PROTOCOL: Neurobiological and Psychological Benefits of Exercise in

Chronic Pain & PTSD

NCT#- 03283163

(1). Rationale:

(a). Statement of the Problem.

The wars in Iraq and Afghanistan are creating a new generation of Veterans, including an increasing number of women Veterans, who present with comorbid PTSD and chronic pain conditions from recent deployment-related physical injuries and exposure to psychological trauma. Health behavior change has become increasingly important in treating these conditions and proactively preventing long-term negative health sequelae, in order to benefit these Veterans directly and reduce the growing challenges to our healthcare system. The proposed CDA-2 program of research will use an innovative translational research approach to study whether a chronic progressive -based exercise program will reduce chronic pain in patients with PTSD and to elucidate and modify potential PTSD-related deficiencies in neurobiological and psychological responses to exercise to optimize the physical and psychological benefits of exercise for these individuals.

(b). Hypotheses or Key Questions.

The overall aims and hypotheses of the current protocol are:

Aim 1: Assess the degree of clinical change in chronic pain and PTSD symptoms between the screening session, baseline and endpoint assessment time-points across a 12-week progressive exercise training program.
Hypothesis 1: As compared to the screening evaluation and baseline exercise assessment, as a result of the progressive exercise training regimen, participants will experience clinically significant reductions in pain related symptoms as well as improvements in symptoms of PTSD by the endpoint exercise assessment (between week 13-15).

Aim 2: Compare the impact of the exercise training program on plasma levels of the anti-stress neuromodulator, allopregnanolone plus pregnanolone (ALLO +PA), among trauma-exposed participants with comorbid chronic pain and vary degress of PTSD symptom severity (CP/PTSD).

Hypothesis2a: At the baseline exercise assessment, ALLO +PA will be lower and increase less in response to the maximum load exercise than during the endpoint exercise assessment (week 13).

Aim 3: Determine whether maximum load exercise-induced increases in plasma ALLO+PA correlate with changes in pain symptoms as measured by the cold pressor test and self-reported pain ratings.
Hypothesis 3a: At the baseline exercise assessment, diminished acute (maximum load) exercise-induced increases in ALLO+PA will be
associated with lesser acute exercise-induced decreases in pain sensitivity and lesser increases in tolerance as measured by the cold pressor test.
Hypothesis 3b: At the endpoint exercise assessment at the end of the progressive, intense exercise training regimen, MAX-EX-induced increases in plasma ALLO+PA will correlate with increases in pain tolerance/decreases in pain sensitivity when compared to baseline pre-training responses.

Exploratory Aim 1: Assess the role of exercise motivation and self-efficacy in relation ALLO+PA responses to exercise at the screening, baseline and endpoint exercise assessments.
Hypothesis: Participants with higher acute exercise-induced increases in ALLO+PA will show significantly higher levels of intrinsic motivation and self-efficacy for exercise, as well as lower levels of pain sensitivity (tolerance and threshold), pain-related symptoms and PTSD severity. Increases in intrinsic motivation will parallel increases in acute exercise-induced increases in ALLO +PA as the participant's progress through the 12-week chronic exercise training regimen.

(c) Specific Objectives.

Our main objective is to first determine if there are clinical, antinociceptive and anti-stress benefits of exercise for the trauma-exposed, chronic pain/PTSD population. Our second objective is to begin to delineate the interrelated pathophysiology of chronic pain and PTSD through our investigation of neurobiological factors such as ALLO+PA. These findings would ultimately inform development of more effective therapeutic interventions for these commonly comorbid conditions. For example, data from this pilot work will be used to compute effect sizes in support of a future clinical trial incorporating individually prescribed exercise regimens and a motivationally based exercise behavior change intervention aimed at reducing pain and PTSD symptoms in our Veterans. Specifically, this CDA-2 will allow the PI to develop a more effective, motivationally based, exercise behavior change protocol that fosters long-term exercise compliance in patients with chronic pain/PTSD which will be used as an adjunct to cognitive interventions for these disorders to be further developed and studied via a larger VA, NIH, or DOD-funded grant for which the PI will apply in years 4-5 of the CDA2.

2. Background and Significance

It is well documented that chronic pain and posttraumatic stress disorder (PTSD) are both disabling and health threatening conditions, adversely affecting the biological, psychological and social domains of those affected, and placing a significant financial strain on the healthcare system.[1] Although reported rates vary, as many as 50-75% of patients who present for PTSD treatment also have a significant chronic pain condition.[2-4] Conversely, among persons presenting for treatment of chronic pain, approximately 20-37% have PTSD.[5] Furthermore, those who suffer from co-morbid chronic pain and PTSD have been found to experience greater pain, affective distress, and disability than those with either pain or PTSD alone.[6-8]

According to Otis, Keane and Kerns[1], chronic pain is considered to be the most frequent complaint made to primary care providers, leading to 100 billion dollars per year loss in productivity and health care costs. PTSD is one of the most prevalent psychological disorders nationally, present in 6 and 12 percent of men and women, respectively. Furthermore, there is a lifetime 30% prevalence of PTSD in Vietnam Veterans, while rates up to ~20% have been reported for returning OEF/OIF Veterans. Finally, 80% of combat Veterans with PTSD also report suffering from chronic pain and researchers believe that the co-prevalence of these conditions impacts negatively on the course of both disorders.[1-2]

Research suggests that the strong relationship between chronic pain and PTSD is maintained by biological, as well as psychosocial factors that include co-morbid depression, anxiety sensitivity, perceived life control, and physical disability.[6] Among OEF/OIF Veterans, the association between pain and PTSD is likely to be particularly strong as the pain and PTSD conditions are more likely to have a recent onset and to be associated with the same traumatic event.[2] Therefore, the need for development of new and more effective treatments to help reduce the overall impact of comorbid chronic pain and PTSD on the lives of Veterans has been heightened within the past decade.[2]

Since chronic pain and PTSD are medically and psychiatrically complex illnesses, it is important to consider the potential impact of long-term exercise on both physical and mental health. Research suggests that a regular program of exercise has the potential to positively impact individuals suffering from both chronic pain and PTSD as well as improve their overall health and well-being. While much is known about the physical health benefits of exercise, its role in the prevention and treatment of mental illness has only recently been acknowledged.[7] According to Smith (2006), "For high risk populations, exercise planning is critical and exercise may provide efficiencies in healthcare…it can also address emotional difficulties in less direct but effective ways as well as increase patients' readiness to address and change psychological concerns over time (p. 199)." Since it is known that only 50% of mental illness can be effectively addressed through existing psychological and psychopharmacological treatments, regular exercise may serve as a cost effective compliment to traditional psychological and psychopharmacological treatments. Moreover, it can provide an alternative for those individuals who are not responding to traditional treatment approaches.[9] In fact, exercise combined with psychotherapy has been found to produce a better treatment response than either of these approaches by themselves.

Exercise may reduce chronic pain and PTSD through biopsychosocial mechanisms, and is considered a necessary component in comprehensive behavioral pain treatment programs because it can foster rehabilitation and provide social reinforcement and a diversion from illness behaviors.[10] In fact, there has recently been a call for more investigations of vigorous or highly intense aerobic

exercise in populations with specific chronic pain types, such as low back pain.[11] With respect to PTSD, most treatment programs support an exercise program as part of the individual's overall recovery process, and there is preliminary literature revealing PTSD symptom reduction following an exercise training intervention.[12] There is also evidence of exercise reducing symptoms associated with PTSD including anxiety, panic and depression.[13] In fact, a recent met-analysis revealed that exercise has effects on depression similar to psychotherapy and equivalent to drug treatment.[14] Moreover, exercise is associated with reductions in anger, hostility and stress, as well as with heightened self-esteem, symptoms relevant to both chronic pain and PTSD.[12,15-16] Taken together, these findings provide promising implications for exercise treatment within the chronic pain/PTSD population.

With regard to the effects of exercise on physical well-being, chronic exercise contributes to improved immune reactivity to stress and improved overall immune functioning.[17] Habitual exercise of sufficient intensity and duration is positively associated with a reduction in coronary heart disease, as well as the prevention and control of obesity, hypertension, diabetes and osteoporosis.[18] Recent research suggests that PTSD mediates the relationship between trauma exposure and negative health outcomes.[19] Metabolic syndrome, a compilation of metabolic risk factors that predict mortality and morbidity (e.g., cardiovascular disease and Type II diabetes) is highly prevalent, affecting 47 million individuals in the United States.[21] Among Veterans, metabolic syndrome has been found in 40% of 253 men and women Veterans presenting for treatment for Gulf War Syndrome. Its highest rate (46%) was in Veterans suffering from comorbid PTSD and depression.[20] Furthermore, neurobiological profiles associated with PTSD, or with comorbid PTSD and depression, predict both PTSD severity and metabolic syndrome risk.[22] Given that depression is a shared factor between chronic pain and PTSD, and exercise is beneficial for the treatment of obesity, diabetes and coronary heart disease, the investigation of exercise as a potential multisystem treatment intervention for men and women suffering from chronic pain and PTSD through impact on a shared pathophysiological substrate is compelling.

While the shared psychological factors in chronic pain and PTSD have been identified, the shared neurobiology is yet to be known.

<u>Neurobiological Factors that Impact both Chronic Pain and PTSD: A Working Model</u>

The neuroactive steroids, allopregnanolone and its equipotent stereoisomer pregnanolone (together termed ALLO +PA) may serve as potential mediators of the pain-trauma interrelationship.[,21-23] These stress buffering molecules have been found to regulate pain.[,22-23] In addition, synthesis of these hormones is regulated by sex steroids such that there are both gender and menstrual cycle phase-related differences in their levels and reactivity that may impact both pain and PTSD symptomatology.

<u>Allopregnanolone & Pregnanolone (ALLO):</u> The neuroactive steroid allopregnanolone (3α,5α-tetrahydroprogesterone) and its equipotent enantiomer, pregnanolone (3α,5β tetrahydroprogesterone) (collectively termed ALLO) are among the most potent positive modulators of the effects of gamma-amino-butyric acid (GABA) at $GABA_A$ receptors. ALLO exerts anxiolysis, as well as analgesia at both supra-spinal and spinal levels. For example, Charlet, Lasbennes, Darbon and Poisbeau[24] showed that intrathecal injection of ALLO (i.e., injection into the fluid bathing the spinal cord at rat vertebral level $L_{5\text{-}6}$) potently increased mechanical- and thermal pain thresholds in naive animals, as will as in animals with experimentally-induced inflammation. Kavaliers and Wiebe[25] similarly showed that intracerebroventricular injection of ALLO increased the thermal pain threshold with more potency than progesterone, while the

$GABA_A$ receptor inactive 3β enantiomer of ALLO was ineffective. In addition, the analgesic effects of ALLO were blocked by $GABA_A$ receptor antagonists and naloxone (an opiate antagonist), indicating that they involved the interactive activation of $GABA_A$ and opiate receptors.

In women with PTSD, cerebrospinal fluid ALLO levels were decreased to 39% of normal and were lowest in participants with comorbid major depression. In addition ALLO levels correlated inversely with PTSD reexperiencing symptoms (r=-0.72) and negative mood[23]. The ratio of ALLO to its immediate precursor, 5α-dihydroprogesterone (5α-DHP) was also decreased, consistent with a block in ALLO synthesis. Similar observations were made in a sample of 90 male OEF/OIF Veterans with PTSD, wherein the serum ratio of ALLO to its precursor progesterone was significantly reduced in those with a Davidson Trauma Severity (DTS) score ≥40 compared to those scoring <10, and in Veterans scoring ≥ 20 on the Beck Depression Inventory (BDI-II) compared to those scoring < 10. [24]Together these data support the idea that a block in ALLO synthesis contributes to the pathophysiology of PTSD and depression symptoms—as well as to potential chronic pain conditions in this population.

Sex-specific factors: Sex-specific factors may also influence the chronic pain-PTSD relationship. As compared to men, women are more likely to suffer from chronic pain conditions such as fibromyalgia, migraine and musculoskeletal pain; women also report pain to be more frequent, severe, and prolonged, and they experience greater pain-related physical, psychological and social disabilities.[28-29] Nevertheless, of the few studies investigating the pathophysiology of co-morbid chronic pain and PTSD, none has been undertaken in women.

Given that ALLO is derived from progesterone, there are sex-differences in its regulation related to the menstrual cycle. Lower levels of ALLO +PA, similar to those seen in men, are found during the follicular phase in women. During the luteal phase, allopregnanolone levels rise markedly in healthy women due to production of progesterone by the corpus luteum after ovulation.[30-31] Work is currently underway in the laboratory of Dr. Ann Rasmusson (primary mentor) to establish whether a luteal phase-related increase in ALLO+PAalso occurs in women with PTSD. As stated earlier, low levels of ALLO+PA are associated with both chronic pain and increased PTSD and negative mood symptoms. Together, these findings suggest that women with chronic pain and PTSD may experience more chronic pain during the follicular phase of the menstrual cycle. However, in women with PTSD, a deficit in the capacity to synthesize ALLO+PA could contribute to a relative deficit in ALLO+PA during the luteal phase as well. Further research is thus needed to enable a better understanding of the potential relationship between ALLO+ PA levels and chronic pain and PTSD symptoms in women, as well as in men. In addition, other neuroactive steroids that positively modulate the action of GABA at $GABA_A$ receptors have been identified—e.g. androsterone, a reduced metabolite of testosterone synthesized by the same enzymes that synthesize ALLO +PA.While less potent than ALLO+PA, androsterone is present at sufficient levels in blood to contribute significantly to GABA tone and have possible effects on pain.[32-33] Thus androsterone too will be measured in the current study (see preliminary data).

Exercise in relationship to ALLO+PA: Exercise training can serve as both a method to enhance mental and physical health as well as a vehicle to better delineate the shared neurobiology in this population. Specifically, exercise may be one means by which these anti-stress hormones (ALLO +PA) can be favorably impacted to simultaneously reduce chronic pain and PTSD symptoms.[35-38] Free fatty acid oxidation during aerobic exercise may acetylate the * chromatin of genes in the pathway for ALLO+PA synthesis. Subsequent demand on these systems via strenuous anaerobic exercise may then trigger/upregulate expression of these genes and thereby increase ALLO synthesis and release. Research providing more definitive data in this area may enable the development of

individually prescribed exercise-based interventions specifically tailored to elevate ALLO+PA levels in individuals suffering from chronic pain and PTSD. **Exercise as a clinical intervention:** Despite the documented benefits of the psychological, physical and neurophysiological benefits of exercise, there is minimal applied research focused on exercise for individuals who suffer from chronic psychological illnesses or on the factors that may mediate the benefits of exercise. This suggests the value of multidisciplinary studies that clarify the potential biological and psychological benefits of exercise-related interventions for complex populations.[7] Up to this point, most studies have examined effects of exercise on individuals with chronic pain only.[11] These findings indicate significant benefit for some chronic pain patients, but the majority of the results are unclear and systematic reviews of these studies suggest various flaws in experimental design, as well as inappropriate matching of exercise frequency, intensity and duration to chronic pain type. Thus, it is recommended that future research in this area be grounded in "existing theoretical principles" of exercise physiology so that clinical trials have strong internal validity.

Furthermore, many individuals in U.S. society are either sedentary or too infrequently active to accrue health benefits from exercise.[39] Most individuals participate in fitness programs for "extrinsic" reasons such as losing weight or becoming more attractive.[52] Such reasons for participation are likely to be related to poor adherence because extrinsically focused individuals may derive less enjoyment from the activity itself and feel more pressure and anxiety as well as a general lack of enjoyment of the exercise routine.[39-40] Individuals with chronic pain and PTSD will likely face similar difficulties, as well as the specific challenges posed by their illness. They may not "feel good" after strenuous exercise because they may not mount sufficient biological responses (e.g. NPY and ALLO) responsible for the post-exercise calm, focus, and improved pain tolerance experienced by healthy individuals. Indeed, pain patients tend to avoid regular exercise due to fear of pain exacerbation.[41] Perhaps similarly, women with a history of sexual trauma are as likely to engage in light or moderate exercise as non-exposed women, but are unlikely to engage in vigorous exercise.[42] Such women are also likely to experience chronic pain as a result of physical violence associated with sexual trauma. Thus an investigation of the impact of vigorous exercise in these populations would help us to better understand the psychophysiological barriers faced by these patients when attempting a regular exercise program.

Summary: There has been a call for research for clinical trials of exercise with high risk populations,[7] such as individuals suffering from chronic pain and PTSD. Therefore, because of the known psychological benefits of exercise on overall mental and physical health, and compelling recent research suggesting that exercise may address the biopsychosocial pathophysiology shared between chronic pain and PTSD (and other commonly comorbid conditions such as depression), we have designed a progressive exercise training program for this population. Our main objective is to determine whether chronic exercise can help reduce clinical symptoms of chronic pain and PTSD, including comorbid symptoms of depression. Secondarily, we will investigate whether chronic exercise also impacts ALLO+PA, as well as nociceptive responses to exercise. We hypothesize that individuals with trauma exposure, chronic musculoskeletal pain and varying degrees of PTSD severity will INITIALLY be unable to experience the "anti-nociceptive and anti-stress" benefits of exercise due to deficits in the release of the antinociceptive molecules ALLO +PA. This may also contribute to amotivation for vigorous exercise and difficulty achieving long-term exercise maintenance, which is our second exploratory objective. We hypothesize that engagement in an enforced laboratory-supported chronic, intense exercise program will progressively enhance the capacity of such patients to synthesize and release ALLO+PA during exercise. This will be associated with a central perception of "reward", reductions in pain sensitivity, reductions in PTSD symptoms, and overall improvements in mood and vigor. These biopsychological benefits may then increase the intrinsic motivation and self-efficacy for exercise and promote the long-term adoption

of exercise outside of the laboratory. Over time, this may help to reduce disability from PTSD severity and chronic pain and improve the overall quality of these participants' lives.

(b). Significance.

This study will provide valuable information about the neurobiological, psychological and physiological impact exercise can provide to Veterans with chronic pain and PTSD—and help bridge the gap in our understanding of the negative physical and emotional sequelae of trauma. This work may also serve as a foundation upon which innovative adjunct or alternatives to current treatments for PTSD and chronic pain can be developed, such as the development of a motivational and theoretically integrative exercise behavior change protocol specifically tailored to the unique needs of this complex population in order to foster long term exercise adherence. Furthermore, individualized prescriptions could continue to be modified.

(c). Relevance to Veterans Health.

The assessment and treatment of chronic pain and Posttraumatic Stress Disorder (PTSD) are national priorities for the Veterans Health Administration (VHA) as we continue to see steep increases in the prevalence of these conditions among returning OEF/OIF Veterans. Recent solicitations from the VA Rehabilitation Research and Development Service (RR&D) related to improving the healthcare for OEF/OIF Veterans emphasize this focus as an important target for rehabilitation research within the VHA. The proposed research supports these initiatives by advancing our understanding of neurobiological and psychological mechanisms underlying chronic pain and PTSD that can be mediated or moderated by exercise training.

(3) Work Accomplished

(a). ***Past work in exercise motivation and change in lifestyle by exercise***

Dr. Scioli's thesis work focused on the interrelationships of various health behaviors such as exercise, smoking cessation and nutritious behaviors. In a sample of 612 undergraduates, significant gender differences were found among exercise, nutritious eating and smoking behaviors. The study found, more men were in the active stages of change as compared to women [$x^2(1)=9.15$, $p<.01$]. Chi square statistics revealed a significant gender difference when comparing exercise and eating nutritiously $z(572)=2.25$, $p<.05$. Specifically, the women were engaging in both behaviors [$x^2(1)=23.92$, $p<.001$] but not the men [$x^2(1)=.004$, $p>.05$] despite more men being in the more active stages of change (action and maintenance). Logistic regression confirmed these results for the women (AOR=2.66, 95% CI=1.79-3.85) while the men's results did not reveal a significant difference ($p>.05$). Additionally, chi square statistics did not reveal a significant difference for exercising and smoking cessation for the women or men respectively [$x^2(2)=0.20$, $p>.05$; $x^2(2)=0.28$, $p>.05$]. Based on these findings, we deduced that health providers and health researchers should not assume that regular exercise is associated with eating nutritiously or a smoke-free status. Further intervention development should be focused on helping men to eat more nutritiously and for women to maintain exercise long-term.

Dr. Scioli's dissertation built upon these findings and investigated exercise motivation as a method by which to identify factors that can predict exercise maintenance. Her work was among the first to integrate the Transtheoretical Model of Health Behavior Change (TTM) and Self-Determination Theory (SDT) in order to better identify such motivational factors that predict exercise maintenance. In a sample of 614 undergraduate students, it was found that the more intrinsic motivational variables were found to be significantly different from exercise maintenance [$F(1,415)=15.51$, $p<.01$, $m^2=29.47$] as well as the earlier stages of change, including action [$F(1,415)=19.49$, $p<.01$, $m^2=5.63$]. Focused mean comparisons revealed that the intrinsic variables were highest in exercise maintenance. From these findings, we deduced that SDT could be integrated with the TTM and may be useful when developing more effective motivationally based interventions than either theoretical perspective by itself. Specifically, the TTM captures the external change process while SDT captures the internal change process for exercise adoption and maintenance. The SDT motivational variables can aid in predicting as well as developing interventions that foster exercise maintenance.

Additionally Dr. Scioli examined associations among self-determined forms of motivation, self-efficacy, body image anxiety (BIA), and exercise stages of change. This manuscript is currently under review. Stepwise discriminant function analyses revealed that exercise maintenance was most strongly associated with integrated regulation, an internalized "self-determined" motivational state, and self-efficacy, Wilk's lambda=.90, $F(2,378)=21.21$, $p<.001$. However, the standardized canconical coefficients revealed self-efficacy was the strongest predictor of maintenance among individuals high in BIA (1.00), while integrated regulation was strongest among those low in BIA (.84). We concluded that future research should focus on the development of interventions that enhance both integrated regulation and self-efficacy among young adult men and women in order to help them sustain exercise long term as well as manage their body image anxiety.

These findings have further helped to develop the exploratory hypothesis of the current proposal in investigating whether such motivational states (integrated regulation and self-efficacy) is associated with NPY and ALLO levels. Specifically, an improvement in NPY and ALLO levels through chronic exercise training could also help to improve the motivational states necessary to adhere to long term exercise training.

Pilot data:

Pilot Project: Specific outcomes related to preliminary study hypotheses (as previously proposed):

Analyses were performed using SPSS bivariate correlation, regression and frequencies for evaluation of assumptions. A square root transformation was used to reduce skewness and improve the normality of the data when needed (e.g. for the variable "change in NPY from baseline to five minutes post-exercise").
Hypothesis: At baseline, NPY and ALLO levels will be lower in the Pain/PTSD group compared to the TC group.

GABAergic neuroactive steroid levels measured at baseline just prior to the initiation of maximum load exercise, at peak exhaustion (~VO_2 max), and 30 minutes after exercise. Steroids were separated by high pressure liquid chromatography (HPLC) and then measured by gas chromatography-mass spectrometry (GC-MS). Consistent with previous work in rodents (Purdy et al., 1996),

allopregnanolone/pregnanolone appeared not to peak until about an hour after the initiation of exercise stress. Examination of the mean change in ALLO (normalized by BMI) from baseline to post thirty minutes of exercise by sex indicated that for both women and men, the TC's had a greater total mean sum of the GABAergic neuroactive steroids as compared to the Pain/PTSD group [Women:2.84 vs 2.45] and [Men: 3.6 vs. 2.44] though men displayed a greater difference between the study groups. No significant differences between the groups were found at this time.

Examination of the mean change in NPY from baseline to post five minutes of exercise (when NPY is at its peak) by sex indicated that for the men, the TC group had a greater mean change in NPY than the PTSD group (m_1=2.35 (SD=1.26) vs m_2=1.84 (SD=.59) respectively. For the women, the pain/PTSD group had a slightly greater mean change than the TC's (m_1=2.3 (sd=.49) and m_2=1.84 (sd=.37) respectively. No significant mean differences were found within or between the two groups at this time.

Additional findings:

To explore the relationship between exercise Vo_2 max and the neurobiological factors of interest in relationship to pain variables, bivariate correlations were conducted. Significant correlations with respect to Vo_2max were found for change in ALLO ($r=.77$, $p<.01$) and for NPY at the anaerobic threshold ($r=.61$, $p<.05$), as well as for change in NPY from baseline to 5' post-exercise ($r=.81$, $p<.01$). Also, a significant relationship was found between the pain threshold after exercise and a) change in ALLO, as well as b) change in NPY ($r=.61$, $p<.05$, and $r=.81$, $p<.01$, respectively). Finally the change in NPY and pain tolerance was significantly correlated ($r=.64$, $p<.05$).

Due to the observed significant correlations between pain threshold and change in ALLO, as well as change in NPY, these variables were entered into a multiple regression equation to predict pain threshold post exercise. It was found to be significant $F(2,9) = 13.38$, $p<.01$. In addition, for the change in NPY variable, the unstandardized partial slope (18.2) and standardized partial slope (1.2) were significantly different from 0 ($t=4.27$, $df=9$, $p<.01$); with every increase in pain threshold, NPY also increased.

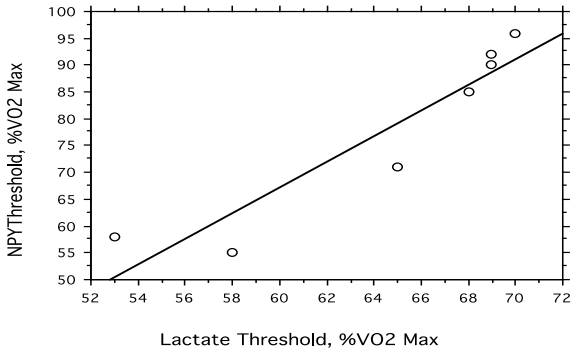
Taken together, these preliminary data 1) trend in the right direction in support of our hypothesis

that NPY and ALLO levels are lower in the Pain/PTSD group as compared to the TC's, particularly for the men, though not significant at this point. 2) Importantly, we found that the changes in ALLO and NPY in response to maximum load exercise challenge were correlated with VO2max, suggesting that regular exercise leading to an increase in VO2max may result in an increase in the capacity for release of both of these antinociceptive molecules—with resultant reductions in pain. This latter assertion is supported by 3) our preliminary data showing that both change in NPY and change in ALLO in response to acute maximum load exercise correlated with pain tolerance and threshold in individuals with and without chronic pain and PTSD.

Prior work in PTSD

As a researcher at the VA National Center for PTSD Clinical Neuroscience and Women's Health Science Divisions since 1994, Dr. Rasmusson brings her considerable expertise in the neurobiology and neuroendocrinology of PTSD and its comorbid psychiatric and medical conditions to this CDA2 proposal. She was the first to demonstrate PTSD-related changes in allopregnanolone and NPY levels in PTSD. Her current work aims to integrate findings regarding the pathophysiology of PTSD and its comorbidities using a systems biology approach. Dr. Rasmusson also brings to this proposal, her expertise and prior experience with a maximum load exercise challenge paradigm in which plasma can be collected for measurement of a variety of compounds. As illustrated below, previous work in her laboratory showed that plasma NPY levels increased significantly during exercise at the lactate threshold, which occurred at a mean of ~75% of VO2 max, in line with previous findings by Pernow (1984).

Thesholds for NPY & Lactate Increases During Exercise Are Highly Correlated



* The threshold for NPY release is defined as the timepoint at which the plasma NPY increased by 30% over baseline and subsequently was sustained at or above this level.

Prior work in Chronic Pain and PTSD:

Dr. Otis is a leader in field of chronic pain and also has expertise in PTSD management. Dr. Otis has been involved in multiple research projects and clinical work geared towards the investigation of CBT treatment within a pain population. He has also

developed and published a CBT pain treatment manual and patient workbook with Oxford University Press under the treatment that Work Series in 2007... This treatment approach emphasized goal setting, increasing physical activity, and teaching patient's ways to challenge maladaptive beliefs about pain. This pain manual has been endorsed by leaders in the pain research field and is being adopted for use in both research and clinical settings nationally.

Dr. Otis's work has not only focused on chronic pain but also on the psychological interplay of the co-occurrence of PTSD. Dr. Otis and colleagues published a review paper that evaluated existing research and theoretical models on the relationship between chronic pain and PTSD (Otis, Keane & Kerns, 2003). In 2005, Drs. Otis and Keane were funded by the Department of Veterans Affairs RR&D Service (Grant #D3322R) to develop an integrated psychological treatment for Veterans with comorbid chronic pain and PTSD. One of the primary goals of this study was to create an integrated treatment for chronic pain and PTSD that amounted to more than simply the sum of parts from each individual treatment. After its development, the integrated treatment manual was pilot tested with six research participants by Dr. Otis and Dr. Scioli. A paper describing the development and implementation of the integrated pain and PTSD treatment, and the results of observed in pilot study participants, published in Pain Medicine (Otis, Keane, Kerns, Monson & Scioli, 2009). Dr. Otis and collaborators also produced several papers that reviewed the mental and physical health problems often faced by OEF/OIF returnees (Scioli, Otis, & Keane, 2009), and addressed the potential interaction between chronic pain and PTSD (Keane, Niles, Otis, & Quinn, In Press). In an effort to describe the specific interactions between chronic pain and PTSD, Dr. Otis and colleagues recently presented data from a sample of 67 Veterans referred for the treatment of chronic pain with a comorbid diagnosis of PTSD. Using hierarchical multiple linear regressions, analyses indicated that the "re-experiencing" cluster of PTSD significantly predicted self-reported pain severity ($F(3,54)=2.75, p<.05$) and the "hyperarousal" cluster of PTSD significantly predicted pain related interference/disability ($F(3,53) = 2.87, p<.05$) (Gregor, Scioli, Schuster, Sanderson, Burnett, & Otis, 2009).

Prior work in exercise testing and exercise training interventions

Dr. Forman brings substantial knowledge and experience in the area of functional assessment and exercise training interventions in addition to related expertise in cellular metabolism and functional capacity. All of his work to date has been with medically complex populations and is therefore translatable to a chronic pain and PTSD population. Specifically, in one of his earliest training studies, he found that older female HF patients, participating in a 10 week resistance training trial had significantly increased muscle strength (increased 43.4 ±8.8% in resistance trainers vs. -1.7 ± 2.8% in controls, p= 0.001), muscle endurance (increased by 299 ±66% vs. 1 ±3%, p= 0.001), and 6MWT distance (increased by 49 ±14 m (13%) vs. -3 ± 19 m (-3%) in controls, p = 0.03). In a subsequent study (16 week program), HF patients (ages 67-82, mean 73 years old) in a strength training arm demonstrated increased skeletal muscle mitochondrial size, (23.4% increased size, p< 0.015) and associated increases in muscle strength and endurance (knee extensor and flexion), as well as increased functional capacity (peak VO_2, VAT, and 6MWT distance)

While on faculty at Boston University, Boston Medical Center was selected by the NHLBI as one of HF-ACTION's (A CHF Trial Investigating Outcomes of Exercise TraiNing) 9 U-site hubs, with Dr. Forman as the U-site principal investigator. Dr. Forman created the infrastructure for recruitment and training into that landmark HF training trial and was commended by the HF-ACTION steering committee for excellent start-up and recruitment. In addition to leading the exercise testing, training, and organization for HF-ACTION, he selected as lead writer on the HF-ACTION baseline data paper focused on older HF patients, showing important age-

related covariates contributing (but not entirely explaining) age-related changes in CPX performance. Age was the strongest predictor of peak VO_2 and the VE/VCO_2 slope in this population of HF patients (accounting for 13% of the variability in peak VO_2 and 4% of the VE/VCO_2 slope after controlling for other variables in the model). BMI, sex, race, and NYHA classification were also independent predictors of peak VO_2; when added to age they accounted for 39% of the variability. Furthermore, adding peak HR increased R^2 from 0.392 to 0.494. Age-related effects were nonlinear and showed splines at age 40 years for peak VO_2 and age 70 years for the VE/VCO_2 slope. These effects do not appear to be mediated via age-related increases in comorbidities.

Dr. Forman has also collaborated with Gloria Yeh and Russell Phillips in the NCCAM Trial Tai Chi Mind-Body Movement Therapy for Patients with Chronic HF. Dr. Forman completed all CPX for that study, which showed that tai chi (TC) improved quality of life, mood, and exercise self-efficacy in patients with HF as compared to a matched attention control population. Dr. Forman also spearheaded a related study comparing TC to aerobic training (AT) in a HF-PEF population. After 12 weeks of training, change in peak VO_2 was similar between groups, but 6MWT distance increased more after TC (+69 ±46 m vs. +10±31 m, p=0.02). Furthermore, while TC and AT were similar with respect to Minnesota Living with Heart Failure score and self-efficacy, POMS-depression scores improved more in TC (-1.7±2.8 vs. +1.6±3, p=0.05). Cardiorespiratory parameters during training showed lower oxygen uptake (4.3 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$ vs. 9.4 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$, p<0.01), respiratory rate and heart rate with TC relative to AT. Dr. Forman recently completed the pilot project *Ubiquitin Proteolysis and PGC-1α in Skeletal Muscle in Heart Failure* which compared functional capacity between HF and controls, evaluating CPX indices, strength testing, body composition, and basic clinical measures. He showed that key aerobic and strength indices were significantly decreased in HF patients (peak VO_2 [15.4±4.2 vs. 23.4±6.6,$mlO_2 \bullet kg^{-1} \bullet min^{-1}$ p<0.0001], VAT [10.9±2.1 vs. 14.4±4.0 $mlO_2 \bullet kg^{-1} \bullet min^{-1}$, p<0.0001], VE/VCO_2 slope [35.7±10.6 vs. 29.1±4.6, p<0.0001], 1RM [154.8±52.0 vs. 195.3±56.8kg, p<0.01], power [226.4±99.2 vs. 313.3±130.6 watts, p<0.01]), and the 6MWT distance (388.8±114.9 vs. 536.5±182.7 meters, p<0.001) reflecting the pathophysiological-associated functional decrements in an HF population. Analyses of gene expression in relation to functional capacity also show several key correlations between generally suppressed in atrophying muscle and generally suppressed aerobic capacity in HF patients. PGC-1α correlated with peak VO_2 (r=0.49, p<0.05) and $P_{ET}CO_2$ (r=0.43, p<0.05). IGFBP5 correlated with peak VO_2 (r=0.60, p<0.01), the VE/VCO_2 slope (r=-0.44, p<0.05), and $P_{ET}CO_2$ (r=0.52, p<0.01), and approached significance with peak VE/VO_2 (r=-0.40, p=0.053). There were significant correlations between expression of genes induced in atrophying muscle and function. Peak VO_2 correlated with MuRF-1 (r=-0.42, p<0.05), FoxO1 (r=-0.50, p<0.01), FoxO3 (r=-0.52, p<0.01), and GLUL (r=-0.36, p<0.05). $P_{ET}CO_2$ correlated with atrogin-1 (r=-0.38, p<0.05) and MuRF-1 (r=-0.38, p<0.05). GLUL correlated with 1RM (r=-0.37, p<0.05) and sub-maximal power (r=-0.36, p<0.05). These data provide strong rationale for further analysis of atrophy-associated gene expression in skeletal muscle following a tailored exercise intervention. This data has led to the funding of Dr. Forman's next project "*Exercise Therapy to Reduce Heart Failure Symptoms; Sorting Mechanisms of Benefit*" which will compare four different exercise regimens (i.e., aerobic, strength, combined aerobic-strength, and inspiratory training) to explore how each modality changes function/symptoms in relation to specific peripheral training effects, i.e., exercise effects on SkMx biology (histology, gene expression), peripheral perfusion, and body compositionwhich will evaluate the effect of varying exercise modalities

In summary, Dr. Forman's work emphasizes his ability to successfully lead and execute successful exercise testing and intervention trails with the primary emphasis on heart failure patients. Dr. Forman has built an exceptional methods for recruitment

and retention of a very medical complex population with heart failure being the emphasis however many of these techniques for recruitment and retention of patients will also be translatable to a chronic pain and PTSD population being recruited as part of this study.

Work within the VA Boston Clinical Studies Unit (CSU)

Dr. Forman is the managing cardiologist of the Clinical studies Unit (CSU) at the Boston VA. The CSU is a center geared to provide services to multiple VA investigators interested in completing research in the area of exercise testing and training. Dr. Forman oversees the day to day running ofr the CSU which houses state of the art exercise testing equipment for performing cardiopulmonary exercise testing and strength assessment. Additionally there is a 1600 square foot exercise training room which is equipped with multiple treadmills, bikes, arm ergometers, free weights and machine weights which is shared by research and cardiac/pulmonary rehabilitation. The CSU is staffed with exercise physiologist, nurses, and cardiologist to provide infrastructure beyond that of equipment which investigators can use. As part of the CSU Dr. Forman is taking part in ongoing work with multiple other VA investigators that are investigating the impact of exercise testing and exercise training outcomes on multiple different health conditions and variables.

In addition Dr. Forman is the Medical Director of cardiac rehabilitation which works closely with pulmonary rehabilitation. Each of these programs cater to a medically complex Veteran population through a multi-session intervention and education program which requires the Veterans to attend classes twice a week for two hours each time (and 60 minutes of exercise and 60 minutes of education). Of those that successfully completed the cardiac rehabilitation program (n=49) it was found that 65% were diagnosed with chronic pain, 22% were diagnosed with PTSD, and that 18% had both pain and PTSD. For the pulmonary rehabilitation program (n=65) it was found that 45% were diagnosed with chronic pain, 29% were diagnosed with PTSD, and that 14% had both pain and PTSD. For both programs patients were found to be able to increase their overall exercise session MET capacity during the course of the exercise program on average of 0.5-1 MET. These findings provide evidence of the staff's ability to retain individuals with both medically and psychiatrically complex conditions as well as see improvements in exercise outcomes.. Therefore, as stated previously, Dr. Forman and colleagues work can be directly translatable to a chronic pain and PTSD population and we will take advantage of the expertise of Dr. Forman and his staff to help retain our participants as well as foster improvements in such exercise outcomes.

(4) Work Proposed.

(a)

Proposed Overall Research Activities and Anticipated Recruitment

Year	Year 1	Year 2	Year 3	Year 4	Year 5

Research Goals	Finalize study staff and lab set up Attain IRB approval for study modifications begin data collection (n=5)	Continue data collection (n=10)	Continue data collection (n=10)	Complete data collection (n=5)	Submit manuscripts of proposed project RESUBMIT Merit Review application

(b) Experimental Plan:

Design Overview: The proposed research will assess the effects of aerobic and anaerobic exercise on ALLO+PA levelsand changes in pain sensitivity among male and female Veterans with trauma exposure, chronic musculoskeketal pain and varying degrees of PTSD symptom severity. A total sample size of 30 participants (15 male & 15 female) , aged 18-60years, will be studied. To control for menstrual cycle effects, the women will be tested during the early follicular phase of the menstrual cycle when estrogen levels are low, and levels of progesterone (the steroid precursor for ALLO+PA) are stable and comparable to those in men. However, we will not be excluding women who are perimenopausal/menopausal. These patients will be scheduled during the same timeline as the male participants.

Recruitment methods Fliers will be posted within the VA and advertisements in the community.

Participant Characteristics: Participants will be receiving care in the VA Boston Healthcare System (VABHS) or recruited from the community. Inclusion criteria for the proposed study will permit the recruitment of women as well as men from all ethnic and racial backgrounds who are at least 18 years of age, and able to speak and understand English. The patient population at the VABHS is 65% Caucasian, 15% African American, 10% Latino, and 10% Asian. We intend to sample a similar demographic population as to that served by the VABHS and will oversample for minorities to ensure that enough are seen.

Inclusion Criteria: Only participants in whom a physical examination, medical history, EKG, and baseline laboratory studies including urine toxicology screens indicate that the symptoms limited cardiopulmonary exercise stress ((MAX-EX) testing will be safe will be included in this study. Also, participants will be required to start at a relatively sedentary level, defined as performing less than 30 minutes/day (150 minutes per week) of moderate physical activity on ≥ 5 days per week. [82] Participants must be free of medications and other substances (e.g., illicit drugs and alcohol) with effects that could hinder data interpretation for 2-6 weeks depending on the medication and frequency of use (which must be cleared by the PI's primary mentor). However, psychotropic medications are allowed as long as the participant has been stable on them for two months. Those who are using tobacco will still be included in the study and will not be required to lower or stop their dosage/intake. If on pain medications with short half-lives,

participants must be off of them for 5 half-lives before testing, generally about 24 hours. Any participant with an ICD-9 or ICD-10 chronic pain diagnosis with a musculoskeletal etiology, as confirmed by the rehab medicine doctor or other qualified pain psychology staff, will be allowed for inclusion in the study. Any participant with a confirmed psychiatric diagnosis of PTSD, including those who are sub-threshold PTSD, or with trauma exposure without a diagnosis of PTSD, other psychiatric conditions, or chronic pain will be included in the study. Individuals in the PTSD group must meet for current chronic PTSD (≥3 months) or sub-threshold PTSD as assessed by the CAPS -5,1-Month Diagnostic Version. Sub-threshold PTSD is determined using the CAPS-5. If a patient endorses 2 or 3 B-E criteria or all B-E criteria without functional impairment – with functional impairment defined as having clinically significant symptoms that interfere with daily activities. Subjects with chronic pain For individuals eligible for the polytrauma group (chronic pain, PTSD and mild and moderate TBI), any participant with a mild or moderate TBI (six months or longer post injury), as determined by the BAT-L will be included.

Exclusion criteria: Participants will be excluded from participation in the study if they have a life threatening or acute physical illness (e.g., cancer), current schizophreniform illnesses, **bipolar disorder**, or active suicidal or homicidal ideation requiring clinical intervention. Individuals with current or past alcohol and/or substance dependence (less than three months from date of screening assessment) will be excluded. Women who are or are planning to become pregnant within the next six months will also be excluded. Individuals seeking pain treatment such as surgical interventions or who have a neuropathic origin to their pain will also be excluded. Participants with chronic pain concerns that cannot tolerate exercising in an upright bike and those who have had a clinical history of coronary artery disease or positive stress test, uncontrolled cardiac arrhythmia, moderate-to-severe aortic stenosis, severe arterial hypertension (systolic >200 mmHg, diastolic>110 mm Hg) and more than first degree atrioventricular block also will be excluded from participation. Finally, individuals taking medications for chronic psychiatric or medical illnesses will not be excluded as long as their medications and medication dosing are stable for two months prior to participation in the study and remain stable throughout the 12 week exercise training protocol and final exercise test. Common medications that will be acceptable include psychotropic medications, steroid contraceptives, and medication for high blood pressure, high cholesterol and diabetes.

****In addition, participants may be excluded from further participation in the study at any point if he/she is unable to provide reliable study data, for example, altering his/her urine sample (in which case he/she would not be paid for the session), providing misinformation during an interview, or misinforming study staff of conditions that may exclude him/her from the study.**

Psychological and Behavioral Measures:
Measures of each of the key domains of the chronic pain experience (i.e., pain, affective distress, and disability), PTSD symptoms, TBI symptoms, exercise behavior, and motivation will be administered. Each measure has substantial evidence supporting its reliability and validity, as well as evidence of sensitivity to treatment effects. The current assessment battery was adapted from a previously funded study of pain and PTSD. Please refer to Table2, at the end of the protocol, for the timeline of administration of the following assessments:

Screening Interview Measures:
To be administered at: Screening Evaluation
Structured Clinical Interview for DSM-5 (SCID)[43] The SCID is a clinician-administered interview used to assess DSM-5 diagnoses. The instrument has been successfully used across diverse clinical populations and is currently in widespread use in both clinical and research capacities where it is generally considered a gold-standard.
Plan for use of SCID assessment data: We plan to use all of the modules of the SCID in order to better assess for eligibility based on the psychiatric inclusion/exclusion criteria. However, since this assessment is being used purely as a screening tool to determine study eligibility, the information will not be used analytically except for that pertaining to depression and PTSD. We will track all participants Axis I diagnoses in order to provide the necessary descriptive data for publications.

Clinician-Administered PTSD Scale-5[44-4](CAPS-5)[46]
To be administered at: Screening Evaluation & Endpoint 13 week exercise test sessions
This 30-item structured interview is designed to assess both the 17 symptoms of PTSD and the 8 hypothesized associated features. The scale yields a dichotomous diagnosis of PTSD, and also provides a continuous score of frequency and severity for each symptom. In addition, a behaviorally anchored probe question is provided for each symptom to increase the reliability of administration. The CAPS-5 is currently in the process of being validated however its previous version demonstrated excellent sensitivity (.81) and specificity (.95).[45]

Plan for use of trauma assessment data: Exposure to potential traumatic experiences (PTEs) will be assessed using the Life Events Checklist (LEC-5), after which a trauma timeline for the participant will be constructed and information about the participant's reaction to the trauma will be obtained to allow us to determine whether the trauma met DSM-5 PTSD criteria, based on the CAPS assessment. Individuals with PTSD must meet for current chronic PTSD.

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To be administered at: Screening Evaluation
This four item measure is designed to screen for potential TBI. This screen is the most widely used TBI screen across all Veteran's Health Administrations nationwide and is recommended for use in the 2008 VA Healthcare Report.

Mini BAT-L:
To be administered at: Screening Evaluation
The BAT-L has a 39-item screener that can be followed up with a larger, more comprehensive assessment (the BAT-L, see below) to further assess the nature of the patient's TBI-related injuries if needed.

VA Boston Assessment of Traumatic Brain Injury (BATL) Military and Civilian versions[48]
To be administered at: Screening Evaluation

The BAT-L is the first validated post-combat semi-structured clinical interview to characterize head injuries and diagnose TBIs throughout the lifespan. Guidelines for establishing a timeline for alteration of mental status, posttraumatic amnesia, and loss of consciousness, the forensic approach to the interview, and diagnostic categories were all refined over time as the distinctive experiences of OEF/OIF/OND Veterans were realized. The BAT-L, unlike existing TBI interviews, includes detailed assessment of blast exposure and blast-related TBI, evaluates TBIs acquired throughout a veteran's lifetime, and includes specific probes targeting the unique experiences of this cohort of Veterans in an effort to help guide the examiner assess the physiological disruption of consciousness in the context of co-occurring traumatic events. TBI is assessed during 3 time epochs: (1) prior to military service (Pre-Military), (2) during active military training and duties (Military: blast-related & other mechanism(s) during combat, training, or other activities during active duty), and (3) after returning stateside (Post-Deployment). The three most severe injuries in each epoch are evaluated.

Self-Report Measures for Cold Pressor Assessment Sessions, Midpoint and/or Exercise/Cold Pressor Test Sessions:

Affective Distress

To be administered at: Baseline & Endpoint exercise test sessions & Midpoint Self-Report Assessment Session

Beck Depression Inventory (BDI)[49]: (Pre-exercise testing)

A 21 item self-report measure of depressive symptom severity that is used to assess the extent to which an individual currently exhibits or experiences each of the behaviors, thoughts, or affective features of depression. The BDI yields a total score for depressive symptom severity as well as two subscales including cognitive and somatic symptoms of depression.

Profile of Mood States (POMS)[50]: (Pre & Post Exercise Testing) The Profile of Mood States (POMS, McNair et al, 1992; Educational and Industrial Testing Services, San Diego, CA) provides continuous measures of several dimensions of mood: anger/irritability, anxiety/tension, depression/dejection, confusion, fatigue, and vigor. This measure reliably gauges changes in negative mood in response to acute mood-altering maneuvers.

The Anxiety Sensitivity Index–III (ASI-III)[51] is an 18-item measure on which respondents indicate, on a 5-point Likert-type scale (0 = "very little" to 4 = "very much"), the degree to which they are concerned about possible negative consequences of anxiety symptoms (e.g., “It scares me when my heart beats rapidly”). The factor structure of the ASI-III has supported a three-factor model, with one higher order factor. The three sub-factors represent Physical Concerns (e.g., “When I feel pain in my chest, I worry that I’m going to have a heart attack”), Cognitive Concerns (e.g., “When my thoughts seem to speed up, I worry that I might be going crazy”), and Social Concerns (e.g., “I worry that other people will notice my anxiety”). All items on the ASI-III evidenced strong loadings (i.e., r’s > .50) on one factor and weak loadings (i.e., r’s < .20) on the other two factors (Taylor et al., 2007). Additionally, the ASI-III shows good internal consistency (α’s = .73 - .91).

To be administered at: Cold Pressor Assessment Sessions & Midpoint Self-Report Assessment Session

Post Traumatic Stress Disorder Symptoms

To be administered at: ; Baseline & Endpoint testing session (pre-exercise testing) & Midpoint Self-Report Assessment Session

PTSD Checklist (PCL-5)[52]: The PCL is a 20-item self-report questionnaire designed to assess PTSD symptomatology. Participants are presented with a list of symptoms of PTSD and asked to indicate the extent to which they have been bothered by each of the symptoms during the past month using a 5-point Likert-type scale. While the psychometrics of the current version of the PCL is in the process of undergoing validation, the previous version of the PCL has been found to be internally consistent and reliable over time and therefore appears to be a valid measure of PTSD. In addition, this previous version has has good sensitivity (.82) and specificity (.83).

Chronic Pain Measures

Pain/Pain Sensitivity/Tolerance Cold Pressor Test [53-54]: A procedure that has been used widely in laboratory studies to measure pain perception and tolerance[73].

To be administered at: Pre Exercise Testing sessions (Cold Pressor Assessment Sessions) & Post Exercise Testing at both exercise test sessions & Midpoint Self-Report Assessment Session

West Haven Yale Multidimensional Pain Inventory[55]: The WHYMPI has been demonstrated to be applicable across a variety of clinical pain conditions. Its brevity, validity/ reliability, self-report nature and ease of scoring make it ideal for both clinical and research purposes. The WHYMPI is sensitive to change following rehabilitation. Please note only the interference subscale of the WHYMPI will be administered in this study.

To be administered at: Screening, Cold Pressor and Exercise Assessment Sessions & Midpoint Self-Report Assessment Session

McGill Pain Questionnaire: Short-Form [56-57]: The McGill short-form questionnaire consists of 15 descriptors (11 sensory, 4 affective) rated on an intensity scale of 0 to 3. This measure has been demonstrated to be a highly reliable measure of pain. Test-retest correlations have been found to range from 0.89-0.96

To be administered at: Screening, Cold Pressor (baseline and post cold pressor) and Exercise Assessment Sessions (baseline, post exercise and post cold pressor) & Midpoint Self-Report Assessment Session

Numerical rating scale: (NRS)[58]. NRS-I, an 11-point numeric rating scale where a score of "0" represents no pain and a score of "10" represents the worst pain imaginable. Participants will be asked to rate their average pain over the past week. According to (Jensen, Turner, Romano & Fisher, 1999), this measure has psychometric properties sufficient for use in clinical research.

To be administered at: Screening, Cold Pressor (baseline and post cold pressor) and Exercise Assessment Sessions (baseline, post exercise and post cold pressor), & Midpoint Self-Report Assessment Session

Pain Catastrophizing Scale: All 13 items on the PCS were drawn from previous experimental and clinical research on catastrophic thinking in relation to pain experience (Chaves and Brown,
1987; Rosenstiel and Keefe, 1983; Spanos et al., 1979). Factor analyses of the PCS have shown that catastrophizing can be viewed as a multidimensional construct comprising elements of rumination("I can't stop thinking about how much it hurts"), magnification ("I worry
that something serious may happen"), and helplessness ("There is nothing I can do to reduce the intensity of the pain"). The factor structure of the PCS has been replicated in several investigations (Osman et al., 1997,2000; Sullivan et al., 1995, 2000; Van Damme et al., 2002).

To be administered at: Screening, Cold Pressor and Exercise Assessment Sessions & Midpoint Self-Report Assessment Session

Exercise Behavior and Motivation Measures

Godin Leisure-time Exercise Questionnaire[59] (The individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits. The participant indicates the frequency, intensity and duration of their exercise behaviors. Reliability estimates range from .83-.85.

To be administered at: Screening, Cold Pressor and Exercise Assessment Sessions & Midpoint Self-Report Assessment Session

Tampa Scale of Kinesiophobia[60-61]: The Tampa Scale of Kinesiophobia is a 17-item self-report checklist developed as a tool to assess fear of movement or re-injury. It has two subscales, activity avoidance and somatic focus. The TSK demonstrates good construct and predictive validity (Roelofs et al, 2004). The total score ranges between 17 and 68, with higher scores representing a higher degree of kinesiophobia and a cut score of 37 or above considered to be a high score.

To be administered at: Baseline & Endpoint testing session (post-exercise testing) and Midpoint Self-Report Assessment Session

Transtheoretical Model of Exercise Stage of Change[62]: A 23-item continuous measure designed to categorize individuals in one of five stages of change (precontemplation, contemplation, preparation, action and maintenance).

To be administered at: Screening, Cold Pressor Assessment Sessions & Midpoint Self-Report Assessment Session

Self-Efficacy for Exercise[63]: Comprised of 18 items used to determine a participant's level of confidence to exercise.

To be administered at: Screening, Cold Pressor Assessment Sessions & Midpoint Self-Report Assessment Session

Bone Mass Density Measures:

Bone Mass Density (BMD) will be measured by dual-energy x-ray absorptiometry (DXA) at Baseline Assessment, visit 2, and at Endpoint Assessment, visit 13 or 14. This would serve as an indicator of the effect of exercise training in the experiment on general

bone health, which is affected by obesity, stress and PTSD, metabolic syndrome, and other conditions found in the population being studied. Central DXA is the most widely-recognized BMD test, measuring bone density at the hip and spine. DXA produces a T-score: 0 indicates normal bone density, within 1 standard deviation of the young adult mean, while between 1 and 2.5 standard deviations indicates low bone mass, and 2.5 standard deviations or more indicates osteoporosis. Dr. Antonio Lazzari will be the responsible investigator for the DXA scans.

To be administered at: Baseline Assessment and Endpoint Assessment

TTM Decisional Balance for Exercise: Part of the decision to move from one stage to the next is based on the relative weight given to the *pros* and *cons* of changing behavior. The pros represent positive aspects of changing behavior, including facilitators of change. The cons represent negative aspects of changing behavior, and may be thought of as barriers to change. The decision-making component of the transtheoretical model is based on a model first conceptualized by Janis and Mann (1968, 1977). They assumed that sound decision making involves careful assessment of all relevant considerations, which are then evaluated in a decisional "balance sheet" of potential gains and losses. The anticipated gains (or benefits) and losses (or costs) can be categorized into eight major types of consequences: gains for self, losses for self, gains for significant others, losses for significant others, approval from significant others, disapproval from significant others, self-approval, and self-disapproval. Gains and losses for self and others represent utilitarian considerations that go into making the decision to change behavior, whereas approval and disapproval for self and others represent instrumental (non-utilitarian) considerations, such as self-esteem, social approval, internalized moral standards and ego ideals. Thus, both individuals and normative reference groups are taken into account regarding instrumental objectives as well as value-based appraisals (Hoyt & Janis, 1975).

Although the Janis and Mann (1977) model proposed eight specific categories of decision-making, only two general dimensions, the pros and cons of behavior change, have been supported consistently by factor analytic studies (Marcus, Rakowski, & Rossi, 1992; O'Connell & Velicer, 1988: Rakowski et al., 1992; Redding, Rossi, Velicer, & Prochaska, 1989; Rossi & Blais, 1991; Velicer, DiClemente, Prochaska, & Brandenburg, 1985). Within the context of the transtheoretical model, the pros and cons were first examined for the problem of smoking cessation (Velicer et al., 1985). This research indicated the existence of a specific functional relationship between decision-making and an individual's stage of change. Subsequent longitudinal research verified the relationship between the stages of change and decisional balance and established the predictive validity of the construct (Prochaska et al., 1985; Prochaska, Velicer et al., 1991). These studies and others across a wide range of problem behaviors have found that the comparative weighing of the pros and cons varies depending on the individual's stage of change (Prochaska, Velicer, Rossi et al., in press). In general, the pros increase as a function of stage whereas the cons decrease. In the precontemplation stage, the cons of changing a problem behavior will be judged by individuals to outweigh the pros. In the action and maintenance stages, the pros outweigh the cons. The positive aspects of changing a problem behavior begin to outweigh the negative aspects of change in the

contemplation stage. That the pros and cons are evaluated approximately equally in the contemplation stage is not surprising. The resulting indecision and lack of commitment are largely responsible for so many individuals becoming stuck in the contemplation stage, substituting thinking for action while continually struggling with weighing the costs and benefits of changing behavior.

The pros and cons of behavior change serve primarily as intermediate outcome variables in the transtheoretical model. The shift in decisional balance tends to be especially striking across the early stages of change, especially the increase in the pros from precontemplation to contemplation. Thus, decisional balance tends to be an excellent indicator of an individual's decision to move out of the precontemplation stage. The relationship between the stages of change and decisional balance has been shown to remarkably consistent across a diverse set of problem behaviors (Prochaska, Velicer, Rossi, et al., in press), including alcohol use, radon gas exposure, mammography screening, HIV risk reduction, condom use, adolescent delinquent behavior, smoking cessation, and weight control (Marcus, Rakowski, & Rossi, 1992; Rakowski et al., 1992; Redding, 1993; Rossi, 1990; Rossi et al., 1993a, 1993b; Rossi & Blais, 1991; Rossi, Rossi, Prochaska, & Velicer, 1992; Velicer et al., 1985). Especially noteworthy is that it is not only the form of the relationship that has been replicated across problem behaviors, but also the magnitude of the change in decisional balance across the stages of change. In progressing from precontemplation to action, the pros of change tend to increase by about one standard deviation, whereas the cons of change tend to decrease by about one-half of a standard deviation. These results have led to the development of strong and weak principals of behavior change (Prochaska, in press).

TTM Processes of Change: Meta-analyses of models of how people change have identified a common set of processes underlying the modification of problem behaviors (Prochaska, 1979; Prochaska & DiClemente, 1982, 1983, 1985, 1986, 1992; Rossi, 1992). These processes of change are overt and covert change strategies and techniques that can be employed by professionals, such as therapists or physicians, or by people changing on their own or with the aid of self-help programs. Ten to twelve processes have been consistently replicated across time, problem behaviors, sex, age, geographical region, and response formats (Prochasks & DiClemente, 1985; Prochaska, Velicer, DiClemente, & Fava, 1988; Rossi, 1992; Rossi & Bellis, 1993). For weight control, 12 processes of change have been identified: *consciousness raising, counterconditioning, dramatic relief, environmental reevaluation, helping relationships, interpersonal systems control, reinforcement management* (sometimes termed contingency management), *self liberation, self reevaluation, social liberation, stimulus control,* and *substance use* (sometimes called *medication*). Brief definitions of the processes can be found linked to the CPRC Transtheoretical Model page. Structural analyses indicate that the processes are organized into two general second order (hierarchical) constructs, reflecting the tendency of individuals to use more than one process of change at a time (Prochaska et al., 1988; Rossi, 1992). This model has been replicated across nine different problem behaviors, including smoking cessation, alcohol use, cocaine use, exercise adoption, dietary fat reduction, HIV risk reduction, psychological distress, weight control, and heroin use (Marcus, Rossi et al., 1992; Prochaska et al., 1988; Redding & Rossi, 1993a; Rossi, 1992; Rossi et al., 1993a; Rossi, Rossi et al., in press; Snow, Prochaska, & Rossi, in press). The two higher order factors are the experimental and the behavioral processes of change. In general, the experimental processes may be characterized as incorporating the cognitive, evaluative, and affective aspects of change whereas the behavioral processes include more specific, observable change strategies. However, these distinctions are not absolutely clear-cut. Across nine different problem behaviors, the

correlation between the experimential and behavioral factors ranged from .51 to .91 (median = .77), indicating a general tendency to use (or not use) all of the processes of change (Rossi, 1992).

The processes of change and the stage of change are integrally related. Transitions between stages are mediated by the use of distinct subsets of change processes (DiClemente et al., 1991; Prochaska & DiClemente, 1983; Prochaska, DiClemente, Velicer, Ginpil, & Norcross, 1985; Prochaska, Velicer et al., 1991). For example, consciousness raising is an experiential process reflecting an individual's attempt to seek out information concerning their problem behavior. Employment of this process predicts successful movement from the precontemplation stage to the contemplation stage. The process of self reevaluation is characteristic of the change from contemplation to action, whereas stimulus control is most frequently employed by individuals progressing from action to maintenance. In general, use of the experiential processes of change tends to peak in the contemplation or preparation stages, whereas use of the behavioral processes tends to peak in the action or maintenance stages. Precontemplators use the processes least of all. Longitudinal data suggest that when individuals (or treatment programs) mismatch processes to stages, action attempts are likely to fail (Fitzgerald & Prochaska, 1990; Gritz, Berman, Bastani, & Wu, 1992; Ockene et al., 1992; Prochaska et al., 1985). These results suggest that stage-specific interventions may accelerate progress through the stages of change. Interventions tailored to participant's stage of change have been developed for smoking cessation (Prochaska, DiClemente, Velicer, & Rossi, in press), exercise adoption (Marcus, Banspach, Lefebvre, Rossi, & Carleton, 1992), and sun exposure (Rossi, Blais, & Weinstock, in press) and have proved successful. Consideration of the processes of change and their relationship to the stages of change is thus important from the standpoint of providing guidance for the development of successful intervention programs applicable not only for individuals who are ready to change a problem behavior but for the vast majority of people who are neither prepared nor motivated to change

The Exercise Motivation Scale (EMS):[64] This measure is comprised of 31 items designed to assess behavioral tendencies according to SDT (Fuzong, 1999). The EMS consists of five subscales measuring SDT extrinsic variants (amotivation, external regulation, introjected regulation, identified regulation, and integrated regulation) and three subscales assessing intrinsic motivation (learn, experience sensation, and accomplish things). Previous studies have demonstrated that this measure has good factorial validity and internal consistency, with Cronbach's alpha values ranging from .75 to .90.[76] In the current study, the Cronbach's alpha for this scale was .88.

To be administered at: Screeing, Exercise Assessment Sessions & **Midpoint Self-Report Assessment Session**

Rate of Perceived Exertion
BORG Scale[67]: A 15-grade scale for self-rating of perceived exertion
To be administered at: Each change of exercise intensity during **both** maximum load exercise tests.

Sleep

The Pittsburgh Sleep Quality Index (PSQI)[65]: a self-rated questionnaire designed to assess sleep quality and disturbance over a one month time span. This measure has been validated on psychiatric patients which yielded a diagnostic sensitivity of 89.6% and a specificity of 86.5% (kappa=0.75, p<.001) when distinguishing "good" and "poor" sleepers. Further, the psychometric and clinical properties of this scale establish its utility in both psychiatric clinical and research settings.

To be administered at: Baseline , Midpoint and Endpoint cold pressor assessment sessions.

Research Procedures:

Participant Recruitment: Participants will be recruited by the study PI and trained research technicians who are approved to work on this protocol. A variety of recruitment methods will be used including; 1) advertisements (e.g., flyers) placed in patient care areas, at VABHS, or approved advertisements on the internet (e.g. craigslist or the NCPTSD website). 2) the screening of referrals to the Center for Pain Management, 3) the screening of referrals to the National Center for PTSD, 4) education of primary care providers at the VABHS and encouragement of referrals, and 5) from pain clinics outside the VABHS who see patients for research that would be eligible for our study. Providers in these settings will be informed of the availability of an exercise program for patients with comorbid chronic pain and PTSD and they will be given a complete list of inclusion and exclusion criteria. The PI will attend at clinical/administrative rounds to introduce the study to providers. When potential participants are self-referred, the patient's primary care provider will be contacted to ensure that there are no clinical contraindications for participation.

Recent statistics indicated that the VABHS Primary Care Clinics has approximately 36, 300 Veterans enrolled and is consistently increasing due to the return of OEF/OIF/OND Veterans. Given that chronic pain has been identified as one of the primary reasons for visits to a primary care provider, it is anticipated that there will be a significant number of chronic pain patients from which to recruit. An examination of the chronic pain population in the VABHS referred to the Center for Pain Management in the past couple of years indicates that approximately 39% are also diagnosed with PTSD.

The National Center for PTSD-Behavioral Sciences Division maintains an electronic database of potential research participants. The database contains relevant screening information from patients and non-patient research participants seen in the PTSD Clinic (e.g., medication status, age, years of education, etc.). Participant entry into the database is done on a voluntary basis and written consent for future contact has already been established. The system currently contains data on over 350 potential research participants. Once IRB approval is in place for this protocol, we will request permission to use this database as a recruitment source.

We will be recruiting through a non-VA research team that works between two local sites - the Brigham and Women's Pain Management Center and the Martinos Center for Biomedical Imaging at Massachusetts General Hospital. Their active study, titled the COMFORT study, is presently recruiting participants for fibromyalgia, and will often receive chronic pain patients who do not have fibromyalgia but may be eligible for our study. We will provide them with recruitment materials (currently approved pamphlets) to provide to patients who are ineligible for their study so that we may be able to boost our recruitment. The study staff with COMFORT will not be screening participants for us, and will only be providing patients who fail screening for the COMFORT study with our information as an alternative study to participate in. No sensitive information that has been collected by the COMFORT staff will be shared with our facility. We will use our approved phone screen to screen such participants as they call into our study. In addition, we will be providing patients at our facility who fail screening the opportunity and information to participate in the COMFORT study in

the same way. We will provide them with contact information for the COMFORT study via a flier the COMFORT study has provided our team. We will not be screening participants for the COMFORT study and any sensitive information we may have collected from participants during our screening session will not be shared with the COMFORT study staff.

With respect to the recruitment of women, my mentor Dr. Rasmusson is a research affiliate of the Women's Health Science Division, National Center for PTSD, which is directed by Dr. Patricia Resick, who is also a consultant on this project. Thus, Drs. Rasmusson and Resick will be instrumental in the recruitment of women into the study from that venue. Patients responding to advertisements or otherwise referred will be directed/asked to telephone the PI or a psychology technician to be scheduled for an in-person screening evaluation. Within the past decade, there is an increasing trend of women Veterans receiving care in the VA due to the significantly increased number of women serving in the current OEF/OIF/OND conflicts. [68] Also, VABHS is a unique site given the co-location of many women Veteran services, such as women's primary care, the Women's Health Sciences Division of the National Center for PTSD, and one of the few Women's Stress Disorder Treatment Teams (WSDTT) in the country. These services draw women Veterans from all over the country. Currently, 3,238 women Veterans are using care at VA Boston, of which we serve 3100 in women's primary care and 276 in the WSDTT. Nevertheless, we anticipate some difficulty reaching our projected recruitment of 50% women Veterans. Therefore, we will also target women in the community (Veterans and non-Veterans) and our research technician will post advertisements in local areas such as community mental health centers, coffee shops, laundromats, local newspapers and college campuses, as well as online sites such as Craigslist. We have already successfully implemented these strategies for our other research studies including women and are confident that we will be able to recruit the required number of women for the proposed study (n = 30) in order to conduct gender comparisons.

Screening Evaluation for Study Eligibility: If considered potentially eligible and interested, participants will be invited for an in-person screening session in which they will first complete the informed consent process, according to the guidelines established by the Institutional Review Board (IRB) at the VABHS. After providing informed consent, the subject will answer assessment questionnaires and receive a physical examination, laboratory blood tests, a urinalysis, a urine toxicology test for illicit drugs, and an EKG. In addition to the initial qualitative "yes/no" test for tobacco use, we will test participants' urine cotinine level using Nymox NicAlert semi-quantitative test strips. Cotinine is the principal metabolite of nicotine and has a longer half-life (18 hrs vs. 2 hrs), and thus can be reliably used to estimate daily intake of nicotine. Cotinine tests will detect any tobacco use for the past few days, and therefore will be sensitive enough to test for any recent tobacco use when participants present for exercise assessment sessions. Although we will not be excluding tobacco users from the study, any level of tobacco use can impact accurate measurement of the antistress and antinociceptive neurohormones under investigation, therefore it is imperative that we are able to capture the level of cotinine for the participants who smoke and verify the non-smoking status of participants who identify as non-smokers. Finally, women will receive a urine pregnancy test at all in person study visits. The physical screening will be performed by Dr. Rasmusson or her medical fellows.

**** Parts of the physical examination, lab tests, or the EKG and psychiatric assessments may be repeated in order to clarify results, or to track or evaluate possible medical/psychiatric problems during the study. To do this, the participant may be asked to return for an extra visit for which he/she will be compensated.**

****If a month or more of time lapses between the screening session and the baseline cold pressor assessment sessions, we will repeat the CAPS-5 to re-determine PTSD status, prior to any study procedures with the exception of the urine testing. Regardless of the outcome of the assessment, the participant will be compensated for the full amount of the cold pressor session.**

Potential chronic pain participants will participate in a one-time meeting with an MD or Co-I, who specializes in rehabilitative medicine, for confirmation of an ICD-10 chronic pain diagnosis and to receive medical clearance to exercise. The screening evaluation will also include a semi-structured interview from which important demographic and descriptive information will be obtained. The assessment will include the Structured Clinical Interview for DSM-5 (SCID) and the Clinician Administered PTSD Scale (CAPS-5). 1. These assessments will be administered in order to confirm a diagnosis of PTSD by the PI or other PhD-level trained staff. The CAPS-5 specifically will be done either in-person or over the phone in a private room during their appointment at VA Boston. CAPS-5 assessments over the phone will only be conducted when the PI, or other approved PhD level staff, is present at VA Boston. If over the phone, the CAPS-5 data will be input directly into our secure data drive via VPN access with a VA-issued laptop, therefore there will be no hardcopy data kept remotely. In the event of an emergency during the CAPS-5 telephone assessment, Dr. Scioli and her team will be on the floor during the assessment and Dr. Scioli, as the PI, will intervene to ensure safety as indicated in the human subjects section, part B, below. The assessor over the phone will be in direct contact with Dr. Scioli via email or text and can indicate and emergency without patient identifiers. VA TBI screen will be administered to identify those potentially suffering from comorbid TBI. These assessments will be audiotaped for purposes of diagnostic consensus and will follow IRB guidelines for storage and disposal based on the VA retention schedule. The PI or other PhD-level trained staff will be administering these assessments for which she has received formal approval. Self-report measures of pain, PTSD and exercise motivation also will be administered. Patients meeting inclusion criteria will be offered participation in the remainder of the study. All patients who decline the study or do not meet study criteria will be given feedback on the evaluation results and offered an alternative treatment (e.g., pain management and/or PTSD treatment offered through the VABHS). Individuals who are not Veterans will be given a referral list of chronic pain and PTSD providers in the surrounding area. The entire screening evaluation will take approximately 3-4 hours to complete. A timeline for the administration of the assessment instruments is provided below, after the next section.

**** The laboratory blood tests will include a complete blood count, other red blood cell or iron indices if indicated, B12 or possibly folate levels, electrolytes, glucose measure(s), liver function tests, a hepatitis screen if indicated, cholesterol or other lipids if indicated, thyroid function tests, or other tests that may be needed to evaluate a specific medical problem you might have. Women may receive a follicular stimulating hormone (FSH) level test to determine if they are perimenopausal.**

****Additional blood tests will be administered during the baseline cold pressor, mid-point and endpoint assessment sessions. These tests will measure vitamin D3, sedimentation rate CBC, C-reactive protein, and a lipid profile in order to explore the potential association of changes among these labs over time with potential improvements in chronic pain symptomatology over time.**

Overview of Experimental Testing Procedures:

****Please note that if an unforeseen circumstance arises such that the in-person scheduled assessment session needs to be cancelled, this session can be reschedule. For women participants, the session would need to be rescheduled during her follicular phase such that it could take up to an additional 28 days for the rescheduled session.**

Scheduling for Women: For each MAX-EX test, female participants will be scheduled between 2 and 7 days after the start of menstruation during the early follicular phase of the menstrual cycle when both progesterone and estrogen levels are at their lowest and comparable to levels in male participants. For women who are perimenopausal/menopausal, they will be scheduled during the same timeline as the male participants.

For participants on any medication that could put them at additional cardiac risk during the MAX-EX test (baseline and endpoint)**, an additional EKG will be done on the morning prior to MAX-EX testing and will be reviewed by the covering cardiologist immediately. Should the EKG indicate that CPX testing will put the participant at any additional cardiac risk, the participant will be withdrawn from the study; however he or she still will be paid in full for the session.**

Cardiopulmonary Exercise Test (CPX): All participants will complete a MAX-EX test within one to five days of the cold pressor test session (see below under Cold Pressor Test Session). During each test, we will be using rigorous means to control for the many confounders that potentially impact baseline NPY and ALLO levels as well as the pattern of neurotransmitters, peptides, and steroids released in response to exercise. Once eligibility is confirmed, the participant will present as scheduled, for the exercise testing session at the Clinical Studies Unit (CSU) and the entire session will take place between 8am and 12pm. In addition to our stringent, inclusion/exclusion criteria, participants will have been instructed to abstain from food and beverages, except for water, after midnight the evening before and to abstain from breakfast at home on the day of the testing procedure. Upon arrival at VABHS, the subject will be given water and power bars (6 kcal/kg) to provide the same baseline caloric load for all participants. The "breakfast" will be provided two hours before exercise, so that feeding-induced increases in ACTH, cortisol, glucose and other reactants will have returned to baseline before the first baseline blood sample is taken. During this time, they will also be completing self-report questionnaires (see Table 2). The MAX-EX testing will be performed in accordance with guidelines published by the American College of Cardiology.[69] Participants will sit in a comfortable chair for 60 minutes prior to testing. A catheter will be placed in a large superficial vein of the left arm. Once ready for exercise testing, the participant will be transported to the exercise testing room via wheelchair. The participant will then be shifted onto the upright testing bicycle and electrocardiogram electrodes will be applied at least 15 minutes prior to testing. During the MAX-EX, oxygen consumption (peak VO_2) and ventilatory anaerobic threshold (VAT),

will be measured in order to assess fitness capacity and correlate with blood lactate, ALLO and NPY levels sampled at each increase in exercise load. Participants will exercise using a standard bike protocol with 2 minute stages. After an unloaded warm-up stage, all subjects will complete the first stage with 50W of resistance. Based on the subject's size and baseline fitness level, the stages will increase in increments of 20, 25, or 30 W at the discretion of our experienced exercise physiologist. Adjustments to incremental increases may also be made by the exercise physiologist to allow subjects to reach their maximum exercise capacity within comparable ~15 minute time frames. Confirmation that the subject reached VO_2 peak will be based on meeting 2 of 3 criteria: 1) respiratory exchange ratio >1.1; 2) plateau of the VO_2 with increased load; 3) achievement of age-targeted heart rate; 4) the patient is no longer able to continue or it is medically unsafe for them to continue. If at any time, participants wish to terminate or are unable to perform the exercise assessment, we will terminate the session after an appropriate and safe cool-down period. During the MAX-EX test itself, plasma will be drawn at the end of each stage, so that changes in plasma levels of the neuromodulators of interest can be linked in real time to changes in the oxidative status of the participant (anaerobic versus aerobic). Blood sampling will be performed at two points prior to exercise (-15 minutes and -0 minutes), during the last 30 sec of each exercise workload, and at 5 and 30 minutes post exercise testing for measurement of the steroids and neuropeptides of interest.

All MAX_EX assessment visits and training sessions will be conducted by a team of ACLS credentialed staff (cardiologist, nurses, and exercise physiologist). A defibrillator and code cart are maintained in the immediate vicinity. Consistently, CR and CSU staff participate in regular mock emergency codes to maintain expertise with emergency management. Furthermore, visits will only be completed during the time that the Urgent Care Center is open and when the hospital code team is available for emergency responses.

Cold Pressor Test (CPT): Measures of pain sensitivity will be obtained using the CPT, a procedure that has been used widely in laboratory studies to measure pain perception and tolerance, [70] as well as self-report measures of pain severity and disability and exercise motivation (Appendix 1). The cold pressor protocol will follow guidelines from a previously published study investigating similar variables.[70]Chronic pain mentor Dr. Otis, who has experience administering the cold pressor test, will provide supervision. Participants will be instructed to hold their right hand in temperature-controlled ice water, inside a cold pressor apparatus, up to their wrist and to keep the hand still. They will be instructed to say when they first experience pain and will be told to withdraw their hand when the pain becomes intolerable. Therefore two measures of pain sensitivity will be derived: "pain threshold" and "pain tolerance". Pain threshold is defined as the number of seconds between hand immersion in the ice water and the first report of "pain." Pain tolerance is defined as the number of seconds between hand immersion and hand withdrawal from the water. A maximum seven-minute time limit for immersion, unknown to the patient, will be imposed. The CPT will be obtained: A) in relation to the acute maximum load exercise assessment (pre- and post-CPX), and B) in relation to progressive exercise training (before, at mid-point, and after completion).

A) Participants will perform baseline pain ratings and the CPT in the late morning **one to five days before** each CPX, two and a half hours after IV placement and the breakfast of power bars provided. Blood will be sampled from the IV for ALLO+PA measurement just prior to the pain ratings and CPT. Participants will have fasted since midnight, as per procedures for the CPX. The post-CPX pain ratings and CPT will be performed on the day of the CPX, immediately after the 30' post-CPX blood drawing for ALLO+PA. Obtaining the baseline and post-CPX pain assessments at the same time of day on two separate days will control for potential effects of diurnal variation on pain sensitivity, as well as ALLO+PA levels.

B) The procedures in A will be completed before and after completion of the chronic exercise training program.

C) In addition, the baseline pain ratings and CPT procedures in A will be performed at the mid-point of the progressive exercise training program.

D) After the first CPT visit, research study staff will program, explain and show the participant how to attach the activity monitor (known as an Actigraph) to record the participant's physical activity during exercise training sessions throughout the progressive exercise training phase of the study. Participants will be asked to wear the monitor only during exercise training sessions (three times per week) to evaluate change in physical activity over time.

****For a timeline of Assessments please refer to Table 2 at the end of the protocol.**

*****Please note that if any abnormalities occur during the MAX-EX testing, the participants physician will be contacted and further testing may be recommended. If referred for further testing participants will need physician clearance prior to being able to continue in the study or may be terminated from their participation in the study.**

Chronic Exercise Rehabilitation Training Program

In an effort to design an effective and safe exercise program for a population with chronic pain and PTSD, we reviewed exercise studies in chronic pain, PTSD, heart failure, and cardiovascular disease populations, which may all share pathophysiological characteristics [7]. We determined that a "progressive" training method is likely to provide the most clinical benefit as well as reduce the risk of exercise related adverse events in this vulnerable population. [80-81]Specifically, we plan to prescribe a 12-week, moderate to vigorous intensity progressive aerobic exercise training regimen to ease sedentary trauma exposed controls as well as chronic pain and PTSD patients into exercise. We believe that this design will both maximize the clinical benefits of the intervention for most patients, as well as allow us to investigate relationships between exercise-induced changes in chronic pain and PTSD symptoms and changes in ALLO+PA physiology.

Progressive Exercise Training: According to Goodrich, Larkin, Lowery, Holleman and Richardson,[73] progressive exercise training can help to minimize the risk or occurrence of a range of exercise-related adverse medical events, particularly with the complex study population which will be starting at a sedentary level and therefore, may not be able to initially achieve the heart rate goals prescribed in standard exercise training protocols.

The exercise prescription will be individually designed and geared toward an intensity manageable by the individual. It will also be relatively easy to integrate into an individual's personal lifestyle. As an example, an individual will be instructed to wear a pedometer and heart rate monitor and progressively increase walking duration and intensity over each week. The devices will be programmed by the exercise physiologist and will allow the participant to walk at a frequency, intensity and duration in accordance with a target heart rate reserve range (HRR) defined by resting and peak heart rates established during baseline MAX_EX testing. The devices will record the activity performed by the participant and allow the exercise physiologist to adjust instruction accordingly when the participant returns to the clinic each week. This will minimize improper performance of the exercise prescription as well as exercise and non-exercise related adverse events. Along with close monitoring by study staff, (i.e. weekly telephone calls and check-ins as well as the end-point in person MAX_EX assessment), we believe that this method would feasibly, safely and effectively promote the progressive realization of potential biological benefits of the full exercise program. Ultimately, this method will start each participant at a level of intensity that matches their capability/ability level and progressively move them towards achieving the heart rate goal of ≥80% of their HRR.

Summary of Approximate Weekly Telephone Calls:

The PI or other trained study staff will provide check-in telephone calls, based on the mutual agreement between participant and study staff, to each participant at week 4, when the participant is primarily exercising at home, and week 10, toward the end of the participant's exercise prescription. Assessments of exercise motivation will be made during these calls. Other data points with these measures will be gathered in person at baseline, midpoint, and endpoint sessions. There will also be "approximately weekly" check-in telephone calls for motivational enhancements without assessments for the purpose of helping the participant maintain compliance with their exercise prescription.. Just prior to each of the assessment based phone calls, the TTM exercise stage of change, self-efficacy, decisional balance and processes of change measures will be administered in order to determine which stage of the telephone script (see Appendix A) to intervene with, as well as which processes of change to highlight during the telephone intervention. Based on the TTM stage of change measure, if a person has not been exercising at all in the past six months and is not planning to at any point in the near future (within the next 6 months), the calls will start at the Pre-contemplation stage in order to help increase readiness for exercise initiation. If the person is contemplating exercising in the near future (at some point in the next 6 months), the calls with start at the Contemplation stage in order to increase readiness. If the person is ready to being exercising at some point within the next month, the calls will begin at the Preparation stage. If the person has begun exercising within the past month, the calls will begin at the Action stage. If the person has been exercising regularly for the past six months, the calls will begin with the Maintenance stage. Please note that we anticipate all participants will start the calls in the Action stage since they will have started their exercise prescription, however, we recognize that over-time, they may encounter real and/or perceived barriers to staying in the action stage and could likely revert to an earlier stage of change. Thus, the staging measure will be needed for the beginning of each call and the additional measures will let the telephone counselor know which processes of change, etc. to highlight during the implementation of the telephone script. The overall goal of the phone sessions are to help increase the participant's motivation to stay on track with their exercise prescription.

This proof-of-concept pilot study is among the first to investigate antinociceptive neurobiomarkers that may be implicated in comorbid chronic pain and PTSD. We think that the exercise training methodology to be employed will yield maximum results (i.e. increases in the capacity for both ALLO +PArelease and improvement in patient symptomatology and overall functioning). This

progressive exercise training method has been found to be efficient and is the standard prescription for most exercise training programs to date.[83] It is also in line with time-based activity pacing used in the rehabilitation of chronic pain populations to minimize disability and maximize activity over time. 74

Taking the above into account for this pilot study, we propose the following exercise prescription after baseline maximum load exercise assessment:

Progressive Exercise Program: Based on the "Active Physical Treatment Model" [75-76] individuals with chronic pain are primarily sedentary and physically deconditioned and need a progressive approach to work up to standard exercise prescriptions as defined by the ACSM.

A. Exercise Prescription:

Weeks 1-2:

Warm-up: 5-10 minutes, light walking at 30-50% of HRR

Exercise: walking for 30 minutes at 40-60% of HRR (based on baseline MAX-EX test)

Cool-down: 5 minutes, gradual reduction in walking intensity to target HRR: 30-50%

Weeks 3-4:

Warm-up: 5-10 minutes, light walking at 30-50% of HRR

Exercise: walking for 30 minutes at 50-60% of HRR (based on baseline MAX-EX test)

Cool-down: 5 minutes, gradual reduction in walking intensity to target HRR: 30-50%

Weeks 5-6:

Warm-up: 5-10 minutes, light walking at 30-50% of HRR

Exercise: walking for 45 minutes at 60-70% of HRR (based on baseline MAX-EX test)

Cool-down: 5 minutes, gradual reduction in walking intensity to target HRR: 30-50%

Weeks 7-12:

Warm-up: 5-10 minutes, light walking at 30-50% of HRR

Exercise: walking/running for 45 minutes at 70-85% of HRR (based on baseline MAX-EX test)

Cool-down: 5 minutes, gradual reduction in walking intensity to target HRR: 30-50%

B. Exercise Implementation:

BaselineInitial MAX-EX test.**Weeks 1- 3:** Exercise 1x/week in clinic and 2x/week at home

** Please note these exercise training sessions will be scheduled based on the mutual agreement between participant and study staff and are therefore subject to change.

Weeks 4-12: Exercise 3x/week at home. Motivational telephone calls by psychologist at weeks 4 and 10. There will also be an approximate 1x/month check in with the exercise physiologist to allow actigraph data to be downloaded and a modification to the exercise prescription if indicated.

****Week 6**: The midpoint check in will consist of implementation of the cold pressor pain threshold test and self-report assessment measures in order to capture change in pain, mood, PTSD and exercise motivation outcome variables.

Week 13-15: Final MAX-EX test.

**Please note, after completion of the study, two follow-up phone calls will be administered at 1-month and 6-months post-study. Please see the timeline of assessments for the questionnaires to be administered during these calls. Such follow-up will allow us to administer the necessary mood, pain, PTSD severity, exercise behavior and exercise motivation questionnaires to help determine if post-exercise intervention improvements have been sustained or help us to identify barriers for sustaining improvements made while in the active phase of the study.

Summary of Exercise Training Implementation: Upon completion of the initial MAX-EX and cold pressor test sessions, each participant will be instructed to return to VABHS for 2 exercise training sessions with our experienced exercise physiologist who will teach them how to conduct their exercise regimens. After these two sessions, the exercise physiologist will instruct the participants to gradually increase the frequency of their prescribed exercise sessions at home to 3x/week by week four. During weeks three and twelve, when the participant is primarily exercising at home, the PI or other appointed and trained research staff will call the participant in order to provide a brief check-in and to discuss any barriers to exercise the participant may be experiencing at home. The PI, who is trained in the identification of barriers to maintaining exercise compliance, will use basic motivational interviewing techniques (i.e. reflective listening) and problem solving strategies, (the current standard of care in this area), in order to facilitate exercise compliance while maintaining participant safety. (Data from this pilot study thus could guide future development of a standardized motivationally based exercise behavior change intervention aimed at promoting long-term exercise adherence in this population.) At weeks 13-15, participants will complete a final MAX-EX, pain ratings, and CPT to assess any changes in their psychological, neurobiological, and pain responses to chronic exercise.

To allow verification of the participant's exercise at home, the participant will wear an actigraph and heart rate monitor to measure overall activity and heart rate, respectively. During exercise, the pre-programmed heart rate monitor will "beep" when the participant needs to increase exercise intensity. Use of this device will ensure that participants are achieving the targeted heart rate range (HRR) in accordance with their individualized progressive prescriptions. This will ensure standardization of the exercise prescriptions and also minimize errors. Participants will be trained in the use of their device during initial exercise sessions in the clinic and will be instructed to call if problems arise. Data collected from the heart rate monitor will be downloaded when the participant returns to the clinic for their monthly check-ins during weeks 4-12 (when they are primarily exercising at home), as well as at the end-point maximum load exercise session. During the check-ins, participants will meet with the exercise physiologist in order to ensure understanding of the exercise prescription and how to perform it properly. The data from the devices will provide objective data to confirm whether the participant is complying with the exercise prescription. The data will also be used to support future funded studies aimed at refinement of individualized exercise prescriptions for chronic pain/PTSD patients, as well as the development of a motivationally-based exercise behavior change protocol tailored to this population that may serve to augment other treatments for pain and PTSD.

Finally, we recognize that throughout a more "chronic" exercise training program of 3 months, participants who are more recent alcohol or substance remitters may face challenges that could increase risk for relapse. Therefore, the PI will monitor participants for relapse risk during the initial and endpoint screening sessions, as well as during the weekly phone call sessions and interim visits to the clinic for exercise training. If the participant reports a lack of appropriate social support or exhibits high levels of acute distress related to craving, psychiatric diagnoses or environmental stressors, he/she will be referred to appropriate clinical care to help with sustainment of remission. The PI will continue consultation with providers in order to assess the efficacy of such interventions. If the participant relapses or continues to display significant levels of distress or risk for relapse such that continued participation in the protocol is contraindicated, the participant will be terminated from the study and referred for further evaluation and clinical care as appropriate.

Blood Drawing: We will draw 10 cc of blood at the screening session. We will draw 20 cc of blood before the CPT or MAX-EX sessions. At the MAX-EX testing sessions only, we will also draw 20 cc at the post MAX-EX (5 and 30 minute) blood drawings. We will draw 4 cc of blood at each step increase in exercise load during the MAX-EX. At the CPT sessions only, we will draw 10 cc of blood at the t post 45 minute CPT blood draw. Previous experiences shows that participants tolerate blood drawing at this level during exercise testing without difficulty**.** Therefore, a total of ~300-316 cc of blood will be drawn during the study which corresponds to a little more than half the amount of a standard blood donation.

Blood Processing: The blood will be collected in EDTA tubes and placed immediately on wet ice; it will be spun within 20 minutes of collection at 3000 rpm for 15 minutes in a refrigerated centrifuge before aliquoting into tubes for storage at -70 degrees C until assays of the neurosteroids/peptides of interest are performed, as well as for DNA and RNA testing in order to assess gene regulation and expression. For the samples that are collected after the CPX tests and at the first exercise training session, Dr. Rao Prabhala will transport the samples, in a safety transport container, to his lab at the West Roxbury VA (room 2c-109, Building 3). There he will conduct molecular profiling in order to better delineate immune cell functioning in relation to the GABAergic neuroactive

steroids we are investigating. Specifically, he will be measuring immune cells (T and B lymphocytes, NK cells and monocytes) and their cytokines at cellular and molecular level.

Biological Assays: The plasma ALLO (allopregnanolone and pregnanolone, which are equipotent stereoisomers) will be measured using gas chromatography-mass spectrometry (GC-MS) after high performance liquid chromatographic (HPLC) separation of the steroids using methods similar to those reported in Rasmusson et al., 2006. The blood, DNA and RNA samples may be sent outside of the VA for analysis, as well as to VA labs, because many of measurements important to this research study cannot be made at VA laboratories. For example, we will send blood plasma samples to the lab of Dr. Grazianno Pinna to assay the full Allopregnanolone pathway: Pregnenolone; Progesterone; Allopregnanolone 3a, 5a; Pregnanolone 3a, 5b and the isomers (IsoAllo 3b, 5a, IsoAllo 3b, 5b). The address and points of contact for this lab are as follows:

Graziano Pinna/Raquel Romay
The Psychiatric Institute, Lab 256
The University of Illinois at Chicago
1601 W. Taylor Street
Chicago IL, 60612

For genomic analyses (e.g. genotyping, gene expression and epigenetics, etc) of our DNA and RNA samples, in which we will address the effects of exercise, one of these laboratories is located at the Boston University Medical School Campus (Evans Building, Room E315 on 72 East Concord street in Boston, MA 02118), with Dr. Huiping Zhang as our point of contact with the facility. To maintain participant confidentiality, these samples will only have the participant research code and will otherwise be stripped of any information that could identify him/her to outside researchers. Approval will be obtained from the VA IRB before such samples or data related to these samples are sent to outside researchers. Only VA-approved non-VA labs that have formally agreed to maintain data confidentiality will be used.

Data Analysis Plan:
Power and Sample Size Considerations: Power calculations were carried out based on available studies in the literature that investigated ALLO in chronic pain populations[42] or ALLO+PA in PTSD populations.[24,35] Achievement of a Cohen's effect size of .35 will suggest statistically and clinically significant effects of the treatment. Thus, in order to obtain a power of 90% at the 5% level of significance (2 tailed), a sample size of 25 participants will be required. Due to an expected drop out rate of 18-20%, the proposed recruitment is 30 participants, yielding a power of .94.

Data Analyses: Baseline demographics and descriptive variables (e.g., age, gender, pain duration) will be summarized for each of the two treatment conditions. Descriptive summaries for continuous variables will be presented in terms of means and standard deviations while discrete variables will be summarized in terms of
relative frequencies and percentages. For aim one, latent growth curve modeling will be performed. This approach is most effective for analyzing change over time, as well as capturing individual differences across all three time-points (baseline CPX assessment, midpoint self-report session, post exercise training CPX assessment). This approach does not assume a linear trajectory and is thus ideal for the current proposal. According to Needham, Espel, Adler and Kiefe[77] with this approach, the latent growth curve analysis will use repeated measures of each construct in order to estimate the underlying growth trajectory by computing the intercept and the slope, also known as the latent factors. The intercept can also be considered the starting point or baseline and the slope is the rate of change across time.

Aim 1 : Hypothesis one will be evaluated by conditional LGMs. The Intercept of the LGM
will be centered on the self report data from the baseline CPX assessment (i.e., first Slope loading will be fixed to 0.0). The intermittent time point (midpoint self-report session) will be freely estimated and the final time point (i.e the self-report data from the 13 week MAX-EX test session) will have a corresponding Slope factor loading fixed to 1.0. Accordingly, the mean and variance of the Slope factor will convey the fixed (average) and random effects (individual differences) of change for the time interval of interest. The two study groups will be dummy coded (using chronic pain/PTSD as the reference condition in the initial models) and included as predictors in the LGM to account for individual differences in symptom reduction (i.e. pain intensity, pain tolerance and threshold, depression and PTSD symptoms) due to treatment assignment. The Intercept will be regressed onto the treatment covariates to examine any pre-exercise training differences among treatment conditions. Moreover, individual differences in pre-treatment functioning will be held constant by regressing the Slope onto the Intercept. Hypotheses 1 will be supported in part by the statistical significance of the study group (dummy code) > Slope paths. In fact, these paths reflect study group x Time interaction effects. The nature of these interaction effects in the LGMs will be characterized using the procedures described by Curran, Bauer, and Willoughby.[78] All outcome measures will be analyzed in this fashion.

Aims 2 & 3: At both exercise assessment time-points, change scores will be computed ALLO+PA and these will be correlated with pain tolerance and pain threshold scores using Pearson or Spearman correlations, as appropriate. For exploratory purposes, ALLO+PA will be used as predictor variables in a regression equation to predict pain outcome (tolerance, threshold and intensity).

Exploratory Aim: Pearson or Spearman correlations, as appropriate, will be computed to assess interrelationships among ALLO+PA exercise motivation, self-efficacy, pain sensitivity, severity and disability, PTSD severity, and depression. Based on the findings of these correlations, biological (ALLO +PA) and/or psychological markers (e.g., self-determination or self-efficacy for exercise) will be entered as predictors in separate multiple regression equations to predict pain sensitivity, pain-related disability, PTSD and depression.

Limitations: The proposed study has several limitations that may be addressed in future research. First, this study does not consider other types of chronic pain conditions (i.e. neuropathic and fibromyalgia). Second, potential effects of additional forms of exercise (i.e. weight training) are not taken into account in a rigorously quantitative way, though we will consider this variable more qualitatively in data analyses. Third, the impact of phase of the menstrual cycle cannot be studied given the time and financial resources available; instead we have elected to study all menstruating women during the follicular phase and

perimenopausal/menopausal women who are within our target age range. During this phase, estrogen and progesterone levels are low and stable and approximate levels seen in men. In addition, previous studies suggest that pain sensitivity is greatest for women during this phase and published data from Dr. Rasmusson's laboratory has shown cerebrospinal fluid allopregnanolone levels in women with PTSD to be substantially lower than in healthy controls during this phase. Finally, the duration and intensity of the exercise component needed to induce changes in the neurobiological parameters of interest is a factor that will have to be considered in greater detail in future studies based in part on pilot data to be collected in the current study.

(c) Human Studies Section

(1). Risk to Subjects:

(a)Human Subjects Involvement and Characteristics: Participants in the proposed research project will be participants who are currently receiving care at VABHS. Due to the lower rates of women in the VA system, women participants will also be recruited from the community since it is often difficult to recruit the required number of women Veterans, among the four study groups, in order to conduct gender comparisons. In addition, while we plan to recruit the majority of our male participants from the VA, when there is also a similar difficulty in recruiting the required number of men Veterans, we will also recruit from the community. The eligibility criteria is as follows: Participants will be 30 participants receiving care in the VABHS or recruited from the community. Inclusion criteria for the proposed study will permit the recruitment of men and women, at least 18 years of age, who are from all ethnic and racial backgrounds, and able to speak and understand English. The patient population at the VABHS is 65% Caucasian, 15% African American, 10% Latino, and 10% Asian. We anticipate that a substantial percentage of the sample will be members of minority groups who are widely served by the VABHS.

Inclusion Criteria: Only participants in whom a physical examination, medical history, EKG, and baseline laboratory studies including urine toxicology screens indicate that maximum load exercise testing will be safe will be included in this study. Participants must be free of medications and other substances (e.g., illicit drugs and alcohol) with effects that could hinder data interpretation for 2-6 weeks depending on the medication and frequency of use (which must be cleared by the PI's primary mentor). If on pain medications with short half-lives, must be off of them for 5 half-lives before testing, generally about 24 hours. Any participant with an ICD9 chronic pain diagnosis, with a musculoskeletal etiology, as confirmed by Dr. Tun, will be allowed for inclusion in the study. Also, any participant with *a* confirmed psychiatric diagnosis of PTSD (PTSD/chronic pain group), or have trauma exposure without a diagnosis of PTSD, other psychiatric conditions, or chronic pain will also be included in the study. Individuals with PTSD must meet for current chronic PTSD ($\geq$3 months) as assessed by the CAPS 1-Month Diagnostic Version.

Exclusion criteria: Participants will be excluded from participation in the study if they have a life threatening or acute physical illness (e.g., cancer), current schizophreniform illnesses or bipolar disorder, or active suicidal or homicidal ideation requiring clinical intervention. Women participants who are pregnant or are intending to become pregnant within the next six months, will be excluded from participation. Individuals with current or past alcohol and/or substance dependence (less than three months from date of screening assessment) will be excluded. Individuals seeking pain treatment such as surgical interventions or who have a neuropathic

originto their pain or fibromyalgia will also be excluded. Participants with chronic pain concerns that cannot tolerate exercising in a reclining bike and those who have had a clinical history of coronary artery disease or positive stress test, uncontrolled cardiac arrhythmia, moderate-to-severe aortic stenosis, severe arterial hypertension (systolic >200 mmHg, diastolic>110 mm Hg) and more than first degree atrioventricular block also will be excluded from participation.

(b) Sources of Materials: A significant source of the data from participants will come from the data that they supply as part of their involvement in this trial (e.g. outcome measures completed by participants). Additional information will come from review of the participant's medical record. The National Center for PTSD-Behavioral Sciences Division maintains an electronic database of potential research participants. The database contains relevant screening information from participants and non-patient research participants seen in the PTSD Clinic (e.g., medication status, age, years of education, etc.). Participant entry into the database is done on a voluntary basis and written consent for future contact has already been established. The system currently contains data on over 350 potential research participants. As indicated in the research plan, we also plan on collecting plasma samples in order to measure ALLO+PA and other steroids of interest pre and post exercise and cold pressor test sessions. We will only use such samples for purposes of conducting the present research and no existing samples will be used. We will only use these biological samples from non-Veterans when we recruit non-Veterans from the community because it is difficult to recruit the required number of men and or women among the four study groups and meet the current eligibility and inclusion criteria.

(c) Potential Risks: The potential physical, psychological or other risk to participants who participate in the proposed research study characterized as minimal. Since participants will be completing questionnaires and receiving an exercise test, there is a slight possibility that some participants may experience psychological discomfort in reflecting on his or her own medical and psychological health conditions. The PI, as a trained clinical psychologist, will be able to provide thorough assessment in the event of a participant's adverse reaction to the questioning and/or intervention. Appropriate intervention and/or referral for more intensive treatment can be provided, if needed. There are additional physical risks associated with the exercise and cold pressor test session which are outlined in the **"Protection Against Risk"** section below as well as our plan to minimize such risks. No other known physical, social or legal risk associated with participation in the proposed research project is identified.

(2). Adequacy of Protection From Risks:

(a) Recruitment and Informed Consent: Issues related to recruitment and obtaining informed consent is relevant to the proposed study. Informed consent will be obtained by the PI or trained research technician at the pre-treatment assessment session. A witness, who is a VA staff member but no identified on the study protocol, will be available to witness the consent. It will be obtained from all study participants prior to participation, according to the institutional guidelines established by the Institutional Review Board (IRB) at the VABHS. Following the completion of the informed consent form, the consent form will be given to the research technician for photocopying for the participant copy as well as scanned into the participant's VA medical record. All participants who

decline the study or do not meet study criteria will be given feedback on the evaluation results and offered an alternative treatment (e.g., PTSD treatment and/or pain management offered through the VABHS or if non-Veteran, a referral to an outside provider).

The information contained within the consents form will include:

- Invitation to participate because the patient meets the criteria for pain and/or PTSD or are trauma exposed but do not meet criteria for pain and/or PTSD.
- Estimated time to complete the screening eligibility session (4 hours) as well as the exercise and cold pressor test session (~4.5 hours)
- Participation is voluntary
- Description of each study procedure (i.e. psychiatric screen, physical exam, lab work, EKG, exercise maximum load test, cold pressor pain threshold test, etc).
- Statement of the freedom to withdraw at anytime without adverse effects on their healthcare at VABHS.
- Description of potential discomforts, risks and inconveniences as well as our plan to minimize such risks.
- No personal benefit will come from participation in the research.
- Participation in research is not necessary to receive care through the pain or PTSD centers at VABHS.
- Amount of compensation provided for participation in each study session.
- Contact information for the PI (copy of consent will be provided to subject)

(b) Protection Against Risk: The primary risk associated with the proposed research plan includes psychological distress resulting from increased focus on ones' medical and psychological health problems within the context of individual interviews about such problems. To address the risk associated with psychological distress that may occur, the PI is a trained clinical psychologist who will be in a good position to provide further evaluation of the patient's distress. This evaluation may include contact with a patient's current healthcare providers, including mental health professionals, if needed. The PI will also be in a good position to make recommendations for further evaluation and/or treatment, and to ensure that such consults are placed on the patient's behalf. In addition, all participants will be provided with the PI's contact information, and encouraged to establish contact as needed. In the event of suicidal or homicidal ideation, a credentialed psychiatrist or a psychologist will evaluate any patient who reports suicidal or parasuicidal or homicidal ideation or behavior at any point during the study and refer the participant for further evaluation and treatment if indicated, against the participants will if necessary. Lastly, in the case of homicidal ideation with explicit intent to harm a named individual, the PI will report the intent to the local police as legally required to protect the named individual. The PI will contact

the participant's mental health provider (if they have one). The participant will be reminded to contact their VA providers, the suicide prevention coordinator, or the Veteran's Suicide hotline if he or she feels at risk in the future.

**Due to the nature of the exercise and cold pressor test session, there are additional risks that we have identified as well as devised a plan to minimize such risks:(1) Blood Drawing and IV Placement: Blood drawing and placement of an IV may be associated with bruising, pain, infection, or rarely, fainting. Sterile equipment and technique by used by qualified personnel while the subject is seated or lying will minimize this risk. The amount of blood sampled during this study over 4 months will be about 240 cc (or about 16 tablespoons which is equal to approximately 1/2 of a standard blood donation).

(2) Breathing mouthpiece: The breathing mouthpiece worn during exercise testing may be uncomfortable. In addition, saliva will tend to accumulate in the subject's mouth when the mouthpiece is in place. This may lead to drooling and will be uncomfortable until subjects have figured out how to swallow with the mouthpiece in place.

(3) Cold Pressor Test: While the experience of pain is an expected part of this procedure, participants will be informed during the consent process that there will be a time limit imposed (without full disclosure of the actual time limit—7 minutes) and are therefore not at risk of freezing or other related injuries to their hand.

(4) Exercise Testing:

a). Men may need to have parts of their chest hair shaved in order to attach electrodes; this hair grows back over the next few weeks.

b). Exercise assessments (clinical treadmill and cardiopulmonary exercise testing) all require people to apply themselves with great effort. Although encouragement and careful medical supervision will help to make these tests as agreeable as possible, some people might still find it unpleasant.

c). Maximal exercise testing is generally associated with a 1 in 10,000 chance of a bad reaction (heart attack of dying). In unselected populations, which include persons referred for exercise testing because of cardiac symptoms, the risk of myocardial infarction or death from exercise testing is approximately 1 in 2500. Specifically, the risk of death has been estimated at <0.01%. In an asymptomatic patient population, selected to have no history, signs, or symptoms of coronary artery disease (as in this study), the risk of harm would be expected to be even lower. However, all those enrolled will have a physical exam immediately before to best insure they are stable and they will have a cardiologist or nurse supervising the performance of the stress test to be sure they are maximally safe and well cared for if any problems develop in accordance with routine VA patient care protocols.

d). The exercise physiologist and Cardiologist/Nurse Practitioner completing the test will be ACLS certified (Advanced Cardiac Life Support). Performance of the testing in the VABHS, Jamaica Plain Clinical Studies Unit (CSU) will allow immediate access to a code cart and defibrillator. Tests will only be completed when the VABHS Code team is also immediately available.

e). Other problems that might also develop from a stress test include heart rhythm abnormalities and skin reactions to the electrode leads. The cardiologist or nurse will administer care for any problem that may arise and coordinate with the subjects' doctors (as long as release of information is provided if the subject is a non-VA patient).

f). It should be pointed out that clinical cardiac stress tests and the experimental maximum load exercise testing described in this protocol are similarly stressful to the myocardium. In addition, the criteria for stopping the maximum load exercise testing are the same as those for the clinical cardiac stress testing. Both tests take participants to maximum "volitional" exercise load unless EKG changes, BP changes, or other symptoms suggest that the participant should end exercise testing prematurely.

(5). Exercising at home:

We anticipate that the same risks during the exercise tests apply to the exercise prescriptions performed at home. However, in both the informed consent and through verbal discussion with each participant, we will encourage them to call 911 or go to the nearest emergency room for evaluation if they experience any chest pain or unusual shortness of breath or weakness while exercising at home. With respect to the chronic pain participants, we will encourage them to call the PI immediately if they experience any unusual, intense increase in their pain intensity levels during or after exercising, in order to be evaluated by Dr. Tun so that he can provide a recommendation for modification of their exercise prescription as needed. Finally, we will also encourage all participants to call us if they experience any physical injury while exercising at home so they too can receive further evaluation by Dr. Tun and modification of their exercise prescription and/or a referral for follow-up care by their primary care doctor (both inside and outside VABHS).

(6) Increase in Anxiety or PTSD Symptoms in Response to Exercise: Some PTSD patients participating in other exercise tests published by other investigators have been reported to have experienced an increase in intrusive thoughts or other reexperiencing symptoms or anxiety in response to exercise. Some patients with PTSD report that this can occur during or in response to everyday attempts to exercise as well. Subjects will be told that they can stop exercising if this occurs. In addition, the PI and primary mentor, Dr. Rasmusson, the psychiatrist present at the exercise testing, will talk with the subject to determine whether any additional treatment should be offered to help with such symptoms. The subject will be instructed to call the Biostudies Unit during the day or the VA operator to get the Biostudies psychiatrist on call after hours if an increase in PTSD or anxiety symptoms persists or occurs after the subject has left the VA. Finally,

while participants are exercising at home, they will be encouraged to call the PI if they experience any increase in their psychological symptoms during or after exercising. The PI will then be able to determine if further intervention is needed.

(7) Harm to the Fetus (Women Only): Cardiac exercise tests or the experimental maximum load exercise testing could cause harm to a developing fetus. Thus an effective method of birth control must be used during enrollment in the study. In addition, urine pregnancy tests will be performed at screening and on the day of exercise testing.

Confidentiality: The confidentiality of the information that is gathered from participants (audiotaped interviews, questionnaires) will be protected through secure storage of such media in a locked cabinet in the PI's office. Additionally, this information will be de-identified for the purposes of analysis and dissemination of findings.

The probability of **ALL of the above stated risks is expected to be low, and the steps detailed, should they be needed, are expected to be effective in minimizing and or reducing such risks.

(3). Potential Benefit of the Proposed Research to the Subject and Others:

The proposed study is consistent with VHA National Pain Management Strategy and overall mission of the National Center of PTSD, which assures that all persons cared for in the VA healthcare system can reliably count on prompt and appropriate treatment of pain and psychological distress. The proposed study seeks to evaluate the efficacy of a potential treatment that may reduce suffering from comorbid pain and PTSD and improve quality of life, overall health and well-being for our Veterans. The proposed study will address the specific objectives of the National Pain Management Strategy and mission of the National Center of PTSD and will directly address the care of participants with PTSD and chronic pain, both high priority problems within the VA.

In addition participants who participate will provide valuable information about the understudied role of exercise in the potential treatment of chronic pain and PTSD. This information will help to inform the further development and refinement of an individualized exercise treatment as well as a motivationally based exercise behavior change intervention to promote long-term exercise adherence, for individuals suffering from chronic pain and PTSD. Thus, there is considerable potential benefit for the proposed research to indirectly help research participants and others who also suffer from chronic pain and PTSD.

(4). Importance of Knowledge to be Gained: Given the high prevalence of both pain and PTSD among Veterans, particularly the high co-prevalence of these two conditions, the current research is important in that it marks a first step toward a more psychologically and neurobiologically based look at the role exercise may play in the treatment for these conditions. More specifically, the proposed research will potentially identify exercise as one mechanism that may serve to moderate or mediate the shared factors that maintain the co-prevalence of these conditions. The delineation of the role of exercise will help to inform new

treatment approaches for comorbid pain and PTSD. One such example is the potential for the development of an exercise behavior change protocol, rooted in the most evidenced-based motivational theories to date, that can either be integrated into the existing cognitive-behavioral interventions or used as an adjunctive treatment by counselors specialized in heath behavior change, thereby improving the efficacy of these interventions for this population.

(5) Resources

(a) Research Space:

(1) The proposed research will be conducted in VA space at VABHS.

(b) Other Research Resources:

The National Center for PTSD, Behavioral Science Division (BSD) at Boston, Massachusetts, under the direction of Terence M. Keane PhD, the academic advisor of the proposed study, as well as the Women's Health Science Division (WHSD), under the direction of Patricia Resick, PhD, a consultant of the proposed study, is at the forefront of efforts to develop effective assessment devices and treatment for PTSD. Current investigations address both psychological and psychophysiological procedures. In addition, the Division staff is engaged in research on basic mechanisms of PTSD as related to cognitive information processing, family and social support factors, and gender issues. Studies of behavioral treatment process and outcome comprise a third major focus of the Division research. Training activities of the Division emphasize both research and clinical skills. Dr. Scioli has also been provided with office space to use at the VABHS, WHSD throughout the duration of this study.

The VA Boston Healthcare System (VABHS) Center for Pain Management, directed by mentor Dr. John Otis, of the proposed study, is a clinical, research, and training center that has the full and continuing support of referring physicians throughout VISN 1. The Center functions as one program among a broad array of psychology programs within Medical Psychology available to practitioners and participants. Over the past several years, the Medical Psychology Section has established an effective collaborative interface with the primary care clinical settings and providers. Dr. Scioli will have access to all primary care facilities at the VABHS and has the support of the Service Line Manager of primary care to recruit participants for her research.

The Clinical Studies Unit (CSU), directed by mentor, Dr. Forman, M.D. is located on the 11th floor, C wing, of the VABHS building. HEAL exercise testing lab is 150 square feet and it is adjacent to the Clinical Studies Unit which provides four 150 square foot rooms that can be signed out for exams, assessment and interviews. Also located on the wing is a 1600 square foot cardiac and pulmonary rehabilitation and research exercise suite. Additionally located directly above this facility are research staff offices. Dr. Scioli will coordinate scheduled exercise testing sessions with the exercise physiologist and the lab will be accessible for the duration of the scheduled exercise test sessions (8am-12:30pm) and supervised exercise sessions, as well as weekly check-in sessions during the

“progressive training program. During this time, Dr. Scioli will have access to the adjacent CSU exam room for her staff to be able to prep the study participant prior to the actual exercise test procedure (i.e. IV set-up and electrode placement) as well as supervised exercise sessions. In fact the cold pressor test sessions will be conducted in this so as to control for room temperature and noise. By collaborating with mentors involved in the CSU lab, this will provide opportunities to establish longer-term collaborations as additional grant mechanisms are awarded and will contribute to the overall infrastructure and running of the CSU lab services.

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