Official Title: Effect of Opioid Taper on Pain Responses in Patients with Chronic Pain

NCT#: 03912298

Date: September 25, 2018

Protocol Details

Basic Info

Confirmation Number:	**chdehdci**
Protocol Number:	**831447**
Created By:	**PENA, JUAN S**
Principal Investigator:	**COMPTON, MARGARET A**
Protocol Title:	**Effect of Opioid Taper on Pain Responses in Patients with Chronic Pain**
Short Title:	**Opioid Taper in Chronic Pain**
Protocol Description:	**The purpose of this study is to determine the effect of opioid taper on pain sensitivity in patients with chronic pain. In a well-characterized sample of men and women with chronic neuropathic pain on high-dose opioid therapy, experimental pain responses (cold-pressor, quantitative sensory testing) will be serially described over the course of and following an individualized opioid taper. In addition, functional improvements and subject-level predictors of response will be described.**
Submission Type:	**Biomedical Research**
Application Type:	**EXPEDITED Category 4**

Resubmission*
Yes

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Training Expiration Date:	**09/21/2020**
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

Disclosure of Significant Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?
No

Penn Intellectual Property*
To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?
No

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Biomedical Research

Clinical Trial*
Is this a clinical trial?
No

Investigator Initiated Trial*
Is this an investigator initiated trial?
Yes

If Yes, please be aware that the investigator may be required to create and manage a record of this trial in https://clinicaltrials.gov.

Drugs or Devices*
Does this research study involve Drugs or Devices?
No

IND Exemption

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https://www.med.upenn.edu/pennmanual/secure/investigational-product-management-at-sites-not-using-investigational-drug-services-(ids).html Please check the box Yes if you have reviewed the guidance.
Yes

Research Device Management*
Please indicate how research device(s) will be managed.
Not Applicable (no investigational devices)

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed.
Not Applicable (no drugs, herbal products or other chemical entities)

Radiation Exposure*
Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?
No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects?
No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)?
Yes

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?
No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?
No

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
No

Cancer Related research not being conducted by an NCI cooperative group*
Does this protocol involve cancer-related studies in any of the following categories?
No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?
Yes

If the answer is YES, indicate which items is is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

CTRC Resources*
Does the research involve CTRC resources?
No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System?
No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?
No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for

research purposes?
No

Trial in Radiation Oncology
Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?
N/A

Study in Radiation Oncology
Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?
N/A

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures*, whether considered routine care or strictly for research purposes?
No

Primary Focus*
Sociobehavioral (i.e. observational or interventional)

Protocol Interventions

	Sociobehavioral (i.e. cognitive or behavioral therapy)
	Drug
	Device - therapeutic
	Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
	Surgical
x	**Diagnostic test/procedure (research-related diagnostic test or procedure)**
	Obtaining human tissue for basic research or biospecimen bank
x	**Survey instrument**
	None of the above

The following documents are currently attached to this item:

There are no documents attached for this item.

Sponsors

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Department budget code

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Funding Sponsors

Name:	**NATIONAL INSTITUTE ON DRUG ABUSE/NIH/DHHS**
Type:	**UPENN Federal**

Funding sponsors billing address
If you have selected a commercial or industry sponsor, please provide the appropriate address and contact information for the Sponsor for the purposes of billing for IRB review fees (initial review, continuing review and convened modification fees apply here). If the Sponsor is not industry/ commercial, this information is not necessary to provide with your application.

Funding sponsors gift
Is this research being funded by a philanthropic gift?
No

Regulatory Sponsor

IND Sponsor

none

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Industry Sponsor

None

Project Funding*
Is this project funded by or associated with a grant or contract?
Pending

Sponsor Funding
Is this study funded by an industry sponsor?
No

Status of contract

The following documents are currently attached to this item:

Grant Application (comptonr21_egrant.pdf)

Multi-Site Research

Other Sites

No other sites

Management of Information for Multi-Center Research

The following documents are currently attached to this item:

There are no documents attached for this item.

Protocol

Abstract
The US is in the midst of an epidemic of prescription drug abuse. According to the CDC, of the 52,404 opioid overdose deaths that occurred in 2015, almost 25% involved a prescription opioid, a number that has quadrupled since 1999. This public health crisis was fueled by well-intended efforts to better treat chronic pain, however, the use of opioids for ongoing pain is not an evidence-based intervention. In fact, outcomes are often poorer for patients on opioids, with counterintuitive improvements appreciated when opioids are tapered. An oft-cited but untested explanation for this finding is opioid-induced hyperalgesia (OIH), or increased pain sensitivity secondary to ongoing opioid use. Unknown is the degree to which OIH contributes to the pain experience or how opioid taper might improve pain sensitivity. Proposed is an observational pilot designed to measure the effect of opioid taper on pain perception in patients with chronic pain. In a well-characterized sample of pain patients on high-dose opioid therapy, we will examine responses to experimental pain (cold-pressor, quantitative sensory) during a prescribed opioid taper. Responses will be measured at weekly intervals over the course of the taper, followed by monthly intervals up to 12months. In addition to characterizing pain perception over time, functional outcomes and variables related to the patient, chronic pain condition, and opioid therapy will be evaluated. It is anticipated that study findings will explicate the role opioid therapy plays in the pain experience of chronic pain patients, thereby providing evidence-based guidance for treatment.

Objectives

Overall objectives
The overall Specific Aim of this proposal is to determine the effect of opioid taper on pain sensitivity in patients with chronic pain. Specifically, in a well-characterized sample of men and women with chronic neuropathic pain and receiving high-dose opioid therapy (200mg morphine equivalents/day [MED]), experimental pain responses will be serially described over the course of an individualized opioid taper to a safer dose of 90mg MED for up to 12 months. Changes will be inspected within-subject over time, and pain perception will be measured with two valid and reliable experimental pain induction techniques commonly used to measure OIH (cold-pressor, quantitative sensory testing); in addition, related functional improvements and subject-level predictors of response will be described. Hypothesis 1. Subjects undergoing opioid taper will have improved pain responses over time compared to within-subject baseline as measured by cold-pressor and quantitative sensory pain testing. Hypothesis 2. Improvements in experimental pain responses will be positively related to improved functional outcomes compared to within-subject baseline as measured by the PROMIS physical, mental and social health measures. Hypothesis 3. Degree of improvement in experimental pain responses related to opioid taper will be predicted by demographic, pain, and opioid use history characteristics of the subject. Data showing that pain perception improves as opioids are withdrawn would provide an evidence-based, mechanistic rationale for opioid taper in patients with chronic pain and have the potential to support a sea-change in opioid prescription practices. In that ongoing opioid therapy brings with it significant health risks for the patient and the community, it is critical that empirical evidence of its efficacy be demonstrated to balance the benefits with the risks of adverse events, potential misuse and abuse, and patient safety.

Primary outcome variable(s)
The primary dependent variable, pain perception, will be measured using two highly reliable and valid pain induction techniques, the cold-pressor test (CPT) and quantitative sensory testing (QST), employing procedures consistent with those described in the literature. Order of pain testing will vary, and three aspects of the pain response will be captured at each study session: evoked pain; temporal summation; and conditioned pain modulation, which map on to the hypothesized peripheral, spinal and supra-spinal mechanisms of OIH.

Secondary outcome variable(s)
Concurrent with pain testing, the presence of opioid withdrawal symptoms using the well-validated clinical opiate withdrawal scale (COWS) will be assessed. Although prescribed analgesics will not be introduced during the taper, the concurrent use of over-the-counter (OTC) analgesics will be recorded. In addition, urine toxicology is collected to ensure that subjects are taking only their prescribed opioid at each pain data collection session. To account for the effects of disease progression and increased physical activity on pain responses, the study physician will evaluate subjects monthly for evidence of

disease progression, and each will be asked to complete a weekly Stanford Physical Activity Scale. To evaluate if opioid taper improves functional outcomes vis-a-vis improved pain responses, the PROMIS (Patient-Reported Outcomes Measurement Information System) person-centered measures will be utilized (http://www.healthmeasures.net/explore-measurement-systems/promis). Specifically, functional and quality of life indicators from the physical health (pain intensity, pain interference, physical function), mental health (life satisfaction), and social health (ability to participate in social roles and activities) PROMIS domains will be collected on a monthly basis and inspected for change in relationship to changes in experimental pain assay performance. Completion of monthly PROMIS measures is standard-of-care at the Penn Pain Medicine Center, so presents no additional burden to study participation.

Background

Prescription Opioid Abuse Epidemic The United States is in the midst of a growing and dangerous epidemic of prescription drug abuse. Of the 1 in 3 Americans who used a prescription opioid in 2015, 11.3 million reported misusing the medication(37) with 1.9 million meeting diagnostic criteria for opioid use disorder (OUD).(38) The Centers for Disease Control and Prevention (CDC)(39) reported that 44 people in the U.S. die from overdose of prescription opioids daily, a number which has nearly quadrupled since 1999.(40) Further, the rapid rise of heroin and illicit fentanyl overdose in US has been tied to prescription opioid abuse; 45% of people who use heroin were also addicted to prescription opioid analgesics.(40,41) This public health crisis has been fueled in part by the large supply of opioids being prescribed in our communities. The quantity of prescription opioid analgesics sold to pharmacies, hospitals, and doctors offices was 4 times greater in 2010 than in 1999(39), and in 2016, clinicians wrote an estimated 215 million prescriptions for opioid analgesics.(42) Critical to addressing problematic prescribing practices is the development of safe and evidence-based practice guidelines for the use of opioids in the treatment of chronic pain. Need for Evidence-based Opioid Prescribing In 2016, the CDC released the Guideline for Prescribing Opioids for Chronic Pain(32), which targeted opioid analgesic prescribing practices as an important means to reduce prescription opioid abuse, OUD, and overdose deaths. Although the guideline included strategies to decrease risk, evidence to support the efficacy of the CDC recommendations is lacking.(20) It reflects concern at the federal level that healthcare providers are overprescribing these medications, particularly for chronic pain. In fact, it is currently estimated that between 5-8 million Americans use opioids on a daily basis for chronic pain relief(20), with a recent analysis showing that over half of all opioid prescriptions written in the VA system are for veterans with chronic pain.(43) Yet, opioid therapy for chronic pain is not an evidence-based intervention. In a recent review, Von Korff(44) argues that outcomes are actually poorer for chronic pain patients on opioid therapy in comparison to those not taking opioids on multiple indicators including functional status, quality of life, return to work, and self-reported disability.(45-47) Recent NIH reviews conclude that evidence for long-term benefits with daily opioid use is limited.(33,48,49) These analyses have prompted renewed calls for tapering patients off opioid therapy(36,50,51), citing reports of decreased pain, improved function and better quality of life.(21,22,51-58) Potential Benefit of Opioid Taper Reduction of Opioid-induced Hyperalgesia (OIH)? There are multiple mechanisms by which opioid taper might improve chronic pain outcomes. A theorized contributor to poor pain relief in this population is the presence of opioid-induced hyperalgesia (OIH)(25,26), defined as a counterintuitive increased sensitivity to pain related to ongoing opioid use.(59,60) Best described in samples of opioid abusers, cross-sectional data suggest a large effect size, indicating that opioid-dependent subjects are 42%76% less tolerant of experimental pain than are matched controls.(29-31,61-63) Cross-sectional data suggest the presence of OIH in chronic pain patients, showing those on opioids to have poor tolerance for experimental heat, cold and pressure pain.(2-11) Assuming a causal relationship between opioids and hyperalgesia, it is hypothesized that tapering opioids would diminish OIH and thereby improve pain responses in patients with chronic pain. Group comparisons reveal that detoxified opioid addicts are more tolerant of experimental pain than those on opioid maintenance therapy(61-65), and with respect to patients with pain, case studies of those with chronic (66,67) or cancer(68-73) pain show significant pain improvement within hours of opioid dose reduction. Conversely, decreased tolerance to experimental thermal pain has been demonstrated in prospective studies of patients with chronic pain following 1-6 months of opioid therapy.(74-76) Characterization of Effect of Opioid-taper on Pain and Function Thus, although there is evidence that patients do better following opioid taper, the degree to which improvements are due to resolution of OIH is unclear. The findings described above suggest that a clearer description of the effect of opioid taper on pain perception is needed, including description of relationship to functional outcomes and identification of subject-level predictors. Relationship to functional outcomes. As noted, accumulating evidence suggests that chronic pain, function and quality of life improve as patients successfully taper their

opioid dose. (21,22,51-58) The degree to which these improvements may be attributed to decreases in perceived pain severity or increases in pain tolerance are unknown. Empirically describing the relationship between pain perception as measured by the standardized CPT and QST assays and functional outcomes can enable prediction of degree of functional improvement to be appreciated as opioid dose is tapered. Predictors of opioid-taper pain responses. To identify chronic pain patients likely to benefit from opioid taper, the role of mediating and moderating variables on outcomes requires description. Predictors for the development of OIH include factors associated with (a) the patient (age, gender, ethnicity)(4,6,9,77-79), (b) the chronic pain condition (duration, severity)(7,8,80,81), and (c) opioid use history, including dose(3,6,9-11,57,82), potency(30), and duration of treatment.(3,5,9,82) Determining the role of these predictors will support guidelines on determination of which patients may benefit from opioid taper. REFERENCES 1. Dowell D, Haegerich TM. Changing the Conversation About Opioid Tapering. Ann Intern Med. 2017 Aug 1;167(3):208-209. doi: 10.7326/M17-1402. 2. Peles E, Schreiber S, Hetzroni T, Adelson M, Defrin R. The differential effect of methadone dose and of chronic pain on pain perception of former heroin addicts receiving methadone maintenance treatment. J Pain. 2011 Jan;12(1):41-50. doi: 10.1016/j.jpain.2010.04.009 3. Wang H, Fischer C, Chen G, Weinsheimer N, Gantz S, Schiltenwolf M. 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Study Design

Phase*
Not applicable

Design
A prospective time-series survey design will be utilized to measure the experimental (CPT and QST) pain responses of chronic pain patients on high-dose opioid therapy (200mg MED) prior to and then regularly during and following a voluntary opioid taper. Data will be collected weekly during the active taper period; once the subject has reached a stable maintenance dose (90 MED), assessments will occur monthly until month 12. Because our previous work has shown stability in pain responses in patients on

high-dose opioid therapy over time (6 months), and the clinical imperative of tapering patients to safer doses, a control group of patients maintained on high-dose therapy is not included. Consistent with expert opinion in the field, a longitudinal within-subject design is planned.

Study duration
The overall duration of the study is two years, during which time all subjects will be enrolled and complete the study. Data will be collected weekly during the active taper period; once the subject has reached a stable maintenance dose (less than or equal to 90 MED), assessments will occur monthly until month 12. If funded, the study would begin Oct 1, 2018.

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.
The study will be staff by a 55% FTE Project Director assisted by two part time graduate student research assistants (10hr/week) who will assist with pain testing and data collection. The project director is well-trained and experienced in all study procedures and human subjects research; with the PI, he will ensure the research assistants are trained and qualified to conduct research. Weekly research meetings between the investigators and study staff will occur to ensure staff are adequately informed about the protocol and their research-related duties. The PI has her own locking office space (Claire Fagin Hall 402, approximately 170 square feet). All faculty offices come equipped with locked filing cabinets, bookshelves, desk, minimum 4 GHz computer with HP printer, Windows XP service pack 3 operating system, Microsoft Office Professional (Word, Excel, PowerPoint, Access), SPSS or SAS statistical analysis software, and e-mail and internet access. With the same resources, an adjacent cubicle space is dedicated to the study research assistant. NHS copier, printer, fax and scanner facilities are available on each floor. Research visits will take place in a private office at the U Penn Pain Medicine clinic.The Penn Pain Medicine Center currently has eight clinical exam rooms, 7 administrative offices (office manager, physician, fellow, and resident offices), 5 support staff offices (2 billing/new patient coordinator, surgical coordinator, and research coordinator offices). There is a large clinical research area which houses the office of the clinical research coordinator along with 3 bays/ exam locations for research patients. Study sessions will occur one of several small (10 ft x 15 ft) private examination rooms located onsite, complete with examining table, chair, bedside stand, desk, computer, and sink.

Characteristics of the Study Population

Target population
The sample will consist of 25 male and female adults with chronic neuropathic pain on opioid therapy and preparing to voluntarily undergo a prescribed opioid taper.

Subjects enrolled by Penn Researchers
25

Subjects enrolled by Collaborating Researchers
0

Accrual
Participants will be recruited from those treated at the large and nationally-renowned Penn Pain Medicine Center at the University of Pennsylvania Penn Medicine Neuroscience Center. The Penn Pain Medicine Center provides interdisciplinary, multimodal pain care to over 12,000 outpatients annually, an estimated 20% of whom are taking opioids on a regular basis. At any one point in time an estimated 50 patients are undergoing opioid taper, up to half of whom are tapered from opioid doses greater or equal to 200mg MED. Due to anticipated rates of dropout, 25% oversampling for these individuals is planned. Results from previous studies have demonstrated moderate to large effect size estimates of opioids on cold-pressor and QST experimental pain responses. Based on these estimates, a sample size

of 25 will have over 99% power to detect differences in outcome. Using an alpha of 0.05/4 (Bonferroni correction) to account for multiple outcomes, we will have over 90% power to detect significant changes at the 0.01 level for all of the outcomes. Cross-sectional and prospective studies demonstrate statistically significant differences in experimental pain responses with changes between 80-90mg MED (10,11,70); since MED decreases in the proposed work will be 110 MED (tapers from 200MED to 90MED), we anticipate having no difficulty discerning taper effects on pain responses.

Key inclusion criteria
(1) between ages of 21-60; (2) documented chronic neuropathic non-malignant pain condition of at least one year duration; (3) on 200mg MED for at least 6 months; (4) have fully engaged in all prescribed non-opioid pain management treatments; (5) willing to undergo prescribed opioid taper; (6) otherwise in good physical and mental health, or in the care of a physician who is willing to take responsibility for such treatment; and (7) able to understand the purpose and instructions of the study, and provide informed consent as approved by the University of Pennsylvania IRB.

Key exclusion criteria
(1) meet diagnostic criteria for an active substance use disorder other than nicotine; (2) be acutely psychotic, severely depressed, and/or in need of inpatient psychiatric treatment, (3) have a neurological or psychiatric illness that would affect pain responses, including anxiety disorders; or (4) have a history of heart disease, stroke, or a pacemaker or uncontrolled high blood pressure. Good cardiovascular health is stipulated to ensure subjects can tolerate the sympathetic nervous system responses associated with the pain induction procedures.

Vulnerable Populations

	Children Form
	Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form
	Fetuses and/or Neonates Form
	Prisoners Form
	Other
x	**None of the above populations are included in the research study**

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
In the event that Penn students or employees present for screening, they will be informed that their decision regarding whether or not to participate will in no way impact their standing at the university.

Subject recruitment
IRB-approved flyers will be made available and posted at the Penn Pain Medicine Center, and treatment clinicians trained to identify potential subjects for study participation. Patients who indicate interest in study participation will meet with the trained RA for screening; if meeting all inclusion and no exclusion criteria, informed consent, using an IRB-approved consent form will be obtained by the study physician in a private room at the Center.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
No

The following documents are currently attached to this item:

Subject recruitment (recruitmentflyertaperstudy7.23.18sp.pdf)

Subject compensation*
Will subjects be financially compensated for their participation?
Yes

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Subjects will be compensated $25 for each completed study visit, and receive this payment in the form of a gift card. Because each subject's taper schedule is individualized, the exact number of visits will vary among subjects, but it is anticipated that subjects will have between 30 to 40 study visits, thus may earn between $750 - $1000 over the course of the year-long study.

Study Procedures

Suicidal Ideation and Behavior
Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?
No

Procedures
Standard of Care: In light of the demonstrated health risks associated with daily opioid doses greater than 90mg MED, current practice at the Penn Pain Medicine Center is to taper all chronic pain patients down to or below this MED and to stabilize on the lowest effective dose as agreed upon by the patient and prescriber. The actual rate of taper varies with tolerability and availability of dosages of opioid, but averages 10-15% decrease/month. Final stabilization dose also varies between patients but the goal to achieve a daily dose of 90mg MED. Prior to attempting taper, an adequate trial of all non-opioid and non-pharmacologic interventions are provided so that the patients chronic pain is under maximal control. Research Purposes: Baseline Study Session: Study data collection will begin immediately following consent, with the collection of urine toxicology, chronic pain and opioid use history, and baseline pain testing (see attached Data Collection Schedule). It is expected that it will take 30min to complete the baseline measures and another 30min to perform the pain testing battery, totaling 60min for the first session; subsequent sessions should last no longer than 30min. Study Sessions. All data collection will take place in a private office located in the Penn Pain Medicine Center, with sessions scheduled within 3hrs of morning opioid dose, and subjects instructed to ingest no caffeine or nicotine for 1hr prior to each session. Concurrent medication use since last visit, and last menstrual period date for female participants will be documented. A withdrawal score and urine sample for toxicology will be collected immediately prior to pain testing to verify compliance with opioid treatment. Sessions will be scheduled to coincide with regular clinic visits as possible. All study data will be collected using REDCap (Research Electronic Data Capture), utilizing PhenX data collection tools as available. Pain Responses: The primary dependent variable, pain, will be measured using two highly reliable and valid pain induction techniques, the CPT and QST, employing procedures consistent with those described in the literature. Order of pain testing will vary, and three aspects of the pain response will be captured at each study session: evoked pain; temporal summation; and conditioned pain modulation, which map on to the hypothesized peripheral, spinal and supra-spinal mechanisms of OIH. Protocols for each assay have been uploaded. Evoked pain perception: The CPT apparatus consists of a circulating water bath maintained at 1°C ± 0.5°C, into which subjects immerse their dominant hand and forearm to elicit a nociceptive response. Elapsed time until pain threshold and tolerance are reached measures evoked pain. A stopwatch is simultaneously activated with arm immersion, and subjects instructed to indicate when the cold sensation becomes a painful sensation (pain threshold), and when the pain becomes subjectively intolerable or spontaneous hand removal (pain tolerance). Immediately after hand withdrawal, subjects are asked to mark maximal pain intensity on a computerized visual analogue scale (Co-VAS, 0-100). Temporal Summation (TS): As a component of QST, a thermal testing analyzer (TSA; Medoc TSA-2001 device) with a sized 30 x 30 mm Peltier thermode, is used for the assessment

of thermal temporal summation (TS), reflecting increased rate of firing of ascending pre-synaptic neuron with ongoing stimulation. Specifically, tonic noxious heat stimulation will be applied to the dominant volar using a ramp-and-hold method. The baseline temperature will be set to 32.0°C and will be increased at a rate of 1°C/s up to a destination temperature of 46.5°C and then will remain constant for 120 sec. Along the entire test duration (a total duration of 135 seconds), subjects continuously will rate the magnitude of their perceived pain using a computerized visual analogue scale (Co-VAS, 0-100). Conditioned Pain Modulation (CPM): Again using QST apparatus, the TSA thermode is applied to the thenar eminence of the dominant hand, and subjects asked to verbally report pain intensity of five (5) heat pain stimuli of 47ºC (starting from 37ºC at an increasing and decreasing rate of 10ºC/s), each lasting 3 seconds with an interval of 12 seconds. Following these baseline measures, subjects are instructed to report the intensity of the same heat pain stimuli with their non-dominant hand immersed in a cold-water bath (12ºC) at 15 and 30 seconds of immersion. Finally, subjects are instructed to remove their hand from the cold water bath, and rate severity of two additional heat pain stimuli administered at 15 and 30 seconds. Comparison of perceived pain severity with and without counter-stimulation (heat pain, ice bath) provides evidence of supra-spinal modulation of pain responses. Concurrent with pain testing, the presence of opioid withdrawal symptoms using the well-validated clinical opiate withdrawal scale (COWS) (94,95) will be assessed. Although prescribed analgesics will not be introduced during the taper, the concurrent use of over-the-counter (OTC) analgesics will be recorded. In addition, urine toxicology is collected to ensure that subjects are taking only their prescribed opioid at each pain data collection session. To account for the effects of disease progression and increased physical activity on pain responses, the study physician will evaluate subjects monthly for evidence of disease progression, and each will be asked to complete a weekly Stanford Physical Activity Scale.(96) Functional Outcomes. To evaluate if opioid taper improves functional outcomes vis-à-vis improved pain responses, the PROMIS® (Patient-Reported Outcomes Measurement Information System) person-centered measures will be utilized (http://www.healthmeasures.net/explore-measurement-systems/promis).(97) Specifically, functional and quality of life indicators from the physical health (pain intensity, pain interference, physical function), mental health (life satisfaction), and social health (ability to participate in social roles and activities) PROMIS domains will be collected on a monthly basis and inspected for change in relationship to changes in experimental pain assay performance. Completion of monthly PROMIS measures is standard-of-care at the Penn Pain Medicine Center, so presents no additional burden to study participation. Predictor Variables. Demographic characteristics of the patient (age, ethnicity, gender), pain severity and chronicity, and a detailed opioid use history will be collected at baseline. The opioid use history assessment will assess the estimated no. months dependent on opioids, MED, and types/potency of opioids predominantly used at admission. Data will be gathered via patient self-report and extracted from the EMR.

The following documents are currently attached to this item:

Procedures (datacollectionschedule.docx)

Procedures (appacoldpressortestinginstructionsandscript.docx)

Procedures (appbquantitativesensorytestinginstructionsandscript.docx)

Deception
Does your project use deception?
No

International Research
Are you conducting research outside of the United States?
No

Analysis Plan
Preliminary Analyses. Preliminary analyses will include generating descriptive statistics for all baseline measures to characterize the sample, including measures of central tendency and variation for continuous variables; for dichotomous/categorical variables, measures will include frequencies and percentages. Distributional properties will be examined to determine if variance stabilizing or normalizing transformations are required. Non-inferential interim analyses will be performed to ensure data collection and archiving procedures are operating correctly. Outliers will be assessed by visual inspection and checked for accuracy. Normality will be assessed using Shapiro-Wilk tests; should violations emerge (i.e., cold-pressor data are anticipated to be bimodal), transformations or non-parametric tests will be used. Due to known differences in pain responses between men and women, sex

as a biological variable will considered in all analyses. Statistical Analyses. The effect of opioid taper on changes in pain responses (CPT, QST), and functional outcomes (PROMIS domains) over time will be examined using longitudinal mixed-effects regression modeling, using general linear regression modeling with regularization as a function of baseline dose, end dose, and taper rate. These longitudinal profiles will be examined using a linear mixed effects framework with SAS Proc Mixed in which all available data collected during follow-up are used. Mixed models can account for the correlation between repeated measures and handle non-excessive missing data better than traditional models and allow for use of time-independent and time-dependent covariates. To assess patterns of attrition over time, a comparison of withdrawal rates and time to withdrawal will be included. Separate mixed effects regression models will be generated for each of the continuous outcome measures of interest (pain responses, functional outcomes). Random slopes and intercepts will be modeled to represent the participant-level deviation from the fixed-effect slope over time and intercept, respectively. Restricted maximum likelihood estimation will be used and the most appropriate covariance structure examined. Scores will be analyzed as repeated observations of the dependent variable, with mean-centered baseline outcome scores serving as a covariate. Other predictor variables will include baseline demographic characteristics of the patient, severity and chronicity of pain suffered, and opioid use history. Baseline measures will be analyzed as time-independent covariates. The Akaike information criterion will be used to evaluate overall model fit and to select the best-fitting longitudinal change pattern. .

The following documents are currently attached to this item:

There are no documents attached for this item.

Data confidentiality

- x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
- x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**
- x **Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**
- x **Wherever feasible, identifiers will be removed from study-related information.**

A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality
All records will be kept strictly confidential. No one except the researchers will know the subjects are in a research study. Data forms for the collection of health and study data will be coded with each subjects unique identification number. No data form will identify the participants by name. Hardcopies of data forms will be kept in locked files with keys held only by the study investigator. No presentation or publication of the results of this study will refer to the individual participants or present information that would identify any participant. All persons working on the proposed work will have completed HIPAA training and the Collaborative Institutional Training Initiative (CITI) Basic Courses in the Protection of Human Research Subjects and Biomedical Focus Responsible Conduct of Research (RCR) modules.

Sensitive Research Information*
Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?

No

Subject Privacy
Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).
Privacy will be strictly maintained in all aspects of participation. Screening and testing sessions will take place in private rooms at the U Penn Pain Medicine Clinic where strict patient privacy is enforced and all staff are HIPAA certified.

Data Disclosure
Will the data be disclosed to anyone who is not listed under Personnel?
Study data will not be disclosed to anyone who is not listed under Study Personnel.

*Data Protection**

- x **Name**
- x **Street address, city, county, precinct, zip code, and equivalent geocodes**
- x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**
- x **Telephone and fax number**
- **Electronic mail addresses**
- x **Social security numbers**
- x **Medical record numbers**
- **Health plan ID numbers**
- **Account numbers**
- **Certificate/license numbers**
- **Vehicle identifiers and serial numbers, including license plate numbers**
- **Device identifiers/serial numbers**
- **Web addresses (URLs)**
- **Internet IP addresses**
- **Biometric identifiers, incl. finger and voice prints**
- **Full face photographic images and any comparable images**
- **Any other unique identifying number, characteristic, or code**
- **None**

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
No

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
No

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
No

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
No

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
Not applicable

Consent

1. Consent Process

Overview
After expressing interest in the study to the co-investigator study physician, the project manager will meet with the prospective participant in a private office to review the consent document as well as provide an oral explanation of the study. Individuals will be given a chance to ask questions before making a considered decision about whether or not to participate in the study. Via the consent process, prospective subjects will be reminded that their participation in this study is entirely voluntary, and that they should carefully read the information in the consent, and ask questions about anything not understood, before deciding whether or not to participate. It will be emphasized that they have the right to refuse to participate in this study, and if they choose not to participate, it will not affect their relationship with the University and their right to health care or other services otherwise entitled. Prospective subjects will also be informed that if they decide to participate, they are free to withdraw consent and discontinue participation at any time without prejudice to future care at the University of Pennsylvania. As stipulated in the consent form, subjects may withdraw consent at any time and discontinue participation without penalty. No legal claims, rights or remedies are waived as a result of their participation in this research study. Consent will be obtained by the study physician.

Children and Adolescents
Not applicable

Adult Subjects Not Competent to Give Consent
Not applicable

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
No Waiver Requested

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects

Written Statement of Research*
No

If no written statement will be provided, please provide justificiation

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks
Cold-Pressor Pain Induction (CP): As it will induce acute pain, the cold-pressor (CP) procedure will cause the subject discomfort. Subjects will be assured via the consent process that they may discontinue their study participation at any time if they decide not to undergo the painful experience. The PI has performed these pain induction techniques on close to 200 subjects in past research endeavors without a single adverse event. Throughout the pain procedures, vital signs will be continuously monitored and staff available to communicate any discomforts they may experience. Potential CP risks to the subjects are minimal; injury including tissue damage is unlikely as exposure time is to be short (5min); the subject can remove the hand from the ice water should it become subjectively intolerable and all trials will be truncated at 300 seconds. No adverse effects have been reported with the CP pain induction technique in over 75 years of published research. Quantitative sensory testing Pain Induction (QST): Like the cold-pressor procedure, the QST is designed to induce acute pain, thus will cause the subject discomfort. Subjects will be assured via the consent process that they may discontinue their study participation at any time if they decide not to undergo the painful experience. Vital signs will be measured before and after the test, and study staff available to communicate any discomforts they may experience. The heat devices are designed not to exceed safe temperatures and have automatic shut-off. Potential risks to the subjects are minimal, which include a burn such as a bad sunburn. These happen very infrequently (1%). Breach of Confidentiality: Participation in this study may constitute a social risk to the participant in that others may learn that he or she takes opioids regularly for chronic pain. Due to the sensitive nature of this information, privacy and confidentiality will be strictly maintained in all aspects of participation. Testing sessions will take place in private rooms where strict privacy is enforced and all research and clinical staff are HIPAA certified.

Potential Study Benefits
The potential benefit for both the participants and broader segments of society is to improve the management of chronic pain so as to improve outcomes in this challenging and growing patient population, including increases in functionality, satisfaction with treatment and quality of life. Better understanding of the pros and cons of opioid therapy for the treatment of chronic pain can guide clinical practice based upon evidence. Participants will be informed that, with the exception of study payment, no direct benefit is expected to accrue to them from participation in the study.

Alternatives to Participation (optional)

Data and Safety Monitoring
The Principal Investigator will have responsibility for monitoring the safety management of this trial, and comply with the reporting requirements. The PI will be responsible for monitoring the data to ensure safety of participants and will closely supervise the research staff by means of regularly scheduled weekly meetings to discuss interactions with the participants. Monitoring meetings will be conducted monthly with the investigative team throughout the study.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment
Participants will be informed that, with the exception of study payment, no direct benefit is expected to accrue to them from participation in the study. Based on the characteristics of the risks associated with study participation, and efforts in place to minimize these risks, the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others. The potential benefit of this study is expected to far outweigh any minimal risk by providing valuable information on the effects of opioid therapy on chronic pain and functionality.

General Attachments

The following documents are currently attached to this item:

Informed consent form (icfopioidtapertrackedchanges9.17.18pc.doc)

Questionnaires (promis-paininterference.pdf)

Questionnaires (cows.pdf)

Questionnaires (lansstool.pdf)

Questionnaires (stanfordexercisequestionnaire.pdf)

Grant Application (comptonr21_egrant.pdf)

Informed consent form (icfopioidtaperfinal.doc)

Additional forms (references.docx)

Recruitment materials (recruitmentflyertaperstudy7.23.18sp.pdf)

Informed consent form (icfopioidtapercleancopy9.17.18pc.doc)

Cover Letter (responsestoirbstipulations9.17.18pc.docx)