widely used and lead to the death of >15,000 people per year). Therefore, reducing the incidence of transition to CBP would have major health, economic and societal benefits. Until recently there were no predictive mechanisms as to who transitions to chronic pain. In a series of studies we have identified brain parameters that put participants at risk for developing chronic pain from subacute back pain. Based on these results we have tested in animal models a novel drug combination therapy, with highly successful results. Here we will test translation of the animal study into a clinical trial. The study will test whether clinical acute back pain patients who are at high risk of transitioning to chronic pain can be properly treated to abrogate this transition.

2.1.2 *Study intervention*

Carbidopa/Levodopa (12.5mg/50mg – 25mg/100mg – 50mg/200mg) and Naproxen (250mg). Carbidopa/Levodopa is a medication approved by the FDA for the treatment of Parkinson's disease and has been used for many years. Levodopa is metabolized to dopamine, which is a known central neurotransmitter. Carbidopa prevents the degradation of Levodopa to permit higher levels of Levodopa to be biologically active.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) used to treat mild-moderate pain. Its mode of action is via non-selective inhibition of the cyclooxygenase enzymes.

U-shaped dose response

The inverted u-shape hypothesis of dopamine refers to the finding whereby too little or too much dopamine can be disadvantageous for certain neural processes, suggesting that the best range of doses for dopamine treatment is somewhere in between these two extremes (i.e., located at the peak of the inverted u-curve). This phenomenon has been documented particularly well in literature investigating working memory and other functions related to the prefrontal cortex (PFC); in many of these studies, a moderate concentration of increased dopamine enhanced performance on cognitive tasks, whereas doses close to either endpoint of the curve proved detrimental. (Stewart 2006, Williams 1995, Arnsten 1998) It is still being debated as to which dopamine receptor subtype is primarily involved in this curve, with D1-receptor activation being the most cited (Stewart 2006, Monte-Silva 2009), although D2-receptor activation has also been shown to produce this inverted curve in other areas, including the motor cortex (Monte-Silva 2009) and the striatum (Gjedde 2010). This is most likely due to the complicated push-and-pull mechanisms of dopaminergic circuitry throughout the brain, such that one region's concentration may have an antagonistic relationship with another's levels (for example, PFC with striatum (Fallon 2013, Cools 2011)). It has also been shown that the effects of dopamine stimulation on a given cognitive phenomenon is inversely correlated to a participant's baseline dopamine levels in target circuitry, which is also important to this curve (Gjedde 2010, Cools 2011, Costa 2014). Thus a participant with decreased dopamine transmission would be hypothesized to benefit from dopamine replacement whereas in a healthy participant or a person with higher levels of baseline dopamine, the same treatment might be detrimental due to this inverse relationship. Although some studies looking at dopaminergic treatment in pain models have suggested that increasing dopamine levels dose-dependently decreased pain (Park 2013) and that due to biphasic dopamine responses, smaller doses of dopamine can facilitate pain whereas larger doses can cause antinociception (Paalzow 1992), our own experiments do not support these findings. In both rats and mice with chronic pain (spared nerve injury, SNI), smaller doses of Carbidopa/Levodopa (in combination with Naproxen) resulted in both acute (1 hour) and long-term (10 days) relief of tactile allodynia induced by the injury; in contrast, doubling this dose resulted in zero change from baseline pain levels (acutely) and did not produce results significantly different from those at the lower dose (chronically).

Four points can be made from this knowledge of the inverted-U curve. First, dopamine treatment appears to have non-linear effects in both humans and animals. Therefore, a simple upward titration that continues to increase in time does not necessarily result in a simple increase in reported levels of pain relief. Second, given that chronic pain patients are hypothesized to have less dopamine than healthy controls (one extreme of the curve) and more dopamine than individuals with mid-to-late stage Parkinson's Disease (the other extreme), we would hypothesize that targeted dopamine levels

should be in between these two ends of the spectrum (again, residing at the peak of the curve). Third and related, continuing to increase dopaminergic levels after initial efficacy is found does not guarantee increased efficacy results and may even cause additional or worsening levels of pain, as well as increased side effects. Fourth, it is clear that baseline levels of dopamine affect dopaminergic treatment efficacy and behavior, and as such, the starting and stopping of titration must be based on an individual's perception of analgesia in order to indirectly account for this. All of these points would suggest that we therefore titrate the dopaminergic treatment upward until an individual's efficacy is found and then cease increasing the dose in order to remain within this optimum middle range. This would provide us with a tightly-controlled, data-driven, and patient-centered approach to the proposed study.

2.1.3 Research background discussion and scientific justification

Over the last 10 years, the Apkarian group has pioneered the development of brain imaging methods that can be specifically used to study brain properties of chronic pain. A large portion of this work targets the CBP brain. A new mechanistic model for transition of acute to chronic pain was proposed and expounded in three review articles (Apkarian 2008a, Apkarian et al 2009, Apkarian et al 2010). It proposes that learning mechanisms within the limbic circuitry give rise to the transition from acute to chronic pain and cause the pain to become more emotional. Within the context of this model we undertook a longitudinal observational brain imaging study, where SBP patients¹ are tracked over a year as they transition to either persistent pain (SBPp; chronicity) or into recovery (SBPr), enabling comparisons of brain parameters in this time window and in contrast to healthy and CBP patients.² We observe that functional corticostriatal connectivity (a dopaminergic circuit), the size of limbic nuclei, and white matter anisotropy PREDICT participants at high risk for transition to chronic pain, with about 90% accuracy. Most of these results are now published.

Given that the human longitudinal study directly implicates brain dopaminergic limbic circuitry in transition to chronic pain, we recently began mouse electrophysiological studies (patch clamp) where we could identify cellular excitability and morphological changes in nucleus accumbens D2 spiny neurons, 5 days after a peripheral nerve injury. When such animals were treated with a combination of Carbidopa/Levodopa and Naproxen (a combination treatment designed to decrease the peripheral nociceptive load as well as the central dopamine deficit), we were able to block the transition to persistent pain (note that the use of either drug alone had little efficacy in diminishing

¹ Subacute back pain (SBP) patients are defined as individuals still experiencing back pain during a window of 4-12 weeks after the onset of this new acute back pain episode

² SBPr denoted individuals seen during the subacute phase of their pain who, at some time after 12 weeks, have demonstrated a reduction in pain from their baseline of $\geq 20\%$; SBPp individuals are those who do not demonstrate this reduction from their baseline pain over a one year observation period; CBP (chronic back pain) individuals are those who have a history of back pain that has persisted for more than 6 months (in the study these were subjects with back pain of at least 5 year duration) but who have not been followed at earlier time points and for whom there is no "baseline" pain level available.

persistence of pain behavior), and also we could show that accumbens D2 spiny neuronal excitability and morphological adaptations were blocked. Therefore, we think we have identified both a critical site of action and a combination treatment that should diminish transition to chronic pain. The current trial tests this idea in humans at high risk to transition to chronic back pain.

2.1.4 Importance of study

CBP is the single largest cause of loss of work and has major personal and societal consequences. The ability to reduce the number of people who develop CBP after an acute back pain episode would reduce health care expenditures, increase overall productivity and improve quality of life. Up to this point in time, no treatment has been shown to be effective at altering what is described as the natural history of low back pain; therefore, if successful, this study would be the first to demonstrate that it is possible to identify individuals who will progress and to interfere medically in order to prevent that progression.

2.2 Rationale

Based on our results demonstrating the importance of dopaminergic pathways in the modulation of chronic pain response, and the additive effect of Naproxen on the response, this study will attempt to affect brain pathways by the administration of Carbidopa/Levodopa and Naproxen.

Our main hypothesis is: SBP patients treated with Carbidopa/Levodopa and Naproxen will show a statistically significant decrease in rate of transition to chronic pain.

Our secondary hypothesis is: The rate of response to Carbidopa/Levodopa and Naproxen is gender dependent.

Our other secondary hypothesis is: Of the three brain biomarkers that define SBP at high risk for chronification, only the extent of corticostriatal information sharing (mPFC-NAc) will show statistically significant reduction in SBP treated with Carbidopa/Levodopa and Naproxen.

Carbidopa/Levodopa will be administered orally as this has been shown to result in increased dopaminergic brain activity, and also because our rodent studies were also done with oral administration of Carbidopa/Levodopa and Naproxen. The dosage chosen is based on obtaining a clinically meaningful dose without resulting in an unacceptably high rate of side effects, which would limit the utility of this approach. The dosage is also derived from our rodent studies, where standard clinical doses were tested, and with such doses neither Carbidopa/Levodopa alone nor Naproxen alone showed any efficacy on pain related outcomes. By dosing three times per day (TID), it is anticipated that stable elevated drug levels can be maintained (this is the regimen we used in rodents as well). It is anticipated, from our animal studies, that 12 weeks of

treatment will be sufficient to alter the course of the transition from subacute to chronic pain. To evaluate whether this intervention has a long-lasting effect, participants will be followed for an additional 12 weeks after treatment has been stopped, to evaluate their pain response and assess whether the treatment benefits are sustained.

This study specifically focuses on people with subacute low back pain because these individuals have a high likelihood of progressing to chronic pain; as our previous work has shown that ~50% of this group develops CBP. Furthermore, we have extensive experience with this population of people, and have shown that we can identify those individuals who will develop persistent pain and those who will recover, based on MRI findings when first seen with SBP.

2.3 Potential Risks and Benefits

Potential Risks

The risks from the study procedures may include possible side effects from the study medications, the MRI procedure, completion of PROs and the blood draw. (See Supplemental Materials for package inserts.)

Study medications

Carbidopa/Levodopa

Carbidopa/Levodopa is a therapy that combines the dopamine agonists Levodopa and Carbidopa. The combination aims at increasing the levels of dopamine in the brain while preventing any similar increase in the rest of the body, hence minimizing side effects. To reduce the incidence of side effects, the dose of medication will be increased slowly, and subject's health will be monitored closely. After completing 12 weeks of treatment, the participant will slowly taper off the study drug.

The list of adverse events noted below derives from the package insert for Carbidopa/Levodopa and was a consequence of AEs reported in clinical trials of individuals with Parkinson's disease who have depleted brain dopamine levels. The incidence and type of AEs occurring in people in this study with normal dopamine levels is not known but may be lower, particularly as the dose of Carbidopa/Levodopa used is at the low end of the therapeutic range.

The most common side effects (prevalence $\geq 1.5\%$) of Carbidopa/Levodopa are shown below and information from the package insert which lists all reported side effects, regardless of prevalence, follows (Sinemet CR, 2011).

Adverse Experience	Carbidopa/Levodopa (n = 524)
Dyskinesia	12.2%
Nausea	5.7%
Hallucinations	3.2%
Confusion	2.3%
Dizziness	2.3%
Urinary Tract Infection	2.3%
Headache	1.9%
Vomiting	1.9%
Constipation	1.5%

As noted, the most common adverse reactions reported with Carbidopa/Levodopa have included dyskinesias, such as choreiform, dystonic and other involuntary movements, and nausea.

The following other adverse reactions have been reported with Carbidopa/Levodopa:

Body as a Whole: chest pain, asthenia.

Cardiovascular: cardiac irregularities, hypotension, orthostatic effects including orthostatic hypotension, hypertension, syncope, phlebitis, palpitation.

Gastrointestinal: dark saliva, gastrointestinal bleeding, development of duodenal ulcer, anorexia, vomiting, diarrhea, constipation, dyspepsia, dry mouth, taste alterations.

Hematologic: agranulocytosis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia.

Hypersensitivity: angioedema, urticaria, pruritus, Henoch-Schonlein purpura, bullous lesions (including pemphigus-like reactions).

Musculoskeletal: back pain, shoulder pain, muscle cramps.

Nervous System/Psychiatric: psychotic episodes including delusions, hallucinations, and paranoid ideation, neuroleptic malignant syndrome, bradykinetic episodes ("on-off" phenomenon), confusion, agitation, dizziness, somnolence, dream abnormalities including nightmares, insomnia, paresthesia, headache, depression with or without development of suicidal tendencies, dementia, pathological gambling, increased libido including hypersexuality, impulse control symptoms. Convulsions also have occurred; however, a causal relationship with Carbidopa/Levodopa has not been established.

Respiratory: dyspnea, upper respiratory infection.

Skin: rash, increased sweating, alopecia, dark sweat.

Urogenital: urinary tract infection, urinary frequency, dark urine.

Laboratory Tests: decreased hemoglobin and hematocrit; abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen (BUN), Coombs test; elevated serum glucose; white blood cells, bacteria, and blood in the urine.

Other adverse reactions that have been reported with Levodopa alone and with various Carbidopa/Levodopa formulations, are:

Body as a Whole: abdominal pain and distress, fatigue.

Cardiovascular: myocardial infarction.

Gastrointestinal: gastrointestinal pain, dysphagia, sialorrhea, flatulence, bruxism, burning sensation of the tongue, heartburn, hiccups.

Metabolic: edema, weight gain, weight loss.

Musculoskeletal: leg pain.

Nervous System/Psychiatric: ataxia, extrapyramidal disorder, falling, anxiety, gait abnormalities, nervousness, decreased mental acuity, memory impairment, disorientation, euphoria, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, increased tremor, numbness, muscle twitching, activation of latent Horner's syndrome, peripheral neuropathy.

Respiratory: pharyngeal pain, cough.

Skin: malignant melanoma, flushing.

Special Senses: oculogyric crises, diplopia, blurred vision, dilated pupils.

Urogenital: urinary retention, urinary incontinence, priapism.

Miscellaneous: bizarre breathing patterns, faintness, hoarseness, malaise, hot flashes, sense of stimulation.

Laboratory Tests: decreased white blood cell count and serum potassium; increased serum creatinine and uric acid; protein and glucose in urine.

Naproxen

A dose of Naproxen 250mg TID will be administered. Participants with uncontrolled hypertension, history of recent myocardial infarction, peptic ulcer disease, renal disease or history of allergies to NSAID medication will be excluded.

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg Naproxen compared to those taking 750 mg Naproxen.

In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-label studies with about 400 pediatric patients with juvenile arthritis treated with Naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

In patients taking Naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1 to 10% of patients are:

Gastrointestinal (GI) Experiences, including: heartburn*, abdominal pain*, nausea*, constipation*, diarrhea, dyspepsia, stomatitis

Central Nervous System: headache*, dizziness*, drowsiness*, lightheadedness, vertigo

Dermatologic: pruritus (itching)*, skin eruptions*, ecchymoses*, sweating, purpura

Special Senses: tinnitus*, visual disturbances, hearing disturbances

Cardiovascular: edema*, palpitations

General: dyspnea*, thirst

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1 to 10% of patients.

Gastrointestinal (GI) Experiences, including: flatulence, gross bleeding/perforation, GI

ulcers (gastric/duodenal), vomiting

General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes

The following are additional adverse experiences reported in <1% of patients taking Naproxen during clinical trials and through post-marketing reports. Those adverse reactions observed through post-marketing reports are italicized.

Body as a Whole: anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)

Cardiovascular: congestive heart failure, vasculitis

Gastrointestinal: gastrointestinal bleeding and/or perforation, hematemesis, jaundice, pancreatitis, vomiting, colitis, abnormal liver function tests, nonpeptic gastrointestinal ulceration, ulcerative stomatitis

Hemic and Lymphatic: eosinophilia, leucopenia, melena, thrombocytopenia, agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia

Metabolic and Nutritional: hyperglycemia, hypoglycemia

Nervous System: inability to concentrate, depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction

Respiratory: eosinophilic pneumonitis

Dermatologic: alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Special Senses: hearing impairment

Urogenital: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis

In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.

Body as a Whole: fever, infection, sepsis, anaphylactic reactions, appetite changes, death

Cardiovascular: hypertension, tachycardia, syncope, arrhythmia, hypotension,

myocardial infarction

Gastrointestinal: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, hepatitis, eructation, liver failure

Hemic and Lymphatic: rectal bleeding, lymphadenopathy, pancytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations

Respiratory: asthma, respiratory depression, pneumonia

Dermatologic: exfoliative dermatitis

Special Senses: blurred vision, conjunctivitis

Urogenital: cystitis, dysuria, oliguria/polyuria, proteinuria

Omeprazole

A dose of Omeprazole 40mg QD will be administered. Participants with known hypersensitivity to any component of the formulation or substituted benzimidazoles are not required to take the medication for participation in the study.

PPI therapy may be associated with increased risk of Clostridium difficile associated diarrhea

Concomitant use of Omeprazole Delayed-Release Capsules with clopidogrel should be avoided.

Use of Omeprazole Delayed-Release Capsules concomitant with St. John's Wort or rifampin should be avoided due to the potential reduction in omeprazole concentrations.

Increases in intragastric pH may result in hypergastrinemia and enterochromaffin-like cell hyperplasia and increased Chromogranin A levels, which may interfere with diagnostic investigations for neuroendocrine tumors

In patients taking Omeprazole the most frequently reported adverse experiences in approximately 1 to 10% of patients are:

Gastrointestinal (GI) Headache, abdominal pain, nausea, diarrhea, vomiting, and flatulence

Interactions with this drug include:

Combination with atazanavir, nelfinavir, saquinavir: not recommended to be taken concomitantly with omeprazole.

May interfere with ketoconazole, iron salts, erlotinib, ampicillin esters, digoxin, and mycophenolate mofetil, clopidogrel, and cilostazol.

Diazepam, warfarin, phenytoin, cyclosporine, disulfiram, benzodiazepines can be prolonged in their elimination when taking in conjunction with omeprazole; monitor and determine need for dose adjustments.

Patients treated with omeprazole and voriconazole may have raised omeprazole levels.

Drug status regarding interactions will be reviewed by the study clinician and the NU pharmacy. Based on this review, participants may be excluded if there may be a drug-drug interaction that would be clinically significant and affecting subject safety (See Section 5.2. Exclusion criteria).

Acetaminophen

The rescue medication for this study, acetaminophen, may cause liver damage and rarely death due to overdosing and/or mixing with alcohol. Early symptoms of liver damage include, but are not limited to, nausea, vomiting, sweating, and general malaise (not feeling well). Participants should not take more than four 500 mg tablets during a 24-hour period. If a participant drinks 3 or more alcoholic beverages per day, then he or she should tell the study doctor. Regular use of acetaminophen and NSAIDs in general may increase the risk of chronic kidney failure, but only in those individuals with pre-existing kidney disease. Acetaminophen has no significant side effects on the kidney if subject's kidney function is normal and the dosing instructions are followed. Prior to receiving study treatment, blood will be tested to see if kidneys and liver are functioning as they should.

Placebo

There is the risk that participants will not get the study drug or normal medication, so they may see no improvement in their condition or symptoms may get worse.

Magnetic Resonance Imaging (MRI)

For the MRI test, participants will lie in a small closed area inside a large magnetic tube for up to 60 minutes at a time. In our previous experience with MR imaging of individuals with chronic and subacute back pain, almost all are able to tolerate periods of testing up to 60 minutes. Some people are scared or anxious in small places (claustrophobic). Because the test requires that participants lay as still as possible with only minimal movements, back pain may worsen during the test. During the test,

personnel will continuously ask participants about their level of pain, and will discontinue the scan at any time requested. Participants will be asked about any concerns they may have prior to testing.

Blood Draw

The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

Patient Reported Outcomes (PROs)

Some of the questions asked may be upsetting, or may cause the participant to feel uncomfortable answering them. If a participant does not wish to answer a question, he or she may skip it and go to the next question.

Potential Benefits

The possible benefits from this study include decreased low back pain and the potential to avoid being in a chronic pain state. It is possible that participants will receive no benefit from taking part in this study.

Taking part in this study may help scientists to better understand how chemical interactions in the brain determine the type of pain, chronic or acute, in an individual following an injury. It will also help scientists to determine if early treatment with Levodopa and/or NSAID may benefit patients with low back pain. This study may also help inform future research studies involving individuals with subacute low back pain.

3 OBJECTIVES

3.1 Study Objectives

The conceptual basis of this study is that persistent pain, following an inciting injury, leads to an aversive learning signal that the corticostriatal system hijacks to reorganize the brain into a chronic pain state. We hypothesize that blocking the emotional/motivational learning response triggered by peripheral nerve injury and integrated within the corticostriatal circuitry, in a critical time window, will decrease the probability of transition to chronic pain. Specifically, the primary hypothesis to be tested in the study is that early treatment with Levodopa and Naproxen in individuals with SBP will block transition to CBP.

3.1.1 *The primary objective of this study is:*

To compare the efficacy and safety of Carbidopa/Levodopa (12.5mg/50mg – 25mg/100mg – 50mg/200mg) plus Naproxen 250 mg administered TID compared to placebo plus Naproxen 250mg administered TID in people with subacute low back pain in reducing the risk of transitioning to persistent low back pain.

3.1.2 *Key secondary objectives include:*

- To evaluate if an interaction exists between change in pain condition and gender
- To examine the correlation of corticostriatal reorganization with change in pain condition

3.2 Study Outcome Measures

3.2.1 *Primary*

The primary outcome measure for efficacy is the percent of participants who have developed chronic back pain. Mean pain levels will be assessed at study baseline (mean pain over the 5 days prior to randomization) and compared to mean pain levels for the 5 days prior to the visit at week 24 (study endpoint). Pain will be assessed using an 11-point NRS scale. Chronic pain is defined as an improvement in mean pain level at study endpoint of <20% compared to the mean pain level at randomization. Improvements of $\geq 20\%$ reflect “recovery” of pain from the baseline values.

3.2.2 *Secondary*

A number of secondary outcome measures will be evaluated (see below). Many of these will add information regarding the response to treatment in this study. Specifically, analyses will be done utilizing not only endpoint data but pain (and other) data collected at each of the clinic visits. This will permit further analyses of the pain data which will complement and extend the responder analysis that is the primary endpoint. Other pain-associated parameters will also be evaluated as covariates in regard to the basic pain

outcome. Additionally, brain parameters obtained by fMRI will be assessed and correlated with the clinical outcome measures. Safety will also be assessed as a secondary outcome measure.

A list of major secondary outcome measures includes:

1. Effect of gender on incidence of transition to chronic back pain
2. Brain biomarkers (obtained at scanning visits)
3. NRS pain score (obtained at each study visit, and daily by smartphone app)
4. McGill Pain Questionnaire (obtained at each study visit)
5. painDETECT instrument (obtained at each study visit)
6. Pain Disability Inventory (obtained at scanning and intermediate visits)
7. Daily NRS mood score (by smartphone app)
8. Beck Depression Inventory – Second version (obtained at each study visit)
9. Positive and Negative Affect Schedule (obtained at scanning and intermediate visits)
10. Pain Catastrophizing Scale (obtained at screening visit)
11. Pain Anxiety Symptoms Scale (obtained at screening visit)
12. Pain Sensitivity Questionnaire (obtained at screening visit)
13. Personal Health History (obtained at screening visit)

Measure 1 will assess the interaction between the primary endpoint and gender. Measure 2 will evaluate the interaction between the primary endpoint and specified brain biomarkers with particular attention to corticostriatal connectivity. In addition, brain biomarker measures will be used initially to identify SBP patients at high risk for pain chronification, that is, identify the study cohort. They are then measured again at end of treatment. There are four predefined measures extracted from these scans: right amygdala volume, white matter fractional anisotropy, mPFC-NAc functional connectivity and mPFC/somatosensory link ratio. Only mPFC-NAc and mPFC/somatosensory link ratio values are expected to reflect treatment effects. Whole-brain exploratory analyses will be used to identify both brain predictors of treatment response and brain reorganization (consequences) in response to treatment.

Measures 3-12 are validated instruments that have been successfully applied to the back pain population. Measure 3 utilizes the same instrument as the primary outcome measure but at different points of time during the trial to permit a more detailed evaluation of overall change in pain with time. Measures 4-6 are expected to reflect the change observed in measure 3, and are thus primarily confirmatory for the main outcome. They will also be used to examine characteristics of the pain that differentiate between treatment responders and non-responders, and this information can be used in future response prediction based studies and in clinical decision making. Measure 7 should generally reflect measures 3 and 8, as well as contribute to treatment response. It should also capture brain properties reflecting treatment response.

Measures 8-12 are expected to contribute to prediction of treatment response. They will be used as covariates in logistic multiple regression exploratory models where brain parameters, pain parameters and personality values are combined to predict treatment effect.

Measures from 13 include age, gender, smoking, past history of comorbidities, and medication use. We will use gender to test its effect on treatment outcome. We use age, education and behavioral outcomes (measures 8-12) as covariates. Demographic outcomes are also used as covariates in the brain outcome comparisons.

Measures 8 and 9 are collected repeatedly, similarly to measures 3-6, as we expect them to change in parallel with treatment.

Interaction of this primary outcome measure with gender will be assessed (key secondary objective of the study).

Interaction of the primary outcome measure with brain biomarker measures will be assessed (the other key secondary objective of the study).

Correcting for covariates of no interest will strengthen our conclusions. In addition, incorporating covariates of interest into our models provide additional explanations for observed results.

4 STUDY DESIGN

This study is a 24-week, flexible dose escalation, double-blind, randomized, placebo-controlled two-arm, parallel-group trial of a pharmacological treatment (Carbidopa/Levodopa plus Naproxen), selected based on positive results from previous preclinical studies, for people with SBP who are at high risk of progressing to CBP.

Individuals with subacute low back pain (new onset back pain that has been present for 4-20 weeks) will be identified and screened. Individuals having a mean pain level over the 5 days prior to baseline of at least 4 (on a 0-10 NRS) and deemed to be at high risk of developing chronic persistent low back pain (based on brain MRI and fMRI parameters – see [Appendix F](#) & [Appendix G](#)) will be entered into the study in order to increase study sensitivity. In addition, individuals who have diabetes, who are not safe to undergo MRI, who are claustrophobic, or who are unwilling to undergo an MRI, will not undergo brain imaging but will be directly entered into the treatment phase of the study and informed that they are assumed to be at risk for chronification. Participants will then be randomized to receive either 12 weeks of Carbidopa/Levodopa plus naproxen and omeprazole, or placebo plus naproxen and omeprazole; acetaminophen will be available as a rescue medication. Omeprazole is prescribed QD as a preventative measure against possible gastric adverse effects of naproxen. All participants will also use a smartphone app to log their back pain intensity, mood, proper medication use, and other information that they may wish to report. The smartphone data are entered every time participants ingest their medication (up to TID) and after termination of treatment (up to TID) until the final study visit.

Mean pain levels will be assessed at study baseline (mean pain over the 5 days prior to randomization) and compared to mean pain levels for the 5 days prior to the randomization study visit. Pain will be assessed using an 11-point (NRS) scale. Chronic pain is defined as an improvement in mean pain level <20% compared to the mean pain level at randomization. Improvements of $\geq 20\%$ reflect “recovery” of pain from the baseline values.

Treatment with Carbidopa/Levodopa will be titrated up to 12.5mg/50mg TID over one week and then continued at that level for 4 weeks. If at the end of the initial 4-week period the participant has “responded or recovered” (had a reduction in pain from baseline of $\geq 20\%$), the participant will be maintained on that dose for the duration of the treatment period (12 weeks total). If there has not been a response, the dose will be increased to Carbidopa/Levodopa (25mg/100mg) TID for the following 4 weeks at which time the pain status will be re-evaluated. Again, if a response has occurred, that dose will be maintained in a blinded manner for the following 4 weeks of treatment; if not, further dose-titration will occur to Carbidopa/Levodopa (50mg/200mg) TID for the final 4 weeks. If a participant experiences an AE at higher doses, then the participant will be

given the next lower dose that s/he was able to tolerate and then be maintained on that dose for the remainder of the 12 week dosing period. Study drug will be tapered off over a one-week period starting after their week 12 clinic visit, and participants will continue to be evaluated to determine persistence of response for another 12 weeks, at which point they will have a final MRI and fMRI scan session. (See [Appendix A](#) for a detailed schedule of events table)

Individuals with subacute low back pain will be studied as they have a higher likelihood of progressing to chronic low back pain than the entire acute pain population. Furthermore, the initial MRI screening will further identify a subset of the subacute low back pain population who has a brain phenotype that, from results of our previous work, makes it highly likely (~90%) that they will develop persistent low back pain with standard treatment. (See [Appendix F & Appendix G](#) for further phenotyping information.) In addition, those participants (defined above) who are eligible but do not undergo brain imaging will also be treated with study medication. It is anticipated that it will require approximately 200 to be enrolled over 20-24 months in order to identify and randomize 126 with a persistent pain to randomize at baseline and have 100 complete the study at week 24. During the treatment period, participants will return to the clinic at Weeks 1, 4, 8 and 12 after randomization to assess pain, proper treatment use and side effects. After 12 weeks, pain will continue to be assessed monthly through PROs, and daily through smartphone app. MRI scans will be conducted at the end of 24 weeks.

4.1 Substudy

Some individuals with subacute back pain who undergo screening for this study will not meet the inclusion criterion of high-risk phenotype for chronification of back pain. These individuals will be offered the opportunity to participate in a substudy under a separate protocol. The substudy will be an observational study designed to follow these back pain participants over time to collect information on pain levels and other subject-reported outcomes. Data from this study could be used to help evaluate the model proposed in the main study.

5 STUDY ENROLLMENT AND WITHDRAWAL

It is anticipated that to obtain 100 evaluable participants at the final study visit we will need to enroll 126 participants to allow for individuals that discontinue participation prematurely. This will require screening approximately 200 participants during the course of the trial. We anticipate telephone screening in the range of 600-700 individuals.

In our prior study of SBP patients, recruitment of an equivalent number of participants resulted in 50% female representation. We will again ensure in this trial that gender is equally represented, as influence of gender on treatment effect is a major secondary aim.

Based on our previous results, we expect 30% minority representation in our sample.

Children are not included in this study because etiology of pain chronification is likely different from adults. Brain anatomical and functional properties in children are also different from adults. Thus, our brain biomarker based predictive model is most likely invalid in children.

5.1 Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Male or female, over the age of 18 years, (no racial/ethnic restrictions)
- Must have an average pain score of ≥ 4 (on a 0-10 NRS) over a 5 day period (average of ~ 15 measures on smartphone app) immediately preceding the baseline visit (visit 2) and also ≥ 4 between the baseline and enrollment visits (visit 2 and visit 3, respectively).
- Must be willing to read and able to understand instructions as well as PROs
- Must be in generally stable health
- Must sign an informed consent document after complete explanation of the study documenting that they understand the purpose of the study, procedures to be undertaken, possible benefits, potential risks, and are willing to participate (See [Appendix B](#) for an example of the ICF)
- Must have a history of low back pain for a minimum of 4 weeks and a maximum of 20 weeks with signs and symptoms of radiculopathy: positive straight leg raising test with dermatomal radiation and/or myotomal weakness and/or reflex asymmetry; pain must radiate into buttock or below. Individuals undergoing MRI must have a high risk phenotype for chronification of back pain (evaluated at baseline T1-MRI, DTI-MRI, and fMRI scans)

5.2 Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Previous (distinct) episodes of back pain onset (more than 3 distinct episodes of back pain lasting for a total of more than 4 weeks) in the previous year
- Evidence of acute vertebral fracture
- Low back pain associated with any systemic signs or symptoms, e.g., fever, chills
- Symptoms of neuropathy due to diabetes Type I or Type II
- Chronic neurologic conditions, including Parkinson's disease, Alzheimer's disease, and other conditions associated with dementia
- Significant other medical disease such as congestive heart failure, coronary or peripheral vascular disease, chronic obstructive lung disease, or malignancy
- History of glaucoma or narrow angle glaucoma
- Presence of undiagnosed skin lesions or history of melanoma
- Presence of severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease
- History of myocardial infarction with residual cardiac arrhythmia
- History of gastrointestinal bleeding or peptic ulcer
- Diagnosis of current depression (assessed via BDI, total > 28 are excluded) or psychiatric disorder requiring treatment, or such a diagnosis in the previous 6 months
- Use of therapeutic doses of antidepressant medications (i.e., tricyclic antidepressants, SSRIs, SNRIs; low doses used only in the evening for sleep will be allowed if dose is not changed)
- Current use of recreational drugs or recent history of alcohol abuse (pattern of drinking having social, financial or physical consequences) or drug abuse
- Current use of medical marijuana
- High dose opioid prophylaxis, defined as > 50mg morphine equivalent/day
- Use of MAOIs, currently or within the past 2 weeks
- Prior use of Levodopa
- Use of any of the following drugs: bromocriptine, linezolid, metoclopramide, phenothiazines, promethazine/codeine, isoniazid, rifampin, pyrazinamide
- Oral iron supplementation
- Contraindications to use of study product, based on any of the following:
 - Hypersensitivity to Carbidopa/Levodopa or other constituents of the Carbidopa/Levodopa capsules
 - Hypersensitivity to lactose or other constituents of the placebo capsules
 - Hypersensitivity to Naproxen or other constituents of the Naproxen capsules
 - Hypersensitivity to Acetaminophen or other constituents of the Acetaminophen tablets
 - Taking concomitant medication which may be adversely affected by

omeprazole to a degree that alters subject's safety

- Currently taking Levodopa or dopaminergic drugs
- In the judgment of the investigator, unable or unwilling to follow protocol and instructions
- For those receiving MRI: Intra-axial implants (e.g. spinal cord stimulators or pumps, All exclusion criteria for MR safety: any metallic implants, pacemaker, brain or skull abnormalities, tattoos on large body parts, and claustrophobia
- Pregnancy or inability to use an effective method of birth control in sexually active men and women while taking the study drug and for one week thereafter. Barrier contraceptives (condoms or diaphragm) with spermicide, intrauterine devices (IUD's), hormonal contraceptives, oral contraceptive pills, surgical sterilization, and complete abstinence are examples of effective methods of contraception.
- Following laboratory abnormalities: liver function tests (SGOT/SGPT) greater than twice the upper limit of normal; unexplained anemia (Hgb 13.5 to 17.5 g/dL for men, 12.0 to 15.5g/dL for women); evidence of renal insufficiency (creatinine >upper limit of normal) or any other abnormality that the principal investigator feels puts the participant at risk during the study. A blood re-test will occur for all enrolled subjects within one month of the first blood draw due to potential risk for renal impairment with NSAIDs at this dosage.
- History of chronic opioid use for pain management.
- Any medical condition that in the investigator's judgment may prevent the individual from completing the study or put the individual at undue risk

5.3 Strategies for Recruitment and Retention

Participants for the study will be recruited from the following sources: (1) advertising in the local newspapers and radio, (2) online advertising (e.g., craigslist.com, social media like Facebook and Twitter; ResearchMathc.org; (3) professionals who see patients with low back pain or related conditions and/or people with low back pain or related conditions, and (4) community advertising (i.e., coffee shops, libraries, train stations and buses). Research Match is a secure online, national recruitment tool that is maintained by Vanderbilt University. ResearchMatch.org allows researchers to conduct feasibility or recruit potential study participants. These recruitment sources have resulted in a steady flow of patients, given that many individuals with SBP have not yet sought medical treatment.

Potential subjects and data may also be identified through reports generated by the Northwestern Medicine Enterprise Data Warehouse (NMEDW), a joint initiative across the Northwestern University Feinberg School of Medicine and Northwestern Memorial HealthCare (NMHC), a corporate parent of Northwestern Memorial Hospital, Northwestern Medical Group, and Northwestern Medicine Lake Forest Hospital. NMEDW data sources include Cerner PowerChart, PRIMES, Epic, IDX, eNOTIS, and 50+ other systems from the campus. Once approved by the treating provider, potential

subjects reported by NMEDW to a study Research Coordinator/Assistant may then be contacted with an opt-out letter followed by telephone calls, and provided detailed study information and encouraged to complete a screening questionnaire.

We anticipate needing to telephone screen 600-700 individuals to identify approximately 300 who may be eligible for the study. Of these, we estimate that 200-225 will actually show for their scheduled screening visit. These estimates are based on our prior experience screening back pain participants for clinical trials.

If potential subjects are interested in the study, they will be able to contact the research staff via the telephone number given on the website or click on a link to complete a brief online screener. To facilitate the recruitment of similar studies on low back pain conducted by Dr. Apkarian's lab at Northwestern, participants who are screened for the current study will be asked if they are interested in learning about other studies on low back pain. If participants agree, they will be referred to and pre-screened for the other low back pain studies.

It is anticipated that, to obtain 100 evaluable participants at the final study visit, we will need to enroll approximately 126 participants to allow for individuals who discontinue participation prematurely. This will mean screening approximately 200 participants during the course of the trial. These ratios are also derived from our previous experience with the SBP trial that has been completed recently, where in the range of 60% of individuals who were screened were eligible. The completion of the clinical enrollment portion of this project in 24 months will therefore require an overall screening rate of 8-9 participants/month (~2 participants/week) from all recruitment sources. Based on our previous experience with longitudinal studies in this population, this is a highly realistic and achievable rate of enrollment from these sources. We have attempted to recruit participants from pain clinics, both in the community and at Northwestern, and have found this not to be a productive means of identifying the subacute back pain population needed for this study.

5.3.1 Recruitment: Media Advertising

Advertising in the media (newspaper and radio) has proven to be extremely effective in identifying people with subacute low back pain in our previous longitudinal study. Expertise in media placement as well as use of an experienced call center will be made available through the recruitment division of the NUCATS Institute. This recruitment service is a core facility for the medical school that provides assistance in recruitment of study participants. A recruitment plan specific for this study will be developed and implemented by the recruitment division staff, working in close conjunction with the investigators and other study personnel. This methodology in the past has yielded 30-40% of participants for trials of this sort.

5.3.2 Recruitment: Online Advertising

Advertisements using online resources (including but not limited to www.craigslist.com, online newspaper classifieds, social media, e.g., Facebook and Twitter, websites for people who work with or have low back pain or related conditions; ResearchMatch.org; and Apkarian laboratory website) has been a fruitful source of SBP patients in our previous work. As with traditional media advertising, we are able to control when and how often we place these advertisements to make maximum use of our staff's time. This approach has generated 20-30% of participants for trials of this sort in the past.

5.3.3 Recruitment: Community Advertising

Given the high reliance on public transportation in the Chicago area, advertising in bus, train, and rail stations/facilities reaches a large number of citizens from broad socioeconomic backgrounds. Ridership reports indicate the Chicago Transit Authority ridership exceeds 2 million bus, train, and rail rides each day. Even short-term advertising in these venues has repeatedly resulted in large numbers of calls that continue to come in over long periods of time. In addition, coffee shops and libraries are opportunities to tap into diverse communities. As with the above approaches, this methodology will be expected to yield approximately 30-40% of the participants for this trial.

5.3.4 Retention

As this is a longitudinal study, the ability to have participants return to collect data at multiple time points is crucial to the success of the research. In our previous longitudinal study, an individualized retention program was developed to ensure optimal maintenance of participants throughout the trial. Specific branding of the study (specific name with associated letterhead, literature, etc.), use of low cost, IRB-approved mementos (e.g., calendars, tote bags, etc.), regular communication via email and/or telephone, and recognition of special events (e.g., birthdays, holidays) will be employed to make participants feel engaged. In our experience, the optimal means to enhance retention is repeated contact with the participants, via telephone or mail service or electronically. Our retention rates have also benefited from the maximum flexibility in the availability of scanning times. We can routinely scan or interview participants any time between 8:00am-9:00pm to accommodate difficult schedules (including weekends), and missed appointments are typically re-booked within 24 hours. Additionally, the frequency of visits and interactions during the initial 6 weeks of the study when participants come in to obtain their study medication (visits 3-6) will also serve to keep the participants invested in the study and enhance treatment adherence. These methodologies have been shown to be effective in other longer-term trials and are an important aspect to ensure participants' continued interest and involvement.

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures

Participants will be assigned to treatment arms (Carbidopa/Levodopa plus Naproxen vs placebo plus Naproxen) based on a computer generated permuted block randomization with block size randomly varied and an allocation ratio of 1:1. Allocation concealment will be ensured by utilization of sequentially numbered containers. An unblinded individual from NUCATS with no other role in the study will be responsible for assuring proper medication assignment to each container. The randomization code will be maintained by NUCATS and will be available in cases of emergency or clinical situations in which knowing the treatment allocation would make a difference in the safety or management of a subject. In such a circumstance, the allocation assignment will be made available after consultation with the site investigator and the principal investigator. At study conclusion, after database lock, the randomization code will be made available to the study statistician and other personnel analyzing the data.

5.4.2 Masking Procedures

Masking will be achieved by over-encapsulation of the Carbidopa/Levodopa capsules as well as Naproxen capsules utilizing larger capsules that will be identical to those to be filled with lactose to be used as placebo. The only person who will know which capsules contain active vs placebo will be the unblinded NUCATS individual responsible for filling the numbered medication vials with the appropriate kind and number of capsules. This person will have no other involvement with study staff or be involved with any study procedures. Naproxen to be provided to both groups will also be masked in order that participants not be aware of which medication is active that they are taking. Unmasking should not be required during the study. If allocation assignment needs to be made available, this will be done based on the circumstances outlined above. If there should be a question regarding proper allocation of treatment product, it would be possible to ascertain placebo from active drug product by opening the treatment capsules and determining if there were an enclosed tablet present. This will be prevented by sealing of all capsules prior to their being placed in treatment vials for dispensing.

Participants will take 2 capsules on a TID schedule and one capsule will be taken QD. TID medications include one capsule of Naproxen and one capsule of either placebo or some dose of Carbidopa/Levodopa. Omeprazole will be taken QD in the morning. In order to assure that participants take their study medication as designed, the Naproxen and omeprazole will be placed in a separate colored capsule from the Carbidopa/Levodopa. Each colored capsule will be dispensed in separate containers and participants will be asked to take one capsule from each container. As they will be differently colored, this should reduce the possibility of error.

5.5 Participant Withdrawal

Participants have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. Withdrawal of full consent for a study means that the participant does not

wish to receive further investigational treatment and does not wish to or is unable to continue further study participation; participant data up to withdrawal of consent will be included in the analysis of the study. Any participant may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the participant appropriate procedures for withdrawal from the study.

5.5.1 Reasons for Withdrawal

Reasons for removal from protocol-required product(s) or observation might include:

- Partial withdrawal of consent
- Withdrawal of full consent
- Administrative decision by the investigator
- Pregnancy in a female subject
- Pregnancy in female partner of a male participant if he is unwilling to use a condom during treatment and for 7 drug half-lives after the end of treatment
- Ineligibility
- Significant protocol deviation
- Patient noncompliance
- Study drug compliance <80%
- AE / SAE
- Disease progression
- Other safety concern by the investigator
- Death
- Lost to follow-up

5.5.2 Handling of Participant Withdrawals or Participant Discontinuation of Study Intervention

Withdrawal of partial consent for a study means that the participant does not wish to take IP(s) or other protocol-required therapies any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in all subsequent study visits or procedures). Participants may decline to continue receiving IP(s) or other protocol-required therapies at any time during the study. If this occurs, the investigator will discuss with the participant appropriate procedures for withdrawal from IP(s) or other protocol-required therapies. These participants, as well as those who have stopped receiving IP(s) or other protocol-required therapies for other reasons (e.g., investigator or sponsor concern) should continue the schedule of study observations. Should a participant (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable

cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the NIDCR. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Inadequate retention and/or recruitment.

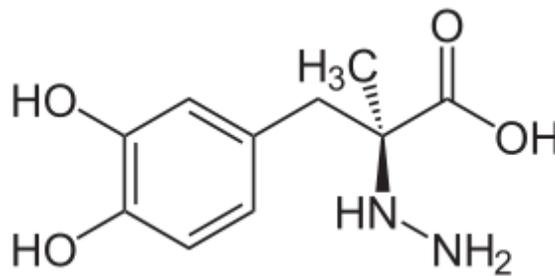
6 STUDY INTERVENTION

6.1 Carbidopa/Levodopa 25-100

6.1.1 Study Product Description

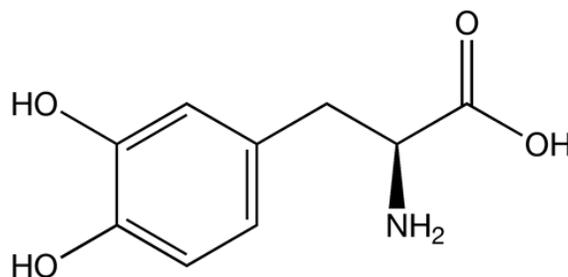
Carbidopa/Levodopa is a combination of Carbidopa and Levodopa for the treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (—)-L- α -hydrazino- α -methyl- β -(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is C₁₀H₁₄N₂O₄•H₂O, and its structural formula is:



Capsule content is expressed in terms of anhydrous Carbidopa which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (—)-L- α -amino- β -(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is C₉H₁₁NO₄, and its structural formula is:



Carbidopa/Levodopa is supplied as tablets containing 25 mg of Carbidopa and 100 mg of Levodopa.

For blinding, the Carbidopa/Levodopa tablets supplied by the manufacturer are over-encapsulated at the clinical site investigational pharmacy, by putting the supplied tablet inside another capsule and filling the remaining space with excipient. The excipient for

the capsules will be Lactose NF. The manufacturer is Humco in Texarkana, Texas. NDC 0395-1501-01. The active ingredient would be the Carbidopa/Levodopa tablets distributed by Caraco and manufactured by Sun Pharmaceutical Industries Ltd., Acme Plaza, Andheri-Kurla Road, Andheri (East), Mumbai-400 059, India.

The capsule shells (hard gelatin) will be manufactured by Capsugel (Coni Snap Size 1). Capsugel provides a certificate of analysis with each capsule batch ordered. Capsugel manufactures gelatin capsules from gelatin that complies with bovine spongiform encephalopathy (BSE) requirements. Capsugel provides confidential detailed information about facilities, processes, articles used in manufacturing, processing, packaging, and storing of empty capsules through Type IV (Excipient) Drug Master Files submitted to the FDA.

Inactive ingredients are lactose NF and gelatin. Carbidopa/Levodopa capsules also contain FD&C Blue #1.

6.1.2 Acquisition

The blinded Carbidopa/Levodopa capsules will be manufactured by the Investigational Pharmacy at NMH, 251 E. Huron St. LC700, Chicago, IL 60611.

6.1.3 Formulation, Packaging, and Labeling

Over-encapsulation is conducted in the Investigational Pharmacy on a segregated and cleaned countertop. Active capsules are prepared by putting the active drug inside an empty gel cap and further filling it with lactose. For the lowest dose of Carbidopa/Levodopa (12.5mg/50mg), the scored tablet will be cut in half by the pharmacy technician. For the highest dose, two tablets will be put into one capsule. A manufacturing record is kept with a listing of all the ingredients, manufacturer, lot numbers and expiration dates of the components used.

6.1.4 Product Storage and Stability

Carbidopa/Levodopa will be stored at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) in a locked cabinet protected from light in a locked room. Carbidopa/Levodopa has a 6-month shelf-life.

6.1.5 Dosage, Preparation and Administration of Study Product

Carbidopa/Levodopa will be administered in this study as an oral capsule. Participants will be titrated up to the therapeutic dose at the beginning of treatment and tapered off at the end of treatment. Participants will always take one capsule TID except during the first week of titration. Both schedules are detailed as follows:

- At treatment initiation, Carbidopa/Levodopa (12.5mg/50mg) QD for 3 days, Carbidopa/Levodopa (12.5mg/50mg) BID for 3 days, and then

Carbidopa/Levodopa (12.5mg/50mg) TID over one week and then continued at that level until 4 weeks is completed (+/- visit window). If at the end of the initial 4 week period the participant has “responded or recovered” (i.e., had a reduction in pain from baseline of $\geq 20\%$), the participant will be maintained on that dose for the duration of the treatment period (12 weeks total). If there has not been a response, the dose will be increased to Carbidopa/Levodopa (25mg/100mg) TID for 4 weeks, after which the pain status will be re-evaluated. Again, if a response has occurred, that dose will be maintained in a blinded manner for the following 4 weeks of treatment; if not, further dose-titration will occur to Carbidopa/Levodopa (50mg/200mg) TID for the final 4 weeks. If a participant experiences an AE at higher doses, then the participant will be given the next lower dose that s/he was able to tolerate and then be maintained on that dose for the remainder of the 12 week dosing period.

- At treatment discontinuation, participants will begin tapering off the medication based on their highest treatment dose. If a participant ended the treatment period on Carbidopa/Levodopa (12.5mg/50mg) TID, then s/he will start with Carbidopa/Levodopa (12.5mg/50mg) BID for 3 days and then Carbidopa/Levodopa (12.5mg/50mg) QD for 3 days before discontinuing it completely. If a participant ended the treatment period on Carbidopa/Levodopa (25mg/100mg) TID or Carbidopa/Levodopa (50mg/200mg) TID, then s/he will start at Carbidopa/Levodopa (25mg/100mg) BID for 3 days and then Carbidopa/Levodopa (25mg/100mg) QD for 3 days before discontinuing it completely.

6.1.6 Modification of Study Product Administration for a Subject

N/A

6.1.7 Accountability Procedures for the Study Product

Study product will be purchased by Northwestern Memorial Hospital Investigational Pharmacy for over-encapsulation. A defined quantity of capsules of Carbidopa/Levodopa, Naproxen and placebo will be supplied by NMH Investigational Pharmacy for distribution to participants. Each of the 126 participants will be provided with vials containing 15, 84, 105, 105, and 9 capsules of Carbidopa/Levodopa or placebo at Visits 3, 4, 5, 6, and 7, respectively. Each of the 126 participants will be provided with vials containing 27, 84, 105, and 105 capsules of Naproxen at Visits 3, 4, 5, and 6, respectively. Participants will be required to record all medication usage using the smartphone app. These data are immediately logged into our server, which provides us routine overview of participants' participation and compliance, and further enhances retention of participants. If participants repeatedly miss entering these values, they are contacted by phone and instructed for compliance. (See [Appendix C](#) for smartphone app usage manual.) Participants will be asked to return all unused study medication at each visit. Unused study medication will be collected at Visits 4, 5, 6, and 7 and counted by the study coordinator. Accountability for study medication will be confirmed at each

participant visit and for each participant at the conclusion of his/her involvement in the study. An overall compliance of 80% is required to remain in the study. A final inventory at study conclusion will be compared with drug supplied, drug participant recorded taking, drug participants actually took, and drug returned. Returned medication will be destroyed through NMH pharmacy drug disposal services after final accountability is determined.

6.1.8 Assessment of Participant Compliance with Study Product Administration

Participants are required to return study medication bottles and any unused medication to the study coordinator at each study visit. Participants will be asked if they missed any days of study medication and if so, how and why. Participant will also be asked if they exceeded taking six capsules per day. The coordinator is responsible for conducting pill counts at each study visit.

6.1.9 Concomitant Medications/Treatments

Participants are asked to discontinue all concomitant pain medications prior to starting study treatment. Participants who refuse to cease pain medication usage between screening and first treatment visit will continue with screening and be asked to rate their pain 15 times (the same as for those who will be scanned with MRI) while they are on their pain medications. If pain is >4, they will undergo an MRI, and if deemed to be part of treatment arm will discontinue their pain medication upon starting the study medication.. Participants will be required to restrict all medications for relief of pain to only those provided during the course of this study (i.e., rescue medication, acetaminophen). Participants will be allowed to continue their existing non-pain medications as long as they are not exclusionary for study enrollment. Concomitant medications not permitted in this study are therapeutic doses of antidepressant medications (i.e., tricyclic antidepressants, SSRIs, SNRIs; low doses used for sleep may be allowed), opioids, MAOIs, dopamine D2 receptor antagonists, and NSAIDs (acetaminophen is allowed).

6.2 Placebo

6.2.1 Study Product Description

The content of the capsules will be Lactose NF. The manufacturer is Humco in Texarkana, Texas. NDC 0395-1501-01. The capsule shells (hard gelatin) will be manufactured by Capsugel (Coni Snap Size 0), which have a volume of 0.5 cc and will hold 300 mg of powder.. Capsugel provides a certificate of analysis with each capsule batch ordered. Capsugel manufactures gelatin capsules from gelatin that complies with BSE requirements. Capsugel provides confidential detailed information about facilities, processes, articles used in manufacturing, processing, packaging, and storing of empty capsules through Type IV (Excipient) Drug Master Files submitted to the FDA.

Inactive ingredients are cellulose and gelatin. Placebo capsules also contain FDC Blue #1.

6.2.2 Acquisition

The blinded placebo capsules will be manufactured by the Investigational Pharmacy at Northwestern Memorial Hospital, 251 E. Huron St. LC700, Chicago, IL 60611.

6.2.3 Formulation, Packaging, and Labeling

Capsule manufacturing is conducted in the Investigational Pharmacy on a segregated and cleaned countertop. Placebo capsules are completely filled with lactose using a capsule maker. A manufacturing record is kept with a listing of all the ingredients, manufacturer, lot numbers and expiration dates of the components used.

6.2.4 Product Storage and Stability

Placebo capsules will be stored at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) in a locked cabinet protect from light in a locked room. Placebo capsules have a 6-month shelf-life.

6.2.5 Dosage, Preparation and Administration of Study Product

The placebo capsule is an oral capsule.

6.2.6 Modification of Study Product Administration for a Subject

N/A

6.2.7 Accountability Procedures for the Study Product

See Section 6.1.7.

6.2.8 Assessment of Participant Compliance with Study Product Administration

See Section 6.1.8.

6.2.9 Concomitant Medications/Treatments

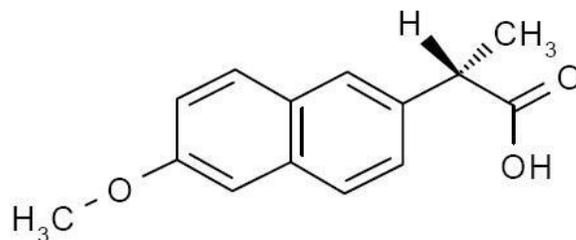
See Section 6.1.9.

6.3 Naproxen 250 mg

6.3.1 Study Product Description

Naproxen is a propionic acid derivative related to the arylacetic acid group of NSAIDs.

The chemical name for Naproxen is (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid. Naproxen has the following structure:



Naproxen has a molecular weight of 230.26 and a molecular formula of C₁₄H₁₄O₃.

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of Naproxen at pH 7.4 is 1.6 to 1.8.

Naproxen tablets are available as white tablets containing 250 mg of Naproxen for oral administration.

For blinding, the Naproxen tablets supplied by the manufacturer are over-encapsulated at the clinical site investigational pharmacy, by putting the supplied tablet inside another capsule and filling the remaining space with excipient. The excipient for the capsules will be Lactose NF. The manufacturer is Humco in Texarkana, Texas. NDC 0395-1501-01. The active ingredient would be the Naproxen tablets manufactured by Amneal Pharmaceuticals.

The capsule shells (hard gelatin) will be manufactured by Capsugel (Coni Snap Size 1). Capsugel provides a certificate of analysis with each capsule batch ordered. Capsugel manufactures gelatin capsules from gelatin that complies with BSE requirements. Capsugel provides confidential detailed information about facilities, processes, articles used in manufacturing, processing, packaging, and storing of empty capsules through Type IV (Excipient) Drug Master Files submitted to the FDA.

The inactive ingredients are Croscarmellose Sodium, Povidone, Magnesium Stearate, lactose NF, and gelatin. Naproxen capsules also contain TiO₂ to make them white in appearance.

6.3.2 Acquisition

The blinded Naproxen capsules will be manufactured by the Investigational Pharmacy at NMH, 251 E. Huron St. LC700, Chicago, IL 60611.

6.3.3 Formulation, Packaging, and Labeling

See Section 6.1.3.

6.3.4 Product Storage and Stability

Naproxen will be stored at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) in a

locked cabinet protected from light in a locked room. Naproxen has a 4-year shelf-life.

6.3.5 Dosage, Preparation and Administration of Study Product

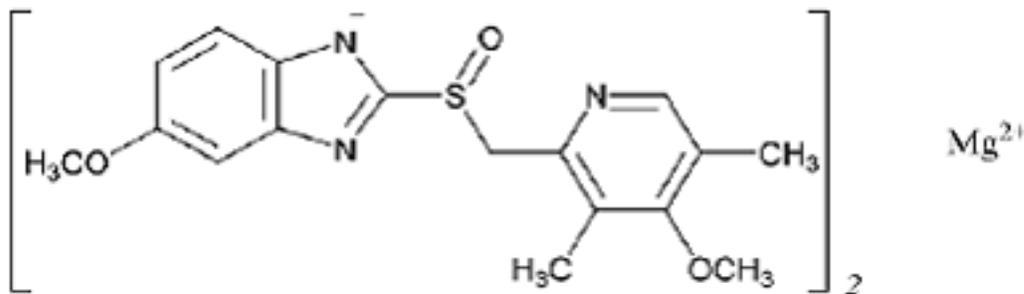
Naproxen is an oral capsule. All participants in both arms will be given a therapeutic dose of one 250mg capsule TID during the treatment period (but not during the tapering down at the end of the study).

6.4 Omeprazole 40mg

6.4.1 Study Product Description

Omeprazole is a proton pump inhibitor that is prescribed to prevent any gastrointestinal upset due to intake of naproxen.

The chemical name for omeprazole is a substituted benzimidazole, 5-methoxy-2-[[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. The structural formula is:



Its empirical formula is $C_{17}H_{19}N_2O_4S$, with a molecular weight of 345.42.

Omeprazole Delayed-Release Capsules, 40 mg, are opaque gold cap and opaque gold body capsules imprinted with "KU" and "136" in black ink.

Inactive ingredients are crospovidone, glyceryl dibehenate, hypromellose, lactose monohydrate, methacrylic acid copolymer dispersion, silicon dioxide, talc, titanium dioxide and triethyl citrate.

Manufactured by: Kremers Urban Pharmaceuticals Inc., a subsidiary of Lannett Company, Inc.

The side effects for omeprazole (given with a capsule of naproxen) include common and less serious symptoms such as headache, diarrhea, nausea, stomach pain, vomiting, and gas. Less common but serious side effects include: rash, face swelling, throat tightness, and difficulty breathing.

6.4.2 Acquisition

The omeprazole capsules will be distributed by the Investigational Pharmacy at NMH, 251 E. Huron St. LC700, Chicago, IL 60611.

Formulation, Packaging, and Labeling

See Section 6.1.3.

Product Storage and Stability

Omeprazole will be stored at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) in a locked cabinet protected from light in a locked room. Omeprazole has a 3-year shelf-life.

Modification of Study Product Administration for a Subject

N/A

Accountability Procedures for the Study Product

See Section 6.1.7.

Assessment of Participant Compliance with Study Product Administration

See Section 6.1.8.

Concomitant Medications/Treatments

See Section 6.1.9.

7 STUDY SCHEDULE

The study duration is 28 weeks, which includes an initial screening period of up to 4 weeks. There will be 8 visits during this time: a Screening Visit, Baseline Visit, and 6 Study Visits. The schedule for the 6 Study Visits after the Baseline Visit will be: Week 0, Week 1, Week 4, Week 8, Week 12, and Week 24. Treatment with study medication will be terminated after Week 12. Follow-up telephone calls at Week 16 and Week 20 will be made to continue evaluation of participants' back pain through PROs to the study end (Week 24). All participants will also use a smartphone app to log their back pain intensity, their mood, proper medication use, and other information that they may wish to report. The smartphone data are entered every time participants ingest their medication (up to TID) and after termination of treatment (up to TID) until the final study visit. Smartphone entries are immediately transmitted through Wi-Fi to a secure web site, downloaded daily to assess compliance, and stored in a second secure server (we have been using such apps for about 6 months and they have been very effective).

Windows for all visits will be ± 1 week except for Visit 4 which will have a 3-day window.

7.1 Screening – Visit 1, Week -4

Screening visit (90 min): Participants will have been prescreened over the telephone prior to being invited to attend this screening visit. Those invited will complete the informed consent process and evaluated with full inclusion/exclusion criteria. Once consented, a medical/pain history and physical examination, including orthostatic BP measurements for participants taking anti-hypertensive medications, will be completed. Urine will be collected for drug screening after participants have signed their consent forms. Blood will be drawn to screen individuals before starting treatment; blood draw will include a CBC, chemistry panel, alcohol levels, and liver function tests. Participants will be asked to assess current back pain intensity on a NRS scale (0-10, no pain to worst possible pain; ≥ 4 required to qualify for study). Participants will complete all PROs electronically and be instructed on the use of smartphone app (if participants do not have a smartphone, they will be given one for the duration of the study) (See [Section 16.2: Data Capture Methods](#)) and return in 1-2 weeks for baseline MR imaging scans (this length of time is adequate to allow scheduling and permit flexibility for participants' preferences). Study staff will ask the participant to discontinue all pain medications (14 days prior to Visit 2). Staff will explain to the participant that s/he can take only the rescue medication provided for pain during this time.

7.2 Baseline Scan – Visit 2, Week -2

Baseline imaging visit (2-2.5 hours): Participants will complete the NRS pain scale, and if score ≥ 4 and their average back pain on the smartphone over the last 5 days is also ≥ 4 , and no changes in clinical status are reported, participant will complete PROs electronically and undergo MRI and fMRI brain scans. This scan data will be used to derive brain biomarkers to determine risk for chronic pain. Only SBP assessed at high risk for chronic pain enter the study.

7.3 Enrollment – Visit 3, Week 0

Randomization and treatment administration (60-90 min). Those participants who meet all entry criteria (except for the first 12 participants, who will be included in the study if they fulfill all entry criteria except for being classified as high risk, as brain parameters derived from these subjects will be used to hone the model predicting risk for chronic pain) will return to the clinic to be randomized to receive either active treatment or placebo in a double-blind fashion, with medication dispensed sufficient until the next visit. For WOCBP, a urinary pregnancy test will be done prior to receiving study medication. Participants will complete the NRS pain scale, pledge to continue to use smartphone app, complete PROs, and have AEs assessed by an unstructured interview of interval medical history since last visit. BP and heart rate will be determined for all participants. Orthostatic BP measurements will be obtained for all participants taking anti-hypertensive medications.

7.4 Intermediate Visit – Visit 4, Week 1 ± 3 Days

Treatment administration (60-90 min). All procedures will be performed as described for Visit 3. Adherence will be assessed by pill counts (participants must take a minimum of 80% of the expected study medication to be considered adherent to study protocol) and participant will be queried about any side effects experienced. Study medication will be dispensed.

7.5 Intermediate Visit – Visit 5, Week 4 ± 7 Days

Treatment administration (60-90 min). All procedures will be performed as described for Visit 3. Adherence will be assessed by pill counts (participants must take a minimum of 80% of the expected study medication) and participant will be queried about any side effects experienced. Study medication will be dispensed.

7.6 Intermediate Visit – Visit 6, Week 8 ± 7 Days

Treatment administration (60-90 min). All procedures will be performed as described for Visit 3. Adherence will be assessed by pill counts (participants must take a minimum of 80% of the expected study medication) and participant will be queried about any side effects experienced. Study medication will be dispensed.

7.7 Intermediate Visit – Visit 7, Week 12 ± 7 Days

End-of-treatment visit (60-90 min). All procedures will be performed as described for Visit 3. Adherence will be assessed by pill counts (participants must take a minimum of 80% of the expected study medication) and participants will be queried about any side effects experienced. Study medication to permit taper and discontinuation of study product will be dispensed. Participants will be allowed to resume former pain therapies for the follow-up period only after IP taper and discontinuation.

7.8 Follow-up Phone Call – Week 16 ± 7 Days

Follow-up phone call (15 min). Participants will be asked if they have had any changes to health/condition and concomitant medications. AEs will be assessed by an unstructured interview of interval medical history since their last visit. Participant also be queried on successful discontinuation of study product and their current pain level using the NRS.

7.9 Follow-up Phone Call – Week 20 ± 7 Days

Follow-up phone call (15 min). All procedures will be performed as described for Week 16 phone call.

7.10 Final Study Visit – Visit 8, Week 24 ± 7 Days

Final visit (1.5-2 hours). All procedures will be performed as described for Visit 2 except for blood draw, with the addition of post-treatment imaging scans. Participants will be queried about any side effects experienced.

The participant will be debriefed once the researchers are unblinded. They will receive communication from the research coordinator by letter, text as follows:

“Dear Participant:

Thank you for agreeing to participate in this important research. The purpose of this study was to see how sub-acute back pain is represented in the brain, and to understand the effects of a new treatment on the body and on the brain.

At the beginning of the study, we took images of your brain (using Magnetic Resonance Imaging, MRI) and identified findings that makes us believe that it was possible that you would continue to have low back pain and therefore you were entered into the study. You participated in a double-blinded study, meaning that neither you nor the study staff knew which treatment you received until the end of the study. Participants were randomized into one of 2 groups: a placebo group or an active treatment group (with naproxen and Levodopa/Carbidopa). In this study, you (did/did not) receive the active treatment. We will only know if the treatment was helpful when all the information from the study has been analyzed. Results of this study will be available for viewing in approximately fall of 2016 at <http://clinicaltrials.gov> (study number NCT01951105)

We greatly appreciate your involvement in making this study possible. If you have further questions about the study, please contact the clinical research coordinator, Elizabeth Hunt, at 312-503-6475. In addition, if you have any concerns about any aspect of the study, you may contact the Office for the Protection of Research Subjects at (312) 503-9338.”

7.11 Interim Electronic Contact

In order to enhance retention of participants in the study and to obtain additional data regarding the course of the participants, participants will be in contact with the site by cell phone on a daily basis. At each of these interactions, the participants will provide an assessment of their level of pain utilizing an 11-point NRS scale.

All participants will also be using a smartphone app to log pain, mood, and medication use daily. These data are immediately logged into the study server, which provides routine overview of participants' participation and compliance and further enhances retention of participants. If participants repeatedly miss entering these values, they are contacted by phone and instructed for compliance. (See [Appendix C](#) for smartphone app usage manual)

7.12 Withdrawal Visit

Early termination visit (1.5-2 hours). If a participant withdraws early or the PI terminates the subject's participation, an early termination visit will be conducted. All procedures will be performed as described for Final Study Visit. All dispensed study medication will be collected and counted. If necessary, study medication to permit taper and discontinuation of study product will be dispensed.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Study Procedures/Evaluations

- Medical history will be obtained through interview. All past medical history will be included. (See [Appendix D](#) for example chart document)
- Medications history will be obtained through interview. Both prescription and over-the-counter medications from the previous two weeks to currently taking will be recorded. (See [Appendix D](#) for example chart document)
- AEs and SAEs will be obtained at each study visit to assess participant safety. (See Section 9.1 Specification of Safety Parameters for further details) (See [Appendix D](#) for example chart document)
- Physical examination will be obtained during the screening visit with the study doctor. Organ systems assessed will be HEENT (Head, Ears, Eyes, Nose, Throat), Chest, Heart, Lungs, Abdomen, Extremities, Skin, Neurological, and Musculoskeletal. (See [Appendix D](#) for example chart document)
- Vital signs obtained by the study coordinator at the beginning of each visit include height (only at screening visit), weight (only at screening visit), BP (orthostatic BP measured for participants taking anti-hypertensive medications), heart rate, and temperature. (See [Appendix D](#) for example chart document)
- Daily subject-reported outcomes: Smartphone app will be used to collect pain, mood, and medication use on a daily basis for the duration of the study. (See [Appendix C](#) for smartphone app usage manual)
- T1-MRI, DTI-MRI, resting state, fMRI scans will be performed as described (Baliki M, 2012) (Mansour A, 2013) twice: baseline (Week -2) and at final study visit (Week 24).
 - All brain imaging is done on two 3.0 T Siemens Trio whole-body MRI scanner with echo-planar imaging (EPI) capability and using a 32 channels head-coil. Both scanners are dedicated for research and shared between 15 NIH funded research groups. The university has guaranteed us access to these magnets for the next 5 years. The magnets are managed by Radiology Department and are fully staffed and equipped. They are core human imaging facilities of NU. Their signal-to-noise ratio is excellent and they have produced very nice results over the last 5 years of operation, and >100 publications.
 - We will acquire four different types of brain images:
 - Anatomical T1-MRI (high resolution anatomical magnetic resonance imaging): voxel size = $1 \times 1 \times 1$ mm, repetition time = 2,500 ms, echo time = 3.36 ms, flip angle = 9° , in-plane matrix resolution = 256×256 ; 160 slices, field of view = 256 mm.
 - Resting state fMRI (functional MRI): multi-slice T2*-weighted echo-planar images with repetition time = 2.5 s, echo time = 30 ms, flip angle = 90° , number of volumes = 244, slice thickness = 3 mm, in-

plane resolution = 64×64 . The 36 slices are covering the whole brain from the cerebellum to the vertex.

- fMRI (functional MRI): multi-slice T2*-weighted echo-planar images with repetition time = 2.5 s, echo time = 30 ms, flip angle = 90° , number of volumes = 244, slice thickness = 3 mm, in-plane resolution = 64×64 . The 36 slices are covering the whole brain from the cerebellum to the vertex.
- DTI-MRI (diffusion tensor imaging): 72×2 -mm-thick axial slices; matrix size= 128×128 ; field of view= 256×256 mm², resulting in a voxel size of $2 \times 2 \times 2$ mm). Images have an isotropic distribution along 60 directions using a b value of 1000 s \times mm⁻².
 - Brain imaging data analysis is done on free-share software including FSL, SPM, FreeSurfer, Caret, MRICron as well as ad-hoc routines written in Matlab, C++, Pearl, Awk. The university maintains a user contract for Matlab and other software that we use routinely.
 - We have a dedicated server for brain imaging data analysis. This is a 23 TByte data management system and with large number of processors, which runs on Linux. This server is our main brain imaging data storage and processing system. It is accessible through Internet, and all data processing is performed on it, mainly by remote access.
- Blood samples will be collected from all participants at baseline scan. Urine samples will only be collected from WOCBP at the first dosing visit.
- Administration of PROs (See Section 16.2 for a comprehensive list)

8.2 Laboratory Procedures/Evaluations

8.2.1 Clinical Laboratory Evaluations

Baseline laboratory values will be collected for determination of inclusion/exclusion criteria and to assess safety and also will be entered into the study database. Repeat laboratory testing will only be done if there is a clinical basis for further testing. Blood and urine samples will be collected at the MRI scanning facility by a RN. Urine pregnancy tests will be processed before starting any study medication. Blood samples will be processed through Pathology Laboratory at NMH, 251 E. Huron St. LC700, Chicago, IL 60611. All results will be faxed to the study doctor for review before participants begin study medications. Samples will not be frozen nor stored for long-term or future use.

Screening Laboratory Evaluations

Hematology - Complete Blood Count (CBC)

(This evaluation will be re-conducted among elderly participants for monitoring at 1 month after beginning treatment)

9 tests will be performed.

- White cell count [3.5-10.5 K/UL, normal reference range]
- Red cell count [3.80-5.20 M/UL]
- Hemoglobin [11.6-15.4 g/dL]
- Hematocrit HCT [34.0-45.0%]
- MCV [80-99 FL]
- MCH [27.0-34.0 pg]
- MCHC [32.0-35.5%]
- RDW [11.0-15.0%]

Hematology - Differential

10 tests will be performed.

- Neutrophils [34-73%]
- Lymphocytes [15-50%]
- Monocytes [5-15%]
- Eosinophils [0-8%]
- Basophils [0-2%]
- Absolute neutrophils [1.5-8.0 K/UL]
- Absolute lymphocytes [1.0-4.0 K/UL]
- Absolute monocytes [0.2-1.0 K/UL]
- Absolute eosinophils [0.0-0.6 K/UL]
- Absolute basophils [0.0-0.3 K/UL]

Chemistry Panel

16 tests will be performed. (This evaluation will be re-conducted among elderly participants for monitoring at 1 month after beginning treatment)

- Sodium [134-142 mEq/L]
- Potassium [3.5-5.1 mEq/L]
- Chloride [98-109 mEq/L]
- Bicarbonate [21-31 mEq/L]
- Blood urea nitrogen [2-25 mg/dL]
- Creatinine [0.00-1.30 mg/dL]
- eGFR – African Am [≥ 60 mL/min/1.73m²]
- eGFR – Non African Am [≥ 60 mL/min/1.73m²]
- Glucose level [65-100 mg/dL]
- Calcium [8.3-10.5 mg/dL]
- Albumin [3.5-5.7 g/dL]
- Total protein [6.4-8.9 g/dL]
- ALT [0-52 Unit/L]
- AST [0-39 Unit/L]
- Total bilirubin [0.0-1.0 mg/dL]

- Alkaline phosphatase [34-104 Unit/L]
- Alcohol levels

Vital signs

- Blood Pressure – diastolic [60-90 mm Hg]
- Blood Pressure – systolic [100-130 mm Hg]
- Pulse [60-100 beats/minutes]
- Respirations [10-16 breaths/minute]
- Temperature [36-37.5°C]

Urine Tests

- A urine test for drug use will be performed on all participants during screening after study consent has been obtained. A negative test result will be required prior to consenting to participate in the study.
- A urine pregnancy test will be performed on all WOCBP prior to starting treatment. A negative test result will be required before receiving study medication.

8.2.2 Special Assays or Procedures

N/A

8.2.3 Specimen Preparation, Handling, and Storage

N/A

8.2.4 Specimen Shipment

N/A

9 ASSESSMENT OF SAFETY

This study will evaluate the efficacy and safety of the combination of two treatments, the fixed dose combination of Carbidopa/Levodopa and Naproxen in people with subacute low back pain. Naproxen is a drug that has an FDA-approved indication for the treatment of pain. Carbidopa/Levodopa is primarily used to treat the symptoms of Parkinson's disease, and is being investigated in this study for off-label central CNS effects that could influence mechanisms associated with chronification of pain. An IND application (IND 118758) for this study has been filed and the study has been determined by the FDA to be exempt.

Both Carbidopa/Levodopa and Naproxen are associated with potential side effects, which have been well known for more than 30 years. In order to reduce the incidence and severity of side effects in this study, doses of both drugs well below the maximum suggested dosage for usual treatment are being utilized: a total maximum daily dose of 150mg/600mg of Carbidopa/Levodopa and 750mg of Naproxen, both given in three divided doses. Additionally, it should be noted that the population being studied is expected to be significantly younger than the typical population of people with Parkinson's disease, and therefore may have a lower incidence of some of the reported side effects which are thought to be at least to some extent age-dependent and disease dependent. Similarly, the GI safety of Naproxen is well recognized to be a function of age.

The only special safety consideration is the development of orthostatic hypotension due to the possible interaction of Carbidopa/Levodopa with antihypertensive medications. In order to assess this potential interaction, orthostatic blood pressure measurements will be done at each visit while participants are receiving study medication. No other special safety considerations appear applicable and further details are provided below.

9.1 Specification of Safety Parameters

In addition to reporting of AEs (see below), BP and pulse rate will be collected at each study visit and entered into the study database for safety evaluation. As noted above, orthostatic blood pressure measurements will be obtained on all participants on antihypertensive medications. Baseline physical examination will be documented, and any interim change reported by the participant will also be entered into the database. Baseline laboratory values will be collected for determination of inclusion/exclusion criteria and will be entered into the study database. Repeat laboratory testing will only be done if there is a clinical basis for further testing. Reporting requirements are detailed below.

9.1.1 Unanticipated Problems

A UP includes any AE, incident, experience, or outcome that meets **all** of the following criteria:

1. **Unexpected** (in terms of nature, severity, or frequency) given:
 - a. the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; **and**
 - b. Characteristics of the participant population being studied.
 - i. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in: **a)** the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document; and **b)** other relevant sources of information, such as product labeling and package inserts; or
 - ii. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the AE.

2. **Related or possibly related** to a subject's participation in the research; and

3. Suggests that the research places participants or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.2 Adverse Events (AE)

An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.1.3 Serious Adverse Events (SAE)

The following events are considered a SAE and would place participants at a greater risk of harm:

- Results in death;
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; or

- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

9.2 Time Period and Frequency for Event Assessment and Follow-Up

UPs will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
 - a. The event is known to occur with the study intervention.
 - b. There is a temporal relationship between the intervention and event onset.
 - c. The event abates when the intervention is discontinued.
 - d. The event reappears upon a re-challenge with the intervention.
 - e. No compelling alternative etiology is discernible.
2. Not Related (Unlikely, Not Related)
 - a. There is no temporal relationship between the intervention and event onset.
 - b. An alternate etiology has been established.

9.3.2 Expectedness of SAEs

The NIDCR Medical Monitor and the Study PI will be responsible for determining whether an SAE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention on the product label.

9.3.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; participant seeks medical attention, needs major assistance with ADL
4. Life-Threatening: An experience that in the opinion of the Investigator places the subject at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
5. Death

9.4 Reporting Procedures

The reporting of AEs, SAEs and UPs will be completed according to the guidelines of the NU IRB.

As of August 20, 2007, NU IRB requires filing of internal or external AEs reports, or safety reports only if they have been determined by the PI to contain a report of UPs involving risks to participants or others.

UPs involving risks to participants or others should be reported to the IRB within 10 working days (unanticipated deaths of participants enrolled at NU or Affiliates need to be reported within 24 hours).

All AEs deemed to be serious, both unexpected and expected, will be reported to the independent safety monitor.

The independent safety monitor is required to review all UPs involving risk to volunteers or others, SAEs and all volunteer deaths associated with the protocol and provide an unbiased written report of the event. The monitor will comment on the outcomes of the event or problem and in the case of a SAE or death comment on the relationship to participation in the study. The monitor will also indicate whether he/she concurs with the details of the report provided by the study investigator.

9.4.1 Unanticipated Problem Reporting to IRB and NIDCR

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an AE, or any other incident, experience, or outcome as an UP to the IRB:

- Appropriate identifying information for the research protocol, such as the title, PI's name, and the IRB project number;
- A detailed description of the AE, incident, experience, or outcome;
- An explanation of the basis for determining that the AE, incident, experience, or

outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to NIDCR within 1 week of the PI becoming aware of the event.
- Any other UP will be reported to the IRB and to NIDCR within 2 weeks of the PI becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the PI.

All UPs will be reported to NIDCR's centralized reporting system via Rho Product Safety:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

9.4.2 Serious Adverse Event Reporting to NIDCR

Any AE meeting the specified SAE criteria will be submitted on an SAE form to NIDCR's centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The PI should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help

Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

The study clinician will complete a SAE Form and submit via fax or email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to Product Safety within 24 hours of site awareness.
- SAEs other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

9.4.4 Events of Special Interest

Special attention will be directed toward the possible interaction of Carbidopa/Levodopa and antihypertensive medications in causing postural hypotension. Orthostatic blood pressure measurements will be made at all visits for participants receiving antihypertensive medications and adverse effects closely monitored to evaluate any signs or symptoms of postural hypotension.

9.4.5 Reporting of Pregnancy

The study will follow our institution's procedure regarding pregnancy during a clinical trial. Female patients will have to have a negative pregnancy test. Both male and female participants agree in their written consent to use double-barrier contraception during the course of the study. If a female participant or partner of a male participant becomes pregnant while taking part in this study, the participant will be instructed to discontinue the study drug and will be withdrawn from the study. Permission of the participant will be requested to notify their physician of pregnancy during participation in this trial and to follow the participant or partner of the participant closely through delivery or termination of pregnancy. Unblinding may occur by a member of the research staff if requested by the subject's physician and/or obstetrician. All pregnancies occurring during the course of the study will be reported to the FDA, NIDCR and the NU IRB.

9.5 Halting Rules

As both treatments being evaluated in this study are medications that have been widely utilized, mainly in Parkinson's patients, for many years, often at dosages considerably higher than will be used in this study, it is not anticipated that discontinuation of the study due to safety concerns will occur. However, a safety review will be triggered if there is the occurrence of any serious, unexpected, and related AEs by the Medical Monitor. Additionally, a safety review will be triggered by finding an increase in the

number of occurrences of expected AEs or SAEs (e.g., GI bleeding, dyskinesia) overall. If the safety review demonstrates evidence of concern, the FDA, NIDCR and the NU IRB will be notified and corrective action will be taken which could include actions such as reduction of the dosage of a given intervention, a reduction in the frequency of administration or possibly a suspension of further administration of study product.

10 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of an Independent Safety Monitor (ISM), who has expertise in clinical trials and in the pharmacology of treatments for Parkinson's disease, particularly Levodopa and Carbidopa/Levodopa. The ISM is independent of the study and will be available in real time to review and recommend appropriate action regarding adverse events and other safety issues. We anticipate safety concerns to be relatively limited due to the fact that (1) the safety profiles of both study medications have been well described over long periods of time, (2) the doses that are being used are at the lower end of the therapeutic range for both Carbidopa/Levodopa and Naproxen, (3) treatment is for a limited period of time (12 weeks) and (4) careful monitoring of safety will be undertaken by the study team with regular oversight by the clinical investigator and the principal investigator.

In addition, a DSMB will be assembled by NIDCR. Its meetings and calendar will operate under a charter that will be approved by the DSMB. The DSMB will meet at least annually.

11 CLINICAL SITE MONITORING

Site monitoring is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the study uses high quality data collection processes. NIDCR or its contractor will conduct clinical site monitoring for this study. The monitor will evaluate study processes based on NIDCR standards and ICH E6 Good Clinical Practice guidelines. NIDCR will receive monitoring reports from the contractor that performs monitoring visits, and reserves the right to conduct independent audits as necessary.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

The basis of this study is the notion that persistent pain, following an inciting injury, leads to an aversive learning signal that the corticostriatal system hijacks to reorganize the brain into a chronic pain state. We hypothesize that blocking the emotional/motivational learning response triggered by peripheral nerve injury and integrated within the corticostriatal circuitry, in a critical time window, will decrease the probability of transition to chronic pain.

The primary hypothesis to be tested in the study, for which we have supporting preclinical data, is that early treatment with Levodopa (in the form of Carbidopa/Levodopa) and Naproxen in individuals with SBP will block transition to CBP.

This will be tested by undertaking a parallel-group double-blind study comparing Carbidopa/Levodopa plus Naproxen to Naproxen alone in individuals with SBP. It is anticipated that there will be a lower number of individuals progressing to CBP in the Carbidopa/Levodopa plus Naproxen group than in the Naproxen treatment alone group.

Key secondary objectives are to evaluate the interaction with gender of the response to pain and to evaluate the correlation between pain response and corticostriatal reorganization.

Our main hypothesis is: High-risk SBP patients treated with Carbidopa/Levodopa and Naproxen will show statistically significant decrease in rate of transition to chronic pain. The null hypothesis is that SBP patients treated with Carbidopa/Levodopa and Naproxen and those treated with placebo and Naproxen show equal efficacy for blocking transition to chronic pain.

Our secondary hypothesis is: Rate of response of high risk SBP to Carbidopa/Levodopa and Naproxen is gender dependent.

Our other secondary hypothesis is: Of the three brain biomarkers that define SBP at high risk for chronification, only the extent of corticostriatal information sharing (mPFC-NAc) will show statistically significant reduction in SBP treated with Carbidopa/Levodopa and Naproxen.

12.2 Sample Size Considerations

We plan to recruit approximately 200 individuals with SBP. During screening, 126 participants will be recruited that are at high risk for developing chronic pain based on brain-based biomarkers. These 126 participants will be randomized to the active treatment arm (Carbidopa/Levodopa and Naproxen) or the placebo treatment arm (placebo and Naproxen). As a conservative estimate, we presume that 100 participants will complete the study. The clinical trial is a two-group design examining the effects of

predicted response on type of treatment. Because our dependent variable is binary (recovered from back pain or not; more than 20% decrease in back pain magnitude between entry and 24 weeks after treatment is classified as recovering from back pain) and we wish to have sufficient power to detect treatment effect, we conducted power analysis based on comparison of independent proportions. Our preliminary data shows that in high-risk SBP ~90% will persist with back pain if treated with standard of care (mostly occasional use of anti-inflammatories). Thus, for power calculations, we assume that 90% of participants that receive placebo will have persisting pain at study end. Calculations in G*Power 3.1.2 9.2 indicated that we will detect significant differences with 80% power if the probability of pain persistence is reduced to .67 or smaller (Type I error rate assumed at .05, two-tailed, $n = 50$ per group). Again, this is a conservative scenario given that our team has extensive experience with participant retention, and we assumed a two-tailed comparison, even though there is no a priori reason for the placebo to outperform the active drug. We are planning to enter 126 participants, so we will have adequate power, accounting attrition. As a supplemental data analysis strategy, Dr. Griffith can model pain trajectory as a continuous variable using mixed modeling approaches, which potentially has more power, but at some cost of model complexity. All effects will be estimated with 95% confidence intervals, consistent with CONSORT guidelines.

Our secondary aim is to determine if there is a gender by treatment interaction effect. Specifically, we want to test the influence of gender on response to active treatment with Carbidopa/Levodopa and Naproxen. Assuming no gender effect on the placebo treatment response rate, then we are left with the active treatment arm. Calculations in G*Power 3.1.9.2 indicated that we will detect an odds ratio of greater than 2.7 (2.5-3.0) with $\geq 80\%$ power with an overall sample size of 50 (assuming $n = \sim 25$ per gender). We assumed a two-tailed comparison because there is no a priori reason for a given gender to respond better to the active drug. Although power will be adequate with this conservative scenario, we will be able to strengthen the analyses, if needed, by removing variance due to nuisance covariates and using longitudinal modeling, as described above. All binary outcomes will be reported based using absolute and relative descriptive statistics, consistent with CONSORT guidelines.

Our other secondary aim is to determine if prevention of chronification of pain is correlated with inhibition of corticostriatal reorganization. These are planned comparisons for brain regional gray matter density and brain functional connectivity strengths, as determined in fMRI, DTI, and T1 scans, collected at time of entry into the study and at 24 weeks after treatment. Our previous published studies indicate that $n = \sim 20$ per group would be sufficient to show medium size effects of recovery from back pain on these pre-specified brain parameters; above calculations indicate that we will have an adequate sample size. If we observe a gender by treatment interaction, then we can also test whether the interaction can also be detected for the pre-specified brain regions.

Additional exploratory analyses will also be conducted in which we examine whole-brain contrasts and whole-brain correlations for parameters of interest. One such analysis entails examining brain parameters that distinguish between treatment responders and non-responders. A second would be to test for treatment by response interaction effect on the whole brain, contrasting anatomical and functional brain states between before and after treatment. We expect to have adequate number of participants per group to detect medium-sized such effects. All whole-brain statistical results will be based on proper correction for multiple comparisons. Post-hoc analyses are then performed for specific brain regions or networks identified from whole-brain analyses.

As it stands, our analysis will have sufficient power, but we will achieve even greater power by including covariates that are associated with pain recovery/persistence in our preliminary data. For example, we have identified extent of radiculopathy as a significant contributor with odds ratio of 2.0. We expect to replicate this finding in this treatment study.

12.3 Planned Interim Analyses (if applicable)

There are no planned interim analyses for efficacy or safety endpoints. It is anticipated that by the time a sufficient number of participants have completed the trial to provide an adequate data set to permit interim assessment of efficacy, all or almost all the participants will have already been recruited. Therefore, no planned interim analysis has been considered. Interim analysis for safety will be undertaken if there is evidence of a concern regarding safety generated from consideration of AE and SAE reporting.

Safety Review

Participants' safety will be closely monitored by the site investigator and the principal investigator in conjunction with the proposed Independent Safety Monitor, who will be available in real time for participant assessment should the need arise. Careful, periodic assessment of all safety data will be undertaken. An inclusion/exclusion criteria checklist will be reviewed for each participant enrolled to ensure that only appropriate participants are included. AEs will be collected at each visit and tabulated by the coordinator during the trial. The site and principal investigator will meet on a monthly basis to review these data and be joined on a quarterly basis by a biostatistician. There will be regular meetings with the Independent Safety Monitor every 6 months, and more frequently if requested. All SAEs will be collected separately and reviewed as such. Those that are unexpected and considered related will be reported to the IRB immediately. An annual report of study progress and adverse effects will be made.

MRI safety is routinely implemented at Northwestern University Center for Translational Imaging, and participants are carefully screened for contraindications at entry and prior to entering the scanner suite. Participants are screened for iron or steel implants or clips from surgery, or metallic objects, such as shrapnel or metal sliver in their bodies, are excluded from the study if present. Dental fillings do not present a hazard.

Efficacy Review

There are currently no plans to perform an interim efficacy analysis or review (please see 12.3 above for rationale).

12.4 Final Analysis Plan

SBP participants who qualify to participate in the study are first instructed to rate their back pain for a week on the smartphone Pain App. If their average back pain over the last 5 days (~15 measures) is $>4/10$, they undergo brain resting state, fMRI, DTI, and T1 scans. The outcome of these scans determine if they are at high risk for transitioning to chronic pain, in which case they are randomized to active or placebo treatment for 12 weeks; followed for another 12 weeks; and then undergo repeat brain scans.

From our previous longitudinal observational study ($n = 68$ SBP patients followed over one year), we have built a statistical model for identifying high risk SBP. The model uses a Naïve Bayes Classifier where 3 independent brain biomarkers are used to predict risk. The three parameters are: from resting state fMRI the strength of functional connectivity between two brain regions, of predefined coordinates (6 mm^3 regions) (right medial prefrontal cortex and right nucleus accumbens, mPFC-NAc); from DTI we derive mean fractional anisotropy for a predefined white matter track (superior longitudinal fasciculus); from T1 we measure the volume of the right amygdala. We have shown that specific ranges of these 3 values, when used in our model, can identify high risk SBP at greater than 90% accuracy.

At termination of study, participants are classified into recovering (r), based on individual back pain (5 day average) decrease $>20\%$, from entry to 24 weeks later. Otherwise they are labeled persisting (p). Therefore, our main outcome is a 2×2 frequency table for treatment type and ratio of $p/(p+r)$. As the total $n = \sim 100$ for this table, we will use a chi-squared test to identify effect of active treatment on risk of pain chronification.

Our secondary aim is to test for an interaction effect between gender and treatment outcome, which we will evaluate within a multiple logistic regression model. Our other secondary aim is to relate brain parameters to treatment outcome. We expect that DTI fractional anisotropy and T1 right amygdala volume will not change with treatment, whereas resting state functional connectivity and fMRI mPFC/somatosensory link ratio will decrease in time in treatment responders. The four brain biomarkers are treated as continuous outcome measures, and tested within a three-way mixed-design ANOVA with factors of treatment type, response type, and time (repeated measure).

All brain imaging data undergo a routine pipeline for quality assessment and standardized preprocessing. Fixed coordinate values are then extracted from each participant and for each modality. These analyses are all performed blinded. Once all data are available and the study is closed, we use appropriate groupings to perform the ANOVA tests.

Whole-brain exploratory analyses will contrast between groups, and correlate pain, anxiety, depression (and other behavioral outcomes) with brain anatomy and function.

All initial preprocessing of these comparisons are also done blinded. All whole-brain comparisons properly correct for multiple comparisons. The design of the contrasts will be repeated measure ANOVA applied over the whole brain, or applied to specific brain structures, or functional network measures. Single parameter whole-brain correlates, with correction for covariates of no interest will also be performed, across the modalities and for multiple behavioral measures.

We will also perform exploratory analyses regarding the contribution of demographics and pain-related behavioral measures to the treatment outcome, as well as to their influence on outcomes as a covariate when combined with brain biomarkers. These would be based on building logistic multivariate regression models.

12.5 Sensitivity analyses

Although our primary analyses will be on N = 100 completers, we will also conduct sensitivity analyses on all enrolled participants (N = 126) assuming a worst-case scenario by imputing baseline-observation-carried-forward for missing data. Because we have a two-group design with a binary outcome, it is possible to visualize how all possible imputation strategies would influence the outcome of the trial (Liublinska 2014). We will calculate propensity scores using logistic regression on participation (1 = included/0 = not included) with other study variables as covariates. We will then compare the treated versus untreated groups on propensity scores, as well as reanalyze the data weighting cases on the basis of propensity scores.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. All source documents pertaining to an individual participant is compiled into a participant folder. Each participant folder includes, but is not limited to, records on personal contact information, demographic information, physical exam, vital signs, personal health history, researcher comments from each visit, PROs, concomitant medication logs, study medication logs, indications of any AEs experienced, clinical laboratory results, and ICFs. PROs will be collected directly into REDCap (REDCap is the source document), but will be printed and maintained with the participant folder. All folders are kept in a locked cabinet, located in a locked room away from all participant activity. Only study coordinators have access to the locked room and cabinet. These paper charts are also kept separate from any hospital records acquired through NMH or the NMFF. Study staff will permit authorized representatives of NIDCR, the NU IRB and defined regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

All brain imaging data are maintained on a secure server, stored under lock at the NMH hospital server banks. Access to these data are password protected, and all brain scan data are anonymized and coded prior to being available on the server. Only NUCATS will maintain the lock for the specific subject-to-data correspondence, and this information is not anticipated to be used, except in some unusual emergency situation (such an event has not arisen in the past >15 years).

14 QUALITY CONTROL AND QUALITY ASSURANCE

NUCATS Institute maintains SOPs that deal with quality control and quality assurance activities related to clinical trials. In brief, data are evaluated for compliance with the protocol and for accuracy in relation to source documents by regular audits from NUCATS staff. All study documents may be reviewed. Ultimate responsibility for QA and QC resides with the site investigator and PI. These responsibilities can be delegated to designated study staff. Staff training is made available by both on-line and live educational forums. All training is tracked by a university employee database.

15 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, as drafted by the US National Commission for the Protection of Human Participants of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.2 Institutional Review Board

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the ICF must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the participant folder. (See [Appendix B](#) for an example of the ICF)

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

N/A

15.5 Participant Confidentiality

We are committed to respect participant privacy and to keep personal information

confidential. When choosing to take part in this study, participants are giving us the permission to use their PHI that includes health information in their medical records and information that can identify them. For example, PHI may include name, address, phone number or social security number. Health information that we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history including back pain history and family history of back pain
- Lab tests, or certain health information indicating or relating to a particular condition as well as information collected by cellphone apps and PROs
- Records about study medication or drugs
- Records about MRI scans
- Substance abuse information: current recreational drug use or history of alcohol or drug abuse

The following groups of people may give the researchers information about research participants:

- All current and previous health care providers, including but not limited to the NMFF, NMPG, NMH.

Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of NU and its clinical partners (or affiliates) will not contain subject's name, address, telephone or social security number or any other direct personal identifier unless disclosure of the direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the PI's office]

- Authorized members of the NU workforce, who may need to see information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study),
- Clinical affiliates, including but not limited the NMFF, NMH, and NMPG. Individuals' participation in this clinical trial will be tracked in an electronic database and may be seen by investigators running other trials and by other healthcare providers having access to this database.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,
- Government agencies and public health authorities, such as the FDA and the DHHS.

The results of this study may also be used for teaching, publications, or presentation at

scientific meetings. However, the individual's name and personal information will not be used.

15.6 Future Use of Stored Specimens and Other Identifiable Data

We foresee that the brain imaging data and related PROs may be used in future studies, either by us or when we make this data available on OpenPain for use by other researchers (Apkarian, 2014). In all such cases all data will be fully anonymized prior to their availability for future use by investigators outside of Apkarian's lab.

16 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate CRFs, and source documentation.

16.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. UPs and AEs must be reviewed by the investigator or designee.

16.2 Data Capture Methods

We plan to use REDCap (<http://www.project-redcap.org/>) as our data management tool. Participant-entered data will be collected directly into the REDCap application as source documents and subsequently printed out for participant files. PROs will not contain any PHI and will be stored in participant's folder (See [Appendix E](#) for examples of PROs). Clinical (e.g., medical history and physical examination, pain evaluations) and functional (e.g., brain phenotype) status assessments will be entered on paper as source documentation and subsequently entered into REDCap as confirmation of a participant's passing or failing inclusion/exclusion criteria. Other data collected by study staff pertaining to the study visit will be entered on paper and subsequently entered into REDCap.

Instruments used for assessing characteristics of back pain:

Numerical Rating Scale (NRS) (Farrar et al, 2001): is an 11-point numerical rating scale used to measure pain intensity, where 0 corresponds to no pain and 10 indicates worst possible pain. The timeframe in question is concerned with the average pain experienced in the past 48 hours. This questionnaire has been extensively used across pain management studies.

McGill Pain Questionnaire - Short Form (sf-MPQ) (Melzack, 1987): is a well-validated pain measure, which permits separation of sensory and affective components of pain, as well as a total score. It also includes a numeric/descriptor scale, a visual analog pain scale (VAS), and a body map to localize the pain. This instrument is very well validated and often used in pharmacological research (Caraceni et al. 2002). However its affective subscale is thought to be relatively rudimentary.

Beck Depression Inventory, second version (BDI-II) (Beck et al., 1996): A 21-item self-report instrument for measuring the severity of depression in adults (and adolescents 13 and up). It is well validated in pain populations, and has been extensively used in

pharmacological research (Rowbotham et al. 1998) and in chronic back pain (Harris & D'Eon, 2008).

Pain DETECT (PD-Q) (Freyenhagen et al., 2006): A 12-item self-report instrument that assesses neuropathic pain properties and was originally developed in a sample of 8,000 low back pain sufferers in Germany. The PD-Q demonstrates high sensitivity (80%) and specificity (85%), and has since been validated in other clinical pain populations.

Personal Health History (PHH): This general questionnaire will assess demographic information (gender, age, marital/relationship status, race/ethnicity, and education), pain history (descriptions, diagnostic testing history, and treatment history), general health history (other medical/surgical history, concurrent medications, health behaviors, a general symptom checklist, and health-care utilization), and work history. The entire questionnaire will be completed at the baseline visit. Participants will be asked about any changes to concurrent medications at subsequent visits. History and physical examination will be done to confirm diagnosis, inclusion and exclusion criteria and assess overall safety.

Positive and Negative Affect Schedule (PANAS)(Watson et al., 1988): is a 20-item self-report instrument that measures the general distress and dysfunction, depression, and state anxiety and more of an individual. The PANAS was developed with a sample of undergraduate students and validated with adult populations. It is comprised of two mood scales, one measuring positive affect and the other measuring negative affect. Each item is rated on a 5-point scale ranging from 1 = very slightly or not at all to 5 = extremely to indicate the extent to which the respondent has felt this way in the indicated time frame.

Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995): The PCS is a 13-item instrument derived from definitions of catastrophizing described in the literature (Chaves & Brown, 1987; Spanos et al., 1979) as well as items from the catastrophizing subscale of the CSQ (Rosenstiel & Keefe, 1983). The PCS instructions ask participants to reflect on past painful experiences, and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on 5-point scales with the end points (0) not at all and (4) all the time. The PCS yields a total score and three subscale scores assessing rumination, magnification and helplessness. The PCS has been shown to have adequate to excellent internal consistency (coefficient alphas: total PCS = .87, rumination = .87, magnification = .66, and helplessness = .78; Sullivan et al., 1995).

Pain Anxiety Symptoms Scale (PASS-20) (Author et al., year): is a 20-item instrument used to measure the relationship between fear and avoidance of pain, and the suffering and disability of chronic pain. The PASS-20 is designed to assess four aspects of pain-related anxiety: cognitive anxiety, escape-avoidance behaviors, fear of pain, and physiological symptoms of anxiety.

Pain Sensitivity Questionnaire (PSQ) (Ruscheweyh et al., 2009): is a 17-item, self-rated

instrument used to assess individual pain sensitivity. This questionnaire is based on pain intensity ratings of daily life situations, which include various modalities (heat, cold, pressure, pinprick) and measures (pain threshold, intensity ratings). Participants are asked to rate pain intensities from a 0-10 scale pertaining to hypothetical situations.

Pain Disability Inventory (PDI) (Tait et. al., 1987): a brief 7 item instrument that was developed to assess pain-related disability, providing information that complements assessment of physical impairment. This self-reported index is based off an 11-point scale ranging from no disability (0) to total disability (10). The PDI is a measure of social participation in relation to pain, which corresponds to **C** (achievements) and **E** (subjective evaluations and reactions) of Dijker's Model (Dijkers, 2005).

Daily NRS Mood Score: is a 21-point numerical rating scale used to measure mood intensity, where 0 corresponds to a neutral mood, -10 indicates sadness, and 10 indicates happiness. The timeframe in question is concerned with mood experienced currently.

16.3 Types of Data

Our research staff will be collecting multiple types of data pertaining to the participants, such as those dealing with safety, imaging, and behavioral and medical participant domains. The safety of the participant will be initially assessed through obtaining a thorough history and assuring that participants meet all the criteria of the inclusion/exclusion checklist, which reviews comorbid illnesses and contraindicated medications. Safety data will continue to be collected at each contact with participants and recorded in the source documents. There will not be a separate safety database. Imaging data will be collected during each of the scanning visits and will be collected based on well-documented protocols. Behavioral data will be provided through selected patient PROs that assess various aspects of pain and overall quality of life. Medical data will be collected primarily during physical examinations and from a baseline blood draw, in addition to follow-up visits throughout the study. These measurements include BP, heart rate, chemistry panel, CBC, drug urine screening, and urine pregnancy screening.

16.4 Schedule and Content of Reports

In order to monitor the progress of the study and to provide quality control, a number of reports will be regularly generated throughout the course of the study. The clinical investigator will have a weekly meeting with all study staff to review the status of the study and address issues that have arisen during the week. At this meeting, a recruitment and retention report will be presented and discussed. Dates of important summary reports (e.g., annual IND report, report to clinical committee, IRB annual renewal, etc.) will be highlighted. In general, a draft of any report to be circulated outside the study team will be prepared at least one week prior to the deadline for the report needing to be sent in order to provide adequate time for review and discussion. It

is anticipated that there will be a data review regarding safety done at least quarterly or more often as requested by the study oversight committee. Outcome data will not be reviewed until after database lock, though the integrity and completeness of data will be assessed on a quarterly basis as part of quality assurance activities. The database will not be locked until all data fields have been checked and any remaining discrepancies dealt with. Once the database has been locked, no further changes will be made and the randomization code can be provided to the study statistician.

16.5 Study Records Retention

Study records will be maintained for at least five years from the date that the grant FFR is submitted to the NIH. No records will be destroyed for up to 3 years after the study has completed. There is no anticipation of a marketing application.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or Good Clinical Practice requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions will be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All serious and significant deviations from the protocol will be documented in the study participant source documents and promptly reported to NIDCR and the local IRB, according to their requirements.

17 PUBLICATION/DATA SHARING POLICY

This study will comply with the [NIH Public Access Policy](#), which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](#) upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as [ClinicalTrials.gov](#), which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIDCR grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

[U.S. Public Law 110-85](#) (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product participant to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product participant to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific [steps to ensure compliance](#) with NIH implementation of FDAAA.

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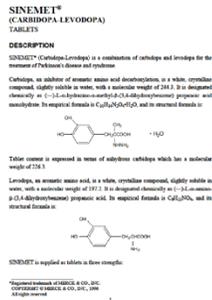
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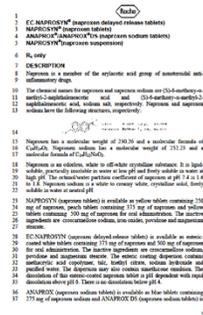
SUPPLEMENTAL MATERIALS

Supplemental materials provided are:

- Package insert for Carbidopa/Levodopa (Double-click to open)



- Package insert for Naproxen (Double-click to open)



- Package insert for Acetaminophen (Double-click to open)



APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

APPENDIX B: CONSENT FORM

APPENDIX C: SMARTPHONE APP USAGE MANUAL

APPENDIX D: CHART DOCUMENTS

APPENDIX E: KEY PROs

APPENDIX F: PROCEDURE FOR DETERMINING HIGH-RISK SUBACUTE BACK PAIN PATIENTS (HIGH-RISK SBP)

APPENDIX G: CASE REPORT FORM FOR PHENOTYPING

APPENDIX A: SCHEDULE OF EVENTS

	S c r e e n i n g	B a s e l i n e S c a n	R a n d o m i z a t i o n	Double-blind Treatment				Follow-Up Phone Call		F i n a l S c a n	E a r l y T e r m
				4	5	6	7				
Visit Number	1	2	3	4	5	6	7			8	--
Telephone Contact								X	X		
Week	-4	-2	0	1	4	8	12	16	20	24	--
Visit Window (Days)	--	7	7	3	7	7	7	7	7	7	--
Study informed consent	X										
Eligibility criteria	X										
Demographic information	X										
Medical/surgical history	X										
Vital signs	X	X	X	X	X	X	X			X	X
Height	X										
Weight	X										
Physical Examination	X										
Prior / Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Washout instructions	X										
Provide daily pain diary	X	X	X	X	X	X	X	X	X		
MRI scan		X								X	X
Review / collect daily pain diary		X	X	X	X	X	X			X	X
Clinical Laboratory Tests	Hematology - CBC ^a	X									
	Hematology - Differential ^b	X									
	Chemistry Panel ^c	X									
	Urine ^d			X							
Rescue medication	X	X	X	X	X	X	X				X
Investigational drug dispensing ^{e, f}			X	X	X	X	X				X
Study drug compliance				X	X	X	X	X			X
AE / SAE reporting			X	X	X	X	X	X	X	X	X
Pain Assessment	NRS	X	X	X	X	X	X	X	X	X	X
	painDETECT	X	X	X	X	X	X	X		X	X
	MPQ	X	X	X	X	X	X	X		X	X
	BDI	X	X	X	X	X	X	X		X	X
	PHH	X									
	PANAS		X	X	X	X	X	X		X	X
	PCS	X									

PASS	X											
PSQ	X											
PDI		X	X	X	X	X	X				X	X

^a Hematology – CBC: White cell count, Red cell count, Hemoglobin, Hematocrit HCT, MCV, MCH, MCHC, RDW, Platelet count.

^b Hematology – Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Absolute neutrophils, Absolute lymphocytes, Absolute monocytes, Absolute eosinophils, Absolute basophils.

^c Chemistry Panel: Sodium, Potassium, Chloride, Bicarbonate, Blood urea nitrogen, Creatinine, eGFR – African Am, eGFR – Non African Am, Glucose level, Calcium, Albumin, Total protein, ALT, AST, Total bilirubin, Alkaline phosphatase.

^d Urinalysis – Alcohol and pregnancy (pregnancy collected before any procedures from WOCBP only).

^e At Visit 3, Carbidopa/Levodopa (12.5mg/50mg) QD for 3 days, Carbidopa/Levodopa (12.5mg/50mg) BID for 3 days, and then Carbidopa/Levodopa (12.5mg/50mg) TID over one week and then continued at that level at Visit 4 for 4 weeks. If at the end of the initial 4 week period the participant has “responded or recovered” (had a reduction in pain from baseline of $\geq 20\%$), the participant will be maintained on that dose for the duration of the treatment period (12 weeks total). If there has not been a response, the dose will be increased to Carbidopa/Levodopa (25mg/100mg) TID at Visit 5 for the following 4 weeks at which time the pain status will be re-evaluated. Again, if a response has occurred, that dose will be maintained in a blinded manner for the following 4 weeks of treatment; if not, further dose-titration will occur to Carbidopa/Levodopa (50mg/200mg) TID at Visit 6 for the final 4 weeks. If a participant experiences an AE at higher doses, then the participant will be given the next lower dose that s/he was able to tolerate and then be maintained on that dose for the remainder of the 12 week dosing period. At Visit 7, participants will begin tapering off the medication based on their highest treatment dose. If a participant ended the treatment period on Carbidopa/Levodopa (12.5mg/50mg) TID, then s/he will start with Carbidopa/Levodopa (12.5mg/50mg) BID for 3 days and then Carbidopa/Levodopa (12.5mg/50mg) QD for 3 days before discontinuing it completely. If a participant ended the treatment period with Carbidopa/Levodopa (25mg/100mg) TID or Carbidopa/Levodopa (50mg/200mg) TID, then s/he will start with Carbidopa/Levodopa (25mg/100mg) BID for 3 days and then Carbidopa/Levodopa (25mg/100mg) QD for 3 days before discontinuing it completely.

^f All participants in both arms will be given a therapeutic dose of one 250mg capsule TID during the treatment period (but not during the tapering down at the end of the study).

APPENDIX B: CONSENT FORM

The following document titled “Consent Form and HIPAA Authorization for Research” is an example of the ICF used by NU’s IRB for this study. (Double-click to open)

APPENDIX C: SMARTPHONE APP USAGE MANUAL

The following document is the usage manual for the smartphone app. (Double-click to open)

Phone Usage Instruction Sheet

Subject ID: _____

How to use the phone for rating your pain

1) Click on the "Pain Rate" icon on the home screen



3) Please enter your subject ID here



4) Rate your current pain level by sliding the GREY box between 0 and 10.



Example: if your pain level is 4 out of 10, then stop the grey box at 4.



APPENDIX D: CHART DOCUMENTS

The following are chart documents used in this study:

- Medical History Form (Double-click to open)

The Medical History Form is a grid with columns for 'Date', 'Time', 'Event', 'Location', 'Duration', 'Frequency', and 'Status'. It lists various medical conditions such as Allergies, Blood Pressure, Diabetes, Heart Disease, and others, with rows for recording data.

- Concomitant Medications (Double-click to open)

- Physical Examination Form (Double-click to open)

The Physical Examination Form is a grid with columns for 'Date', 'Time', 'Event', 'Location', 'Duration', 'Frequency', and 'Status'. It lists various physical exam findings such as Heart, Lungs, Abdomen, and others, with rows for recording data.

- Vital Signs Form (Double-click to open)

The Vital Signs Form is a grid with columns for 'Date', 'Time', 'Event', 'Location', 'Duration', 'Frequency', and 'Status'. It lists various vital signs such as Temperature, Heart Rate, Blood Pressure, and others, with rows for recording data.

- Adverse Event Form (individual) (Double-click to open)

Confidential

Eff
Pa

Adverse Events

(con_1) Record ID _____

Adverse Events

Were any adverse

e
 v
e
n
t
s

e
x
p
e
r
i
e
n
c
e
d
?

N
o

Y
e
s

Adverse Event 1

(please type AE name)

Adverse Event 1 - Additional Comments/Description

Was the AE expected?

Yes

N
o

Start Date

Stop Date

93

Severity

M
 o
d

Mild

The image shows a form titled "Adverse Event Form" with various sections for reporting adverse events, including patient information, event details, and a table for tracking events.

- AE/SAE/UAP Tracking Master Log

The image shows a large, multi-column table used for tracking adverse events, with columns for event type, date, and other tracking information.

- AE/SAE Log (Double click to open)

The image shows a form titled "ADVERSE EXPERIENCE FORM" with a table for recording adverse experiences and a list of checkboxes for reporting details.

- Unanticipated Problem Form (UP)

The image shows a form titled "Unanticipated Problem Form (UP)" with sections for reporting unanticipated problems, including a table for tracking and a list of checkboxes for reporting details.

- Serious Adverse Event (SAE) Report Form

The image shows a form titled "Serious Adverse Event (SAE) Report Form" with sections for reporting serious adverse events, including a table for tracking and a list of checkboxes for reporting details.

- SAEs Cumulative Tracking Log



The image is a small, low-resolution thumbnail of a table. It appears to be a tracking log with multiple columns and rows. The columns likely represent different categories of data, such as dates, patient identifiers, and event descriptions. The table is oriented vertically on the page.

APPENDIX E: KEY PROs

The following documents are the PROs used in this study:

- Numerical Rating Scale (NRS) (Double-click to open)



- McGill Pain Questionnaire - Short Form (sf-MPQ) (Double-click to open)



- Beck Depression Inventory, second version (BDI-II) (Double-click to open)



- Pain DETECT (PD-Q) (Double-click to open)



- Personal Health History (PHH) (Double-click to open)

- Positive and Negative Affect Schedule (PANAS) (Double-click to open)

- Pain Catastrophizing Scale (PCS) (Double-click to open)

- Pain Anxiety Symptoms Scale (PASS-20) (Double-click to open)

- Pain Sensitivity Questionnaire (PSQ) (Double-click to open)

APPENDIX F: PROCEDURE FOR DETERMINING HIGH-RISK SUBACUTE BACK PAIN PATIENTS (HIGH-RISK SBP)

This step is necessary to identify who of the recruited subacute back pain patients fulfills the criteria for high risk SBP, as the latter are entered into the clinical trial while others are excluded. Given MRI/fMRI brain scans are collected, as explained in the section 8.1 study procedures/evaluations, we perform several analyses to obtain brain parameters that define which patients are high risk SBP/non high risk SBP. Following are the specific steps:

Brain parameters validation:

The MRI facility at Northwestern University recently updated one of their MRI scanners. To be able to use the prediction model that we have developed on the previous scanner, we need to validate the brain parameters obtained on this new scanner. To do so, we will enroll in this study the first 12 eligible participants to gather brain data and update our model. Based on our prediction model, that is designed to maximize participant to be included in the treatment arm, the likelihood of exclusion from this study is 20%. This exclusion rate leads to a maximum of 2-3 participants, out of these first 12, that could be excluded from this study. Once the updated prediction model will be finalized with the data from the first 12 participants, we will use this model to retrospectively stratify them into high-risk or low-risk SBP and take the appropriate decision regarding study continuation.

Quality control pipeline:

A robust quality control pipeline has been established in the Apkarian's lab and is detailed in the publication (Huang et al., 2012). Briefly, each imaging modality (fMRI, T1, DTI) is assessed for excessive motion or bad signal to noise ratio. Four different metrics are evaluated for each subject: for T1, the volume of seven ROIs and the stretch factor (transformation required to move the native-space brain to template space) is obtained. For fMRI, the temporal signal to noise ratio is calculated. For DTI, the mean FA and mean diffusivity is obtained for specific ROIs and for white matter. These metrics must be met for the obtained scans to be accepted and to start the analysis for each modality.

Anatomical parameter:

Subject's structural T1 images are analyzed with FSL subcortical segmentation tool "FIRST" (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>). From the FIRST result that includes 14 subcortical regions, we extract the volume of the right amygdala, which is our main

structural parameter of interest. This parameter is established from patients in our longitudinal study of SBP (amygdala results are in a manuscript currently in preparation; the study details are described by Baliki (Baliki et al., 2012). We have shown that chronic back pain (CBP of duration > 5 years) and persisting SBP patients have a lower right amygdala volume. The latter data provides us with the normative distribution of amygdala volumes. If the obtained result is within this distribution then the value is used with no further manipulation. However, occasionally FIRST segmentation may fail, in which case the obtained volume would underestimate amygdala volume. In such cases the volume measure need to be checked manually, and might be further augmented manually.

Functional parameters:

Subject's T2* resting state functional images are analyzed with FSL tools. First, we use "FEAT" (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT>) to pre-process the data and correct resting images for motion. To produce the final filtered functional data that we use for analysis, we use "MELODIC" toolbox (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC>) to regress-out any signal found in ventricles and in white matter as this is considered artifacts. We also remove the whole brain global signal. To allow comparison between participants, these filtered functional data are finally registered to a standard brain and down-sampled to a 6x6x6 mm voxel size. A c program produced in house called "ABLM" (for Apkarian Brain Linkage Map), described and results reported by Baria (Baria et al., 2013), is used to provide the number of functional connectivity link of each brain voxels. We then extract the average number of links from the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC) and also from sensory regions (somatosensory cortex S1 and anterior cingulate cortex). The link ratio of mPFC-NAc/sensory is then calculated (link ratio). We also extract mPFC-NAc correlation coefficient based on coordinates reported by Baliki (Baliki et al., 2012).

White matter parameter:

Subject's diffusion tensor images (DTI) are analyzed with FSL tools. We use the diffusion toolbox "FDT" (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT>) to pre-process the DTI images. First, we correct each participant DTI images for "Eddy current" (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide#Eddy_Current_Correction) and then apply a "dtifit" algorithm (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide#DTIFIT>) to obtain a diffusion tensor model value at each white matter voxel. We further extract the mean FA value of a group of voxels that were identified in our previous publication (Mansour et al., 2013).

Bayesian Model for identifying high risk SBP:

For predicting high-risk/non-high-risk SBP at 6 months from brain parameters collected at entry time, assuming that the a priori incidence of high-risk SBP 0.6, we construct the following model:

We want to identify participants, with high specificity, to be non-high risk SBP (non-HR SBP), exclude them from the trial and assume all others are high-risk SBP. Each individual participant parameter is first tested for being in the range of already existing data, otherwise we manually review data extraction steps.

For amygdala volume (Amyg), although alone has a ROC D of 0.77 for predicting high-risk SBP, its Bayesian prediction curve is bimodal: for volumes $> 1600 \text{ mm}^3$ $P(\text{non-HR SBP}/\text{Amyg}) > 0.7$; while for volumes > 900 and $< 1200 \text{ mm}^3$ $P(\text{non-HR SBP}/\text{Amyg}) < 0.35$. In other ranges prediction is less certain.

For DTI group mean fractional anisotropy (gFA), ROC D is 0.95 for predicting high-risk SBP. Bayesian prediction curve is unimodal: for $\text{gFA} < 0.53$ $P(\text{non-HR SBP}/\text{gFA}) < 0.2$; while for gFA values > 0.57 $P(\text{non-HR SBP}/\text{gFA}) > 0.8$.

For fMRI mPFC-NAc correlation coefficient (mPFC-NAc r), ROC D is 0.8 for predicting high-risk SBP. Bayesian prediction curve is unimodal: for correlation coefficients > 0.3 $P(\text{non-HR SBP}/\text{mPFC-NAc r}) < 0.35$; while for values < -0.1 $P(\text{non-HR SBP}/\text{mPFC-NAc r}) > 0.9$.

For fMRI mPFC/somatosensory link ratio (mPFC-S1 LR) ROC D is 0.78 for predicting high-risk SBP. Bayesian prediction curve is unimodal but only predictive for high values: for $\text{LR} > 1.2$ $P(\text{non-HR SBP}/\text{mPFC-S1 LR}) < 0.1$; while for LR values < 0.7 $P(\text{non-HR SBP}/\text{mPFC-S1 LR}) = 0.6$.

For all unspecified values we assign a $P=0.5$.

Best prediction of non-HR SBP would be $(1-0.7)*(1-0.8)*(1-0.9)*(1-0.6)=0.0024$

Participants with P-values < 0.05 are designated non-HR SBP. The model is slightly inflated, as these parameters are not fully independent of each other. However, the procedure provides with a robust decision making algorithm, where specificity of non-HR SBP participants is emphasized.

We assess performance of this classification based on the 69 SBP participants where we know their classification as persisting (=high-risk) or recovering (=non-high risk) SBP at 6 months from entry into the study. In this data set, the model shows that only 26% are assessed as non-HR SBP, which is 65% of recovering SBP (% with high specificity) and only 7% of persisting SBP (% false). Thus, we expect $>90\%$ of those classified as non-HR SBP to recover from back pain without treatment. More importantly, we expect to exclude only 26% of SBP from entering into the clinical trial.

Table below is an excel sheet that calculates and classifies SBP into non-HR SBP. Data are shown for 5 participants.

Non-High Risk SBP Classifier

Amyg	MPFC - NAC	FA	link ratio	P(nonHR amyg)	P(non HR mPFC- Nac)	P(nonHR FA)	P(nonHR link ratio)	total 1-p	non HR SBP
1787	0.100659 0.072483	0.568133	0.507062392	0.7	0.5	0.5	0.6	0.03	1
1453	2	0.574221	0.331351597	0.5	0.5	0.8	0.6	0.02 0.06	1
1189	0.136514 0.095017	0.535257	0.459744165	0.35	0.5	0.5	0.6	5	0
1648	7	0.548217	0.405086864	0.7	0.5	0.5	0.6	0.03	1
1235	0.132299	0.546297	0.699325003	0.5	0.5	0.5	0.6	0.05	0

It is important and clinically highly significant to validate this model as for the first time it provides a means of identifying back pain patients that do not need treatment. The latter can be achieved by simply following the non-HR SBP that were not included in the treatment trial. Therefore, we would like to add this as another secondary aim of the study.

References:

Baliki MN, Petre B, Torbey S, Herrmann KM, Huang L, Schnitzer TJ, Fields HL, Apkarian AV (2012) Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature neuroscience* 15:1117-1119.

Baria AT, Mansour A, Huang L, Baliki MN, Cecchi GA, Mesulam MM, Apkarian AV (2013) Linking human brain local activity fluctuations to structural and functional network architectures. *NeuroImage* 73:144-155.

Huang L, Wang X, Baliki MN, Wang L, Apkarian AV, Parrish TB (2012) Reproducibility of Structural, Resting-State BOLD and DTI Data between Identical Scanners. *PLoS one* 7:e47684.

Mansour AR, Baliki MN, Huang L, Torbey S, Herrmann KM, Schnitzer TJ, Apkarian AV (2013) Brain white matter structural properties predict transition to chronic pain. *Pain* 154:2160-2168.

APPENDIX G: CASE REPORT FORM FOR PHENOTYPING

The following document is a case report form used to phenotype participants into high-risk and not high-risk SBP groups. (Double-click to open)

Effect of L-Dopa in the Transition from SBP to Chronic Pain
 Subject ID: _____ Subject Initials: _____ Date: _____

Parameter	Value	Range	P	P _{obs}
1 Amyg (mm ³) ¹		>500 to <1200	0.35	
		1200-1600	0.50	
		>1600	0.70	
2 gFA ²		<0.53	0.20	
		0.53-0.57	0.50	
		>0.57	0.80	
3 mPFC-NAc r ³		<-0.10	0.90	
		-0.1-0.3	0.50	
		>0.30	0.35	
4 mPFC-S1 LR ⁴		<0.7	0.60	
		0.7-1.20	0.50	
		>1.20	0.10	

Risk:

p = [P _{1,obs}][P _{2,obs}][P _{3,obs}][P _{4,obs}]	≥ 0.05	not high-risk SBP
	< 0.05	high-risk SBP

¹ Amygdala Volume
² Group Fractional Anisotropy
³ mPFC-NAc correlation coefficient
⁴ mPFC-S1 Link ratio

Signature: _____ Date: _____

