Cover Page – Study Protocol

Study: Reduction of Opioid Dose Using Conditioning & Open-Label Placebo (COLP) in Intensive Rehabilitation

NCT: 03906721

Date: 02/07/2020

ORGANIZATION OF DETAILED PROTOCOL

Title: Reduction of Opioid Dose Using Conditioning & Open-Label Placebo (COLP) in patients with Spinal Cord Injury, Polytrauma and Burn Injury

Protocol #: 2017P001673

Date: 02/07/20

BACKGROUND AND SIGNIFICANCE

Summary and overview:

I. Pain and Opioids

The management and control of pain is one of medicine's biggest challenges. Pain can be defined as an unpleasant sensation that can be either acute or chronic and that is a consequence of complex neurochemical processes in the peripheral (PNS) and central nervous system (CNS). Clinicians have regularly battled these processes through the use of pharmacological or non-pharmacological treatments.

Over the past decade, increased attention has been given to the ineffective treatment of pain with the clarion call for physicians to treat pain as the 'fifth vital sign'[1]. The National Institutes of Health Committee on Advancing Pain Research, Care, and Education reported that the incidence of chronic pain is approximately 100 million people in the USA, a number that exceeds that of diabetes, heart disease, and cancer combined [2]; the need for the treatment of pain is high. As a result of the focus on pain management, there has been an increase in the amount of opioid medications prescribed by physicians attempting to treat patients with chronic pain. The increase in opioid supply coupled with public perception that medications prescribed by a physician are 'safe', even for recreational use, has been associated with a shift from the abuse of illicit substances to the widespread misuse of opioid medications [3].

Pain remains a significant problem for many with spinal cord injury (SCI). Recent data from the national Model Spinal Cord Injury Systems indicate a pain prevalence ranging from 81% at 1 year after injury to 82.7% at 25 years [4], usually pain is of difficult control in SCI patients, and opioids are often used as a part of the analgesic treatment protocol, unfortunately, adequate pain relief by opioid treatment comes with adverse effects that diminish quality of life (QOL). Overall, opioid usage in patients hospitalized in the Comprehensive Rehabilitation Program still

is high due to the complexity of their injuries, including polytrauma, burnt and patients with severe injuries, which require appropriate and aggressive pain management. Moreover, these side effects have a detrimental impact for the recovery of these patients. Neuroendocrine down regulation, digestive and addictive issues are part of the negative consequence of opioid treatment that can be prevented by adapting new methods for opioid usage in this population.

A. Placebo

Placebo effects are often considered the effects of an "inert substance," but that characterization is misleading and inaccurate. In a broad sense, placebo effects are improvements in patients' symptoms that are attributable to their participation in the therapeutic encounter, with its rituals, symbols, and interactions. These effects differ from those of discrete therapies and are precipitated by the contextual or environmental cues that surround medical interventions, both those that are fake and lacking in inherent therapeutic power and those with demonstrated efficacy. This diverse collection of signs and behaviors includes identifiable health care paraphernalia and settings, emotional and cognitive engagement with clinicians, empathic and intimate witnessing, and the laying on of hands [5].

A.1. Neurobiology of placebos

Converging evidence substantiates the view that placebo responses are a complex psycho-neurobiological phenomenon that involves the activation of distinct brain areas and peripheral physiology including the release of endogenous substrates such as opioid and non-opioid components (e.g., dopamine, cannabinoids) that mediate placebo analgesia (figure 1).

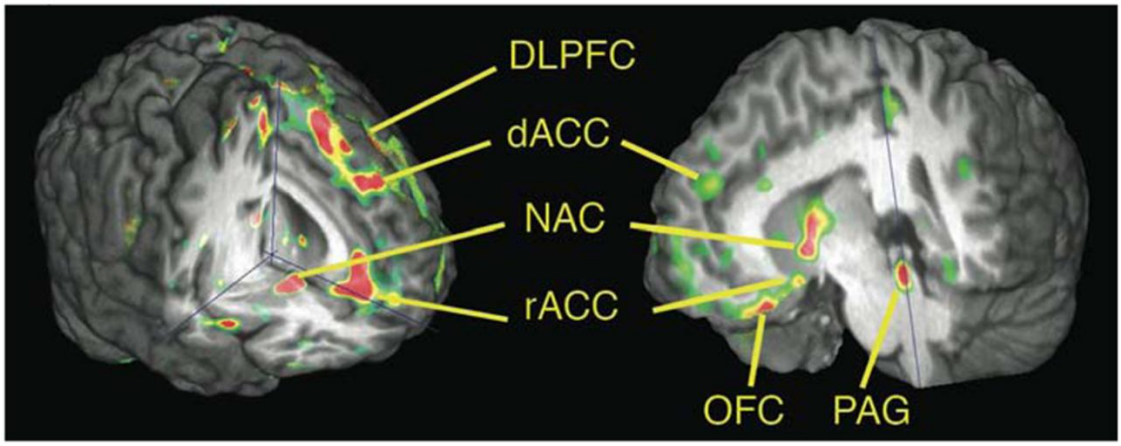

Figure 1. Neural structures involved in placebo effect and endogenous analgesia detected using brain imaging methods. DLPFC, dorsolateral prefrontal cortex; dACC dorsal anterior cingulate cortex; NAC, nucleus accumbens; rACC rostral anterior cingulate cortex; OFC, orbitofrontal cortex; PAG, periaqueductal grey matter.

Pharmacological agents with opioid-like properties exert their effects by interacting with one or more subclasses of the three main opiate receptors; mu (μ), delta (δ), and kappa (κ). In spinally transected dogs, Martin and colleagues demonstrated that opioid agents acted over μ and κ receptors preferentially [6]. Agonist activation of opioid receptors leads to several events which serve to inhibit the activation of the neuron. Mu and delta agonists have been shown to depress cyclic AMP formation. Mu and δ and on occasion κ receptors can induce a membrane hyperpolarization through the activation of an inwardly rectifying potassium channels. In pharmacological induced conditioning, these at membrane events act under a "learning" paradigm, presented in the form of conditioning. Thus, every time the receptor is exposed to the effects of the acting drug in the acquisition phase, it also creates a memory to the association between the unconditioned stimulus (UCS) and the neutral stimulus (NS), this response will be unconditioned, and latter during the evocation phase, the exposure only to the neutral stimulus will evoke a response to the presence of placebo.

Recently there have been several proposals suggesting that combining the principles of pharmacological-induced conditioning and placebo effects could lower the dosage of opioids for patients and still provide the same level of pain relief [7] [8]. One of the strategies proposed for this objective is to combine principles of pharmacological-induced conditioning and open-label placebo effect. These mechanisms are also of differential importance and it seems they are dependent on 1) whether the patient has direct experience with a pharmacologically active

substance treatment during the intervention --"*pharmacological placebo effect*"-- or 2) whether the effect is due to other mechanisms (e.g., expectation, hope, anxiety reduction, responses to the ritual of treatment, emotional support). A pharmacological placebo effect necessarily implies a direct experience with a pharmacologically active substance during the treatment.

A.2. Psychological mechanisms of placebo

The effects of symbols represented by a diverse set of therapies or medical devices, and clinician interactions can dramatically enhance the effectiveness of a placebo. Associative learning (conditioning) and conscious and non-conscious expectancy formation are the two main psychological mechanisms that contribute to the placebo effect [9]. These mechanisms are also of differential importance and it seems they are dependent on two main learning routes. 1) A conditioning or associated learning process whereby whether the patient has direct experience pairing a pharmacologically unconditioned active substance treatment with a conditioned stimulus (like pills or injections) --"*conditioning placebo effect*"-- or 2) whether the effect is due to other psychological mechanisms (e.g., expectation, hope, anxiety reduction, responses to the ritual of treatment, emotional support). Patients responding to placebo or any other particular intervention can often be identified by asking what is expected, therefore, expectations of therapeutic success is postulated as the underlying psychological mechanism in the placebo responder [10].

B. <u>Pharmacological-induced conditioning</u>

Conditioning dose extension capitalizes on classic conditioning mechanisms and differential reinforcement rates of the medication. The reinforcement rate is gradually decreased (i.e. the pharmacological agent is intermittently replaced by a placebo). Therefore, placebo effects can contribute to the pharmacological effects of a drug and help to sustain therapeutic responses [8]. By employing this method, clinicians can manipulate drug dosage in a safe and optimal way, as the binding receptors are being conditioned to respond to a neutral stimulus, so it can evoke a conditioned response (figure 2). Open-label placebo mechanisms is an emergent ethical approach that seeks to elicit placebo effects in patients with honestly prescribe placebos. [11]

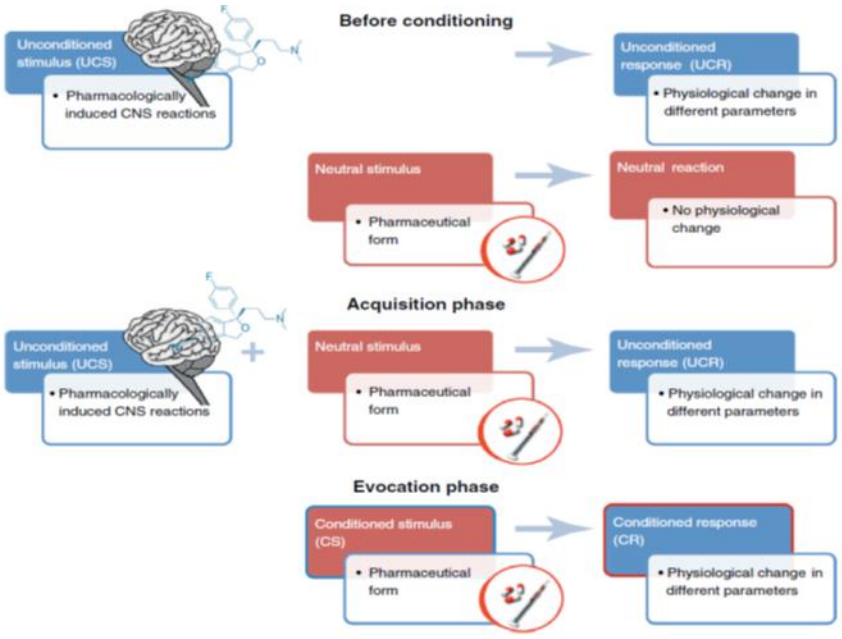

Figure 2. Classic conditioning with pharmacological stimuli. In the acquisition phase, the pharmacological agent is paired with a neutral stimulus, such as the pharmaceutical form. Thus, the pharmaceutical form alone can elicit a conditioned response in the evocation phase. From TRENDS in Pharmacological Sciences

The idea to extend the efficacy of a drug by applying principles of conditioning has been tested previously in animal models; mechanisms of placebo mediated analgesic dose-extension in pain are based on memory-related analgesia response. Using the mice model of the hot-plate test, pharmacological opioid and non-opioid conditioning was obtained. Conditioned cues were paired by presenting the hot-plate stimuli simultaneously with the unconditioned pharmacological agent, either the opioid agonist morphine hydrochloride or non-opioid aspirin and this model was effective to elicit placebo mediated analgesia shaped by the learning experience provided by the presentation of the paired stimuli which proved to conditioned for opioid receptors [12].

Human models for conditioning dose extension have been limited to a handful of small trials, one of the first studies adopting dose-extending placebos explored decrements in peripheral leukocyte counts in 10 patients treated for multiple sclerosis with 4 intravenous cyclophosphamide treatments paired with a conditioned stimulus. Eight of 10 patients showed a decreased peripheral leukocyte count when a placebo was given after cyclophosphamide [13]. Notably, Ader and colleagues demonstrated that placebos given in a context to elicit conditioned responses can be used with corticosteroids in patients to reduce the symptoms of psoriasis [14]. Studies have also

been performed in children with attention deficit hyperactivity disorder [15], and adults with chronic insomnia [16].

B.1 Open Label Placebo (OLP)

The use of placebos in the clinical arena represents an ethical challenge as deception or concealment is usually thought to be necessary; an alternative strategy to harness placebo effects is the use of open-label prescribed placebos, where patients are aware of the placebo or non-active substance and no deception obscures the rationale behind this particular form of intervention. Open-label placebo (OLP) also known as "honest placebo" bypass ethical issues related to using placebo without deception or concealment. OLP involves the presentation of the placebo to the patient and explaining the purpose and possible benefits of this option. A pre-specified script was used where negative connotations related to placebo are decreased. The script offers clear and concise information to the patients on how the placebo effect relies on various neurotransmitters and activation of specific quantifiable and relevant of the brain that release these chemicals (Finnis 2010). (Ballou S, Kaptchuk TJ, Hirsch W, Nee J, Iturrino-Moreda J, Kelly M, Cheng V. Kirsch I, Jacobson E, Conboy L, Lembo A, Davis RB. Open-label vs. double-blind placebo treatment in irritable bowel syndrome: Study Protocol for a randomized controlled trial (2017, in press.) The first such study exploring the use of OLP involved a sample of patients with irritable bowel syndrome (IBS), who were randomized to OLP versus no-treatment control (n=80) [11]. Among OLP patients, 60% reported "adequate relief" of their IBS symptoms versus 37% "adequate relief" in NTC patients. Recently our group of collaborators presented one of the most compelling data favoring the use and application of open placebos. This randomized controlled trial was performed to investigate whether placebo effects in chronic low back pain could be harnessed ethically by adding open-label placebo (OLP) treatment to treatment as usual for 3 weeks (n=83) . The results showed pain reduction on the composite Numeric Rating Scales (30% vs 9% improvement pain and in the disability measurements (29% vs 0%, $p<.001$) with a large effect size [17]. Similarly, a group of researchers from Charite University demonstrated improved symptomatology, in subjects with a small sample allergic rhinitis by using open-placebo [18]. Mechanistic research is just beginning but a recent study suggests that regions that are usually associated with double blind or deceptive placebo responses are involved minus pre-frontal activation. (Schafer SM, Colloca L, Wager TD. Placebo-induced decreases in the neurological pain signature do not always correspond

to pain relief. Abstract 4272. Organization for Human Brain Mapping Conference June 14-18, 2015.)

B.2 A combined model: **Conditioning Open Label Placebo (COLP)**

This proposal is, to our knowledge, the first to propose a conditioning open-label placebo paradigm (COLP) that combines 1) conditioning dose-extension model and 2) an open-label placebo paradigm. We anticipate that a combined strategy would be more likely to be successful than any of these two strategies separately. Future studies could disentangle these two options.

It seems reasonable to propose that we can extend the analgesic effects of opioids through the use of placebo, which in turn, might reduce the total drug dosage and its undesirable side effects, by doing so; we can also expect patients will benefit from the reduction in the risk of opioid dependence. Finally, this approach may also represent a cost-benefit advantage in the treatment of pain. Our proposed study design tests the following hypothesis whether patients in Group 1 will have superior or equivalent pain relief compared to Group 2.

In this six-day experiment, patients will be randomized to either:

- Group 1. 100% dose + COLP (three days), then 50% dose + COLP for following three days
- Group 2. 100% standard dose (six days)

II. <u>All patients in Group 1 and Group 2 will have access to rescue medication and received all usual auxiliary therapies such as OT, PT, and SPL</u>

RATIONALE

We propose that in severe devastating conditions where long-term treatments are needed, as in the case of pain in spinal cord injury (SCI), polytrauma or burn injury patients from the Comprehensive Rehabilitation Program at Spaulding Rehabilitation Hospital, COLP may offer an innovative treatment protocol for symptoms control, especially when highly addictive agents are used. Under these circumstances, patients may benefit from the systematic use of both placebo mechanisms and the medication by itself. Additionally, practical issues of how to integrate conditioned placebo effects into clinical practice warrant further investigation.

We hypothesize that a COLP model can be implemented for safe opioid dose management; this model is also intended to extend opioid's therapeutic effect and may help to reduce risk for

opioid addiction in our target patients. Lower doses might also help in reducing side effects, such as constipation that is a common adverse event and of relevant importance in patients with limited mobility, COLP can facilitate adequate dosage control and give room for latter opioid attrition. Moreover, administrating fake pills to harness placebo effects poses an ethical challenge for physicians and researchers, to avoid this we proposed the model of open or disclosed placebo, which seems to be also efficient based on previous research [17] (Kaptchuk 2010).

The rationale behind the use of conditioning and the smell and taste of inert substances, is based on the separation between the endogenous opioid system and non-opioid mediated mechanisms in relation to placebo analgesia and conditioning. Behavioral studies have shown that the placebo response can be blocked by the opioid antagonist naloxone [19]. Therefore, the proposed model is a reinforced conditioned placebo paradigm that also introduces sensory stimuli in the form of taste and smell, thus, active intervention will have the following assembly; *opioid - conditioning with a Placebo pill + odorous stimuli/tasteful stimuli as boosters of conditioning*.

To the best of our knowledge, no one has directly tested the potential of COLP on pain and spinal cord injury (SCI), polytrauma or burn injury patients from the Comprehensive Rehabilitation Program at Spaulding Rehabilitation Hospital. Our trial design will directly compare two groups; 1) an open COLP opioid regime (conditioned response to placebo), 2) and a control group of patients receiving the standard of care. By having these 2 groups we will be able to compare the combined effect of conditioning and open placebo (COLP) against the "standard of care" treatment. All patients enrolled will have access to rescue medication. Also, by separating these two groups, we might be able to differentiate pharmacological and psychobiological responses between the use of placebos as a therapeutic alternative to opioid usage, and the standard of care in patients with pain of difficult control that usually are exposed to highly addictive agents.

In summary, there is an urgent need to address the opioid epidemic and the devastating consequences it has in patients with pain, this problem is inherent to the clinical approach used in opioids for pain management. This is a feasibility, "proof-of-concept, pilot trial". In this proposal, our research group will test whether drug conditioning using COLP is effective in controlling pain in patients affected with SCI, polytrauma or burn injury patients from the Comprehensive Rehabilitation Program at Spaulding Rehabilitation Hospital.

Sponsors

. This study is supported by Spaulding Research Institute, the Discovery Center for Recovery from Chronic Pain, and the Gordon Center for the Cure and Treatment of Paralysis.

SPECIFIC AIMS

AIM 1: To determine the feasibility of whether COLP can be compared to usual care in a randomized trial, and to obtain data for power calculation for future studies.

III.

Sub Aim 1.1: *Effects of COLP on pain interference and pain behavior.* These subdomains, parts of the Spinal Cord Injury – Quality of Life (SCI-QOL) measurement system, will allow for the evaluation of psychosocial and behavioral issues patients may have, and how these might change as a result of COLP and opioid dose reduction.

Aim 2: To obtain actual pilot data on whether COLP can reduce dose of opioid medication needed for successful pain relief, by using conditioned open-label (COLP) in patients receiving this intervention (Group 1) compared to patients undergoing standard pharmacological treatment (Group 2).

We seek to determine whether COLP can elicit detectable changes on pain tolerability that can be measured by total dose of morphine equivalents (primary outcome) and standardize clinical measurements of pain. Rescue analgesic therapy will be also monitored as a marker of intervention efficacy.

Aim 3: To explore neurophysiological and biochemical markers associated to placebo analgesia in subjects exposed to COLP, when compared with the TAU group.

We will collect electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS), and pinprick blood samples to investigate patterns of cortical activation, cerebral metabolism, and metabolomic profiling.

Hypothesis: Our hypothesis is that COLP can allow stable pain relief at 50% dose of the active drug, and that will be superior or no different to 100% dosage after three days.

This protocol will advance the field of pain medicine and rehabilitation by applying a pharmaco-behavioral model for the reduction of opioid usage in patients with pain and SCI, polytrauma or burn injury patients from the Comprehensive Rehabilitation Program at Spaulding Rehabilitation Hospital. Values of morphine equivalence will serve as standardized opioid dosage method, among

narcotic agents, while clinical pain evaluations and the use of rescue medication will serve as measurements of efficacy.

IV. INVESTIGATORS

a. **Ross Zafonte, DO**
b. **Kevin O'Connor MD**
c. **León Morales-Quezada, MD, PhD**
d. **Douglas Sohn, MD**
e. **Timothy Young, MD**
f. **David Crandell, MD**
g. **Jeffrey Schneider, MD**

Medical monitor

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator.

V. SUBJECT SELECTION

We will recruit 60 inpatients. All subjects must meet clinical criteria for the use of opioids as a treatment for pain management.

Eligible subjects will be considered for enrollment if they meet the following *inclusion criteria*;

- Men and women aged 18 or older with traumatic and non-traumatic SCI (ASIA A-D), polytrauma or burn injury patients from the Comprehensive Rehabilitation Program at Spaulding Rehabilitation Hospital,
- SCI, polytrauma or burn injury patients from the Comprehensive Rehabilitation Program at Spaulding Rehabilitation Hospital and pain of no more 5 years of evolution,
- Patients admitted to the Spaulding Comprehensive Rehabilitation Unit at Spaulding Rehabilitation Hospital,

- Who have; above, at, or sub-lesional neuropathic pain and/or nociceptive pain (musculoskeletal or visceral) that is moderate or severe in nature (average VAS scale score of 4 or greater at time of enrollment),
- Respiratory and hemodynamically stable,
- With current narcotic use for pain control,
- Narcotic usage of no more than 120 mg of morphine equivalent

Subjects will be excluded if;

- History of alcohol or drug dependence, as self-reported,
- A history of bipolar disorder or psychosis, as self-reported,
- Any substantial decrease in alertness, language reception, or attention that might interfere with understanding,
- Current usage of narcotic medication with dosage higher than 120 mg of morphine equivalent or 80 mg of a short-acting oxycodone,
- Current use of ventilator,
- Compromised medical status due to uncontrolled pathology such as cancer, heart failure, kidney or liver insufficiency, or any other condition which jeopardizes patient's participation to the study
- Pregnancy or breastfeeding. Females in childbearing age who are eligible to participate in the study, will be tested for pregnancy by serum hCG test

For patients allocated to the control group, no immediate opioid dose reduction intent will be required for inclusion. Subjects in this group will receive a standard dosage of medication for pain control as prescribed by their treating physician.

Concurrent Pain Medication Use: Although pain medications can confound the effects of COLP for opioid control, we consider it to be unethical to require subjects to discontinue non-opioid pharmacologic treatment for pain over the course of the study. In addition, to increase generalizability, it is important to recruit subjects using diverse pain medications. For inpatients, we understand that it may not be possible to keep stable doses of medications. Thus, we will notify the patient's physician and nurses of his/her participation in the study to facilitate involvement. We will track any medication changes as they may occur. We will not withdraw the subject if he/she must change medications/dosage***. During the development of the trial intervention, all patients enrolled and who are experiencing pains will have access to rescue medication***. Quantification of rescue medication will be an outcome measure, therefore rescue medication will

not affect their participation in the study, we expect patients requesting rescue medication in case COLP or standard of care is ineffective for adequate pain control.

VI. SUBJECT ENROLLMENT

Subjects with neuropathic or nociceptive pain and who meet the inclusion/exclusion criteria will be eligible for this study. We will enroll 60 subjects for this study.

Eligible subjects will be considered for enrollment if they meet the following *inclusion criteria*;

- Men and women aged 18 or older with traumatic and non-traumatic SCI (ASIA A-D),
- SCI, polytrauma or burn injury patients from the Comprehensive Rehabilitation Program at Spaulding Rehabilitation Hospital and pain of no more 5 years of evolution,
- Who have; above, at, or sub-lesional neuropathic pain and/or nociceptive pain (musculoskeletal or visceral) that is moderate or severe in nature (average VAS scale score of 4 or greater at time of enrollment),
- Respiratory and hemodynamically stable,
- With or without current narcotic use for pain control,
- Narcotic usage of no more than 120 mg of morphine equivalent

Subjects will be excluded if;

- History of alcohol or drug dependence, as self-reported,
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- Pregnancy or breastfeeding. Females in childbearing age who are eligible to participate in the study, will be tested for pregnancy by serum hCG test

For patients allocated to the control group, no immediate opioid dose reduction intent will be required for inclusion. Subjects in this group will receive medication for pain control as prescribed by their treating physician.

Subjects will be recruited through the following means:

1. Study staff will identify possible subjects by screening SRH inpatient medical records and/or by physician referral.
2. Flyers will be posted in the hospital.
3. Inpatients attending educational talks where the trial will be presented to the patients and their relatives

Study staff will screen the patient's medical records through SRH admission lists. If there is a potential candidate, they will ask the treating physician to confirm eligibility and to approach the patient to introduce the study. If a potential candidate learns of the study through other means, the treating physician needs to confirm eligibility and confirm that the study staff may discuss the study with the patient. Once patient agrees to meet with study staff, further study details will be discussed. Patients may also be referred to study staff by clinical staff. If patient learns about the study and initiates discussion with their physician, study staff will be notified for further discussion.

VII. STUDY PROCEDURES

Study Overview: We will conduct an assessor blind controlled clinical trial, patients in the COLP group will be fully informed about the interventions they will be allocated for. The treating physicians and other personnel like the staff who talks to patients after randomization about the intervention, and the nurses who do the conditioning will be aware of patient allocation.

Pre-screening procedures:

If the subject has been approved to participate by the treating physician, the co-investigator will discuss details of the study and answer questions both prior to and during the first study visit.

Subject Randomization:

The subjects will be randomly assigned for the intervention to receive either the experimental procedure (COLP) or to receive standard of care treatment. Randomization will be performed using the order of entrance to the study and a previous randomization list generated by a computer using blocks of four, to minimize the risk of imbalanced groups.

Study Design and Flow:

This study contains 1 experimental arm and one control group. The experiment will run in a parallel design, with each subject having 06 days of participation. For each group, subjects will have evaluations prior to the start of the trial (Baseline), and evaluations after the 06 days of study participation.

For this open placebo- opioid dose reduction study, we will enroll a total of 60 subjects with SCI, polytraumatized or burnt patients from the Comprehensive Rehabilitation Program at Spaulding Rehabilitation Hospital and ongoing neuropathic and/or nociceptive pain. Subjects will be evaluated using the following tools: Morphine Equivalent Dose Conversion (MEDC); Modified Brief Pain Inventory (BPI); Spinal Cord Injury – Quality of Life measurement system (SCI-QOL); and Numerical Opioid Side Effects (NOSE). Medication changes, side effects, and pain level as measured by the Visual Analog Scale (VAS) will also be recorded daily for each patient.

We will also perform neurophysiological and metabolomic phenotyping, using the following measures, electroencephalography (EEG) for quantitative assessment (qEEG), functional near-infrared spectroscopy (fNIRS) and metabolomics assessment.

Experimental treatments will take place at Spaulding Rehabilitation Hospital (SRH). We will coordinate with the appropriate care outlets to ensure that the procedures of the study will not interfere with their standard of care at Spaulding. This includes, but is not limited to: physicians, therapists and nurses working with the patient. We will schedule inpatients as their clinical schedule allows.

After enrollment, subjects will be randomized to receive COLP treatment or to receive standardized opioid dosage. Baseline assessments will be performed, and subjects on the COLP group will undergo 3 consecutive days of 100% dose + opioid conditioning paired with taste and odorous placebos (pill, and smell), followed by 3 days of 50% dose + COLP, where active opioid

medication will be alternated with full placebo dosages with the goal to decrease the therapeutic opioid dose by 50% (figure 4 and 5).

Treatment regime and schedule for patients in the COLP group will include a short-acting opioid prescribed on a schedule of 3-4 times per day, this will be considered the active agent for the pharmaco-conditioning intervention, subjects will have access and receive rescue medication if necessary (PRN). Other forms of analgesics (NSAID's and combos) will be prescribed under the criteria of treating physician, if combined agents containing opiates are used, a morphine equivalence calculation will be applied.

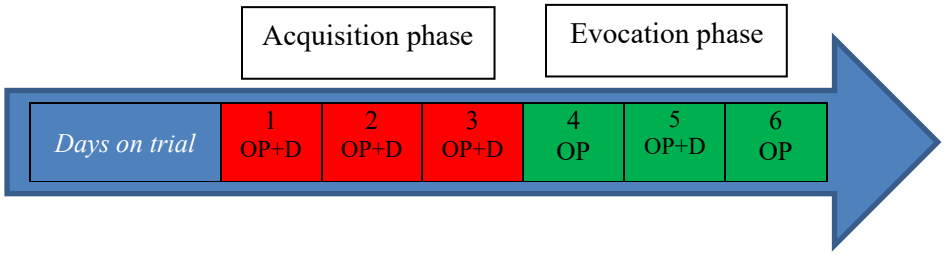

Figure 4. Proposed treating scheme for COLP group. Days 1 to 3 will include the acquisition phase where opioid medication will be prescribed on a schedule of 3-4 times per day and paired with open-placebo. Days 4 to 6 will be the evoked phase, and patients will receive full opioid dosage on alternating days with open placebo. During the evoked phase we expect to reduce opioid use by 50% approximately, and the open-placebo will keep therapeutic effect due to opioid receptors conditioning. OP; open-placebo, D; opioid drug. Open-placebo will have a characteristic smell and taste, days using only open-placebo (with characteristic smell and taste) will include a form of placebo drug pill to substitute the active drug.

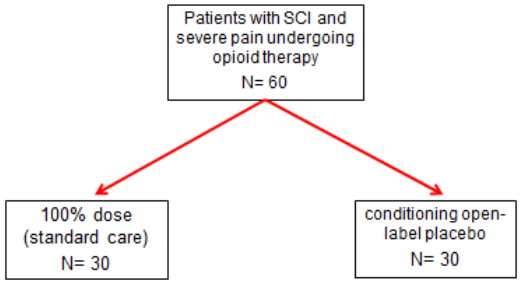

Figure 5. Patient allocation into standard of care or COLP.

For subjects allocated in the control group, the customarily treatment routine will be followed for SCI, polytrauma or burn injury patients from the Comprehensive Rehabilitation Program, this will

include all pharmacological agents being used for pain control. Total narcotic dosages will be registered at the beginning and end of the trial. Morphine equivalent values are going to be used to standardized dosages among agents.

Study Visit Outline:

Screening Procedures: Prior to the subjects' participation (this applies to both COLP and control group); a review of inclusion/exclusion criteria will be conducted to determine the subject's eligibility for enrollment. Study procedures will be reviewed with the subject, and documentation of informed consent will be obtained. At screening, the following procedures will take place:

- Discuss study-specific procedures with the subject;
- Review inclusion and exclusion criteria;
- Review of medical history;
- Obtain a signed and dated consent form;
- Demographic Data
- Randomization

Assessments and evaluations: During the study the subject will undergo several evaluations.

- Recording of analgesic medication and rescue medication usage (including opioids, NSAIDs, AEDs, and combos).
- Morphine equivalent dose conversion (MEDC)
- Modified Brief Pain Inventory (BPI)
- Spinal Cord Injury – Quality of Life (SCI-QOL) measurement system
- Numerical Opioid Side Effects (NOSE)

Time Period	Assessment	COLP group N=30	Control group N=30
Pre-screening	*Screening and Consent*	*X*	*X*
Before and after intervention	*Medication and rescue recording*	*X*	*X*
	MEDC	*X*	*X*
	BPI	*X*	*X*
	SCI-QOL	*X*	*X*

	NOSE	*X*	*X*
	qEEG	*X*	*X*
	fNIRS	*X*	*X*
	Metabolomics	*X*	*X*
Intervention		Conditioned open-label placebo	Standard of care

Table 1. Assessments and interventions per group. MEDC; morphine equivalent dose conversion, BPI; Modified Brief Pain Inventory, SCI-QOL; Spinal Cord Injury – Quality of Life measurement system; Numerical Opioid Side Effects, NOSE, qEEG; Quantitative electroencephalography, fNIRS; Functional near-infrared spectroscopy.

DETAILED STUDY OUTLINE

60 subjects are going to be enrolled for this protocol. Each subject who agrees to participate in the study will go through the screening procedures as outlined above and will be randomized to receive either: COLP or standard of care opioid management (a total of 30 per group). For those patients who agreed to participate in the study, baseline tests will be performed. Including:

- Information of pharmacological treatment protocol for pain control (including agents use as rescue option)
- Morphine equivalent dose conversion (MEDC)
- Modified Brief Pain Inventory (BPI)
- Spinal Cord Injury – Quality of Life measurement system SCI-QOL
- Numerical Opioid Side Effects (NOSE)
- Quantitative Electroencephalography (qEEG)
- Functional near-infrared spectroscopy fNIRS
- Metabolomics assessments

After the above information and assessments are collected, subjects will be randomized to one of the two groups (COLP or Standard of care).

Patients in the COLP group will receive their analgesic treatment through Spaulding Pharmacy in a specially prepared package, containing the opioid medication and a placebo pill with specific taste and odor. This package will be administered orally for 3 days representing the acquisition

phase. After the initial 3 days the evoke phase will follow, and the patient will receive a package containing the opioid agent and placebo, and in alternate days an inert opioid placebo pill resembling the physical characteristics of the opioid agent plus the placebo with characteristic taste and smell (3 days). Once the experiment period finish (a total of 6 days), measurements and assessments will be collected again, and the participant will be asked about his/her preference to continue under this analgesic regime, or to receive the standard of care treatment.

Patients in the standard of care group will receive their analgesic treatment through Spaulding Pharmacy as prescribed by their treating physicians. The treatment regime will include an opioid medication at the standard recommended dosage. Subjects in this group will receive the treatment orally for 6 consecutive days. Once the experiment period has finished, measurements and assessments will be collected again, and the participant will continue his/hers prescribed treatment.

All patients in both groups will have access to analgesic rescue medication if requested and will be able to terminate study participation at any time.

Description of Assessments:

Morphine Equivalent Dose Conversion (MEDC) – main outcome: The opioid morphine equivalent conversion factor, is used to standardized opioid usage having as a reference morphine as main indicator for analgesic potency. For drug utilization, there is a need to present usage data consistently, considering dosing requirements. One method of representing opioid use at the population level is through the application of Defined Daily Doses (DDD), however, this represents a problem partly because opioids require highly individualized dosing and need to be titrated to pain response, rather than having standard therapeutic dose ranges. Oral morphine equivalents are based on the idea that different doses of different opioids may give a similar analgesic effect. Where the doses of two different opioids are considered to give a comparable analgesic effect, they are deemed to be equianalgesic doses [20].

Modified Brief Pain Inventory (BPI): The BPI is a short self-assessment questionnaire that provides information on various dimensions of pain including how pain developed, the types of pain a patient experiences, and time of day pain is experienced, as well as current ways of alleviating pain [21]. The BPI also consists of the VAS Pain scale, a simple 10- point scale (0 = ‘‘no pain’’, 10 = ‘‘pain as bad as you can imagine’’) measuring a patient’ worst pain and least pain, on average and at present time. The Brief Pain Inventory provides information on the

intensity of pain (the sensory dimension) as well as the degree to which pain interferes with function (the reactive dimension). According to several previous studies on pain in spinal cord injury, the BPI is an effective measure, as shown by both our group [22] and other studies [23].

Spinal Cord Injury – Quality of Life measurement system (SCI-QOL): This measurement system was developed to address the shortage of relevant and psychometrically sound patient reported outcome measures available for clinical care and research in spinal cord injury (SCI) rehabilitation. For the purpose of this research, the Pain Behavior subdomain will be the primary component of this scale to be used. This 7-item fixed-length scale measures manifestations of pain. These actions or reactions can be verbal or non-verbal and involuntary or deliberate. They include observable displays, and verbal reports of pain. This scale includes a small subset of the PROMIS Pain Behavior item bank ($i = 4$) and three new items. These items were calibrated in a SCI sample, but final scores are transformed to the PROMIS general population referenced metric. Due to the small number of component items, Pain Behavior was developed as a fixed-length scale rather than an item bank [24]. Although this scale is standardized for SCI, the content can be applied to other types of patients with severe pain.

Numerical Opioid Side Effects (NOSE): Opioid therapy may be associated with adverse effects—which may affect the patient's perception of the overall satisfaction with opioid therapy. The Numerical Opioid Side Effect (NOSE) assessment tool is a simple, rapid, self-administered instrument which has the potential to be utilized in a busy pain clinic setting in efforts to document and longitudinally follow trends of opioid adverse effects [25].

All questionnaires and assessments will be administered in the privacy of the patient’s room or in a secluded area of the hospital. If subjects, feel uncomfortable in answering any of the questions or performing the assessments they may stop at any time.

Only an authorized, blinded member of the research staff will be conducting the assessments.

A visual analog scale for Pain, Medication Dosage Diary, and Side Effects Log are ancillary forms that will help to monitor medication efficacy, management, and the occurrence of adverse effects associated with the treatment. Nursing staff will collect this information by mid-day and capture the results in the subject chart.

Quantitative electroencephalography (qEEG): stands out as a valuable, non-invasive tool because it provides reliable and relevant information about brain functioning during rest, sensory stimulation and cognitive tasks. In addition, this technique is safe, low-cost, and employs an easy methodology, thus making it an appropriate tool for use in clinical practice. qEEG at rest and during pain processing event-related potentials (ERP's) at the patient's bed side. The qEEG and ERP's recordings will be processed for analytical purposes, standard EEG metrics will be explored (e.g. spectral analysis, connectivity, source localization), while ERP's will provide information related to pain and values of valence and arousal.

Functional near-infrared spectroscopy (fNIRS): this method is based on near-infrared light absorption fluctuations that depend on concentration changes of the chromophores O2Hb and HHb in the tissue under investigation. We will use it to investigate cerebral metabolism of oxygenated (O2Hb), deoxygenated (HHb) and total hemoglobin (tHb) during pain processing ERP's. Changes in tHb, defined as the sum of the changes in O2Hb and HHb, can be used as a measure of blood volume changes. fNIRS can provide the equivalent of cortical BOLD signal, similar to fMRI.

By combination qEEG and fNIRS data, we will be able to explore the effects of conditioning from a mechanistic perspective, we expect to find some reliable neurophysiological markers associated with the processing of placebo analgesia at a cortical level.

Metabolomics assessment: Metabolomic assessment will be performed in pathways associated with cognitive and cellular metabolism, metabolites such as indole-3 propionic acid, tryptophan, serotonin, kynurenine, and tyrosine will be analyzed seeking for alteration associated with cognition, while uric acid, xanthine, tyrosine, kynurenine, and tryptophan will provide information related to energetic efficiency. Samples are collected by pinprick system, and analysis will be done using liquid chromatography (LC) technique and by employing Electrochemical Array Detection (ECA). All assessments including pain related clinical outcomes will be taken at baseline and after intervention.

Description of Intervention:

We will use an open-label placebo method to facilitate endogenous opioid receptor conditioning, Oxycodone an active short-acting opioid will be administered in a schedule of 3-4 times per day, simultaneously, an inert pill (placebo) will be ingested while the patient is exposed to an odor of particular characteristics (e.g. lavender or roses like smell) a compound pharmacy will prepare the placebo pill.

Oxycodone Intervention and Rescue Medication:

All patients enrolled in this study will receive oxycodone as primary opioid medication for pain control. A short-acting form of the oxycodone will be prescribed 3-4 times per day, the accepted range dosage for this medication will be from 15 to 50 mg PO per day (Q24H), treating physicians will decide the oxycodone dosage to effectively control pain. We expect patients enrolled in this study to take an average of 40 mg of oxycodone per day (Q24H).

In case pain persists and the maximum oxycodone dosage has been reached, and alternative option for rescue medication will be prescribed by clinical staff and subject will be terminated from the study.

SRH pharmacy will receive the placebo pills from the compound pharmacy (Johnson Compounding and Wellness Center, Waltham, MA) and repack it into single units that will be dispensed on a daily basis for those subjects in the COLP group. The standard treatment group will receive their medication through SRH pharmacy supply.

Medical orders for the COLP or the standard treatment groups are going to be placed in the inpatient orders through EPIC and by study physician.

Placebos and standard medication will be stored and dispensed on the OMNI-ATM's machines located in the SCI floor at SRH

Both components of the COLP method will be dispense by the nursing team, which will need to observe and assure the participant is taking the pills, participants in Group 2 will receive the pills together for five days in the following order; 1st the long-acting opioid and 2nd the placebo pill. After the first 3 days are completed, the evoke phase will be started by providing a placebo pill and alternating with placebo/opioid days (figure 4), patients will be exposed to the same odor used during the first 3 days of the acquisition phase.

Study termination:

If a subject's pain increases by more than 3 points in the VAS score in 24hrs, his/her participation in the study will be terminated.

VIII. BIOSTATISTICAL ANALYSIS

The statistical analysis methods will consist of paired t test where mean, standard deviations, and p-values will be obtained to compare results at two-time points. Analysis of covariance (ANCOVA) tests for morphine equivalent dose, BPI, SCI-QOL, SSE, and total rescue medication usage assessments per group. The paired t tests will compare the change variable from pre-to post interventions between groups.

Analysis of covariance will be used to test the main and interaction effects of categorical variables (SSE, SCI-COL) on a continuous dependent variable (MEDC), controlling for the effects of selected other continuous variables (BPI), which co-vary with the dependent.

For Physiological Markers continuous variables will be compared using one-way analysis of variance, and categorical variables will be analyzed using a chi^2-test. Kruskal–Wallis test was used to compare the effects of COLP and TAU intervention on standard qEEG metrics and fNIRS values (e.g. power and coherence or tissue oxygenation respectively). The dependent variables for qEEG metrics in each bandwidth are going to be calculated as the difference between pre and post interventions. Exploratory investigations will be done by applying network and Bayesian methods, to evaluate for predictors of response.

For each fNIRS scan session, we will perform a standard general linear model (GLM) analysis to test the statistical significance of the detected hemodynamic response to the pain processing stimuli from the ERP's.

Metabolomic data will be managed as continuous and analyzed using linear regression modeling. Matrix correlations will be used to integrate metabolomic data with the rest of the clinical and physiological outcomes.

A standard of care comparison group will generate statistical data for sample size calculation for future studies. By comparing both groups, the chance to get a significant effect size improves beyond the test of statistical significance alone. Journals will find the information clinically relevant if a control group is included. The control group will help to compare the natural course of hospitalization.

Study Design and Flow:

This study contains 1 experimental arm and one control group. The experiment will run in a parallel design, with each subject having 6 days of participation. For each group, subjects will have evaluations prior to the start of the trial (Baseline), and evaluations after the 6 days of study participation.

For this open placebo- opioid dose reduction study. We will enroll a total of 60 subjects with SCI and ongoing neuropathic and/or nociceptive pain. Experimental treatments will take place at Spaulding Rehabilitation Hospital (SRH). We will coordinate with the appropriate care outlets to ensure that the procedures of the study will not interfere with their standard of care at Spaulding. This includes, but is not limited to: physicians, therapists and nurses working with the patient. We will schedule inpatients as their clinical schedule allows.

After enrollment, subjects will be randomized to receive COLP treatment or to receive standardized opioid dosage. Baseline assessments will be performed, and subjects on the COLP group will undergo 3 consecutive days of opioid conditioning paired with taste and odorous placebos (pill, and smell), followed by 3 days of the evoked response phase, where active opioid medication will be alternated with full placebo dosages with the goal to decrease the therapeutic opioid dose by 50% (figure 4 and 5).

Treatment regime and schedule for patients in the COLP group will include a short-acting opioid prescribed on a schedule of 3 to 4 times per day, this will be considered the active agent for the pharmaco-conditioning intervention, subjects will have access and receive rescue medication if necessary (PRN). Other forms of analgesics (NSAID's and combos) will be prescribed under the criteria of treating physician, if combined agents containing opiates are used, a morphine equivalence calculation will be applied.

The sample size calculation was performed under some assumptions as no published data is available for comparison, the calculation showed that a sample size of 60 participants would provide at least 80% power (alpha=0.05) to detect an effect size of 0.9 (considering the treatment difference between the two independent groups) in our main outcome between the COLP, 50%, and control groups. Although this sample is small and may rely on statistical assumptions, this is a realistic sample for an initial exploratory study as the effect size of 0.9 is consider smaller than

those required for a clinical trial. Finally, there will also be good statistical power to detect moderate effects of treatment on the secondary outcomes.

IX. RISKS AND DISCOMFORTS

Pharmacological treatment: All patients will be exposed to opioid treatment as a part of their treatment regime. Opioid use, both short term and long term, is associated with a high rate of multiple adverse effects. Adverse effects occur at all dose ranges, although the frequency increases with daily opioid use (as compared to intermittent use), higher doses, long-term therapy, polypharmacy and decreased renal or hepatic function promote the occurrence of adverse events. As many as 80% of patients experience at least one adverse event [26] the most common are gastrointestinal and CNS side effects. Across studies, a high percentage of patients experience dry mouth (42%), constipation (20–41%), sweating (34%), weight gain (29%), somnolence (14–29%), problems with sleep (25%), memory deficits (24%), loss of appetite (23%), nausea (17–33%), concentration deficits (19%), fatigue (19%), sexual dysfunction (18%), dizziness (12–22%), vomiting (11–15%), pruritus/dry skin (10%) and urinary retention. While tolerance develops to most side effects, constipation does not improve with time and prophylactic measures to improve laxation are required. All subjects involved in this study will be monitored by medical and nursing personnel during study participation, with special attention to the adverse events mentioned above. Treating physicians will have the right to discontinue opioid usage, in the event of this to happen, last dosage will be recorded, and patient participation will be terminated. A rescue medication will be used if pain cannot be controlled. Treating physicians will have the right to discontinue opioid usage, in the event of this to happen, last dosage will be recorded, and patient participation will be terminated.

Risks/benefits of short-acting oxycodone: Oxycodone hydrochloride tablets are an immediate-release oral formulation, indicated for the management of moderate to severe pain when the use of an opioid analgesic is appropriate. Physical dependence and tolerance are not unusual during chronic opioid therapy, however, during hospitalization, acute pain management is tailored to receive the minimum efficacious dose of opioid to prevent dependence. Significant tolerance should not occur in most patients treated with the lowest doses of oxycodone. It should

be expected, however, that a fraction of patients will develop some degree of tolerance and require progressively higher dosages of oxycodone hydrochloride tablets to maintain pain control during chronic treatment. The dosage should be selected according to the patient's individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effects of opioids is usually parallel the tolerance of side effects, except for constipation.

Oxycodone hydrochloride tablets have been evaluated in open label clinical trials in patients with cancer and nonmalignant pain. Oxycodone hydrochloride tablets are associated with adverse experiences like those seen with other opioids. Serious adverse reactions include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock (see **OVERDOSAGE, WARNINGS in packet insert**). The less severe side effects noted on initiation of therapy with oxycodone hydrochloride tablets are also typical of other opioid drugs. These effects are dependent on dose, the clinical setting, the patient's level of opioid tolerance and a host factors specific to the individual. They should be expected and managed as part of treatment. The most frequent side effects include nausea, constipation, vomiting, headache, and pruritus. In many cases the frequency of AEs during initiation of opioid therapy may be minimized by careful customization of starting dosage, slow titration and the avoidance of large rapid swings in plasma concentration of the opioid. Many AEs will abate as therapy continues and some degree of tolerance is developed. Others may be expected to remain throughout therapy.

The main disadvantage of using a LAO is that OxyContin is **NOT intended for use as a prn analgesic.** This represents a problem when SCI patients are exposed to physical demanding tasks during intensive rehabilitation. OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), if the pain is mild, or use for an extended period of time, as in the case of pain as a result of physical manipulations.

Behavioral assessments/Questionnaires: All questionnaires and clinical evaluation scales will be administered in the privacy of a closed room. There are no potential risks posed to participants with respect to behavioral tasks and questionnaires. If participants become fatigued during testing or are uncomfortable answering any personal questions, they will be informed that they are allowed to take a break at any point during the experiment and that they may end their participation at any time.

Electroencephalography (EEG): The EEG procedures are performed to measure the electrical activity in the brain and to examine the dynamic changes. It also allows for a better understanding of the effects of electrical activity generated in different areas of the brain. EEG only measures brain activity and does not induce any electrical current. These procedures are non-invasive and have been used extensively in clinical practice for diagnosis of neurological conditions such as epilepsy. Therefore, EEG poses no significant risk or anticipated discomfort.

Near-Infrared Spectroscopy: fNIRS: is a safe technique and poses non-significant risk to participants – it is utilized as a non-invasive monitor or brain oxygenation. The effect of radiated heat due to NIR absorption is low – less than 0.5°C – since emitted light power is comparable to the NIR part of sunlight. The conducted heat due to semiconductor junction of the LED can cause temperature increases up to 9°C. It has been shown that adjusting operational parameters by amplitude modulating or time multiplexing the LED decreases the temperature increases of the skin significantly. Skin will be monitored before, after and during the procedure. With these safety measures the potential skin damage is minimized. The side-effect profile includes skin irritation/redness at the site of the stimulation.

Metabolomics: for this assessment, we will perform finger capillary blood collection, which involves puncturing the dermis layer of the skin, this method is commonly used, especially for blood glucose testing. In order to prevent spread of infectious diseases, all personnel will be trained on the collection procedure, we will make sure that the collecting environment is clean and secure, prior to the procedure, a member of the research team will wash well his/her hands, and wear gloves, participant will be asked to perform hand wash with soap and dry with a clean towel, the finger to be punctured must be free of visible infection or wound, using the thumb and index finger, study staff will grasp the participant's finger, and will apply alcohol swab to clean the finger area to be punctured, and dry the area with sterile gauze or cotton ball. The site of puncture should be slightly posterior from the tip of the finger over the dorsal area of the hand, a disposable new lancet would be used and discarded immediately after following finger puncture. While continuing grasping the finger with one hand, blood will be drawn into the tip, and one drop of blood will be collected using a special pipette, once the sample is collected a drop of blood will

be applied over the test-stripe container. The container will be closed and marked with a special ID number, no personal information will be used for sample's ID.

Limitations: This is a proof-of-concept and feasibility trial, sample size calculation and statistical power where calculated based on some assumptions. If success in this protocol is obtained, further research will be conducted with the intention to prove efficacy and differences between different dosage alternatives.

X. POTENTIAL BENEFITS

The results of this study may benefit subsequent future subjects to the application of COLP therapy regime. In addition, the results from this investigation will provide a ground for future studies on opioid management. Furthermore, those subjects presenting adequate responses to the COLP intervention will benefit from having their opioid agent reduced so adverse events occurrence might decrease as well. Overall, SAOs offer flexibility of pain management in a challenging and dynamic clinical environment. Current standard of practice favors the use of SAOs over LAOs due to risk of dependence and benefit pertaining to insurance coverage. Short-acting oxycodone administration will facilitate the conditioning processes due to the increased frequency of medication administration, thus strengthening the relationship between the pairing of the neutral stimuli (placebo) and the active drug.

XI. MONITORING AND QUALITY ASSURANCE

Data for this study will be collected from subjects in several forms: scores from a multitude of questionnaires measuring pain, sensation, quality of life as well as demographic data. All data will be assigned a subject number, and the accompanying name will be deleted, so that it is de-identified. Data on paper (i.e. IRB approved questionnaires in subject folders) will be kept in a secured and locked storage room, of which only research staff have access to. Electronic data will be kept in a secured database which only study staff will be able to access.

Safety will be monitored by the opioid effects list. Adverse events, data, and procedures will be reviewed by PI and clinical team. All expected and unexpected adverse outcomes will be reported to the IRB according to the Adverse Event Reporting guidelines.

A study staff member will administer exams and the other evaluations. Prior to being added to the study, the study staff member will be trained in the techniques of how to present and conduct themselves in the hospital environment, as well as all aspects of the evaluations. This study staff member will be then evaluated by an investigator. The investigator will give confirmation that the study staff member is qualified to administer the evaluations, prior to performing study procedures.

References

1. Stayner, R.S. and D.J. Copenhaver, *Opioids, pain management and the law.* Curr Opin Anaesthesiol, 2012. **25**(5): p. 566-71.
2. Simon, L.S., *Relieving pain in America: A blueprint for transforming prevention, care, education, and research.* Journal of Pain & Palliative Care Pharmacotherapy, 2012. **26**(2): p. 197-198.
3. Gordek, H., R. Folsom, and T.G. Virag, *Substance abuse and mental health services administration.* 2013.
4. Cardenas, D.D., et al., *Gender and minority differences in the pain experience of people with spinal cord injury.* Arch Phys Med Rehabil, 2004. **85**(11): p. 1774-81.
5. Kaptchuk, T.J. and F.G. Miller, *Placebo effects in medicine.* New England Journal of Medicine, 2015. **373**(1): p. 8-9.
6. Martin, W.R., et al., *Morphine physical dependence in the dog.* Journal of Pharmacology and Experimental Therapeutics, 1974. **189**(3): p. 759-771.
7. Colloca, L., et al., *Learning potentiates neurophysiological and behavioral placebo analgesic responses.* Pain, 2008. **139**(2): p. 306-314.
8. Doering, B.K. and W. Rief, *Utilizing placebo mechanisms for dose reduction in pharmacotherapy.* Trends in pharmacological sciences, 2012. **33**(3): p. 165-172.
9. Price, D.D., D.G. Finniss, and F. Benedetti, *A comprehensive review of the placebo effect: recent advances and current thought.* Annu. Rev. Psychol., 2008. **59**: p. 565-590.
10. Pearce, J.M., *The placebo enigma.* Qjm., 1995. **88**(3): p. 215-20.
11. Kaptchuk, T.J., et al., *Placebos without deception: a randomized controlled trial in irritable bowel syndrome.* PLoS One, 2010. **5**(12): p. e15591.
12. Le Bars, D., M. Gozariu, and S.W. Cadden, *Animal models of nociception.* Pharmacological reviews, 2001. **53**(4): p. 597-652.
13. Giang, D.W., et al., *Conditioning of cyclophosphamide-induced leukopenia in humans.* Journal of Neuropsychiatry and Clinical Neurosciences, 1996. **8**(2): p. 194-201.
14. Ader, R., et al., *Conditioned pharmacotherapeutic effects: a preliminary study.* Psychosomatic Medicine, 2010. **72**(2): p. 192.
15. Sandler, A.D., C.E. Glesne, and J.W. Bodfish, *Conditioned placebo dose reduction: a new treatment in ADHD?* Journal of developmental and behavioral pediatrics: JDBP, 2010. **31**(5): p. 369.
16. Perlis, M., et al., *Durability of treatment response to zolpidem with three different maintenance regimens: a preliminary study.* Sleep medicine, 2015. **16**(9): p. 1160-1168.
17. Carvalho, C., et al., *Open-label placebo treatment in chronic low back pain: a randomized controlled trial.* Pain, 2016.
18. Schaefer, M., R. Harke, and C. Denke, *Open-Label Placebos Improve Symptoms in Allergic Rhinitis: A Randomized Controlled Trial.* Psychotherapy and Psychosomatics, 2016. **85**(6): p. 373-374.
19. Amanzio, M. and F. Benedetti, *Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems.* The Journal of Neuroscience, 1999. **19**(1): p. 484-494.
20. Nielsen, S., et al., *Comparing opioids: a guide to estimating oral morphine equivalents (OME) in research.* National Drug and Alcohol Research Centre, University of NSW, 2014.
21. Cleeland, C.S. and K.M. Ryan, *Pain assessment: global use of the Brief Pain Inventory.* Ann Acad Med Singapore, 1994. **23**(2): p. 129-38.
22. Fregni, F., et al., *A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury.* Pain, 2006. **122**(1-2): p. 197-209.

23. Bryce, T.N., et al., *Pain after spinal cord injury: an evidence-based review for clinical practice and research. Report of the National Institute on Disability and Rehabilitation Research Spinal Cord Injury Measures meeting.* J Spinal Cord Med, 2007. **30**(5): p. 421-40.
24. Tulsky, D.S., et al., *Overview of the Spinal Cord Injury--Quality of Life (SCI-QOL) measurement system.* J Spinal Cord Med, 2015. **38**(3): p. 257-69.
25. *The Numerical Opioid Side Effect (NOSE) Assessment Tool.* Journal of Cancer Pain & Symptom Palliation, 2005. **1**(3): p. 3-6.
26. *Long-acting Opioids for Chronic Non-cancer Pain: A Review of the Clinical Efficacy and Safety*2015, Ottawa ON: 2015 Canadian Agency for Drugs and Technologies in Health.