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The Role of N-acetyl-L-Cysteine (NAC) as an Adjuvant to Opioid Treatment in Patients with Inadequately Controlled Chronic Neuropathic Pain

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THE ROLE OF N-ACETYL-L-CYSTEINE (NAC) AS AN ADJUVANT TO OPIOID TREATMENT IN PATIENTS WITH INADEQUATELY CONTROLLED CHRONIC NEUROPATHIC PAIN

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Abstract

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Introduction. While opioid medications are commonly prescribed for management of neuropathic pain (NP), long-term use has been associated with increased risk for overdose, drug interactions and addiction. New strategies are necessary to better manage chronic pain, thereby reducing need for opioid medications and their associated adverse consequences. N-acetyl-L-cysteine (NAC), an over-the-counter supplement, has shown promise in the treatment of psychiatric and addictive disorders. In addition, NAC has shown promise for reducing physiological signs of NP in laboratory rat models, prompting this study.

Purpose. The present study was an open-label clinical trial of NAC as an adjuvant to opioid treatment for poorly controlled, chronic NP. It examined whether 1200 mg NAC twice daily for 4 weeks was associated with: lower ratings of patient-reported pain; reductions in PRN opioid medication for breakthrough pain; and improvements in physical and mental health quality of life (QoL). The study also examined whether appraisal of pain impacts response to medication.

Method. Participants were N=28 chronic NP patients who consented to study participation. This consisted of 2 baseline assessments, 4 weeks of NAC and 1 post-trial follow-up visit. The majority (N=17) dropped out or were excluded during baseline. Of the remaining participants, N = 11 started the study medication and N=10 completed the study, with daily recordings of pain severity ratings and use of PRN opioid medication. Small sample size limited analyses to qualitative case reviews and effect sizes.

Results. Over 90% of participants receiving NAC completed the study. Case review found varied results. While 4 of 10 participants showed decrease in average pain ratings during NAC, estimated effect sizes for the whole sample were small, bordering on negligible (ω^2 from .003 to .027) as were those for PRN opioids (Partial Eta-Squared=.0003). Effect size for mental health QoL was medium (Cohen's *d*=.421).

Conclusions. With N=10, findings must be interpreted with caution. Nonetheless, the study found some albeit small evidence supporting NAC for improving mental health QoL and pain ratings. Several participants reported improvements in pain and mental health domains while taking NAC. NAC was well tolerated with minimal side effects. Lessons from this study will inform design and implementation of future NAC studies.

The Role of N-acetyl-L-Cysteine (NAC) as an Adjuvant to Opioid Treatment in Patients with Inadequately Controlled Chronic Neuropathic Pain

Pain is an integral part of life and is essential for survival, however, for many, it progresses beyond an acute condition and into a serious, debilitating, and chronic problem with little or no relief. It is estimated that between 19% and 25% of the U.S. population has chronic or recurrent pain, 10% report pain lasting a year or more, and 40% of the U.S. population report that pain had a moderately or severely degrading impact on their life (National Center for Health Statistics [NCHS], 2004; Kennedy, Roll, Schraudner, Murphy & McPherson, 2014)

Chronic pain is a general term that includes a large sample of diseases, illnesses, disorders and traumas (Turk & Melzack, 2011). A subset within the chronic pain grouping is chronic neuropathic pain. Neuropathic pain, or neuropathy, is defined by the International Association for the Study of Pain as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (Treede et al., 2008). A number of conditions can cause neuropathic pain and it is present in approximately 1-8% of the general population (van Hecke et al., 2014; Dworkin et al., 2007; Torrance, Smith, Bennett & Lee, 2006; Bouhassira, Lantéri-Minet, Attal, Laurent & Touboul, 2008). Neuropathic pain is generally very difficult to treat, and there are very few approaches available to prevent the development of neuropathic pain.

The range of diseases, illnesses and injuries which can result in neuropathic pain present a significant challenge in diagnosis and treatment in the clinical setting, and measurement in the research setting. While numerous treatments are available, patient response to these treatments are extremely variable and there is little understanding of which patients will benefit from a particular treatment. Complicating this further is that a portion of individuals receiving treatment will not receive any benefit from any of the available treatment approaches. A lack of response to the traditional treatment approaches, such as SSRIs, will often result in the transition to the use of long

term opioids for the management of pain. Patients utilizing long term opioid treatment for the management of their pain will often receive additional as-needed opioid medication to treat periods of increased, or breakthrough, pain.

Use of opioids in the management of chronic neuropathic pain is a common general practice (Dworkin et al., 2010), however, it is not without controversy (Fields, 2011, Dowell, Haegerich & Chou, 2016). Long term use of opioids presents some unique challenges. Management of pain is essential; however, the possibility of tolerance and dependence is a very real concern for these patients. Anywhere from 3-30% of patients prescribed long term opioids become dependent on opioids (Boscarino et al., 2010; Elander, Lusher, Bevan & Telfer, 2003; Adams et al., 2006). This concern has prompted the search for novel, non-narcotic, approaches to the management of neuropathic pain for patients who do not respond to traditional treatments.

There are a number of challenges in testing the efficacy of novel treatment approaches to chronic neuropathic pain. Research suggests that, for chronic pain patients, the psychological aspects of pain are the most salient features of the pain response (Horstman & Flax, 1999; Beecher, 1956; Ferrari, 2002; Fields, 1991). There is growing literature highlighting the importance of psychological factors in the experience of neuropathic pain, and in the assessment of these factors in novel treatment approaches (Sullivan, Lynch & Clark, 2005; Haythornthwaite & Benrud-Larson, 2000; Danie et al., 2008; Sullivan, Lynch, Clark, Mankovsky & Sawynok, 2008). Among the psychological factors that appear to impact the pain experience, the strongest empirical support is for catastrophizing (Turner & Aaron 2001) and fear avoidance (Vlaeyen & Linton 2000). Furthermore, it has been suggested in the research that the inclusion of assessments of Health-Related Quality of Life (HRQoL), including social and emotional functioning, should be assessed when analyzing analgesic efficacy (Baron, Binder & Wasner, 2010). Researchers have also suggested that the lack of treatment efficacy found in novel analgesics may be due to a focus on limited variables (e.g. pain level) and a lack of recognition of the importance of assessing multiple domains of functioning

beyond just the level of pain experienced (Foster, Hill & Hay, 2011; Turk & Okifuji, 2002; Turk & Rudy, 1988).

The present study grew out of research on Reactive Oxygen Species (ROS) and their role in the maintenance of chronic neuropathic pain (Kwak, Lim & Baek, 2011). N-Acetyl-L-cysteine (NAC), a ROS scavenger, NAC has shown promise at reducing physiological signs of neuropathic pain in laboratory rat models (Kim et al., 2004; Kim et al., 2006). In a human clinical trial investigating this supplement, researchers found that NAC administered pre and post operatively resulted in reductions in post-operative morphine use compared to a control group (Orban et al., 2006). Additionally, this over-the-counter herbal supplement has shown some efficacy in the reduction of cravings in patients with cocaine, marijuana, and nicotine addiction (Dean, Giorlando & Berk, 2011). These findings prompted the present study of NAC for patients with inadequately controlled chronic neuropathic pain.

The present study was the first to evaluate the potential benefits of NAC as an adjunct to opioid treatment for patients with poorly controlled neuropathic pain. Bearing in mind the risks associated with long-term opioid use, the importance of identifying nonopioid treatment alternatives thereby reducing the need for opioids is imperative. The purpose of the present study is to examine the addition of NAC to opioid treatment for poorly controlled, chronic neuropathic pain. We begin with a review of the literature focusing on chronic neuropathic pain, multidimensional measurement of pain outcomes, theories of chronic pain, and an overview of N-Acetyl-L-cysteine research to date. Given the variability in response to treatments, and the difficulty in measuring successful treatment response, the current study used several psychosocial variables to assess the efficacy of a novel treatment approach.

In order to determine if NAC was a beneficial adjunct to opioid treatment in this population, the following hypotheses were tested: 1) Compared to baseline, study participants will report a reduction in their use of opioid medications to manage breakthrough pain, using measures of daily

morphine equivalent dose (MED). 2) Past week VAS severity ratings for Average, Worst and Least amount of pain will be lower over the 4-week clinical trial period than those reported at baseline. 3) Upon completion of the 4 week medication trial, participants will have higher physical and mental health related quality of life scores (as measured by the Short Form-12 survey) than obtained at baseline. 4) After completing the 4 week medication trial, participants with a more positive appraisal of their pain (Low catastrophizers on the pain catastrophizing scale) will have lower Visual Analogue Scale pain ratings than participants with more negative appraisals of their pain (High catastrophizers). We reviewed the individual level data to further explore the clinical utility of NAC as an adjunct to opioid treatment for chronic neuropathic pain and identify any trends in the data. Finally, lessons learned from participant identification, study recruitment, baseline assessment measures, retention of patients in the clinical trial and 1-month follow-up procedures will be presented with focus on informing design and implementation of future NAC studies.

Review of the Literature

Chronic Pain

Chronic pain is a well-documented and prolific area of research. Chronic pain can consist of a number of different pain experiences (i.e. neck pain, lower back pain, migraines, pelvic pain). By definition it continues beyond the time expected, and shows few signs of going away (Friedman & Silver, 2007). It is a complex condition, but pain is generally defined as chronic pain when it lasts longer than six months (Turk, Wilson & Cahana, 2011). A number of different factors can result in chronic pain, including tissue trauma, acute illness, inflammation and nerve damage (Turk & Melzack, 2011). According to the National Center for Health Statistics (2006), approximately 25% of the adult U.S. population has chronic or recurrent pain, and one in ten Americans reported experiencing pain with duration of a year or more (Turk & Melzack, 2011). It is estimated that the average prevalence of chronic pain across the globe is currently at 20% (Boris-Karpel 2010). Chronic pain can contribute to declines in physical and social role functioning as well as psychological stress and suffering. Furthermore, it is estimated that chronic pain costs our society billions of dollars each year through lost work productivity, including unemployment and disability benefits, and increased health care costs associated with having the disorder. According to the Gaskin and Richard (2011, 2012), the cost of pain in the United States was recently estimated to be between $560 and $635 billion annually, including direct health care expenditures of $261 to $300 billion. Chronic pain is such a far reaching and severe problem that the U.S. Congress designated the period from 2001–2010 as the Decade of Pain Control and Research (Kerns, Sellinger & Goodin, 2011).

Neuropathic Pain. Chronic neuropathic pain is one particularly challenging subtype of chronic pain and was the focus of the current study. The International Association for the Study of Pain defines neuropathic pain as "pain arising as a direct consequence of a lesion or disease affecting

the somatosensory system" (Treede et al., 2008). A myriad of conditions can cause neuropathic pain, or neuropathy, and it is typically the result of damage to the nervous system (e.g. the peripheral nerve, the dorsal root ganglion or dorsal root, or the central nervous system) (Woolf & Mannion, 1999). Approximately one third of cases of neuropathy are the result of diabetes, while another third of cases are the result of autoimmune disorders, tumors, heredity, nutritional imbalances, infections or toxins and the remaining third of cases are idiopathic, or of an unknown cause (Loeser, 2001).

Given the range of diagnoses that can result in neuropathic pain, precise incidence rates are not available, however in the general population, prevalence rates seem to be between 1% and 8% (Dworkin et al., 2007; Bouhassira, Lantéri-Minet, Attal, Laurent & Touboul, 2008; Smith & Torrance, 2012). Torrance and colleagues (2006) surveyed a random sample of 6,000 adults as part of 6 family practices in 3 cities in the U.K. The authors mailed a validated survey, the Leeds Assessment of Neuropathic Symptoms and Signs score (S-LANSS), for the identification of pain of a predominately neuropathic origin. The authors found that of respondents (N=2,957) the prevalence of any chronic pain was 48% and the prevalence of pain of predominantly neuropathic origin was 8.2%. In a French study, a nationwide postal survey was conducted with a representative sample of 30,155 subjects (Bouhassira, Lantéri-Minet, Attal, Laurent & Touboul, 2008). A validated questionnaire, the *Douleur Neuropathique 4* (DN4), was returned by 24,497 (81.2%) of those sampled. The authors found that 31.7% of respondents reported any chronic pain and the prevalence of pain of predominately neuropathic origin was 6.9%. Prevalence studies focused on some of the more common conditions which result in neuropathic pain show that approximately 26.4% of individuals with type 2 diabetes experienced peripheral diabetic neuropathy (Davies, Brophy, Williams, Taylor, 2006), 8.0% of individuals diagnosed with herpes zoster experienced postherpetic neuralgia after 30 days (Choo, Galil, Donahue, 1997), and 37.0% of those with chronic low back pain had a predominantly neuropathic component to their pain (Freynhagen, Baron, Gockel, Tolle, 2006). These studies affirm the large variability in the development of neuropathic

pain conditions. Such variability among subgroups of neuropathic pain demonstrates the complexity of this disorder, and makes research difficult. While exact numbers of remittance in chronic neuropathic pain is unknown, one small study (N=29) found that n=16 patients suffering from diabetic neuropathy experienced complete remittance in their symptoms after 12 months (Young, Ewing & Clarke, 1988), suggesting that for most patients, neuropathic pain becomes chronic.

The range of diseases, illnesses and injuries that can result in neuropathic pain presents certain challenges for the study of the risk factors for developing neuropathic pain. From the limited research available it is known that individuals with chronic neuropathic pain are significantly more likely to be female, middle age (50–64 years), divorced/separated, living in subsidized housing, unable to work, less educated and smoke (Torrance, Smith, Bennett & Lee, 2006; Smith, Torrance, Bennett & Lee, 2007). Another study found this population more likely to have a manual profession and live in a rural area (Bouhassira, Lantéri-Minet, Attal, Laurent & Touboul, 2008) compared to general population rates.

Despite the many different triggering disorders, there are common signs and symptoms associated with neuropathy (Smith & Torrance, 2012). Clinically, neuropathic pain is characterized by spontaneous ongoing or shooting pain which can be evoked after noxious or non-noxious stimuli. The diagnosis of neuropathic pain is only made when the history and signs are indicative of neuropathy in conjunction with neuroanatomically correlated pain distribution and sensory abnormalities within the area of pain (Hansson, 2002). Questionnaires for screening and assessment are also identified as useful tools for identifying the presence and quality of neuropathic pain (Baron, Binder & Wasner, 2010).

A variety of pharmacological treatment options are available for the treatment and management of neuropathic pain. First line medications include tricyclic antidepressants (Finnerup et al., 2015), selective serotonin norepinephrine reuptake inhibitors (e.g. duloxetine, venlafaxine, milnacipran) (Dworkin et al., 2010; Sindrup, Gram, Brøsen, Eshøj & Mogensen, 1990), and topical

Lidocaine, Gabapentin and Pregabalin (Freynhagen, Strojek, Griesing, Whalen, Balkenohl, 2005; Finnerup, Otto, McQuay, Jensen, Sindrup, 2005). Second-line medications, typically used with patients who have not responded to the first-line medications, include Tramadol and opioid analgesics (Dworkin et al., 2010; Finnerup et al., 2015). In some cases, however (i.e. acute neuropathic pain, neuropathic pain due to cancer) these opioid medications are the most appropriate.

An interdisciplinary approach is recommended for the management of neuropathic pain. Components of this approach include pharmacological (i.e. tricyclic antidepressants, opioids) as well as non-pharmacological (i.e. cognitive behavioral therapy, physical therapy, occupational therapy) treatments. Several meta-analyses focused on treatment of neuropathic pain have been published (Cruccu, Gronseth & Alksne, 2008; Finnerup, Otto, McQuay, Jensen & Sindrup, 2005) supporting an approach which maximizes benefits of pharmacological treatment while minimizing harm in terms of side-effects, comorbidities, and drug interactions.

Despite the recommendations that prescription opioids be a second-line medication for neuropathic pain management, their use has been increasing rapidly for the past several years (Compton & Volkow, 2006, Compton, Jones & Baldwin, 2016) and is a standard practice (Dworkin et al., 2010; Baron, Binder & Wasner, 2010). Currently, the prescription of opioids is a common approach for the management of neuropathic pain. When utilized to manage neuropathic pain, opioids are prescribed using long term prescriptions for daily medication, (Dworkin et al., 2010) often in conjunction with a lower dose narcotic to help control pain flare ups or "breakthrough" pain (Smith, Datta & Manchikanti, 2012). Randomized clinical trials have shown satisfactory pain relief for patients with postherpetic neuralgia (Raja, Haythornthwaite, Pappagallo, 2002; Watson, Babul, 1998) and diabetic peripheral neuropathy (Watson, Moulin, Watt-Watson, Gordon, Eisenhoffer, 2003). It is generally accepted that a reduction in pain by 30%, as measured by patient self report, is considered clinically meaningful (Rowbotham & Peterson, 2001). One study, looking at a number of neuropathic pain conditions found that an orally administered opioid, levorphanol, reduced pain

by 36% and 21% in high and low doses, respectively (Rowbotham, Twilling, Davies, Reisner, Taylor, Mohr, 2003). These studies suggest that opioids for the management of pain can be effective and will likely continue to be utilized for the foreseeable future.

Despite the efficacy of treating neuropathic pain in some patients, between 12% (Watson & Babul, 1998) and 35% (Rowbotham et al., 2003; Haythornthwaite & Pappagallo, 2002) of patients receiving opioid medications discontinued their use because of inadequate pain management. Despite therapeutic levels of pharmacologic agents, they experienced minimal to no pain relief. This data suggests that there remains room for improvement in the approaches for managing pain within this population. There is also growing concern over the potential for misuse of opioids prescribed for pain relief.

While there is little debate about short term use of opioids for acute pain, prescription of opioids for treatment of non-cancer chronic pain, including neuropathic pain, remains controversial and hotly debated (Fields, 2011; Compton, Jones & Baldwin, 2016). Central to this debate are two related but different concerns; tolerance to opioid medication and addiction to opioid medication (Vondrackova, Leyendecker, Meissner, Hopp, Szombati, Hermanns, 2008; Silverman, 2009). Analgesic tolerance has been consistently observed in animal studies (Chang, Chen & Mao, 2007). Analgesic tolerance and dose escalation to maintain analgesia in chronic pain patients is not uncommon. A mild physical dependence is expected and demonstrable in patients receiving opioids for pain management. What is unknown though, is whether the development of physical dependence is a clinically significant problem in patients with neuropathic pain.

Related to the concerns about tolerance and dose escalation is the growing reluctance among some providers to prescribe these medications. Their concern is that the most powerful opioid analgesics are also those most likely to be abused and result in addiction (Ballantyne & LaForge, 2007). Unfortunately, with the rise in legitimate prescription opioid use, there has also been a substantial increase in prescription opioid misuse and use related mortality (Chou et al., 2009).Those

providers in favor of a broader acceptance for the use of opioids argue that iatrogenic, or medically induced, addiction is rare, and that it is unreasonable to withhold adequate treatment from patients suffering from of severe pain (Edlund, Steffick, Hudson, Harris & Sullivan, 2007). While much remains unknown, any treatment approach that can potentially lessen the reliance on opioid analgesics while maintaining sufficient or at least comparable pain relief is worthy of further study.

Measurement of Treatment Efficacy

Challenges in the management of neuropathic pain also make outcome measurement a formidable task. Measuring the efficacy of a new treatment can be especially difficult given the complex, multidimensional, and subjective nature of the pain experience (Turk & Melzack, 2011). Current research suggests that sufficient pain relief is variable depending on the pharmacological approach and the underlying cause of neuropathic pain, however, approximately one-half of neuropathic pain patients do not experience sufficient pain relief (Moore, Derry, Eccleston & Kalso, 2013). Sufficient pain relief is generally accepted to be at least a 30% decrease in pain (Hansson, Lacerenza & Marchettini, 2001; Von Korff, Kolodny, Deyo & Chou, 2011), though some studies look for as much as a 50% decrease in pain (Moore, Derry, Eccleston & Kalso, 2013). Traditionally, the measurement of pain is done through the use of subjective pain rating scales, such as the Visual Analogue Scale (VAS). The VAS consists of a line, usually 100 mm long, which denotes the extremes of pain at its ends (e.g. 'no pain' at one end and 'worst pain imaginable' at the other). The patient marks the severity of their pain at a particular point along the line. The distance of the mark along the scale is taken as the pain score (Price, McGrath, Rafii & Buckingham, 1983). Another common approach for measuring pain is through direct questioning about the pain (e.g. intensity, location, descriptors, and qualities), however, this approach assumes that a reduction in pain will translate into physical, emotional, and overall improvements. Numerous studies have shown that changes in pain severity may have only a limited relationship to patient's ratings of emotional and

physical improvement and satisfaction (Dougados, LeClaire & van der Heijde, 2002; Farrar, Young, LaMoreaux, Werth & Poole, 2001; Dawson et al., 2002; Waddell, Nachemson & Phillips, 2000). The traditional outcome domain of symptom reduction alone is inadequate when evaluating response to treatments for chronic disease states and symptoms that are subjective, such as pain. As such, although pain reduction is an important outcome, and might be a pivotal outcome for pain clinical trials, it is important to consider other outcomes in addition to pain (Turk et al., 2003).

There is a growing body of literature highlighting the importance of additional factors, including psychological factors, in the experience of neuropathic pain (Sullivan, Lynch & Clark, 2005; Haythornthwaite & Benrud-Larson, 2000; Daniel et al., 2008; Sullivan, Lynch, Clark, Mankovsky & Sawynok, 2008). Severe pain causes fatigue, impaired concentration, compromised mood, degraded sleep, and a diminished overall activity level. Thus, there is a need for a way of assessing multiple areas of functioning and well-being in clinical research to assess the full impact of pain treatment. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus meeting made several recommendations in assessing chronic pain in clinical trials (Turk et al., 2003). The IMMPACT group represents a variety of disciplines and includes; anesthesiology, clinical pharmacology, internal medicine, law, neurology, nursing, oncology, outcomes research, psychology, rheumatology, and surgery. The goal of this group was to develop consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain (Turk et al., 2003). They suggested 4 core chronic pain outcome domains to be measured in pain treatment research: (1) pain intensity, (2) physical functioning; (3) emotional functioning; and (4) participant ratings of overall improvement. It is recommended that 2 or more of the 4 core chronic pain outcome domains be used to evaluate the clinical importance of improvement or worsening for chronic pain clinical trial outcome measures. Two areas of functioning highlighted by the IMMPACT recommendations include the assessment of emotional functioning and an assessment of overall, or global, improvements. The recommendations

emphasize that assessments of global functioning should evaluate diverse aspects of an individual's life including: the ability to carry out household chores, walking, work, travel, self-care, strength and endurance (Turk et al., 2003). For the assessment of emotional functioning, the IMMPACT recommendations suggest that emotional functioning could include emotional distress (Turk et al., 2003) and/or coping through emotional approaches. With the importance of multiple forms of measurement in pain research being highlighted, researchers are utilizing the assessment of pain severity, physical functioning, emotional functioning, and global improvements in functioning as unique outcomes in pain research that are important in fully assessing the multidimensional nature of pain (Turk et al., 2003; Mikail, DuBreuil, D'Eon, 1993; De Gagne, Mikail & D'Eon, 1995; Holroyd, Malinoski, Davis & Lipchik, 1999).

The areas outlined for the assessment of global improvements in functioning are all areas that are commonly assessed by Health Related Quality of Life Measures (HRQoL) (Turk et al., 2003). One meta-analysis looked at 39 articles of RCTs in which neuropathic pain and HRQoL were measured (Haanpää et al., 2011). Of the 5 types of measures employed only two were found to have utility in measuring changes in HRQoL in neuropathic patients. The most prominent HRQoL measure identified was the Medical Outcomes Study 12-Item Short Form Health Survey (SF-12). The SF-12 was first developed in 1996 as a shorter alternative to the SF-36, the most widely used generic QoL measurement tool in the world. Initial validation of the SF-12 found that it was a reasonable replacement for the SF-36 (Ware & Kosinski, 1996; Ware, Kosinski & Keller, 1998). Subsequent validations have confirmed the SF-12 as a valid replacement for the Short Form-36 (SF-36) with valid constructs (Gandek, Ware, Aaronson, Apolone, Bjorner, Brazier et al., 1998; Jenkinson et al., 1997). Since that time the SF-12 has been one of the most widely used measure of QoL among individuals from all over the world with various health issues and disease states. There are many advantages to using the SF-12 to measure QoL. First it is very brief, taking approximately 2 minutes to complete (Wu, Hays, Kelly, Malitz & Bozzette, 1997), which can help keep completion

rates high and limit bias due to incomplete data. Second, it has multiple administration modes available, including paper and electronic versions, and standard (4-week) and acute (1-week) recall versions. Research supports the use of HRQoL measures such as the SF-36 and the briefer, but comparable revision, the SF-12, in studies measuring HRQoL

The assessment of emotional functioning includes emotional distress (Turk et al., 2003) and/or coping through emotional approaches (Smith, Lumley & Longo, 2002). While several measures are available for the assessment of an individual's emotional understanding of pain, the Pain Catastrophizing Scale (PCS) is one of the most commonly used scales with a large body of research supporting and validating it (Sullivan, Bishop & Pivik, 1995; Keefe, Rumble, Scipio, Giordano & Perri, 2004). The PCS is a 13-item instrument used to assess catastrophic thinking in response to pain, and has been shown to have high internal consistency ($\alpha = 0.91$) and high test-retest reliability ($r=0.78$) (Sullivan Bishop & Pivik, 1995; Van Damme, Crombez, Bijttebeir, Goubert & Van Houdenhove, 2002). Furthermore, the measure is easy to administer, score and it is very short. While many measures are available that assess a variety of coping skills and include catastrophizing, few other measures look solely at catastrophizing. For instance, the Coping Skills Questionnaire had comparable reliability and validity to the PCS, but is a total of 72 questions, making it too long for use in clinical settings (Robinson et al., 1997). The PCS assesses at attitudes toward pain, specifically catastrophizing attitudes, such as; magnification of pain experience, rumination on pain and perceived helplessness. Use of well validated measures, with a strong research base, can allow for the identification of and change across a range of psychosocial factors. These factors may show the efficacy of a novel treatment approach across multiple domains, including but not limited to overall pain and allow for comparison across studies.

Etiology of Chronic Pain

Many theories exist to explain the development and maintenance of chronic pain as well as the resulting level of disability. A comprehensive review of all the theories lies beyond the scope of the current literature review. The current study explored the development of disability resulting from chronic neuropathic pain, how individuals feel about their level of disability resulting from chronic neuropathic pain, and how feelings about this disability impact severity of pain experiences in a neuropathic pain sample. How pain disability is maintained, and specifically, the psychological factors associated with its maintenance, was a primary focus of this study. With these psychological factors as the primary focus, the number of relevant theories for the development and maintenance of chronic neuropathic pain diminishes, but still remains large.

In the chronic pain literature, a variety of theories are available to explain the development of disability, and the role that feelings about disability may play in the maintenance of this disability. In a review comparing the theoretical perspectives of chronic pain maintenance, Novy and colleagues (1995) categorized pain theories into two broad groups: restrictive and comprehensive. The restrictive theories are those that ignore plausible views of chronic pain or potential interrelations among them as being unimportant or of secondary concern. Whereas the comprehensive theories, as their name suggests, take into account broad perspectives on physiological and psychological processes. These theories suggest that the limited focus of the restrictive theories are inconsistent with the empirical literature and the multifaceted nature of chronic pain (Novy, Nelson, Francis & Turk, 1995). Due to this inconsistency, restrictive theories, such as mind-body dualism, sensory, information-processing, and sociogenic theories will not be discussed in this proposal (Novy, Nelson, Francis & Turk, 1995). Comprehensive models of chronic pain, those taking into account the biomedical considerations with attention paid to psychosocial components of pain, have supplanted discipline-specific or one-dimensional conceptualizations of chronic pain. Currently, multidimensional and multimodal approaches to understanding pain are

considered state of the art and are the preferred approach (Turk & Melzack, 2011). Comprehensive perspectives appear to represent the most up-to-date theoretical perspectives and are the most capable of broad-based utility.

The current study examined the factors that impact the pain experience, specifically those factors with the strongest empirical support, including: catastrophizing (Turner & Aaron 2001; Vlaeyen & Linton 2000) and health related quality of life (Jensen, Chodroff & Dworkin, 2007). Three of the most prominent comprehensive theories presented here include operant conditioning theory, the biopsychosocial theory, and the fear- avoidance theory. The reasoning behind the decision to utilize the Fear-Avoidance model to guide the current study is also discussed.

Operant Conditioning Theory. The Operant conditioning theory of chronic pain was first described by Fordyce (1976), and it suggests that an individual experiencing pain through noxious stimulus desires to withdraw and escape. Through this theory, chronic pain is viewed as a subjective internal experience that may be maintained even after the initial physical causes of pain are removed. In this model, psychological factors are treated as secondary reactions to sensory stimulation (Turk, Dobson & Keith, 1996), and chronic pain includes pain behaviors, namely actions, verbalizations, or facial expressions that occur in response to pain (Fordyce, 1976). Pain-behaviors are thought to occur because the person gains positive effects and/or avoids negative effects, and this is more important than what initially may have caused pain (see Figure 1.). Operant conditioning theory states that what becomes 'chronic' in chronic pain is the pain behavior, the suffering, and the disability. Therefore, instead of looking for and treating underlying pathology, the focus of treatment is on the pain behavior or the symptoms themselves, as these may be maintained through reinforcement rather than physical stimuli (Fordyce, 1974). While the theory has some

research support (Fernandez & McDowell, 1995; Gatchel, Polatin & Mayer, 1995), findings are inconsistent, and there are many criticisms of the theory. The most relevant criticism for the current study was that this theory focuses exclusively on motor behavior, and fails to consider subjective, emotional, or cognitive aspects of chronic pain (Turk, 1996). Additionally, this theory has been criticized for emphasizing pain behaviors rather than emphasizing the pain itself (Turk, 1996). Furthermore, in neuropathic pain, the initial physical causes of pain may not have been removed and is therefore not reinforced by motor behaviors.

Figure 1. Examples of operant conditioning procedures in chronic pain. Pain exacerbation contingent on activity functions as a punisher, leading to a decrease of activity levels and/or avoidance of the specific activity on top line. Verbal or nonverbal pain expressions that elicit attention from others increase in frequency on second line. The pain decrease that occurs during rest reinforces its occurrence, leading to higher frequency of rest on third line. Adapted from " Operant learning theory in pain and chronic pain rehabilitation." by R. Gatzounis, M. Schrooten, G. Crombez & J. Vlaeyen, 2012. Operant learning theory in pain and chronic pain rehabilitation. *Current Pain and Headache Reports, 16*(2), p. 119.

Biopsychosocial Theory. Another theory of neuropathic pain comes from a biopsychosocial perspective. It was first proposed by Engel (1977) as a general approach for the identification of factors relevant to the development of health or illness (Camic & Knight, 2004). The biopsychosocial theory suggests a complex interaction between the biological, psychological, and social factors involved in pain experience, health, and wellbeing (Turk, 1996b). The biopsychosocial model takes into account the multi-dimensional nature of pain and thus recognizes the biological,

psychological, and social components involved in both the development and maintenance of chronic pain (see Figure 2; Gatchel, 2004).

Research into the psychological factors of pain lends support to the biopsychosocial model. In a systematic review of the psychological factors in the development of chronic pain, Pincus and colleagues (2002) found considerable research support indicating that distress, depressed mood, and somatization were psychological factors involved in the development of chronic lower back pain. Gatchel and colleagues (2007), in a comprehensive review of the biopsychosocial model, identify research supporting the theory that emotions, such as depression, anxiety, and anger, impact the pain experience. They go on further to say that these emotions can impact pain experience by acting as antecedents, maintaining factors, and/or consequences. In a separate article, Gatchel (2004) reviews how emotional states, such as prolonged stress and pain can lead to the breakdown of muscle, bone, and neural tissue, which results in additional pain. These studies illustrate the psychological factors that impact pain and chronic pain.

According to the biopsychosocial model, the social component of pain also plays an important role in the development and maintenance of chronic pain. Pain can impact the role people play within their family, within the workplace, and within their community (Gatchel & Epker, 1999). Spouses or family members who are overly solicitous and give the pain patient significant attention may also inadvertently reinforce the patient's pain behaviors and their sick role (Keefe, 1992). Additionally, social constructs such as gender, religion, and cultural can impact pain expression (Thernstrom, 2010).

There is support for a bidirectional relationship between emotions, cognitions, and social factors, and pain. In a review of studies to identify predictors of recovery versus continued disability in chronic pain patients, Vlaeyen and Morley (2005) found psychosocial factors (i.e. maladaptive attitudes and beliefs, heightened emotional reactivity, lack of social support, job dissatisfaction, substance abuse, compensation status, prevalence of pain behaviors, and psychiatric diagnoses) were

associated with continued disability. Furthermore, factors such as severity of injury and the physical demands of one's job were not found to be associated with continued disability (Gatchel & Epker, 1999; Vlaeyen & Morley, 2005).

The biopsychosocial theory does not identify specific pathways to disability, but identifies all pathways as potentially leading to disability in chronic pain. This theory combines psychological factors such as past experience, attention, and emotion with biological factors. Pain, theoretically, becomes less of a signal and more of a process (Kugelmann, 1997). Therefore, there is a need to consider the patient's daily activities in context with the meaning the patient construes from his or her situation when assessing the pain experience (Clancy & McVicar, 1991). The complexity inherent in this theory is one of its greatest criticisms. As a comprehensive overview of many factors contributing to a complex problem, critics suggest that the biopsychosocial theory is too all encompassing and functions as an 'eclectic approach' of understanding health and illness (Wood, 2012). For the purposes of looking at specific factors impacting the maintenance of chronic pain, this approach may be too inclusive and would likely make it difficult to identify and integrate the specific factors of focus.

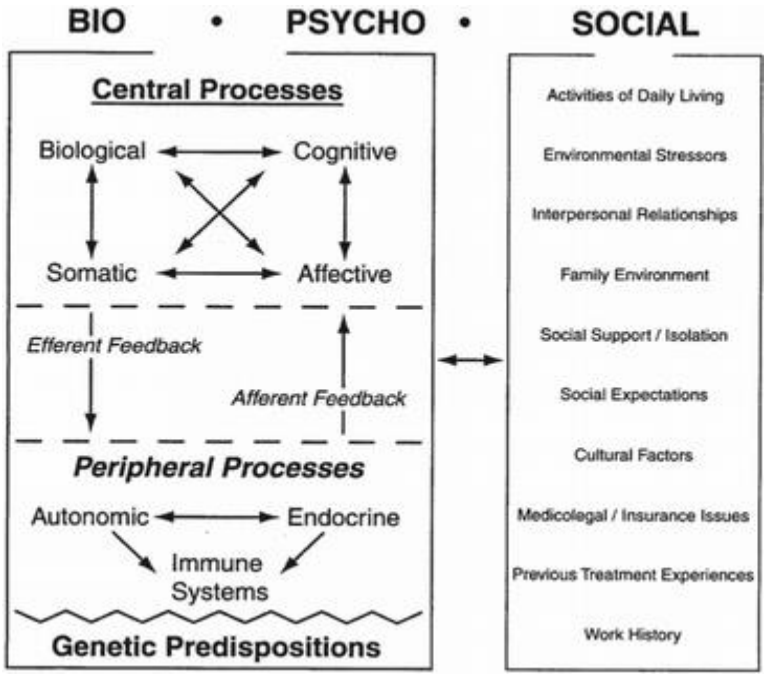


Figure 2. The biopsychosocial model of chronic pain. Adapted from: "The biopsychosocial approach to chronic pain: scientific advances and future directions", 2007, R. Gatchel, Y. Peng, M.

Peters, P. Fuchs & D. Turk, *Psychological Bulletin, 133*(4), p. 581.

Fear Avoidance. The Fear-Avoidance model postulates that long term pain and disability is increased when an individual's perceptions of the likely impact of pain lead to safety behaviors such as escape and avoidance (Vlaeyen & Linton, 2000). Furthermore, this model posits that some individuals are more likely than others to experience a catastrophizing cognitive style which maintains the fear of pain and re-injury. The fear-avoidance model (see Figure 3) includes the fear of movement and catastrophizing thoughts about pain as major contributors to the pain experience.

Figure 3. Fear avoidance model of chronic pain. Adapted from "Fear avoidance and its consequences in musculoskeletal pain: A state of the art," J. W. Vlaeyen and S. J. Linton, 2000, *Pain*, 85, p. 329.

According to the fear-avoidance model, the onset of chronic pain begins with an initial pain, injury or disease that then interacts with an individual's predispositional factors (i.e. affect, genetics, personality). Following this interaction, the pain is interpreted by the individual. Those who

interpret their pain as transitory will approach activities until their pain subsides. In contrast, those who interpret their pain as threatening (pain catastrophizing) go on to develop pain related fear. The latter leads to avoidance behaviors (lack of self-efficacy), and hypervigilance to bodily sensations. These behaviors are often followed by disability, disuse, depression and an intensification of the pain experience (Turk & Wilson, 2011). The avoidance of physical activity can be reinforcing when individuals believe that their avoidance prevents the experience of pain. This is further maintained by an unwillingness to engage in activities that could cause pain. The theory goes on to posit that pain catastrophizing is also influenced by negative affectivity, helplessness and threatening illness information (Vlaeyen & Linton, 2000).

There is a substantive body of research that supports the fear-avoidance model of chronic pain. First, a large number of cross-sectional studies have shown that pain-related fear is indeed one of the most potent predictors of observable physical performance and self-reported disability levels (Tota-Faucette, Gil, Williams, Keefe & Goli, 1993; Hildebrandt, Pfingsten, Saur & Jansen, 1997). For example, fear avoidance predicts pain intensity following treatment (i.e. high scores on catastrophizing are associated with high pain intensity) (Samwel, Evers, Crul & Kraaimaat, 2000).

Second, the notion that pain-related fear is a precursor of disability, rather than a consequence of it is also supported by research. A study by Klenerman and colleagues (1995), which looked at back pain patients in a primary care setting, found indications of fear avoidance were among the most powerful predictors of chronic disability 1 year later. Fear-avoidance is also predictive of post treatment pain intensity. That is, negative orientation towards pain (catastrophizing) was predictive of higher levels of pain intensity after treatment as compared to those with a more positive orientation toward their pain (Tota-Faucette et al., 1993; Samwel, Evers, Crul & Kraaimaat, 2000). Several studies have found that fear avoidance contributes in an important way to disability, suffering, and health care use in patients with chronic pain, often more than pain intensity (Vlaeyen, Kole-Snijders, Boeren & Van Eek, 1995; McCracken, 1998; Asmundson,

Kuperos & Norton, 1997; Crombez, Vlaeyen, Heuts & Lysens, 1999). According to the fear-avoidance model, patients are likely to maintain engagement in daily activities when acute pain is perceived as non-threatening, which promotes functional recovery. In contrast, a vicious cycle may be initiated when the pain is catastrophically misinterpreted, leading to avoidance/escape and hypervigilance behaviors.

Despite much research support, the fear-avoidance model also has limitations. First, it does not discuss the origin of pain related fear or the relationship between muscle disuse and reactivity. Second, fear-avoidance doesn't fully incorporate the role of illness information in the maintenance or remittance of pain, specifically information and feedback about diagnostic tests provided by medical specialists and therapists (Vlaeyen & Linton, 2000). Despite these limitations, and given the compelling research to date, the fear-avoidance model is the most appropriate for explaining the role of catastrophization and health related quality of life in pain maintenance. This interplay of emotions, cognitions, and physical activity in the development of chronic pain supports the further study of various psychosocial variables in chronic pain related research.

Catastrophizing

Historical overview of catastrophizing. The term catastrophizing has been used in the pain field for several decades, and recurrent features in all conceptualizations of catastrophization include attention to negative aspects of events, persistent negative thinking, and perceived inability to handle the situation (Chaves & Brown, 1987; Spanos, Radtke-Bodorik, Ferguson & Jones, 1979). Currently, the most common definition of pain catastrophizing is "an exaggerated negative mental set brought to bear during actual or anticipated pain experience" (Sullivan et al., 2001). This is a broad definition which identifies that catastrophizing involves a fixed pattern of thinking ("mental set") which is disproportionate in regard to the circumstances ("exaggerated"), focused on

unpleasant aspects ("negative") and activated when the individual confronts imaginary or actual pain ("brought to bear") (Sullivan et al., 2001).

The term catastrophizing was originally introduced by Albert Ellis, the founder of rational-emotional therapy (Ellis, 1962), and later adapted by Aaron Beck (Beck, 1976). In their early work, the term catastrophizing was used to describe a maladaptive cognitive style among patients with depressive and anxiety disorders. This cognitive style was understood as a tendency to magnify or exaggerate possible negative aspects of future events.

Several articles were seminal in developing the framework for our current conceptualization of catastrophizing in chronic pain (Spanos, Radtke-Bodorik, Ferguson & Jones, 1979; Rosenstiel and Keefe, 1983; Chaves and Brown, 1987). First, Spanos and colleagues (1979) asked university students to participate in a cold pressor procedure as a means of inducing pain in the laboratory without causing permanent tissue damage. They interviewed the participants after the cold pressor procedure and categorized individuals based on the content of their reported thoughts. Patients were then assigned to one of four treatments: hypnosis plus analgesia suggestion, hypnosis alone, suggestion alone, or no hypnosis and no suggestion. Patients then participated in the cold pressor procedure again and reported pain. Those reporting worry, fear, and/or an inability to divert attention away from pain were classified as catastrophizers (i.e., "I kept thinking I can't stand this much longer, I want to get out") while others were classified as noncatastrophizers. The authors found that individuals who engaged in catastrophizing thoughts reported the highest levels of pain, and showed no response across any of treatment the conditions. In contrast, those participants who were classified as noncatastrophizers showed significant reductions in pain reporting, some as much as a 50% reduction in pain following treatment.

A second influential study on catastrophizing was completed by Rosenstiel and Keefe (1983), who created a 50 item questionnaire, Coping Strategies Questionnaire (CSQ), to categorize individuals into 7 coping subscales, including a catastrophizing subscale (increasing activity level,

diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, praying or hoping, and catastrophizing). In one study, the CSQ was used to examine catastrophizing in rheumatoid arthritis (RA) patients (Keefe, Brown, Wallston & Caldwell, 1989). The authors had each participant complete the CSQ and pain scale on two separate occasions, 6 months apart. They found that patients classified as high catastrophizers experienced greater pain intensity when compared to those with lower catastrophization scores. Furthermore, they found that over the 6 month period, catastrophization scores remained stable. The CSQ was used in a series of studies focusing on chronic pain patients, which consistently found that individuals who obtained high scores on the catastrophizing scale experienced higher levels of physical and emotional distress in relation to their pain condition when compared to participants that did not catastrophize (Keefe, Brown, Wallston & Caldwell, 1989; Keefe et al., 1987; Crisson & Keefe, 1988).

Chaves and Brown (1987) looked at coping strategies dental patients reported using during a stressful dental procedure. In a sample of patients undergoing dental surgery (N=75), they found that individuals differed noticeably in the thoughts they experienced during such procedures. Individuals who engaged in catastrophic thoughts (i.e., "I'm afraid that my pain might get worse") tended to magnify or exaggerate the threat value or seriousness of pain sensations. These individuals were more likely to experience high levels of distress during their dental procedures. In the sample, 44% of patients employed cognitive strategies to minimize pain and stress, while 37% engaged in cognitive strategies which exaggerated the fearful aspects of their experience. A small proportion, 19%, denied any cognitive activity during the procedure. The authors were able to differentiate and label there 3 different groups; copers, catastrophizers, and deniers. The most common strategy employed by copers was attentional diversion, while the most common strategies employed by catastrophizers were nonimaginary negative thoughts.

Catastrophizing and chronic pain. Individuals who score higher on measures of catastrophization consistently report higher ratings of pain intensity. This relationship is one of the

most robust findings in the catastrophization literature. This relation has been observed in a wide range of situations involving both acute and persistent pain, in healthy individuals, and in patients who suffer from chronic conditions (for a review, see Sullivan et al., 2001). Catastrophizing is also related to how people behave when confronting pain. For example, catastrophizing has been associated with "pain behaviors", which are the motor and verbal responses that some people express when confronting pain (e.g. rubbing the pain area, frowning, or complaining about how much it hurts) (Nicassio, Schoenfeld-Smith, Radojevic & Schuman, 1995). Additionally, catastrophizing has also been linked to a heightened use of health care and increased medication use (Bedard, Reid, McGrath & Chambers, 1997).

Catastrophizing has also been linked to higher levels of disability (Sullivan et al., 2001; Keefe et al., 2004). This link, between catastrophizing and heightened disability, has been found in patients with acute pain (Swinkels-Meewisse, Roelofs, Oostendorp, Verbeek & Vlaeyen, 2006) as well as in patients with chronic pain conditions (Peters, Vlaeyen & Weber, 2005; Severeijns, Vlaeyen, van den Hout & Weber, 2001; Turner, Jensen, Warms & Cardenas, 2002). Furthermore, catastrophization has been found to be strongly associated with increased reports of pain and decreased pain tolerance (Edwards, Haythornthwaite, Sullivan & Fillingim, 2004). There is consistent evidence that individuals who catastrophize report their pain as being more intense, express more worries and suffer more adverse consequences as a result of pain than people who do not catastrophize (Sullivan et al., 2001; Keefe et al., 2004).

Catastrophizing is also closely related to negative emotionality. It has repeatedly been associated with broad negative emotional responses such as depressed mood and anxiety (for a review, see Keogh & Asmundson, 2004). Measures of catastrophizing overlap, to a large extent, with measures of negative emotionality. Some research suggests that, after controlling for the broad measures of negative emotionality, catastrophizing contributes minimally to the prediction of pain (Hirsh, George, Riley & Robinson, 2007). However, other research suggests that catastrophizing is

a unique and free standing construct that remains important despite controlling for negative emotionality (Sullivan et al., 2001). For example, a recent clinical study showed that some pain patients presented with either catastrophizing or depressed mood, whereas others displayed elements of both (Linton et al., 2011). These findings indicate that it is important to separate catastrophizing from other aspects of negative emotionality in clinical and research contexts.

Catastrophizing and response to medication. The role of catastrophizing has mainly been studied in persistent and pathological pain situations. Few studies have looked at the role catastrophizing plays in relation to clinical medication intervention trials of pharmacotherapies (Mankovsky, Lynch, Clark, Sawynok & Sullivan, 2012). In the limited research to date, investigators posit that pain catastrophizing might interfere with the effectiveness of pharmacological interventions for pain management.

One study (N=84), looking at response to topical analgesics in patients with neuropathic pain, found that higher scores on a measure of pain catastrophization prospectively predicted poorer response to treatment (Mankovsky, Lynch, Clark, Sawynok & Sullivan, 2012). Using a 0-10 numerical rating scale of pain at baseline and throughout the course of treatment, the authors found that catastrophizers presented with higher initial ratings of their pain when compared to non-catastrophizers. Additionally, they found that catastrophizers were less likely to report moderate to substantial reductions in pain ratings over the course of treatment than non-catastrophizers (Mankovsky et al., 2012).

Haythornthwaite and colleagues (2003) examined the efficacy of an opiate medication for post-herpetic neuralgia (PHN), a neuropathic pain state. A total of 68 PHN patients were recruited from community clinics and entered the study. Of those, 49 participants completed a battery of psychological measures at study conclusion. Participant pain ratings along with questionnaire measures of perceived interference due to pain, overall activity level, depressive symptoms, and pain coping strategies were collected through these psychological measures. Results indicated that that

catastrophizing at baseline predicted a higher level of pain 8 weeks later, an effect that was independent of baseline pain and depressive symptoms.

The research into the role of psychological variables in response to pharmacological interventions is limited. Available research suggests high levels of catastrophizing and maladaptive coping predict poorer response to pharmacological interventions for neuropathic pain (Sullivan et al., 2001).

Health Related Quality of Life

Historical overview of Health Related Quality of Life. Currently, Health Related Quality of Life (HRQoL) is viewed as a multidimensional construct incorporating an individual's evaluation of their life with respect to three fundamental domains of functioning: (1) biological, (2) psychological, and (3) social. A balanced measure of HRQoL captures all of these domains and summarizes them in a single metric (WHO, 1993).

The term Quality of Life (QoL) was introduced in the middle of the last century and appeared in the medical literature in the 1960s (Schuessler & Fisher, 1985). Since its introduction, QoL has been defined in different ways by nearly every academic discipline. A review of QoL studies identified over 100 definitions of QoL (Taillefer, Dupuis, Roberge & Le May, 2003). Initially, QoL in medicine was regarded as an objective concept with a focus on independence and functioning (e.g. activities of daily living). In the early 1980s, however, influences from social science resulted in a greater focus on the subjective aspects of QoL (Musschenga, 1997). Quality of Life has primarily been regarded as a multidimensional construct including at least the individual's subjective perception (Taillefer, Dupuis, Roberge & Le May, 2003). Some authors aim to include "all domains of a person's life", while others take a more modest approach. The medical field has shown increasing interest in a consensus on the QoL concept, however, to date, no consensus has been reached and a large number of different conceptual models are currently used (Taillefer, Dupuis,

Roberge & Le May, 2003). The breadth of this construct is daunting, and has been noted as an obstacle to achieving consensus on what constitutes QoL (Koot, 2001).This lack of consistent theory has created research problems, and makes the study of QoL very challenging.

In an attempt to narrow the QoL construct, Health Related Quality of Life (HRQoL) was introduced. This construct mainly focuses on health specific aspects of well-being and functioning (Koot, 2001). Qualitative and quantitative empirical data support conceptualizing HRQoL into dimensions of physical, emotional and social functioning, and wellbeing (Sartorius et al., 1993). For instance, a large World Health Organization research project involving adult individuals from fifteen nations revealed that physical fitness, social integration and support, psychological stability and ability to fulfill daily tasks seemed to contribute to HRQoL across ages, sex and cultures (Sartorius et al., 1993, Bullinger, 2002).

Health Related Quality of Life and pain. Given the complexity and individuality of chronic pain presentations, it is often difficult for patients to fully describe how pain has impacted their life. Assessment of HRQoL encompasses the aspects of health and well-being valued by patients. Specifically, measures of HRQoL can assess a patient's physical, emotional, and cognitive function, and their ability to participate in meaningful activities within their family, workplace, and community.

Health Related Quality of Life is an important area of focus for pain research because it encompasses many of the aspects of functioning that are seldom assessed in medical research. The subjective nature of pain means that two individuals, with similar pain ratings and disability, may have different emotional wellbeing and role functioning (Gordon, 1993). Specifically, one person might view this pain as a serious disability, while another, with the same degree of pain, might view it as simply an annoyance or inconvenience. While a medical focus on the physiological outcomes is important, this is often of limited interest to the patients, in part because it doesn't result in tangible improvements (i.e. ability to work, increased mobility). Health Related Quality of Life assessments

are capable of measuring tangible improvements in functioning as a result of treatment, even in the absence of any changes in pain perception.

In a review, Jensen and colleagues (2007) found 52 studies that examined the association between neuropathic pain and HRQoL. The authors identified several common domains of HRQoL found across most studies (physical functioning, emotional functioning, sleep, and role and social functioning). These studies consistently found that the presence of neuropathic pain was associated with impairments across these major domains when compared to those without neuropathic pain. Furthermore, they found that participants who rated their pain severity as higher experienced increased impairments in major domains of HRQoL compared to those with lower ratings of pain. The assessment of HRQoL is an important component in identifying whether treatments that reduce pain have additional benefits for QoL (Jensen, Chodroff & Dworkin, 2007).

One study compared two HRQoL measures (SF-36 and Nottingham Health Profile) in patients with neuropathic pain. They found, in a sample of (N=126) participants, that those with neuropathic pain had significantly worse scores on both measures when compared to the general population (Meyer-Rosberg et al., 2001). The authors found that patients who reported a high Visual Analogue Scale score for pain reported lower global health ratings. This study further confirms the role that pain can play on HRQoL and the utility of HRQoL measures.

N-acetyl-L-cysteine (NAC)

Research is constantly being conducted to investigate alternatives to current pharmacological treatments for pain treatment. One particular agent that has shown promise in studies of neuropathy is N-acetyl-L-cysteine (NAC), a parmaceutical drug and nutritional supplement, available over the counter, with many uses in medicine. N-acetyl-L-cysteine has been used for over 30 years as a treatment for acetaminophen overdose (Buckley, Buckley, Whyte, O'Connell & Dawson, 1999) and carbon monoxide poisoning (Kelly, 1998). As more is understood about the actions of NAC, the

clinical applications have also broadened. Recently, NAC has emerged as a promising treatment for a variety of medical (Dodd et al., 2008; Adair, Knoefel & Morgan, 2001) and psychiatric disorders (Dean, Giorlando & Berk, 2011, Deepmala et al., 2015). Data are also emerging which suggest that NAC be effective for addiction and neuropathic pain.

A derivative of the amino acid cysteine and an antioxidant, NAC, which appears to affect neuropathic pain by acting as a free radical scavenger has shown particular promise for treating neuropathic pain. The use of NAC in restoring (Dean, Giorlando & Berk, 2011) and helping to enhance glutathione concentrations (Chopra & Tiwari, 2012) is well established. Glutathione is an antioxidant that neutralizes Reactive Oxygen Species (ROS) through direct and indirect scavenging. Reactive Oxygen Species are chemically reactive molecules which contain oxygen and form as a natural byproduct of the normal metabolism of oxygen (Devasagayam et al., 2004). A growing body of research support that ROSs play an important role in cell signaling and that increased levels of ROS can result in significant damage to cell structures (Devasagayam et al., 2004).

Reactive Oxygen Species have been shown to be involved in persistent neuropathic pain. Kim and colleagues (2004), in a study of rat spinal nerve ligation model (SNL) of neuropathic pain, implicated ROS in the pathology of neuropathic pain. They showed that ROS scavengers ameliorated SNL-induced mechanical allodynia and prevented the development of neuropathic pain in these rats. Naik and colleagues (2005) showed that NAC significantly reduced the increased sensitivity to mechanical, thermal, and cold allodynia tests in a peripheral neuropathy model (chronic constriction injury of sciatic nerve) in rats. Further, they noted that glutathione levels were decreased following injury. In another study, looking at rats with induced diabetic neuropathy, the authors found that NAC was able to reduce the physical signs of pain (decreased tail-flick latency and decreased motor coordination) when compared to a control group (Kamboj, Vasishta & Sandhir, 2010). This research supports the role of NAC in attenuating oxidative stress associated with neuropathic pain, and further supports the role of NAC as a potentially beneficial treatment for

neuropathic pain patients. N-acetyl-L-cysteine, an antioxidant and precursor to glutathione synthesis, acts by directly scavenging free radicals as well as by increasing glutathione synthesis, results in increased cellular clearance of ROS, decreased oxidative stress, and subsequently, decreased pain.

Orban and colleagues (2006), in a small (N=31) clinical research study, investigated the role of NAC in decreasing pain intensity, measured by self report of pain and decreased morphine use. They found that NAC did not decrease the pain intensity or decrease the recovery time. However, they found that patients treated with NAC (1200 mg NAC prior to and 600 mg NAC post procedure) showed a significant reduction in post operative morphine use (0.22 mg/kg vs. 0.47 mg/kg, $p<0.05$) in the first 48 hours post-surgery compared to the control group. In this study, NAC was well-tolerated with no difference in the occurrence of adverse events between the treatment groups.

Neuropathy is a common serious adverse effect of chemotherapy. In a small (N = 14) randomized study looking at the protective effects of NAC in colon cancer patients receiving oxaliplatin chemotherapy patients were randomized to receive NAC (N = 5) or placebo (N = 9). Results showed a significant benefit of NAC over placebo in preventing development of oxaliplatin induced serious sensory neuropathy (Lin et al., 2006).

Truini and colleagues (2015), conducted a double-blind, placebo controlled design, to test NAC induced changes in quantitative sensory testing and laser-evoked potentials in healthy volunteers. Participants (N = 10) were tested on their response to thermal-pain perceptive thresholds and laser evoked potential measures in two separate sessions after the administration of either oral placebo or oral NAC. Findings indicate that NAC reduced pain rating to laser stimuli but left thermal-pain thresholds unchanged. Responses also show that NAC resulted in significantly greater changes than placebo. Given the small sample size of these studies the results should be interpreted cautiously, however it lends further support to the small, but growing, literature suggesting the possibility of NAC as a favorable treatment option for neuropathic pain.

Data are emerging which suggest that ROS play a role in the pathophysiology of addiction to drugs of abuse as well as pain (Knackstedt et al., 2009; Cunha-Oliveira, Rego & Oliveira, 2009; Huang et al., 2009). For instance, LaRowe and colleagues (2013) in a larger (N=111) double blind, placebo controlled trial found no changes in cocaine use for participants randomized to receive daily doses of 1200mg of NAC, 2400mg of NAC or placebo. However, while no effects were observed for reducing cocaine use in cocaine dependent individuals, researchers did find that subjects who had already achieved abstinence prior to trial entry showed longer time to relapse and lower self-reported cravings. LaRowe and colleagues (2006), in a small (N=15) double blind, placebo controlled trial, found that patients taking NAC reported less desire to use, less interest in response to cocaine slides and watched cocaine slides for less time. Similar results have been found for nicotine dependence (Knackstedt et al., 2009), marijuana dependence (Gray, Watson, Carpenter & LaRowe, 2010), methamphetamine dependence (Mousavi, et al, 2015), pathological gambling (Grant, Kim & Odlaug, 2007) as well as other studies of cocaine addiction (Mardikian, LaRowe, Hedden, Kalivas & Malcolm, 2007; LaRowe, Mardikian & Malcolm, 2006).

Furthermore, NAC has shown promise in the treatment of a number of additional psychiatric conditions, such as obsessive-compulsive disorder (Lafleur et al., 2006), schizophrenia (Berk et al., 2008a) and bipolar disorder (Berk et al., 2008b). For a comprehensive review of clinical trials investigating NAC in treating psychiatric and neurological conditions consult Deeplmala and colleagues (2015).

The doses of NAC used in a range of studies, ranging from 400mg/day to 3000mg/day for 2 to 24 weeks, were well-tolerated (Gray, Watson, Carpenter & LaRowe, 2010; Knackstedt et al., 2009; LaRowe, Mardikian & Malcolm, 2006; LaRowe et al., 2007; Mardikian et al., 2007). No patients experienced serious adverse events, and no patients were discontinued from the studies due to serious adverse events related to NAC.

While research on NAC is limited, there are studies which suggest that NAC may be a promising adjunct to standard treatments for neuropathic pain and addiction. The available research suggests that ROS are critically involved in the maintenance of neuropathic pain and that NAC, as an ROS scavenger may have utility in decreasing not only pain but also the potential for addiction to the opioid medication used for pain management. The available research in support of NAC makes it worthy of further study as an adjunct to current pain treatment regimens.

Statement of Problem and Hypotheses

Chronic neuropathic pain is a serious health concern effecting between 1% and 8% of the United States adult population (Dworkin et al., 2007; Torrance, Smith, Bennett & Lee, 2006; Bouhassira, Lantéri-Minet, Attal, Laurent & Touboul, 2008). Numerous treatment options are available for managing this pain, however, individual response to treatment is extremely variable (Cruccu, Gronseth & Alksne, 2008). Opioid medications are one of the frequently used treatment options for the long term management of neuropathic pain (Dworkin et al., 2010). While there are many advantages to prescribing opioids for this patient group, including relief of pain, improved mood, and increased functioning, long-term use of such medications is associated with increased risk for overdose, drug interactions, medication diversion, physical dependence and addiction (Ballantyne & LaForge, 2007). Despite the frequency of their use to treat pain, evidence on the efficacy of long-term opioid therapy for chronic pain is limited (Chou et al., 2014) and can lead to adverse consequences. For instance, in 2013 an estimated 1.9 million people abused or were dependent on prescription opioid pain medications (SAMHSA, 2014). In light of this, recent guidelines from the Centers for Disease Control (CDC) emphasize the importance of nonopioid medications and recommend that nonopioid therapy be the preferred treatment for chronic pain (Dowell, Haegerich & Chou, 2016). It is imperative, therefore, that we develop new strategies to aid in the management of chronic pain thereby reducing the need for opioid medications.

Research investigating the benefits of novel uses for existing drugs and alternatives to current pharmacological therapies is ongoing. One drug that has shown promise as a novel treatment for chronic neuropathic pain is N-acetyl-L-cysteine (NAC). An over-the-counter supplement, NAC has been studied as an adjunct to existing treatments for a number of psychiatric disorders including, schizophrenia (Berk, Copolov, Dean, Lu, Jeavons, Schapkaitz et al., 2008), bipolar disorder (Berk, Copolov, Dean, Lu, Jeavons, Schapkaitz et al., 2008), and obsessive-compulsive disorder (Lafleur et al., 2006). Additionally, NAC has been studied as a stand-alone treatment for several substance use

disorders, including marijuana (Gray, Watson, Carpenter & LaRowe, 2010), nicotine (Knackstedt et al., 2007) and cocaine (Mardikian et al., 2007) as well as for treatment of pathological gambling (Grant, Kim & Odlaug, 2007).

The present study grew out of research on Reactive Oxygen Species (ROS); specifically, the role of ROS in the maintenance of chronic neuropathic pain (Kwak, Lim & Baek, 2011). As a ROS scavenger, NAC has shown promise at reducing physiological signs of neuropathic pain in laboratory rat models (Kim et al., 2004; Kim et al., 2006). These findings prompted the present study of NAC for patients with inadequately controlled chronic neuropathic pain.

Present study data were collected through a 4 week, open label clinical trial of NAC as an adjuvant to opioid treatment for poorly controlled, chronic neuropathic pain. Reductions in amount of opioids taken to relieve breakthrough pain and/or a decrease in pain severity ratings were the primary outcome measures. The latter has often served as a proxy for improvements in other areas impacted by chronic pain such as level of functioning and life satisfaction. However, research has suggested that pain and functioning may not be as closely linked as previously assumed (Dougados, LeClaire, van der Heijde, 2002; Dawson et al., 2002). Pain reduction alone does not guarantee that physical or emotional functioning will improve (Turk & Melzack, 2011). As such, even though pain ratings are often the primary outcome in evaluating pain treatments, it is important to consider other outcomes to capture the various aspects of pain that can change as a result of treatment.

The current study followed the recommendation of a multidisciplinary workgroup of pain specialists to include measures that related to pain intensity, participant ratings of overall improvement and satisfaction with treatment, and physical and emotional functioning (Turk et al., 2003). Self-reported use of opioid medications for break through pain, pain severity ratings (average, highest, lowest) and measures of physical and emotional functioning were collected at baseline, during the 4-week medication trial and at the 4-week follow-up visit.

The present study examined the role of NAC for decreasing pain ratings (VAS scores), reducing use of PRN opioid pain medication, and improving physical and mental health related quality of life scores. Additionally, we examined whether appraisal of pain impacts response to study medication. Findings must be interpreted cautiously due to the small sample size, but are promising and support further research. Case studies of individual participants provide additional depth to the study findings. Given the severity of the problem of chronic pain and the consequences associated with opioid medications, the use of NAC in this population is worthy of further exploration and remains a promising contribution in the national effort to identify suitable and well tolerated alternatives to the reliance on opioid pain medications.

Hypotheses. The present study had 3 specific aims and evaluated the following 4 hypotheses:

Specific Aim 1: Conduct an open label pilot study of an over-the-counter pharmaceutical drug and nutritional supplement, N-acetyl-L-cysteine (NAC) as an adjuvant to opioid treatment in patients with inadequately controlled chronic neuropathic pain.

1.1: Examine changes from baseline in participant self-reports of pain (by Visual Analogue Scale), doses of PRN opioid medication use and/or health related quality of life over the 4 week trial period and at 1 month post-trial follow-up.

Hypothesis 1: Compared to baseline, study participants will report a reduction in their use of opioid medications to manage breakthrough pain, using measures of daily morphine equivalent dose (MED).

Hypothesis 2: Past week VAS severity ratings for Average, Worst and Least amount of pain will be lower over the 4-week clinical trial period than those reported at baseline.

Hypothesis 3: Upon completion of the 4 week medication trial, participants will have higher physical and mental health related quality of life scores (as measured by the Short Form-12 survey) than obtained at baseline.

1.2 In light of the lower than predicted sample size (which limited statistical testing of Hypotheses 1-3), case study methods were used to examine individual participant pain rating and PRN medication use profiles from baseline to the 4 week medication trial as well as the 1 month post-trial follow-up visit. The purpose was to identify and characterize participant subgroups with common patterns of response over the 10 week study period, with the goal of identifying participant subgroups that merit further investigation.

Specific Aim 2: *E*xamine the influence of catastrophic thinking on response to study medication.

Hypothesis 4: After completing the 4 week medication trial, participants with a more positive appraisal of their pain (Low catastrophizers on the pain catastrophizing scale) will have lower Visual Analogue Scale pain ratings than participants with more negative appraisals of their pain (High catastrophizers).

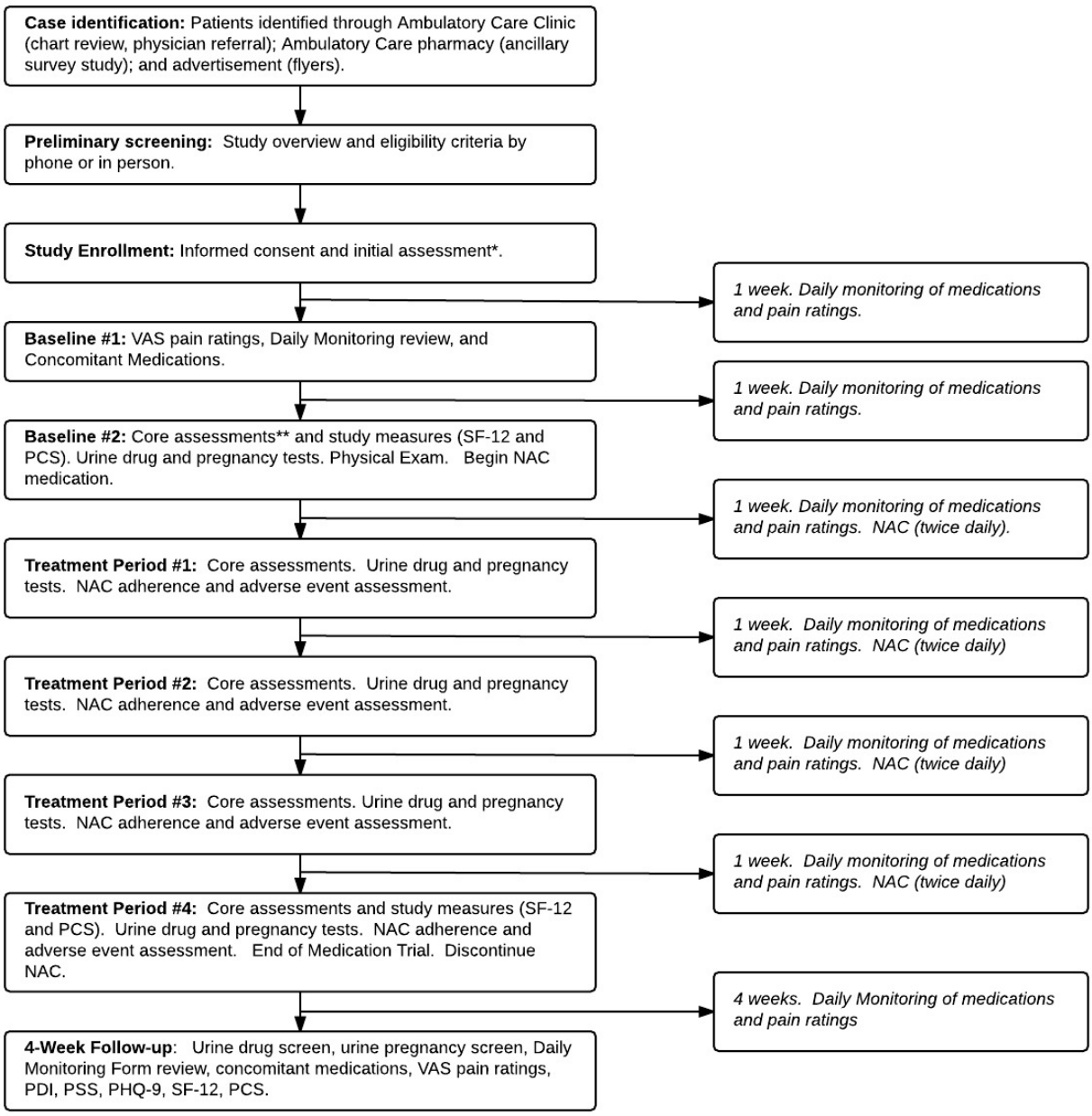
Specific Aim 3: If pilot data support future study of NAC as an adjuvant in the treatment of chronic neuropathic pain, explore feasibility issues for a future randomized clinical trial with a focus

on potential barriers to participant identification, study recruitment, baseline assessment measures, retention of patients in the clinical trial and 1-month follow-up procedures.

Methods

Study Design and Overview

The present study was part of a larger project examining whether N-acetyl-L-cysteine (NAC), an over-the-counter medication that decreases levels of oxidative stress and pain, may be a promising adjunct to standard treatments for clinical neuropathic pain. Specifically, the present dissertation examined the relationship between catastrophization and health related quality of life (HRQoL) and patient response to 2400mg of NAC taken daily over a 4 week time period. Study participants were primary care patients prescribed both a stable dose of an opioid or gabapentin as well as "breakthrough", or as-needed, opioid medication to treat their poorly controlled neuropathic pain. Patients who met study criteria and provided informed consent completed a 2-week baseline period followed by a 4 week open-label trial of NAC. Throughout this 6 week period, participants recorded their quantity and frequency of opioid or gabapentin use, and corresponding pain intensity ratings on a daily basis. They also noted their adherence to the prescribed NAC dosing schedule of 1,200 mg every 12 hours. Finally, they completed a follow-up assessment at 4 weeks post-discontinuation of the NAC medication. The flow chart of study visits is outlined in Figure 4.



***** *Initial Assessment measures include: urine drug test, pregnancy test, demographics, medical history, concomitant medication inventory, Visual Analogue Scale (VAS) pain ratings*

*****Core assessment includes: Daily Monitoring Form review, concomitant medications, Visual Analogue Scale (VAS) pain ratings, Pain Disability Index (PDI), Perceived Stress Scale (PSS), Patient Health Questionnaire (PHQ-9).*

Figure 4. Study Flow Chart

Study eligibility criteria. Initial study inclusion criteria were as follows: 1) between the ages of 18 to 65; 2) scored ≥3 on the ID-Pain measure; 3) currently taking a stable (same dose and dosing schedule for at least 6 months) dose of opioids for control of their neuropathic pain*; 4)

taking short-acting opioid medication on an "as-needed" or PRN basis to control breakthrough pain; and 5) rated their pain for the previous week as 5 or higher on the 10-point Visual Analogue Scale (VAS). Patients were excluded from the study if they: 1) were pregnant or nursing; 2) had a serious, unstable medical or psychiatric illness that the investigative team felt would preclude them from safely participating in the study; 3) had an active stomach ulcer or a history of seizures or asthma; 4) reported using non-opioid medications on an as needed or PRN basis, to control their neuropathic pain; 5) tested positive for one or more illicit drugs by urine assay; 6) had uncontrolled hypertension; and/or 7) were unable to comprehend spoken English.

**Note: In November, 2014, inclusion criteria were broadened to include patients taking a stable (same dose and dosing schedule for at least 6 months) dose of either opioids or gabapentin for control of their neuropathic pain. This expansion in the inclusion criteria for the study was prompted by low rates of patient eligibility, caused in part by changes in primary care clinic prescribing practices. All other study criteria remained unchanged.*

Preliminary chart reviews. To estimate rates of patient recruitment into the NAC study, a chart review was conducted with a focus on patients who had been prescribed any opioid medication. From April, 2014 to November, 2014, primary care patient charts were reviewed, tallying rates at which each clinical trial exclusion criterion was met by a given patient. Since one patient could endorse more than one criterion, rates do not sum to 100%. Also, despite best efforts to minimize duplicates, in the absence of any identifying information (which was not recorded), it is likely that some patient records were tallied more than once. With those caveats in mind, during the 6 month review period, N = 1072 charts were examined and findings are summarized in Table 1. The most frequent criterion leading to disqualification was absence of a neuropathic pain diagnosis (90.6%), followed closely by the absence of a stable opioid medication (86.1%).

Table 1.

Prevalence rates for study exclusion criteria in a chart review sample of N =1072 patients with an opioid prescription.

Variable	Prevalence rate N (%)
Age (>65)	207 (19.4%)
No diagnosis of neuropathic pain	969 (90.6%)
Not prescribed a stable opioid*	1003 (86.1%)
Not prescribed PRN opioid	747 (70.2%)
Seizures	34 (3.2%)
Asthma	164 (15.3%)

* Note that this review was conducted prior to the expansion in study criteria to include not just opioid but also Gabapentin prescription for management of chronic pain.

Recruitment site and procedures. Study participants were identified through the Virginia Commonwealth University Health System (VCUHS). This large, urban care system serves approximately 1,500 patients with a diagnosis of neuropathic pain annually. The initial sample of potential participants (N=275) was identified between May, 2014 and June, 2015 from 3 sources: Ambulatory Care Clinic (n=220, 80%), Ambulatory Care Pharmacy (n=2, 0.7%), and through study fliers posted in prominent places throughout VCUHS (n = 53, 19.3%).

Study recruitment. Potential participants were contacted and study inclusion/exclusion criteria were discussed. If interested, those eligible proceeded with informed consent and enrolled in the study. Figure 5 summarizes the progression from potential participant identification through study completion.

Case identification. Several methods were used to identify potential study participants. In the ambulatory care clinic, 2 approaches were used. First, the research assistant (RA) would review medical records of patients scheduled to be seen in primary care on a given day, to identify those who might meet the aforementioned study inclusion/exclusion criteria. Second, primary care physicians were informed about the study on an ongoing basis, emphasizing eligibility criteria, and

encouraging practitioners to refer potentially eligible patients to a member of the research team. In addition, flyers describing the study were posted in strategic places and circulated around the hospital, with information about how to contact the PI or member(s) of the research team about the study. Lastly, for 3 months (November, 2014- January 2015), potential participants were identified through an ancillary study taking place in the VCU Ambulatory Care Pharmacy where they were informed about the study.

Of the N = 275 persons identified, N = 88 were duplicates, yielding a sample of N = 187 unique potential participants. Of these, N = 20 could not be reached by phone to schedule an appointment; N = 27 missed or cancelled one or more appointments; and N = 35 were missed due to limitations in RA and other staff member time and availability (see Figure 2).

Initial contact. Next, a member of the research team met with potential participants, typically before or after a scheduled medical appointment, to talk about the study. Patients who expressed interest were escorted to a more private room or place in the waiting areas to discuss study participation.

Of the N = 105 individuals contacted by the research team, N = 23 declined screening. The remaining N = 82 were provided with inclusion/exclusion criteria by study personnel and of these, N=50 indicated they did not meet study criteria. Specific reasons included: over 65 years of age (N=1), ID-Pain ratings < 3 (N=2), not prescribed a stable opioid medication or Gabapentin (N=17), not prescribed an "as needed" or PRN opioid medication (N=16), reported a sub-threshold (<5) average pain score for the previous week (N=4), had a history of seizures (N=1) or asthma (N=8), or reported illicit substance use (N=1).

Informed consent. The remaining N = 32 patients who met study criteria were invited to participate in the study. Of these, N = 4 chose not to participate in the study. The remaining 28

provided informed consent and proceeded to baseline assessment. This study was reviewed and approved by the VCU Institutional Review Board (IRB) with an Investigational New Drug (IND) approval from the Food and Drug Administration.

Participants

Participants were N=28 individuals with chronic, non-cancer, neuropathic pain who were identified through the VCU health system, met study criteria, and provided informed consent. All were receiving medical care and long-term medication management of chronic pain through the VCU Primary Care clinics. Of these, N = 17 did not complete the baseline period for the following reasons: lost to follow up despite repeated attempts to contact (N = 7), no longer meeting study inclusion criteria (e.g. no longer taking PRN opioid, no longer taking stable opioid or gabapentin, evidence of illicit drug use) (N = 5), study physician or primary care physician recommendation that they not participate (N = 2), or participant decision to discontinue study participation (N = 3). The remaining N = 11 (39%) proceeded with the open-label NAC trial and were instructed to take 2400 mg NAC daily for 4 weeks. Medication was dispensed weekly during the active treatment phase of the protocol. One participant was subsequently withdrawn from the study because of an allergic reaction during week 1 of the active phase. The remaining N = 10 completed the 4-week trial and the one month follow-up assessment. The final sample was predominantly female (63.6%); Black (72.7%); never married (81.8%); with a mean age of 49.9 years (SD= 7.1, Range = 18-64 years of age).

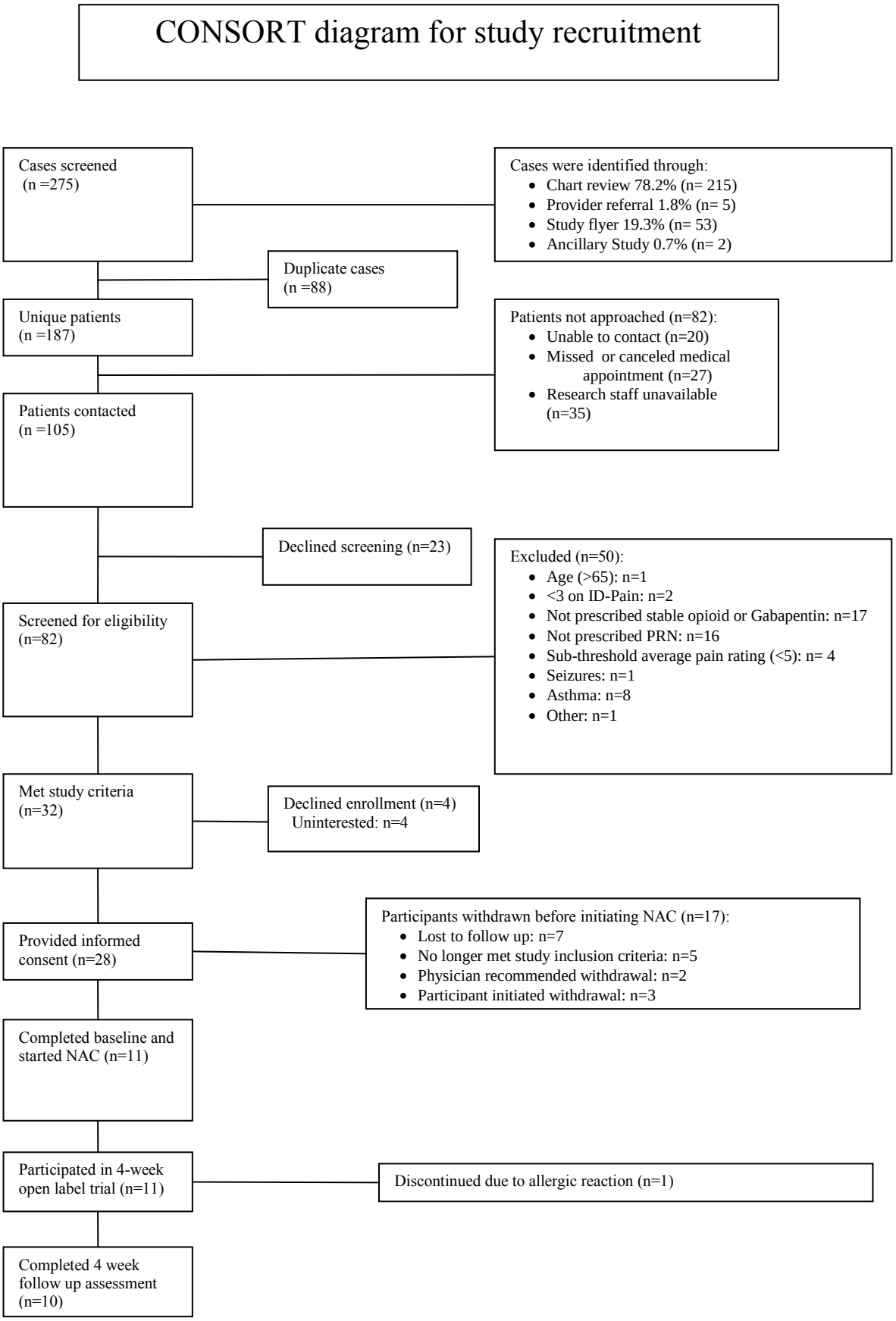


Figure 5. CONSORT diagram

Procedure

Preliminary screening for study eligibility. When first contacted, either by phone or in person, patients were verbally prescreened using several questions about primary inclusion and exclusion criteria. To confirm eligibility, they were routinely asked to rate their pain experience (past week) on a scale of 1-10, affirm use of "as needed" opioid pain medication, and score $\geq$ 3 on ID-Pain scale. Individuals who remained eligible and expressed interest in study participation proceeded with informed consent. This occurred at the initial visit or an appointment was set to complete these procedures.

Informed consent and study enrollment. Patients who met study criteria and had interest in study participation were given a copy of the Research Consent Form and proceeded with screening assessment. The RA reviewed the document with them, explaining the schedule of 8 study visits over the 10 week time period (see Figure 6), they included: Screening Visit, two Baseline Visits, four weeks of treatment with a visit at the end of each week, and a Follow-Up Visit four weeks after completing the NAC treatment phase. The RA explained that these survey questions would focus on: pain, mood, stress, general functioning, demographics. Compensation for study participation was also reviewed, and the RA informed them that urine tests would be conducted to assess for illicit drug use, and, in women, pregnancy.

The RA reviewed potential risks and discomforts of study participation, alternatives to participation, and an explanation of the voluntary nature of participation. Further, the RA informed participants that all data was confidential and that if published or presented, that the findings would not contain any identifying information. For patients who were interested in participating in the study and who meet the eligibility criteria, the RA obtained written informed consent for study participation. Participants who were no longer interested in participating were thanked for their time and not enrolled in the study.

Initial assessment. Upon completing informed consent, the following information was collected; 1) demographics; 2) medical history; 3) a Concomitant Medication inventory (including questions about prescription, non-prescription, and medical/nutritional supplement use); 4) a urine drug test (testing for cocaine, cannabis (THC), and amphetamines); and for women of childbearing age, 5) a urine pregnancy test.

After affirming participant eligibility, they received the Daily Monitoring Form and the RA explained it was used for tracking both stable and PRN pain medications (including Gabapentin after inclusion criteria were amended). They were instructed in how to record dose taken, time each dose was taken, and Average and Worst VAS pain ratings at the time medications were taken. Upon completing initial assessment, participants were given an appointment for a follow up in 1 week and compensated with a $5 gift card for their time and effort. See Figure 6 for the measures collected at each study appointment. If the participant was found to no longer be eligible (e.g. they are pregnant, using illicit substances) they were informed of this, thanked for their time, provided with study compensation and withdrawn from the study.

		Demographics	Physical Examination	Urine Drug Screen, Pregnancy Test	Daily Monitoring Form	VAS	SF-12 (HRQoL)	Catastrophizing (PCS)	Disability (PDI)	Stress (PSS)	Mood (PHQ-9)	Concomitant Medication	NAC Pill Count	Compensation
	Screening	X		X		X								$5
Baseline	Baseline Week 1				X	X						X		$10
	Baseline Week 2		X	X	X	X	X	X	X	X	X	X		$10
Intervention	Treatment Week 1			X	X	X			X	X	X	X	X	$30
	Treatment Week 2			X	X	X			X	X	X	X	X	$30
	Treatment Week 3			X	X	X			X	X	X	X	X	$30
	Treatment Week 4				X	X	X	X	X	X	X	X	X	$50
	4 week follow up				X	X	X	X	X	X	X	X		$10*

* a bonus gift card of $25 was also given at this visit if the participant completed all study visits.

Figure 6. Study procedures and measures by study visit.

Baseline period. Following study enrollment and initial assessment, participants returned for two baseline appointments.

Baseline 1. At Baseline 1, participants Daily Monitoring Forms with medication use and pain ratings were reviewed and new forms were provided. Any questions about the study were answered and the next appointment was made for approximately 1 week later. Participants were also thanked for their continued participation and compensated with a $10 gift card for their time and effort.

Baseline 2.

Physical Examination. At baseline 2, the participant completed a physical examination with the study physician. In addition to an evaluation of general appearance, review of body systems, and assessment of vital signs, the study physician assessed for any medical conditions that would preclude study participation. If the participant was approved for continued study participation, he/she proceeded with Baseline 2 assessment measures.

If participant was not approved for medical reasons, this was explained to them. After answering any questions they were thanked for their time, provided compensation for the visit and withdrawn from the study.

Medication. The treatment consisted of the addition of NAC to the participants existing medication regimen. The treatment adjuvant, NAC, was provided as 600-mg capsules. The active treatment period lasted for four weeks. Each week, participants were provided a one week supply of NAC (+/- two days) and written and verbal instructions on how to appropriately take the study medication. Participants were instructed to take two, 600 mg capsules, twice daily (in the morning and in the evening). They were told if they missed a dose of the study medication, they should either take the dose (if it is more than six hours before their next scheduled dose) or skip the dose of NAC (if it was six hours or less until their next dose). Participants were also reminded to note all such events on their Daily Monitoring Forms. They were also instructed to return their NAC pill bottles and any remaining study medication at each subsequent study appointment and they were told that pill counts would be conducted to confirm their reported medication usage.

The study medication, NAC, is an herbal dietary supplement regulated as a food by the FDA. Dietary supplements containing NAC are widely available in health food stores and on the Internet. FDA regulations concerning the manufacture of these products are different than those for prescription drugs, but all domestic and foreign companies that

manufacture dietary supplements for distribution in the United States, must comply with the Dietary Supplement Current Good Manufacturing Practices (cGMPS) for quality control (http://www.fda.gov/Food/DietarySupplements/default.htm). The NAC medication used in the current study was provided by General Nutrition Centers (GNC) in 600mg capsules. Concentration and bioavailability of the NAC medication was not established for the current study.

Baseline 2 measures. After completion of the physical examination, the following were completed: 1) pregnancy test; 2) urine drug test; 3) Visual Analogue Scale (VAS); 4) Pain Catastrophizing Scale (PCS); 5) Short Form Health Survey-12 (SF-12); 6) Pain Disability Index (PDI); 7) Patient Health Questionnaire (PHQ-9); 8) Perceived Stress Scale (PSS); 9) Concomitant Medication inventory. Additionally, completed Daily Monitoring Forms were reviewed and collected from the participant. Blank Daily Monitoring Forms were provided. A one week supply (+/- 2 days) of the study medication was provided and a follow up visit was scheduled for the following week. Participants were also thanked for their continued participation and compensated with a $10 gift card for their time and effort.

Treatment Period. At the conclusion of baseline 2, participants entered the active treatment period. The active treatment period lasted for four weeks. Participants followed up with in-person clinic appointments weekly for the four weeks of active treatment and were provided with a one week supply (+/- 2 days) of the study medication.

Treatment 1. The following measures were completed:1) VAS; 2) PDI; 3) PHQ-9; 4) PSS; 5) urine drug screen; 6) pregnancy test; 7) Adverse event assessment; 8) medication compliance assessment; and 9) Concomitant Medication inventory. Additionally, completed Daily Monitoring Forms were reviewed and collected from the participant. Blank Daily Monitoring Forms were

provided. At the completion of this appointment, a one-week supply (+/- two days) of study medication was provided and a follow up visit was scheduled for the following week. Participants were also thanked for their continued participation and compensated with a $30 gift card for their time and effort.

Treatment 2-3. Identical measures were collected, and procedures followed, for Treatment 2 and Treatment 3, as were followed in Treatment #1 visit.

Treatment 4. This appointment marked the conclusion of the active treatment period. At this appointment, all the measures collected at the Treatment 1-3 visits were collected (VAS, PDI, PHQ-9, PSS). In addition to these measures the following measures were collected; 1) PCS; 2) SF-12. Completed Daily Monitoring Forms were reviewed and collected from the participant. At the conclusion of this appointment a 4 week supply of blank Daily Monitoring Forms were provided and participants were asked to continue tracking their stable and PRN pain medications (including Gabapentin) that they were currently taking, dose taken each day, time each dose was taken, and pain ratings prior to taking medication. Finally, a follow up visit was scheduled for approximately 4 weeks after Treatment #4. Participants were thanked for their continued participation and compensated with a $50 gift card for their time and effort. Urine drug screens and pregnancy tests were no longer collected at this appointment.

4-Week Follow-up. Participants returned for an in-person follow up visit approximately 4 weeks after they completed taking the study medication. At this final study visit, participants completed 1) VAS; 2) PCS; 3) SF-12; 4) PDI; 5) PHQ-9; 6) PSS, and 7) Concomitant Medication inventory. Participants returned their Daily Monitoring Forms and they were reviewed with the RA for errors. Participants were also thanked for their continued participation and compensated with a

$10 gift card for their time and effort. They were provided with an additional bonus gift card for $25 if they attended all study appointments. This appointment marked the conclusion of their study participation and no further visits were scheduled.

Compensation. Participants were compensated for their time and effort. They received $5 for completing the Screening Visit, $10 for completing Baseline week 1, $10 for completing Baseline week 2, $30 for completing each of the first three, weekly Treatment Visits, and $50 for completing the final weekly Treatment Visit. At the final visit, the 4-Week Follow-Up, participants received a $10 gift card and an additional $25 if they have attended each of their study visits. Thus, the potential maximum compensation for this study was $200.

Reminder Calls and Missed Appointments. The business day prior to each scheduled study appointment the RA would call to remind the participant about the appointment date, time, and location. If the participant was unable to make the appointment it was rescheduled. If a participant missed a scheduled appointment the RA would attempt to reach the participant by phone to reschedule the appointment. A discrete voicemail message was left requesting a return phone call if the participant was unavailable. Participants who could not be reached were called every week throughout the study or until contact had been established. The RA called the participants' back-up contacts if contact could not be established with the participant. Participants were withdrawn from the study if contact could not be reestablished or, if when contact was reestablished, the participant requested to be withdrawn from the study. The same procedures were followed for all study appointments and documented in the participants' study chart.

Research Personnel. Research personnel included graduate and undergraduate research assistants. All research personnel completed the CITI online training in human subjects' protection.

In addition, Drs. Svikis and Dillon conducted a variety of protocol-specific (e.g., participant recruitment, forms administration, standard operating procedures, emergency procedures, adverse event reporting procedures, etc), and intervention-specific training activities prior to study start and during the course of the study. The trainings included both didactic and hands-on/experiential learning activities. Additional booster trainings were conducted with research staff throughout the course of the study.

Measures and Participant Information

Demographics. Basic demographic information was collected at baseline using an RA administered self-report questionnaire. Questionnaire items included: age; race (Caucasian, African American, Hispanic, Other), years of education, marital status (single/married), employment status (full time/part time), receipt of disability. This information was collected at study enrollment.

Medical and Medication History. A brief medical history was obtained with particular focus on duration of pain, as well as comorbid psychological and medical diagnoses. Information about pain medications type, dosage and frequency of use for both stable dose and "break through" drugs as well as concomitant medications (e.g., prescription, non-prescription and medical/nutritional supplements). This information was reported by participants at study enrollment and confirmed through chart review after completion of the study visit.

Visual Analogue Scale (VAS) of Pain Severity. Visual analogue scales are a measurement instrument for subjective characteristics or attitudes that cannot be directly measured (i.e. cravings, anxiety) and is regularly used to assess pain (Wewers & Lowe, 1990). The VAS uses a 100 mm long horizontal line to demarcate the possible range of pain ratings from "0" no pain at all to "100" worst pain imaginable at the other. Participants are asked to characterize pain severity by making a

vertical line crossing the horizontal line at a particular point along the line. The measurement continuum is also believed to provide greater sensitivity than a numerical scale (Flaherty, 1996). Test–retest reliability of the VAS for pain has been reported to be high for the VAS (r = 0.73-0.82) (Good et al., 2001). Participants completed the Visual Analogue Scale (VAS) at each study visit.

Participants rated their Average, Worst, and Least pain for the previous week on a 100mm line. The VAS rating was converted into a score ranging from 0 to 100.

Pain Catastrophizing Scale (PCS). The Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995) is used to assess catastrophic thinking in response to pain. The 13 item questionnaire asks participants to rate frequency of specific pain-related thoughts and feelings using a 5-point Likert scale (0, not at all to 4, all the time). The PCS has been shown to have high internal consistency (α = 0.91) and high test-retest reliability (r=0.78) (Sullivan Bishop & Pivik, 1995; Van Damme, Crombez, Bijttebeir, Goubert & Van Houdenhove, 2002). This information was collected at three time points; Baseline #2, Treatment #4 and 4-Week Follow-up.

The total PCS score (0-52) of participants were used to identify a median of 25.5 (SD = 10.70). Participants were divided into Low catastrophizers or High catastrophizers using the median split of the PCS total scores. Additionally, three sub scores were calculated from the PCS (e.g. magnification, rumination, and helplessness) using criteria established by Sullivan and colleagues (1998). For the subscales, a sum of the response to a subset of responses were used. Rumination was calculated using responses to questions 8, 9, 10 and 11. Magnification was calculated using response to questions 6, 7 and 13. Helplessness was calculated using responses to questions 1, 2, 3, 4, 5 and 12.

Short Form-12 Health Survey Questionnaire (SF-12). The SF-12 is a brief version of the Short Form-36 (SF-36) health-related survey instrument (Ware, Kosinski & Keller, 1995, 1996).

The SF-12 requires 2-3 minutes to complete (Ware & Gandek, 1998) and measures of patient's physical (PCS) and mental (MCS) functioning. Both scales have good internal consistency (PCS α = 0.82; MCS α = 0.85). This information was collected at three time points; Baseline #2, Treatment #4 and 4-Week Follow-up.

The present study examined the scores obtained from the Physical Component Summary (PCS) scale and the Mental Component Summary (MCS) scale. Criteria for calculation of the PCS and MCS were obtained from *A guide to the integration of certified Short Form survey scoring and data quality evaluation capabilities* provided by QualityMetric Incorporated (Maruish & DeRosa, 2009).

ID-Pain Questionnaire. The ID-Pain questionnaire is a 6 item screener for neuropathic pain (Portenoy, 2006). The ID- Pain has been used to assess neuropathic pain general populations (Ohayon & Stingl, 2012), primary care settings (Haanpää, 2009), as well as for neuropathic pain within specific population, such as osteoarthritis (Ohtori et al., 2012) and breast cancer (Reyes-Gibby, Morrow, Bennett, Jensen & Shete, 2010). The measures requires 1-2 minutes to complete and is scored by adding the responses. All "Yes" answer to questions 1–5 are scored as 1, while a "yes" answer to question 6 is scored as −1. A total score of ≥ 3 was established as the minimum cut off for identifying neuropathic pain (Portenoy, 2006). In the initial scale development study conducted by Portney (2006), the ID-Pain items were found to accurately predict diagnoses of neuropathic pain determined by pain specialists, with concordance *c* indices in the studies of 0.73 and 0.69. The ID-Pain questionnaire is highly correlated with the Douleur Neuropathique 4 (DN4) (r = 0.8), another measure of neuropathic pain (Padua et al., 2013). The ID-Pain showed sensitivity 78% and specificity 74% (Padua et al., 2013). Participants with a score lower than three were withdrawn from the study. This information was collected at study enrollment.

Patient Health Questionnaire – 9 (PHQ-9). The nine-item PHQ-9 is a self-report measure designed to measure depressive symptoms (Kroenke, Spitzer & Williams, 2001). The PHQ-9 has been used for both diagnostic and treatment monitoring purposes. The PHQ-9 assesses DSM-IV diagnostic symptoms of depression with Likert-type ratings on a "0" (not at all) to "3" (nearly every day) scale (Range = 0-27). Psychometrics have been assessed in a number of settings, including, primary care (Spitzer, Kroenke & Williams, 1999), ob/gyn (Spitzer et al., 2000), and in a general, non-medical population (Martin et al., 2006). The PHQ-9 has demonstrated high internal reliabilities (α = .89 and .86) and forty-eight hour test-retest reliability (α = .84) (Kroenke, Spitzer & Williams, 2001). The PHQ can be meaningfully applied as a diagnostic proxy for depression (score > or = 10 has 88% sensitivity and 88% specificity), and provides a continuous measure of severity (Total Score). The PHQ – 9 has been found to be a practical and responsive tool among both men and women (Löwe, Schenkel & Carney-Doebeling, 2006). This information was collected at every study visit.

Daily Monitoring. Daily Monitoring Forms were used to assess pain medication use. The Daily Monitoring Form is a paper-and-pencil record that was completed by participants daily. Participants recorded both their stable and PRN pain medications (including Gabapentin after inclusion criteria were amended) that they were currently taking, dose taken each day, time each dose was taken, pain ratings (Average and Worst) prior to taking medication. During the treatment period participants were also asked to record when they took the NAC medication on the Daily Monitoring Form. Participants returned the completed Daily Monitoring Forms at each subsequent study appointment. Further instructions for filling out the Daily Monitoring Form were provided as needed. This information was collected at every study visit from Baseline #1 through the 4-Week Follow-up.

Information on opioid medication, collected on the Daily Monitoring Form, was converted into morphine equivalents dose (MED). The potency of one opioid medication is not necessarily the same as another and the MED was calculated using a formula that allows the standardization of opioid pain medication. A calculator was used to convert prescribed opioid medications (i.e. Tramadol, oxycodone, Fentanyl) into MED. For the purposes of this study, MED was calculated by following the criteria outlined in McPherson (2010). Specifically, the online calculator provided by the Washington State Agency Medical Directors' Group was used for such calculations (http://www.agencymeddirectors.wa.gov/).

Study Phase. The data were divided into three discrete time points, or phases, because of the possible changes in slope due to the addition or discontinuation of the study medication. The Pre-NAC Phase consisted of Baseline 1, and Baseline 2; the NAC Phase consisted of Treatment 1 through Treatment 4; and the Post-NAC Phase consisted of the 4-Week Follow Up.

Data Management. Data were entered continuously throughout the study by RA's. Data were reviewed for missing, illogical, out of range, and inconsistent values; accuracy of key variables such as gender, age, race, medication adherence, pain ratings. Any problems that were encountered that needed correction and clarification were addressed by the project coordinator with the RA's.

Participant confidentiality was maintained through a numbered reference system with participants names appearing on the "key", which was kept by the project coordinator. Data were entered into a REDCap database, which uses a MySQL database via a secure web interface. Access to the study's data in REDCap was restricted to the members of the study team by username and password.

Data Analysis Plan

Demographics. Statistical analyses were performed using SPSS v.23.0 (SPSS, Chicago, IL). The data set was prepared and assessed for any outliers or missing data. Descriptive analyses to describe demographic characteristics (e.g., age, race, education) were calculated.

Hypotheses. The hypothesized relationships between the study medication and reductions in opioid use was examined (Hypothesis 1). A mixed linear model was fit with Time, NAC (Yes or No), and MED (Daily reported morphine equivalent doses). The model included an effect for day/time (1 to the maximum reported days for each subject), NAC use on the day (Yes or No) and the interaction between day/time and NAC use. An AR(1) variance-covariance matrix was used to model the within subject correlation. Nonsignificant interaction terms were removed from the model. Additionally, a mixed linear model was fit to the data to examine the impact of time and NAC use on pain ratings (Average, Worst) for each day.

A hypothesized relationship between the study medication and reductions in global assessments of pain was examined (**Hypothesis 2**). A repeated measures analysis of variance was conducted with global pain ratings (VAS) as the DV and the repeated factor of time (Baseline #1 [week 1], Baseline #2 [week 2], Treatment Period #1 (week 3), Treatment Period #2 (week, 4), Treatment Period #3 (week 5), Treatment Period #4 (week 6), and 4-week follow up (week 10). Additionally, a repeated measures analysis of variance was conducted with global pain ratings (VAS) as the DV and the repeated factor of phase of study (Pre-NAC [Baseline #1, Baseline #2], NAC [Treatment Period #1, Treatment Period #2, Treatment Period #3, Treatment Period #4], Post-NAC [4-Week Follow Up]).

The hypothesized relationship between the study medication and improvements in HRQoL was examined (**Hypothesis 3**). Paired samples t-tests were performed to compare HRQoL subscores across three time points (Baseline 2, Treatment period 4, and 4-Week Follow Up). Paired-samples t-tests were run for both the MCS and PCS scores derived from the SF-12 across the three time points.

A hypothesized relationships between appraisal of pain and global pain experience was examined (**Hypothesis 4**). A mixed between-within subjects analysis of variance was conducted with appraisal of pain (Low catastrophizer, High catastrophizer) as the between-subjects independent variable (IV). The dependent variable (DV) was the global pain rating as measured through the Visual Analogue Scale (VAS) score measured at each time period (Baseline #2 [week 2], Treatment #4 [week 6], and 4-Week Follow Up [week 10]) across three separate ratings; Average, Worst, and Least pain for the previous week. The within-subjects factor was time (Baseline #2 [week 2], Treatment #4 [week 6], and 4-Week Follow Up [week 10]).

Results

Data Analysis

Outliers and Tests of Normality. Prior to any analysis, the data was examined for normality of distribution and for the presence of outliers. Descriptive statistics (mean, standard deviation, median) were generated for the demographic variables collected at baseline. Given that this is an open label study, without a control group, each participant acted as their own control. Frequency distributions of continuous variables were examined for evidence of non-normality and outliers. If the data contained outliers and there was a meaningful rationale to remove them (e.g., outliers were not expected), they were coded as missing. If by removing outliers the data were normal, no further changes were made to the variable. In one participant, at Treatment 4 appointment, an obvious error was made in identifying the least, average, and highest pain scales at one visit (e.g. the rankings were in the single digits and the least pain exceeded the highest and average). In this case a mean substitution for the Average, Least, and Worst pain ratings were used.

Initial examination of the data showed that while the sample was slightly skewed and kurtotic, the values were not above 1.5 on either statistic. Variables were normally distributed and within expected ranges.

Characteristics of the Sample

Demographics: Demographic characteristics for participants who initiated NAC treatment (N=11), those who did not (N=17) and the total sample (N=28) are shown in Table 2. Participants who initiated NAC had an average age of 49.9 years (SD= 7.1, 18-64 years old). They were almost two thirds female (63.6%) and they identified themselves either as Black (72.7%) or Caucasian (27.3%). Participants reported a mean of 12.4 years formal education (SD = 1.2, range 10-14 years) and most were single (never married) (81.8%) at the time of study participation. Participants who did not initiate NAC were similar on age, education, marital status, and receipt of disability. Participants who did not initiate NAC were nearly twice as likely to be male (70.6%) compared to those who did initiate NAC (36.4%). They were also less likely to have a disability case pending (35.4% vs. 45.5%) or be African American (64.7% vs. 72.7%).

Table 2.

Participant Characteristics: Initiated NAC (n =11) and Enrolled (N=28)

	Initiated NAC treatment (N=11) Total (%) or M (SD)	Did not initiate NAC treatment (N=17) Total (%) or M (SD)	Total Sample (N=28) Total (%) or M (SD)
Age (years)	49.9 (7.1)	47.7 (8.5)	48.3 (7.9)
Gender			
Female	7 (63.6%)	5 (29.4%)	12 (42.9%)
Male	4 (36.4%)	12 (70.6%)	16 (57.1%)
Education (years)	12.4 (1.2)	12.1 (2.0)	12.2 (1.8)
Marital Status			
Married/cohabitating	1 (9.1%)	2 (11.8%)	3 (10.7%)
Single/divorced/widowed	9 (81.8%)	14 (82.4%)	23 (82.1%)
Separated	1 (9.1%)	1 (5.9%)	2 (7.1%)
Ethnicity			
Caucasian	3 (27.3%)	6 (35.3%)	9 (32.1%)
African American	8 (72.7%)	11 (64.7%)	19 (67.9%)
Disability	4 (36.4%)	6 (35.4%)	10 (35.7%)
Disability case pending	5 (45.5%)	6 (35.4%)	11 (39.3%)
Employed (part or full time)	2 (18.2%)	5 (29.4%)	7 (25.0%)

Neuropathic Pain. Neuropathic pain symptoms for participants who initiated NAC treatment, those who did not and the total sample are presented below (Table 3). A cut off score of $\geq$3 was established by Portenoy (2006) to identify neuropathic pain and was used as an inclusion criterion for the current study. Participants who initiated NAC tended to report higher rates than those who did not initiate NAC of their pain feeling "like pins and needles" (100% vs. 94.4%), and "like electric shocks" (81.2% vs. 72.2%). Participants who did not initiate NAC reported higher rates of their pain feeling like "burning" (83.3% vs. 72.7%), "numb" (88.9% vs. 63.6%), and "worse with the touch of clothing or bed sheets" 44.4% vs. 27.3%). Participants who did not initiate NAC also reported more frequently that pain was "limited to *(their*) joints" (11.1% vs. 0%).

Participants ID-PAIN responses are presented below (Table 4). Participants who initiated NAC tended to endorse fewer ID-PAIN responses than those who did not initiate NAC; 3 ID-PAIN

responses (63.3% vs. 47.1%), 4 ID-PAIN responses (27.3% vs. 29.4%), and 5 ID-PAIN responses (9.1% vs. 23.5%).

Table 3.

ID-Pain responses

	Initiated NAC (n=11)	Did not initiate NAC (N=17)	Whole sample (n=28)
ID-PAIN Question	Yes	Yes	Yes
Did the pain feel like pins and needles?	100%	94.4%	96.4%
Did the pain feel like burning?	72.7%	83.3%	78.6%
Did the pain feel numb?	63.6%	88.9%	78.6%
Did the pain feel like electric shocks?	81.2%	72.2%	78.6%
Is the pain worse with the touch of clothing or bed sheets?	27.3%	44.4%	39.3%
Is the pain limited to your joints?	0%	11.1%	7.1%

Table 4.

Percentage of ID-PAIN responses endorsed

Number of ID-PAIN responses endorsed	Initiated NAC (n=11)	Did not initiate NAC (N=17)	Whole sample (n=28)
3 responses endorsed	63.6%	47.1%	53.6%
4 responses endorsed	27.3%	29.4%	28.6%
5 responses endorsed	9.1%	23.5%	17.9%

Medical and Pain Diagnoses. Participants reported their current medical and pain diagnoses at study enrollment and these were confirmed through chart review. There was no significant difference in number of medical diagnoses for participants who initiated NAC (M=11.18, SD=4.62) and participants who did not initiate NAC (M=8.18, SD=3.64; t (26) = -1.92, p = .066). Similarly, there was no significant difference in scores for participants who initiated NAC (M=2.73, SD=1.10) and participants who did not initiate NAC (M=2.59, SD=1.23; t (26) = -.30, p = .763) on

number of pain diagnoses. The most common pain diagnoses, assessed at study enrollment, include: chronic pain diagnosis with an unspecified etiology (e.g. "chronic pain", "knee pain", "shoulder pain", "back pain", "hip pain"), diabetic neuropathy, fibromyalgia, unspecified neuropathy (e.g. "neuropathy", "polyneuropathy"), arthritis, and gout.

Pain Medications. Participant reports of pain medications they were prescribed at study enrollment are presented in Table 5. Most frequently prescribed medications for both those who initiated NAC and those who did not were Oxycodone and Tramadol. The percentage of participants who were prescribed Oxycodone (54.5% vs. 35.3%) and Gabapentin (81.8% vs. 41.2%) at baseline was higher than the percentage of participants who did not initiate the 4 week trial. However, participants who initiated NAC were prescribed Hydrocodone (9.1% vs.23.5%), Tramadol (36.4% vs. 52.9%), Oxycontin (0% vs. 11.8%), and Lyrica (9.1% vs. 23.5%) less frequently than participants who did not initiate NAC.

Table 5.

Pain medications prescribed at study enrollment (N=28)

Medication	Initiated NAC (n=11)	Did not initiate NAC (N=17)	Whole sample (n=28)
Hydrocodone	9.1%	23.5%	17.9%
Tramadol (Ultram)	36.4%	52.9%	46.4%
Oxycodone	54.5	35.3%	42.9%
Morphine	9.1%	11.8%	10.7%
Oxycontin	0	11.8%	7.1%
Hydromorphone	9.1%	0	3.6%
Fentanyl	9.1%	0	3.6%
Gabapentin	81.8%	41.2%	57.1%
Lyrica	9.1%	23.5%	17.9%
Nortryptyline	9.1%	0	3.6%
Cymbalta	0	5.9%	3.6%

While pain medications were reported at study enrollment, stable pain medication and PRN medication were not differentiated until participants returned for Baseline visit 1. Therefore, this information is only available for the N = 11 individuals who began the open label trial of NAC. The PRN opioid and stable pain medications prescribed to this subgroup are summarized in Tables 6 and 7, respectively. Detailed descriptions of PRN opioid and stable pain medications, dosage and frequency for all study participant who initiated study medication are presented in Table 8.

Table 6.

PRN opioid medications of participants initiating NAC (N=11)

Hydrocodone	9.1%
Hydromorphone	9.1%
Oxycodone	45.5%
Tramadol	36.4%

Table 7.

Stable pain medications of participants initiating NAC (N=11)

Gabapentin	63.6%
Fentanyl Transdermal	9.1%
Methadone	9.1%
Morphine	9.1%
Oxycodone	9.1%

Table 8.

Stable and PRN pain medications of participants initiating NAC (N = 11)

Participant	Stable dose medication	PRN medication
002	Morphine 15mg. 1 tab every 12 hours	Oxycodone 5mg. 1 tab every 8 hours as needed
003	Methadone 10mg. 2 tabs every 8 hours	Hydromorphone 4mg. 1 tab every 4 hours as needed
006	Oxycodone 10mg. 1 tab every 4 hours	Tramadol 50mg. 2 tabs every 8 hours as needed
007	Fentanyl 50 mcg/hr, replace every 72 hours	Oxycodone 10mg. 1 tab 4x day as needed
012	Gabapentin 600mg. 2 tabs 2x day	Oxycodone 5mg. 1 tab every 8 hours as needed
013	Gabapentin 300mg. 1 tab 2x day	Tramadol 20mg. 1 tab every 6 hours as needed
016	Gabapentin 300mg. 1 tab AM, 2 tabs PM	Tramadol 50mg. 2 tabs every 8 hours as needed
017	Gabapentin 800mg. 1 tab 3x day	Oxycodone 5mg. 1 tab 4x day as needed
019	Gabapentin 300mg. 1 tab in AM, 2 tabs in PM	Hydrocodone 7.5mg. 1 tab every 6 hours as needed
022	Gabapentin 400mg. 1 tab 3x day	Oxycodone 30 mg. 1 tab every 6 hours or as needed
024	Gabapentin 300mg. 1 tab 3x a day	Tramadol 50mg. 1 tab every 6 hours as needed.

Eleven participants started NAC medication. Ten of those participants completed the full four week course of study medication. One participant experienced an allergic reaction (e.g. "itching") while taking the NAC medication and attributed the allergic reaction to the NAC. It is unclear if the reaction was to the NAC medication or to other causes, however the Primary Investigator, in consultation with the study physician, elected to discontinue the participant in the study.

Primary Analyses

Hypothesis 1. Compared to baseline, study participants will report a reduction in their use of opioid medications to manage breakthrough pain, using measures of daily morphine equivalent dose (MED).

The first hypothesis, using a mixed linear model and MED tracked daily, examined whether there was a decrease in overall opioid use, measured as daily MED, during the three distinct phases of the study (Pre-NAC, NAC, and Post-NAC). In this model the interaction term was not significant ($F_{38, 512} = 0.57$, $p = 0.9822$), therefore it was dropped from the model and the model was refit using the main effects of day/time and NAC use. In the reduced model neither the effect of day/time ($F_{86, 550} = 0.89$, $p = 0.7367$) nor NAC use ($F_{1, 550} = 0.15$, $p = 0.6973$) was a significant predictor of daily MEDs, partial eta squared =.0003. The results are summarized in Tables 9-11.

Table 9.

Descriptive statistics for MEDs across study phases

Period	n	Mean	Standard Deviation	Standard Error
Pre	174	101.24	89.93	6.82
NAC	286	104.560	96.66	5.72
Post	187	88.03	102.70	7.51

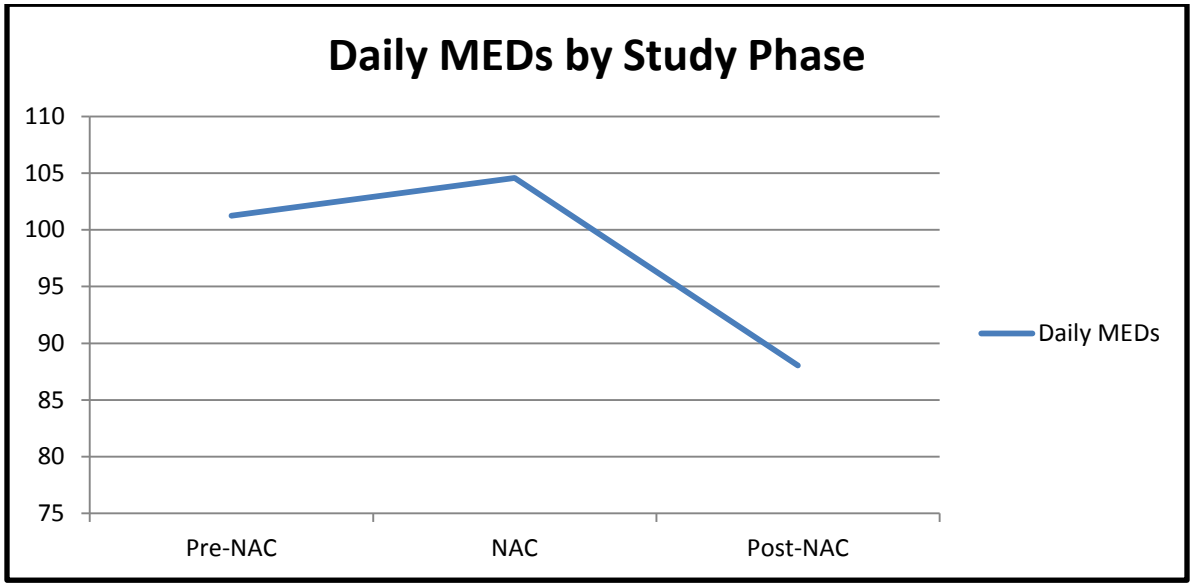


Figure 7. Mean daily MEDs across 3 study phases

A Mixed Linear Model was fit to the data to examine the impact of time and NAC use on the Average pain score for each day. In this model the interaction term was not significant ($F_{38, 567}$ = 1.00, p = 0.4788) therefore it was dropped from the model and the model was refit using only the main effects of day/time and NAC use. In this reduced model neither the effect of day/time ($F_{86, 605}$ = 0.84, p = 0.8394) nor NAC use ($F_{1, 605}$ = 1.73, p = 0.1891) was a significant predictor of average pain score, partial eta squared =.0029.

Table 10.

Descriptive statistics for Average pain ratings across 3 study phases.

Period	n	Mean	Standard Deviation	Standard Error
Pre	180	6.38	1.58	0.12
NAC	308	5.95	1.96	0.11
Post	214	6.80	1.18	0.08

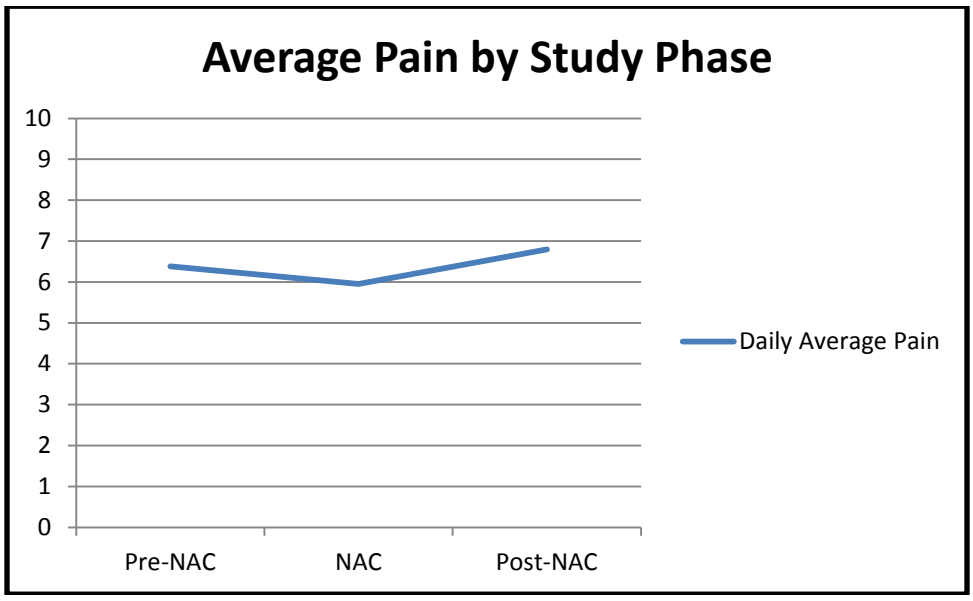


Figure 8. Mean Average pain ratings across 3 study phases

A mixed linear model was fit to the data to examine the impact of time and NAC use on the Highest pain score for each day. In this model the interaction term was not significant ($F_{38, 566} = 0.60$, $p = 0.9714$) therefore it was dropped from the model and the model was refit using only the main effects of day/time and NAC use. In this reduced model neither the effect of day/time ($F_{86, 604} = 0.80$, $p = 0.9038$) nor NAC use ($F_{1, 604} = 0.30$, $p = 0.5841$) was a significant predictor of highest pain score, partial eta squared =.0005.

Table 11.

Descriptive statistics for Highest pain ratings across 3 study phases.

Period	n	Mean	Standard Deviation	Standard Error
Pre	180	7.47	1.85	0.14
NAC	308	6.94	2.33	0.13
Post	213	7.91	1.30	0.09

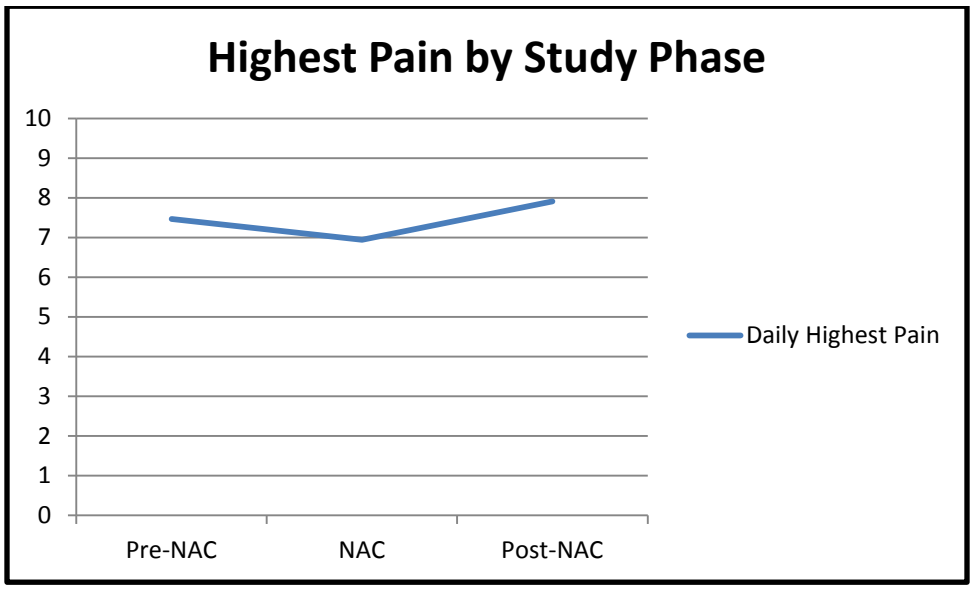


Figure 9. Mean Highest pain ratings across 3 study phases

A mixed linear model was fit to assess the effect of NAC on daily MED throughout the study (Baseline 1 thorough 4-Week Follow-up). No significant effects were found for NAC on MED. Additionally, a mixer linear model was fit to Average and Worst pain and no significant effects were found for either. Given the small sample size, the results cannot be fully interpreted. Effect sizes were presented for decreases in MED as well as average and worst pain ratings.

Hypothesis 2. Past week VAS severity ratings for Average, Worst and Least amount of pain will be lower over the 4-week clinical trial period than those reported at baseline.

The second hypothesis was tested with RMANOVA using VAS ratings obtained weekly about average, worst and least severe pain experienced during the previous week. Assessment time points included Baseline Weeks 1 and 2, Treatment Weeks 1-4 and 4-Week Follow-up. Analyses were conducted separately for the 3 pain categories (average, worst, least). The results are summarized in Tables 12-14.

A repeated measures analysis of variance was conducted to compare average pain ratings from the VAS across all study time points. There were no significant effects for time, Wilks' Lambda = .173, F (6, 4) = 3.189, p = .141, multivariate partial eta squared = .827, ω^2 = .003.

Table 12.

Descriptive statistics for Average VAS ratings across all study visits.

Study appointment	N	Mean	Standard Deviation
Baseline 1	10	69.80	13.32
Baseline 2	10	71.40	15.02
Treatment 1	10	60.30	18.09
Treatment 2	10	61.60	18.14
Treatment 3	10	62.50	19.42
Treatment 4	10	65.90	21.13
4-week follow up	10	64.00	17.98

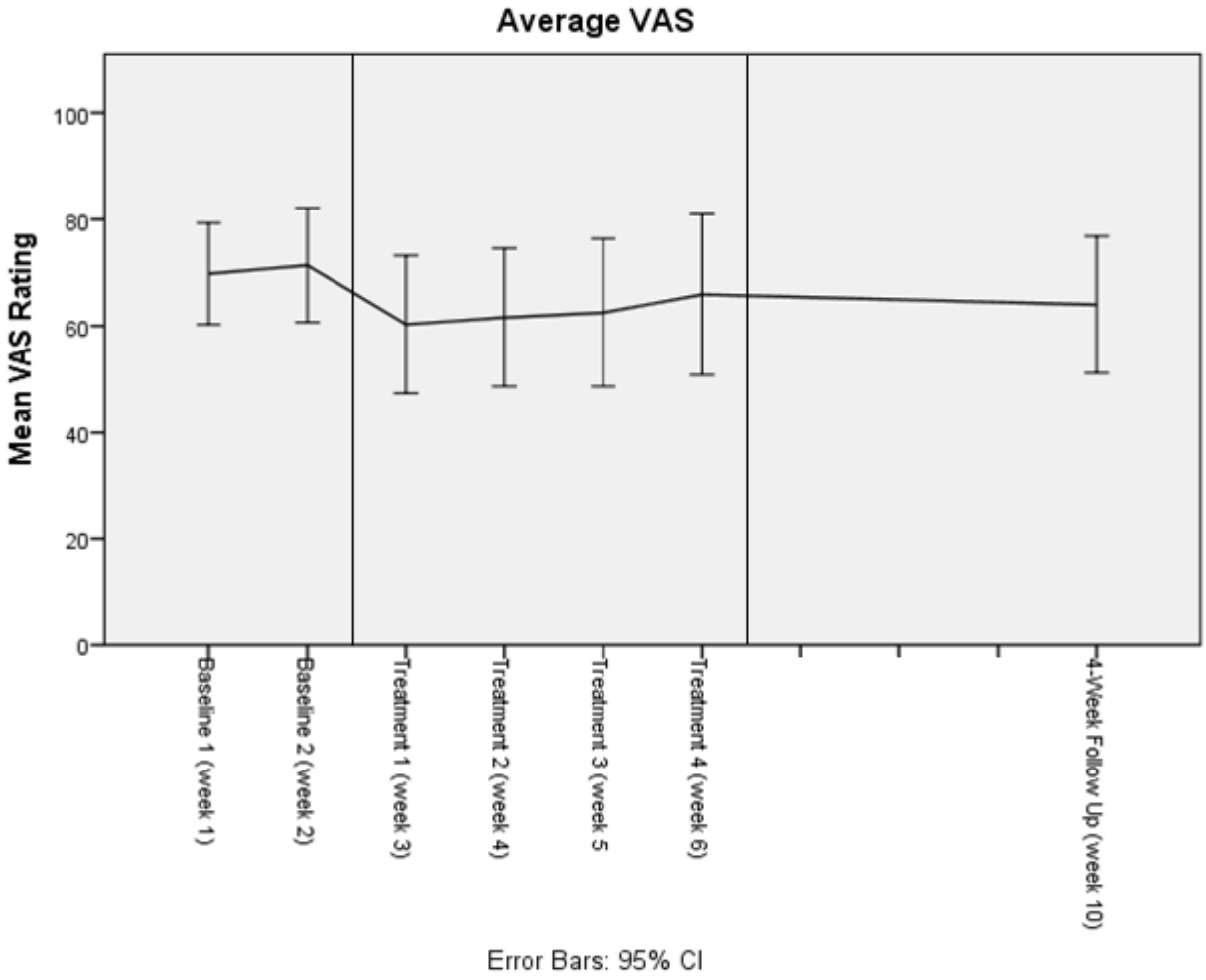


Figure 10. Average VAS ratings across all study visits

A repeated measures analysis of variance was conducted to compare highest pain ratings from the VAS across all study time points. There were no significant effects for time, Wilks' Lambda = .453, F (6, 4) = 0804, p = .615, multivariate partial eta squared = .547, ω^2 = .001.

Table 13.

Descriptive statistics for Highest VAS ratings across all study visits.

Study appointment	N	Mean	Standard Deviation
Baseline 1	10	86.60	12.24
Baseline 2	10	89.30	11.66
Treatment 1	10	84.10	16.41
Treatment 2	10	83.60	16.87
Treatment 3	10	78.80	18.54
Treatment 4	10	80.30	19.64
4-week follow up	10	82.80	19.65

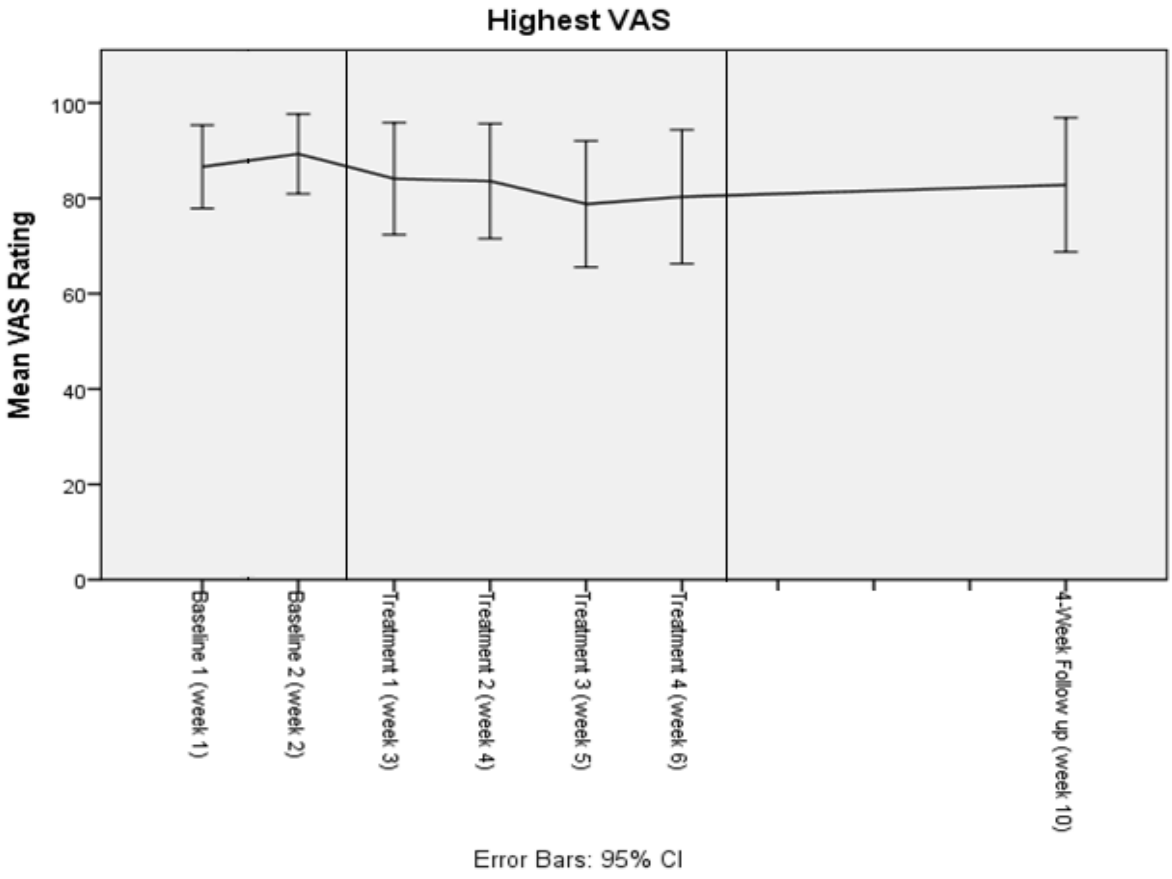


Figure 11. Highest VAS across all study visits.

A repeated measures analysis of variance was conducted to compare least pain ratings from the VAS across all study time points. There were no significant effects for time, Wilks' Lambda = .521, F (6, 4) = .613, p = .718, multivariate partial eta squared = .479, ω^2 = .003.

Table 14.

Descriptive statistics for Least VAS ratings across all study visits.

Study appointment	N	Mean	Standard Deviation
Baseline 1	10	43.90	14.08
Baseline 2	10	38.80	17.82
Treatment 1	10	41.30	19.59
Treatment 2	10	46.20	21.48
Treatment 3	10	47.10	22.30
Treatment 4	10	48.70	20.28
4-week follow up	10	45.40	20.40

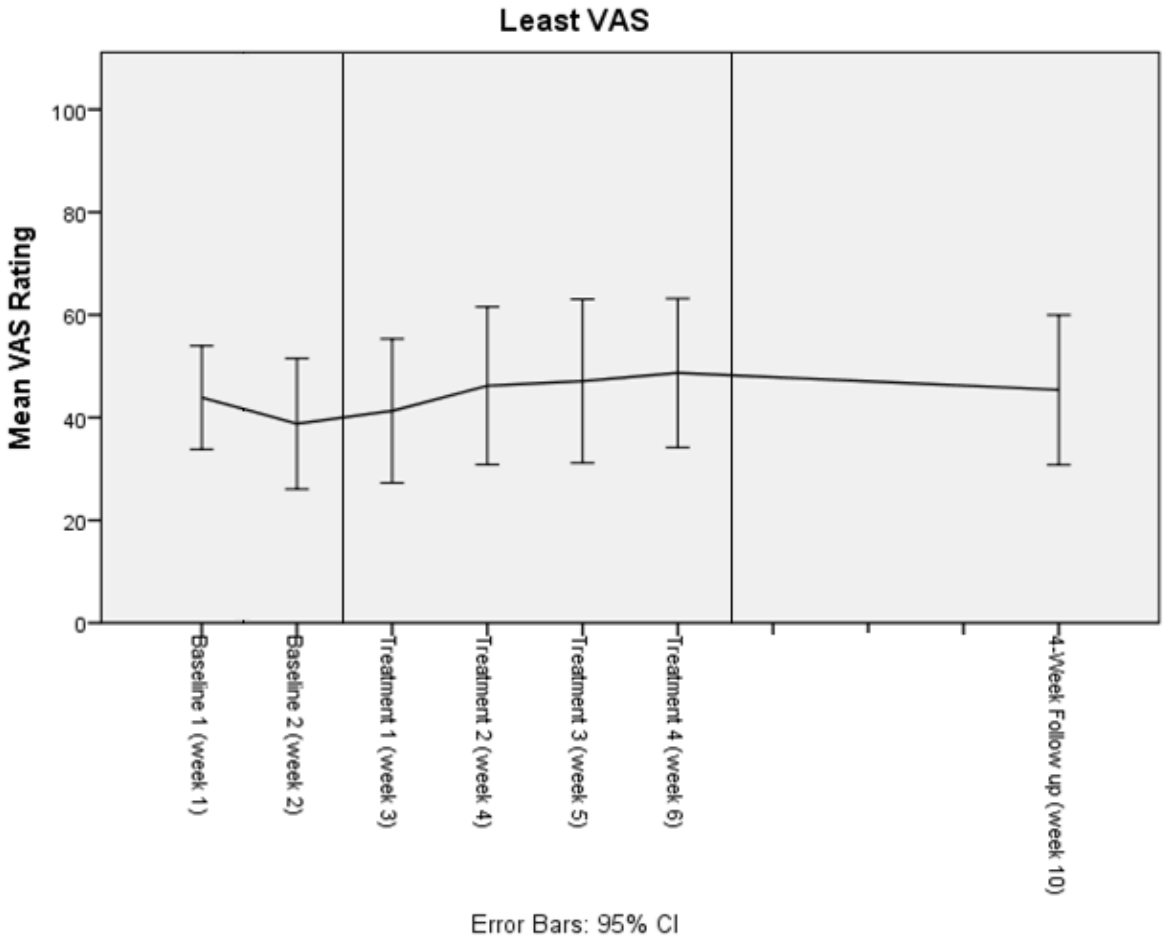


Figure 12. Lowest VAS ratings across all study visits

To explore possible changes across the three distinct phases of treatment (Pre-NAC, NAC, and Post-NAC) a RMANOVA was conducted on the mean pain rating for each phase of the treatment. Analyses were conducted separately for the 3 pain categories (average, worst, least). The results are summarized in Tables 15-17.

A RMANOVA was conducted to compare Average pain ratings from the VAS across the three phases of the study. There were no significant effects for time, Wilks' Lambda = .677, F (2, 8) = 1.911, p = .210, multivariate partial eta squared = .323, ω^2 = .027.

Table 15.

Descriptive statistics for Average VAS ratings across 3 study phases.

Study appointment	N	Mean	Standard Deviation
Pre-NAC	10	70.60	13.89
NAC	10	62.57	17.95
Post NAC	10	64.00	17.98

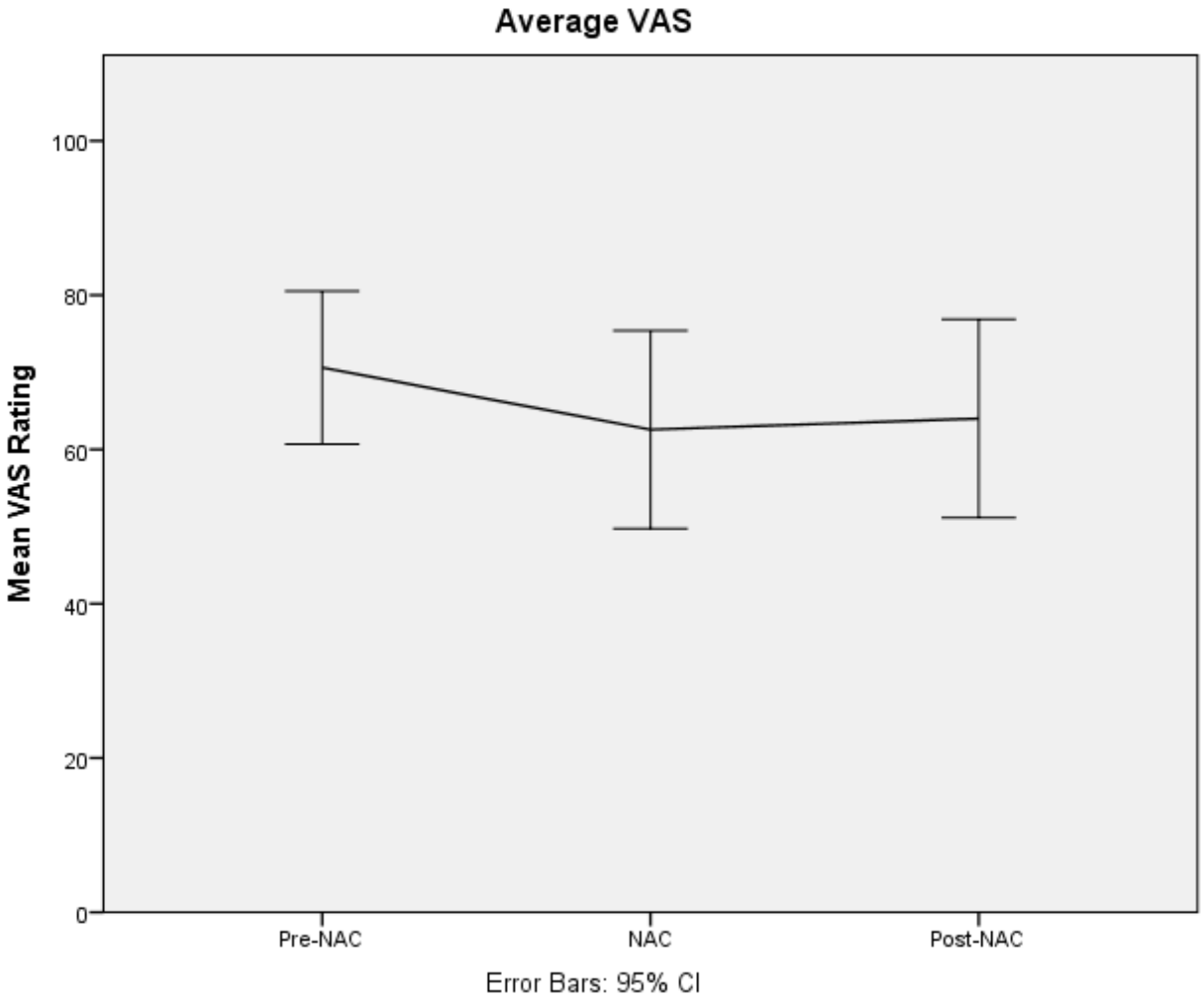


Figure 13. Average VAS ratings across 3 study phases.

A RMANOVA was conducted to compare worst pain ratings from the VAS across the three phases of the study. There were no significant effects for time, Wilks' Lambda = .678, F (2, 8) = 1.904, p = .211, multivariate partial eta squared = .322, $\omega^2 = 0.017$.

Table 16.

Descriptive statistics for Highest VAS ratings across 3 study phases.

Study appointment	N	Mean	Standard Deviation
Pre-NAC	10	87.33	11.81
NAC	10	81.70	16.42
Post NAC	10	82.80	19.66

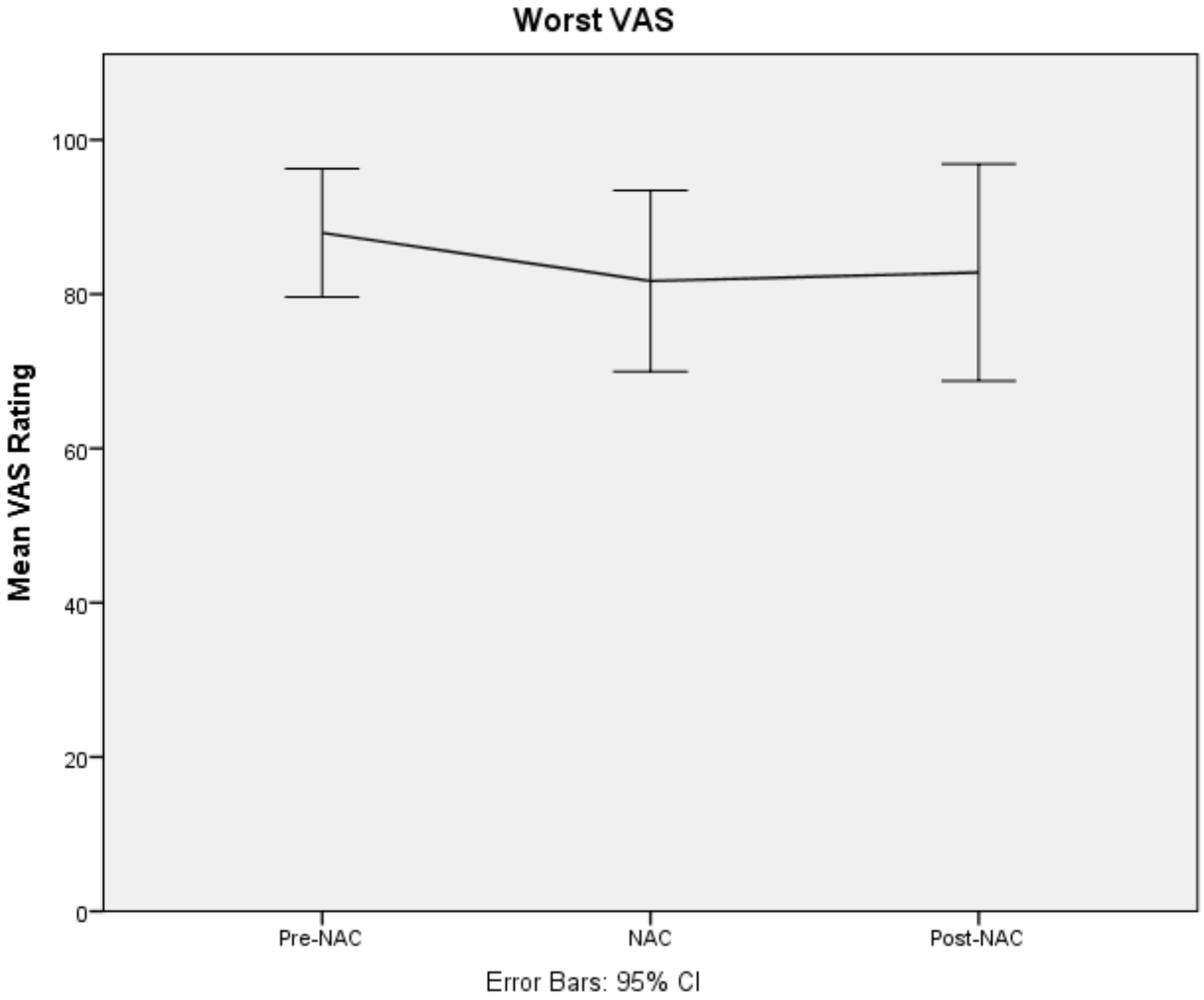


Figure 14. Highest VAS ratings across 3 study phases

A RMANOVA was conducted to compare least pain ratings from the VAS across the three phases of the study. There were no significant effects for time, Wilks' Lambda = .887, F (2, 8) = .508, p = .620, multivariate partial eta squared = .113, ω^2 = -0.003.

Table 17.

Descriptive statistics for Least VAS ratings across 3 study phases.

Study appointment	N	Mean	Standard Deviation
Pre-NAC	10	41.40	14.26
NAC	10	45.83	20.52
Post NAC	10	45.40	20.40

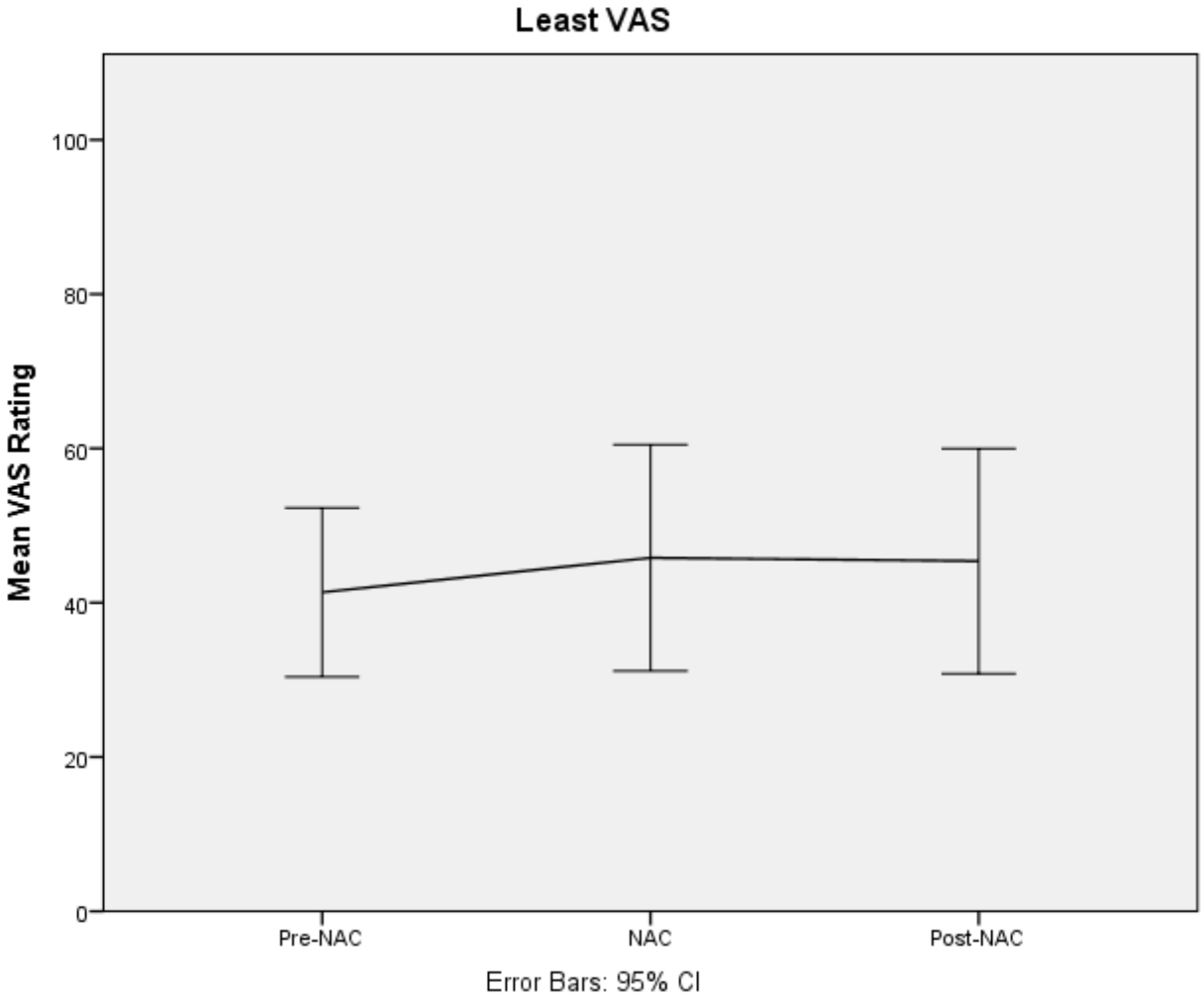


Figure 15. Least VAS ratings across 3 study phases

Repeated measures analysis of variance were performed to assess the effect of NAC on VAS ratings (average, worst, least) across all study visits. No significant time effects were found for NAC on global pain ratings measured through the VAS. Additionally, repeated measures analysis of variance were performed to assess the effect of NAC on VAS ratings (average, worst, least) across the three distinct phases of this study (Pre-NAC, NAC, Post-NAC). No significant time effects were

found for NAC on global pain ratings in the different phases of the study measured through the VAS. Given the small sample size, the results cannot be fully interpreted. Effect sizes were observed for improving global pain ratings while taking the study medication.

Hypothesis 3. Upon completion of the 4 week medication trial, participants will have higher physical and mental health related quality of life scores (as measured by the Short Form-12 survey) than obtained at baseline.

To test the **third hypothesis**, that the addition of NAC will result in improvements of health related quality of life (HRQoL), paired-samples t-test were used to compare Baseline 2, Treatment period 4, and 4-Week Follow Up assessment data. Changes in HRQoL were measured using two subscores derived from the SF-12, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) score. Paired-samples t-tests were run for both the MCS and PCS scores derived from the SF-12 across the three time points. Results are presented in Figure 16 and 17.

A paired samples t-test was conducted to evaluate the impact of the NAC medication on participants HRQoL. There were no statistically significant changes in the PCS scores between Baseline 2 (M = 27.53, SD = 8.68) to Treatment period 4 (M =28.63, SD = 10.73), t (9) = -.74, p = .48, Cohen's d = -0.113.

There were no statistically significant changes in the PCS scores between Baseline 2 (M = 27.53, SD = 8.68) and 4-Week Follow-up (M =27.40, SD = 7.45), t (9) = .09, p = .93, Cohen's d = -.016).

There were no statistically significant changes in the PCS scores between Treatment period 4 (*M* =28.63, SD = 10.73) and 4-Week Follow-up (*M* =27.40, SD = 7.45), *t* (9) = .70, *p* = .50, Cohen's *d* = .133.

There were no statistically significant changes in the MCS scores between Baseline 2 (M = 52.86, SD = 11.24) to Treatment period 4 (*M* =49.64, SD = 11.24), *t* (9) = 1.40, *p* = .20, Cohen's *d* = .261.

There were no statistically significant changes in the MCS scores between Baseline 2 (M = 52.86, SD = 11.24) and 4-Week Follow-up (*M* =47.71, SD = 13.20), *t* (9) = 1.40, *p* = .29, Cohen's *d* = .421.

There were no statistically significant changes in the MCS scores between Treatment period 4 (*M* =49.64, SD = 11.24) and 4-Week Follow-up (*M* =47.71, SD = 13.20), *t* (9) = .35, *p* = .73, Cohen's *d* = .145.

Paired samples t-tests were performed to assess changes in HRQoL across the three time points. Two different subscores (PCS and MCS), derived from the SF-12, were used to assess these changes. No statistically significant changes were seen from Baseline 2 to Treatment period 4, Baseline 2 to 4-Week Follow Up, or Treatment period 4 to 4-Week Follow Up. Given the small sample size, Hypothesis 3 cannot be fully interpreted. Small effect sizes were observed for study medication for improving HRQoL.

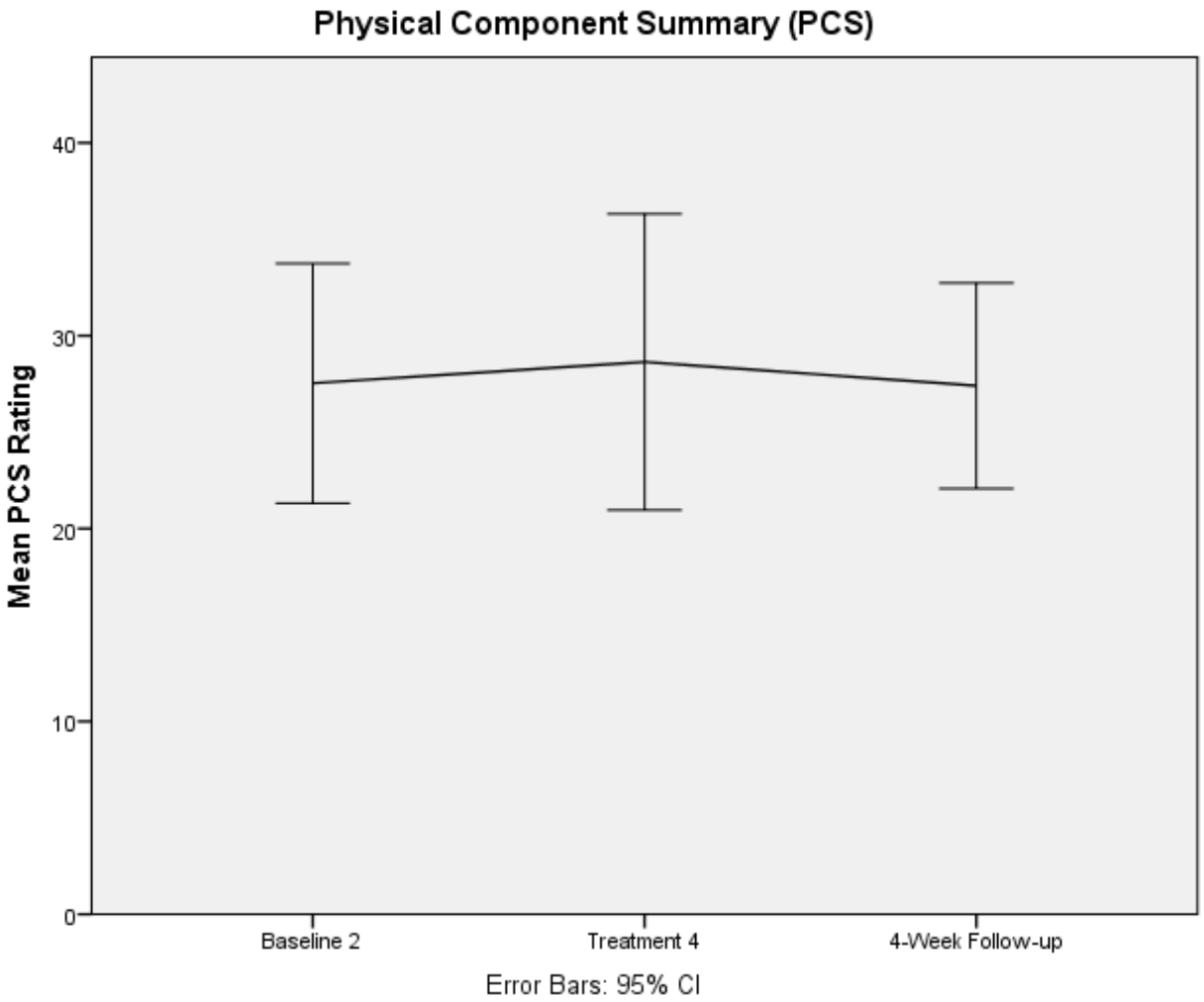


Figure 16. PCS scores across 3 study phases.

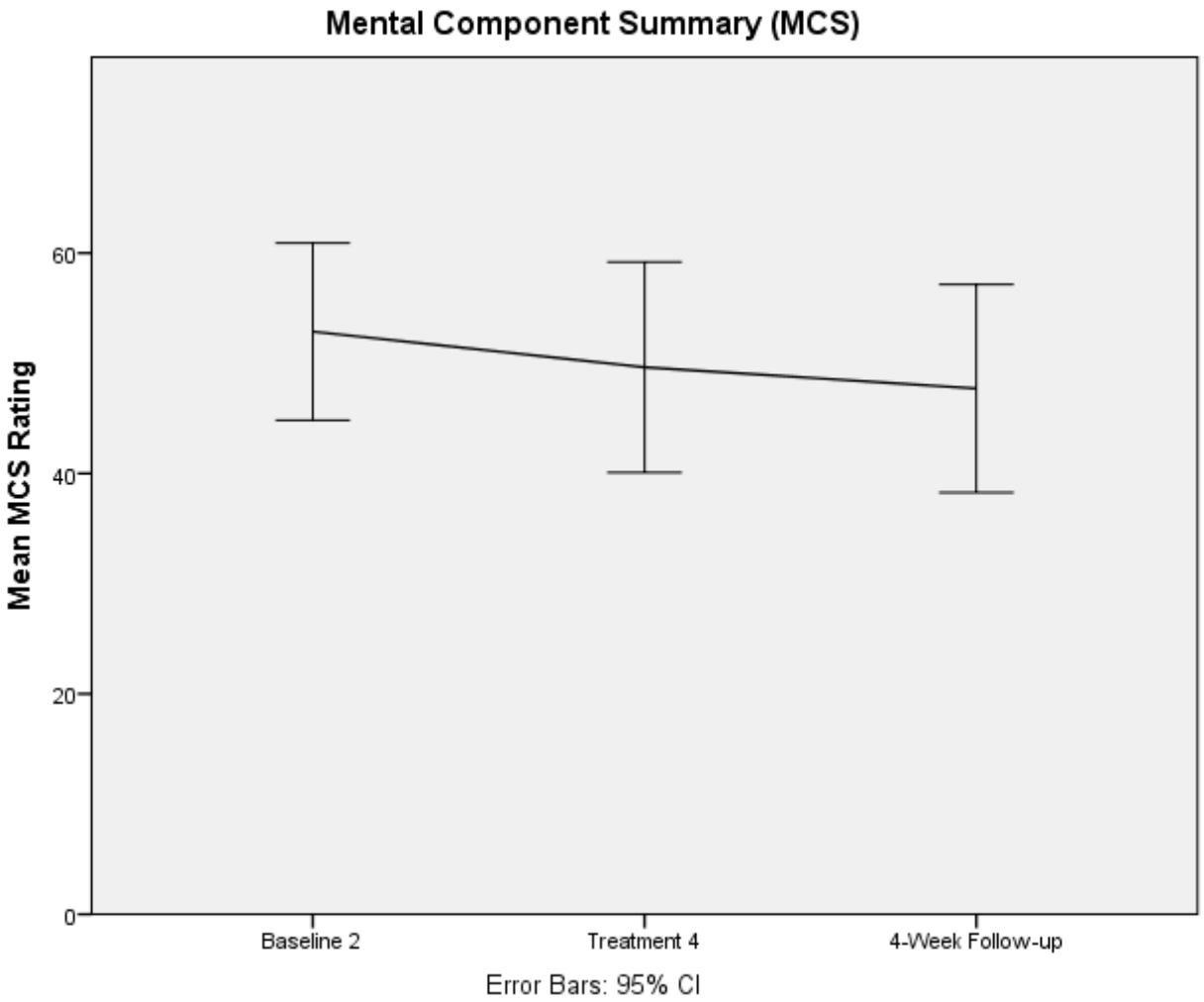


Figure 17. MCS scores across 3 study phases.

Hypothesis 4. After completing the 4 week medication trial, participants with a more positive appraisal of their pain (Low catastrophizers on the pain catastrophizing scale) will have lower Visual Analogue Scale pain ratings than participants with more negative appraisals of their pain (High catastrophizers).

To test the fourth hypothesis, a mixed between-within subjects analysis of variance was conducted to assess the impact pain appraisal (Low catastrophizers, High catastrophizers) on average VAS ratings for the past week, across three time periods (Baseline 2, Treatment 4, and 4-Week Follow Up). There was no significant interaction between participants catastrophizing and time,

Wilks Lambda = .72, F (2, 7) = 1.38, *p* = .31, partial eta squared = .28. There was no main effect for time, Wilks Lambda = .74, F (2, 7) = 1.26, *p* = .34, partial eta squared = .26, and neither group showing significant changes in average pain ratings across the three time points (see Table 18). The main effect comparing the two approaches to pain was significant, *F* (1, 8) = 13.80, *p* = .006, partial eta squared = .633.

Table 18.

Pain catastrophizing and Average VAS pain ratings across 3 time points.

	High catastrophizers			Low catastrophizers		
Time period	N	Mean	Standard Deviation	N	Mean	Standard Deviation
Baseline #2	5	81.40	10.45	5	61.4	12.18
Treatment #4	5	82.2	11.03	5	41.4	25.47
4 week follow up	5	74.4	4.72	5	53.6	20.84

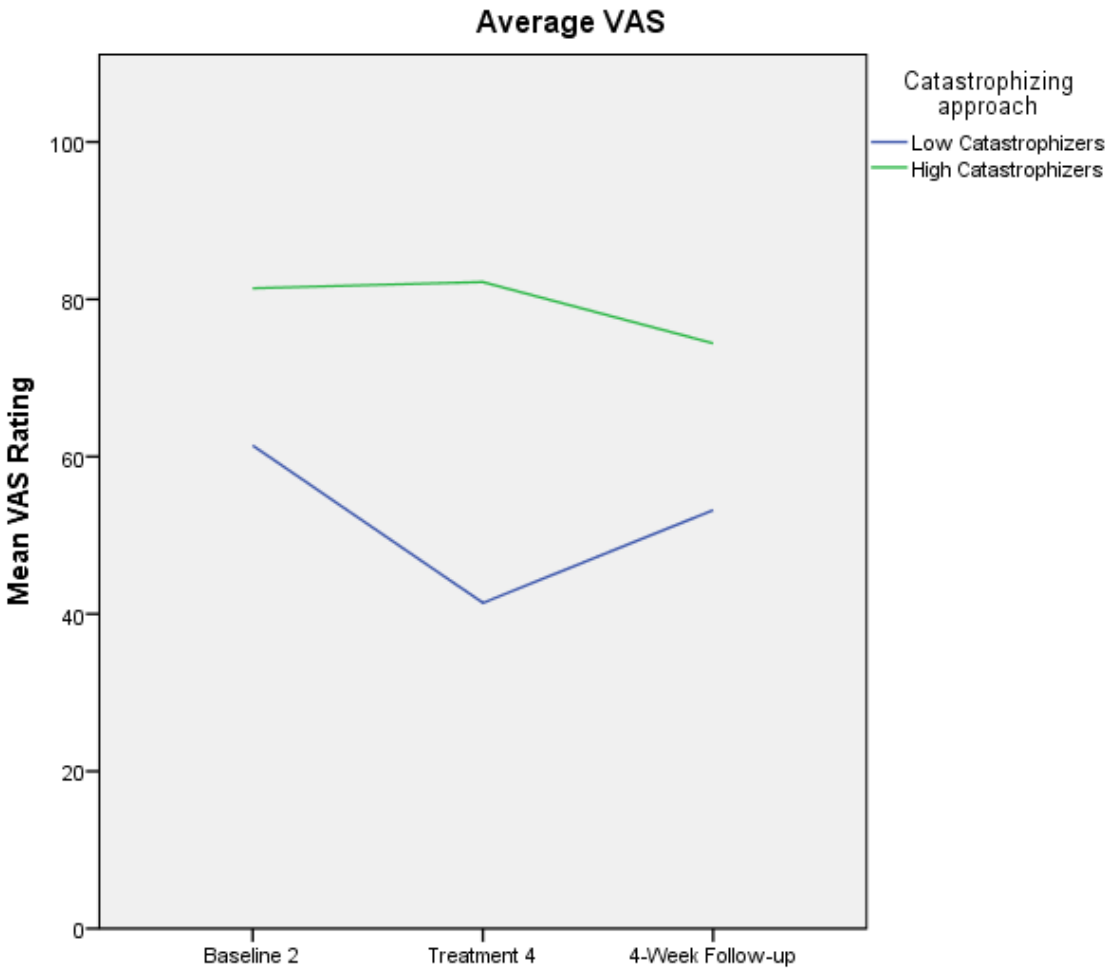


Figure 18. Average VAS ratings across three time points for Low and High catastrophizers.

A mixed between-within subjects analysis of variance was conducted to assess the impact pain appraisal on Worst VAS ratings for the past week, across three time periods. There was no significant interaction between participants catastrophizing and time, Wilks Lambda = .86, F (2, 7) = .59, p = .58, partial eta squared = .14. There was no main effect for time, Wilks Lambda = .67, F (2, 7) = 1.74, p = .24, partial eta squared = .33, and neither group showing significant changes in Worst pain ratings across the three time points (see Table 19). The main effect comparing the two approaches to pain was not significant, F (1, 8) = 2.62, p = .14, partial eta squared = .25.

Table 19.

Pain catastrophizing and Worst VAS pain ratings across three time points

	High catastrophizers			Low catastrophizers		
Time period	N	Mean	Standard Deviation	N	Mean	Standard Deviation
Baseline 2	5	94.60	3.00	5	84.00	15.05
Treatment 4	5	90.00	5.70	5	62.40	36.59
4 week follow up	5	87.00	6.04	5	78.60	28.09

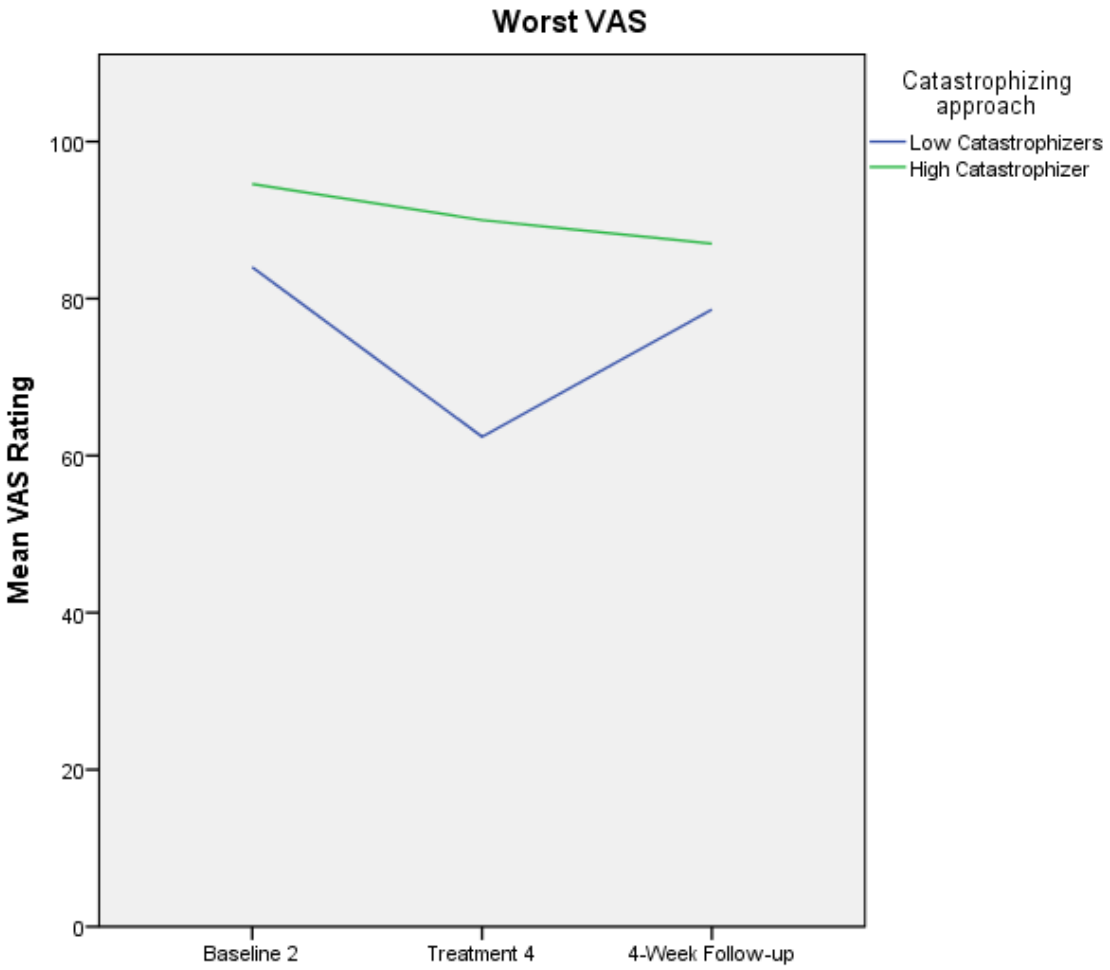


Figure 19. Worst VAS ratings across three time points for Low and High catastrophizers.

A mixed between-within subjects analysis of variance was conducted to assess the impact pain appraisal on Least VAS ratings for the past week, across three time periods. There was no significant interaction between participants catastrophizing and time, Wilks Lambda = .67, F (2, 7) =

.1.75, *p* = .24, partial eta squared = .33. There was no main effect for time, Wilks Lambda = .78, F (2, 7) = 1.01, *p* = .41, partial eta squared = .23, with neither group showing significant changes in Least pain ratings across the three time points (see Table 20). The main effect comparing the two approaches to pain (Low catastrophizers, High catastrophizers) was not significant, *F* (1, 8) = 2.16, *p* = .18, partial eta squared = .21.

Table 20.

Pain catastrophizing and Least VAS pain ratings across three time points

	High catastrophizers			Low catastrophizers		
Time period	N	Mean	Standard Deviation	N	Mean	Standard Deviation
Baseline 2	5	46.6	10.97	5	31.00	21.02
Treatment 4	5	58.60	16.62	5	35.4	23.34
4 week follow up	5	50.20	18.90	5	40.60	22.83

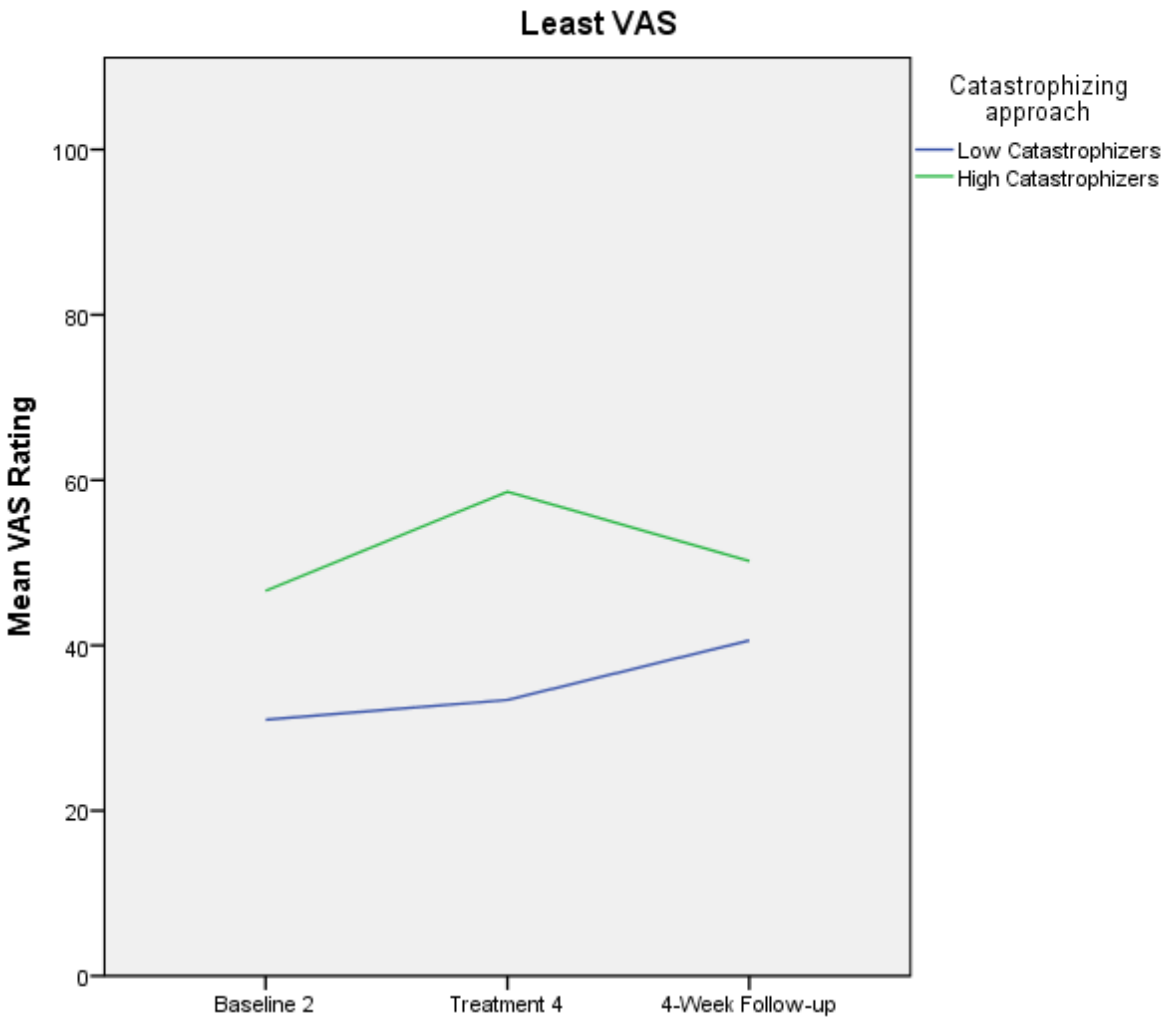


Figure 20. Least VAS ratings across three time points for Low and High catastrophizers.

A mixed between-within subjects analysis of variance was conducted to assess the impact of two approaches to pain appraisal (Low catastrophizers, High catastrophizers) on participants' global pain ratings (average, worst, least), across three time points (Pre-NAC, NAC, Post-NAC). No significant interactions were found between approach to pain appraisal and global pain ratings across the three time points. Given the small sample size, Hypothesis 4 cannot be fully interpreted. Main effect comparing the two types of pain appraisal was significant for difference in the global pain ratings between the two appraisal approaches and this was unrelated to the intervention.

Summary of All Participants

Active medication period. Across all study participants (N =10), self-report VAS scores show Average pain ratings over the course of the study medication period trended downward in N = 4 participants, with the remaining N = 6 participants' ratings remaining stable compared to baseline. When participants' Worst pain ratings were examined, N = 8 remained largely unchanged (flat line), with a slight decreases for N = 2 participants. For the Least pain ratings, only N = 1 participant showed a decline over the 4 weeks, with 5 showing no change and 4 showing an increase over the 4 weeks.

Responses on the Pain Disability Index were mixed. Half (N = 5) of the sample reported largely stable responses from study enrollment through the medication trial while N = 3 reported consistent decreases in disability after initiating the study medication. Two participants had variable responses with decreases for one or two weeks followed by a return to baseline ratings during the active study medication period.

When looking at participants across their reported catastrophizing thoughts, N = 2 participants show increases in catastrophic thinking at the conclusion of the study medication while N = 4 showed declines and the remaining N = 4 participants showed little or no changes in their catastrophic thinking.

On the SF-12 quality of life measure, over half (N=6) of participants reported improvements in physical functioning during the 4-week study period. For mental health quality of life, half of participants reported no change during the study period, with N = 4 reporting improvements and N = 1 reporting decrements.

Five participants noted a decrease in depressive symptoms during the medication period, with N = 3 reporting increases and N = 2 reporting no change. Stress was also assessed and while taking the study medication, N = 5 of the participants reported decreases in their perceived stress and only N = 1 reported an increase, the remaining participants did not report any change.

4-Week Follow-up. At the 4-Week Follow-up visit none of the participants reported continuing the NAC medication despite its availability as an over the counter medication. At the one month, post-trial follow-up visit, a variety of patterns were seen. For average VAS pain ratings, N = 1 of the participants showed an increase in average pain; N = 2 showed an increase for Worst pain and N = 2 reported an increase in Least pain scores. The others either stayed stable (N = 8 for average; N = 8 for worst and N = 3 for Least) or decreased for each rating scale. Half (N = 5) of the sample reported only minimal changes from study enrollment through the final study visit 4-weeks on the pain disability index. Of the remaining N = 5 participants, N = 3 reported increases in disability at the 4-Week Follow-up and N = 2 reported decreases in disability.

Interestingly, over half (N = 6) of the participants reported that their physical functioning decreased after discontinuing the medication, whereas N = 3 reported an increase in functioning and N = 1 reported no change. Four participants reported decreases in their mental health quality of life after discontinuing medication and N = 2 remained stable, while the remaining individuals reported improvements.

Several participants (N = 4) who reported an initial decrease in catastrophizing thoughts from baseline reported increases in catastrophic thinking after the medication trial ended. Alternatively, N = 2 participants who reported an increase in catastrophic thinking after starting the medication reported a decrease in catastrophic thoughts after discontinuing the medication.

After the study medication was discontinued, N = 3 participants reported decreases in their depressive symptoms while the remaining reported no changes. When the study medication was discontinued, N = 3 participants reported increases in their stress while N = 2 reported decreases, the remaining N = 5 reported no changes.

Case Studies

Given the sample size, both clinical and statistical considerations suggest the value of stepping down from the aggregate and focusing on the individual. Presented below are three case narratives of participants enrolled in the NAC study. Cases were chosen to illustrate the range of participant responses to the NAC medication; more effective, less effective, and mixed response.

Participant 017. Participant 017 (DR) was a 52 year old African American female. She was on disability (physical) and unemployed. She did not smoke and was single. Her medical problems included: chronic pain, left shoulder pain, carpal tunnel syndrome, diabetes, degenerative disc disease with sciatica and radiculopathy, coronary artery disease, diastolic dysfunction, chronic obstructive pulmonary disease, gastroesophageal reflux disease, hiatal hernia, Lymphedema, morbid obesity, obstructive sleep apnea, hypertension, uterine fibroids, and depression. She was prescribed and reported taking acetaminophen-oxycodone (Percocett) and Gabapentin for her neuropathic pain. She reported taking the same dose of acetaminophen-oxycodone (5mg 4x per day as needed) and Gabapentin (800mg three times a day) for the 9 months prior to study enrollment. In addition, she was prescribed the following for non-pain related conditions: loratadine, metformin, venlafaxine, verapamil, medroxyprogesterone, albuterol, Symbicort, esomeprazole, ferrous sulfate, Flonase, lasix, potassium chloride, and spironolactone. She also reported taking Aspirin (81mg/day). The participant discontinued her Symbacort between Treatment Visit 2 and 3 and was started on Flovent.

DR enrolled in the study and expressed interest in "anything that might help" her pain. She scored a 4 on the ID-PAIN scale (-1 to 5), reporting that her pain felt "like pins and needles", "hot/burning", "electric shocks", and was "made worse with the touch of clothing or bed sheets". She participated in all her treatment visits and completed Daily Monitoring Forms as instructed throughout the study. Between the week 3 and 4 Treatment Visits, however, DR experienced stomach flu, with symptoms she reported made her unable to take her NAC or "much" of her pain

medication during this time period. The participant reported that she took her NAC (1200mg), gabapentin (800 mg), and acetaminophen-oxycodone (5 mg) on 3/17/15 at 6pm and next reported taking her NAC (1200mg), gabapentin (800 mg), and acetaminophen-oxycodone (5 mg) on 3/20/15 at 6pm. She missed 5 scheduled doses of the study medication and these were confirmed during weekly pill counts.

Her self-report Visual Analogue Scale (VAS) ratings (Figure 21) show that her highest and lowest pain experienced over the course of the study remained stable or with a slight downward trend. Her average pain, reported at weekly visits, shows a noticeable decrease following NAC initiation. Her mean average pain rating prior to taking NAC was 93 (SD = 7) and while taking NAC was 71.25 (SD = 18.2). A slight return to pre-NAC VAS scores are observable at her treatment period 4 visit, likely a result of having the flu and not being able to take NAC or pain medications. By removing this aberrant pain rating and treating Treatment 3 as her last treatment visit a mean pain rating of 62.67 (SD = 7.37) was observed.

Her responses in the Pain Catastrophizing Scale (PCS) show (Figure 22) that there is an overall decrease in catastrophizing thoughts and decreases in 'Rumination', 'Magnification', and 'Helplessness' while taking the NAC medication. These measures of catastrophizing returned close to pre-NAC levels after NAC was discontinued, with the exception of 'Magnification', which remained stable after stopping NAC. Self-report pain disability ratings (PDI), where zero indicates no disability and 10 indicates complete disability, a downward trend is visible after she starts the study medication (Figure 24). She reported no disability in 5 of 6 areas after her final week of medication. Her PDI scores generally increased across 5 of 6 areas at her 4 week follow up visit. Her responses to the Perceived Stress Scale (PSS) also showed a decrease from 18 at Baseline to 11.50 (SD=1.29) while taking NAC (assessed at multiple time points) and rebounded to 23 after she discontinued taking the NAC medication (Figure 25). There was no discernible pattern for the variations in her rating of depressive symptoms (Figure 23)

During the treatment phase of the study she subjectively reported, at different treatment visits, that she "knows it helps nerve damage" and that NAC "helps with stingy and needle feeling" in her feet. Additionally, the participant reported that the medication is "helping neuropathic pain" and that she has felt a decrease in neuropathic pain in her hands. Despite the subjective reports of improvement while taking NAC, the participant did not report taking the medication after it was no longer provided for her study participation. No reason for not taking the NAC medication was given by the participant.

No serious adverse events were reported during study participation. She reported several side effects which included nausea (ongoing), diarrhea (ongoing), hot flashes (reported 1 time only), and acid reflux (reported 1 time only). Reports of side effects were mild and NAC was generally well tolerated.

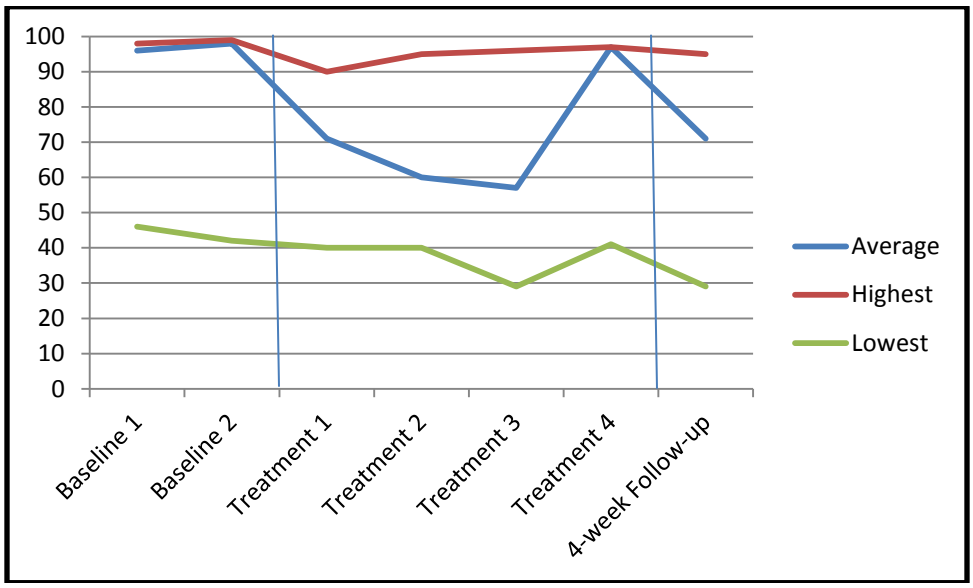


Figure 21. VAS ratings provided by participant #017.

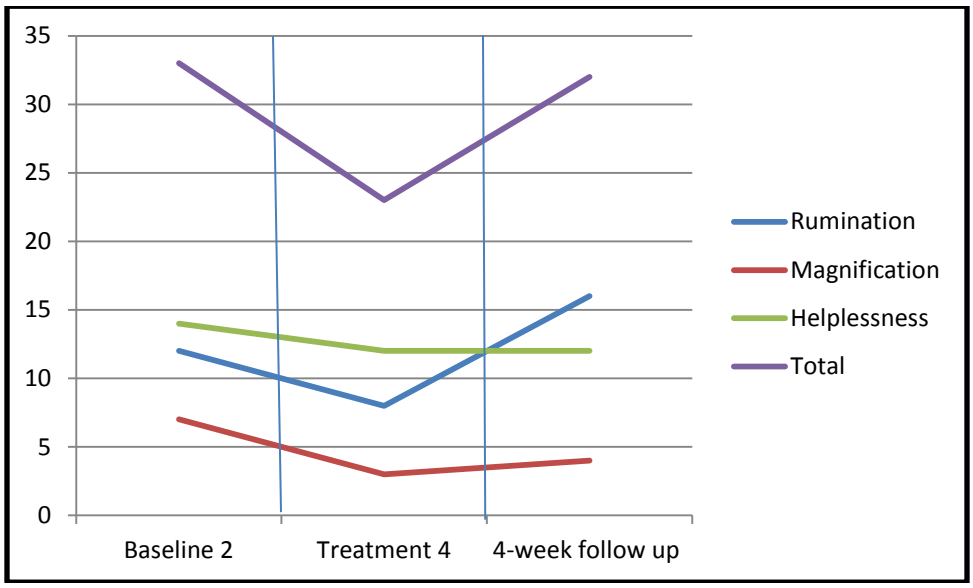


Figure 22. Pain catastrophizing scores for participant #017.

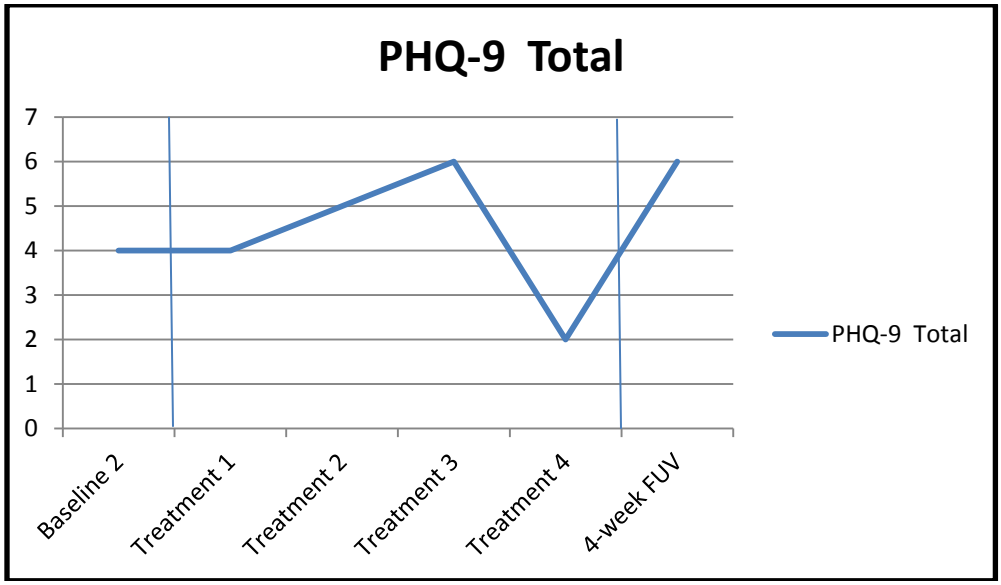


Figure 23. PHQ-9 scores of depression for participant #017.

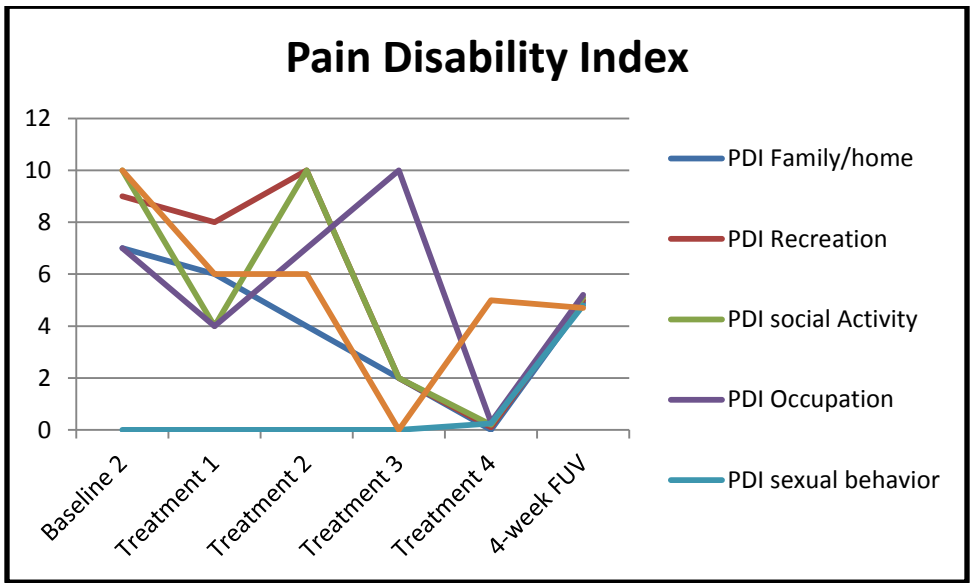


Figure 24. Pain disability for participant #017.

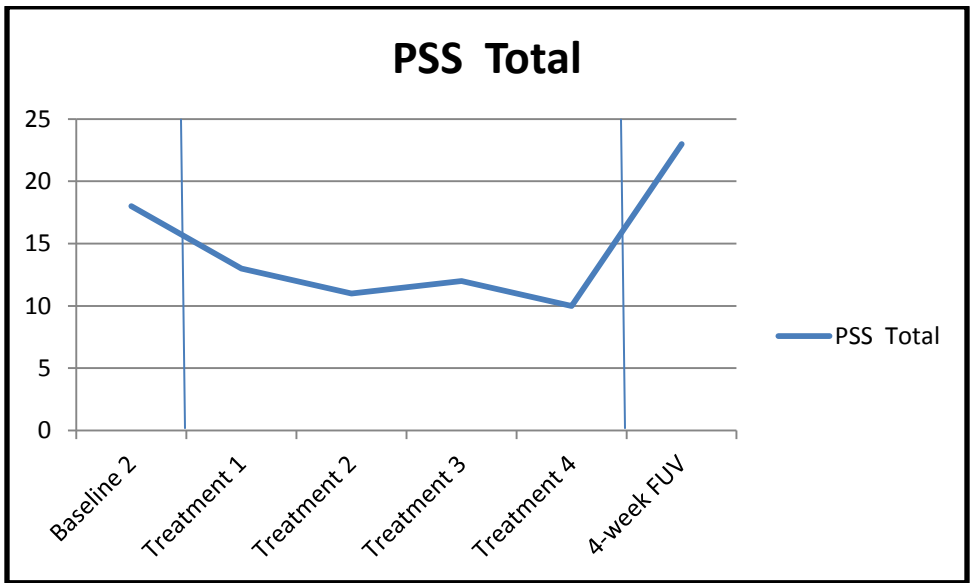


Figure 25. Perceived Stress Scale for Participant #017.

Participant 007. Participant 007 (RJ) was a 43 year old African American female. She was married and did not smoke. She was not on disability but did have a disability case pending (physical). She was employed part time. Medical problems included: lupus, chronic abdominal pain, depression, kidney infection, and gastric bypass. She was prescribed oxycodone (10mg 4x per day as needed) as a PRN opioid medication and the Fentanyl transdermal patch as a stable pain medication (50 mcg/hr, replace every 72 hours) for her neuropathic pain. She reported receiving the same prescription of the oxycodone for at least 2 years before entering the study and the same

prescription of Fentanyl transdermal patches for 7 months prior to starting the study. Additionally medications, for non-pain related conditions, included: cyanocobalamin, esomeprazole, lasix, Golytely Powder, hydroxychloroquine, magnesium citrate, potassium chloride, zinc sulfate, Senna, amitriptyline, duloxetine. She also used the following over the counter medications: Vitamin A, Vitamin E, and a daily multivitamin. All medications were confirmed through chart review.

She scored a 3 on the ID-PAIN scale (-1 to 5), and endorsed that her pain felt "like pins and needles", "hot/burning", and "electric shocks". Her self-report VAS ratings (Figure 26) show that her Highest, Lowest and Average pain experienced over the course of the study remained stable or with a slight upward trend. As shown in Figure 27, her responses on the PCS show there was an overall decrease in catastrophizing thoughts and decreases in 'Magnification' and 'Helplessness' while taking the NAC medication. These measures of catastrophizing returned to pre-NAC levels after NAC was discontinued. 'Rumination' remained stable throughout the intervention and after discontinuation of the NAC. Her responses on the PSS also show a general downward trend while taking the study medication which continues after the medication was discontinued (Figure 28). She showed a decrease in pain related disability across all areas of functioning but a return to at or above baseline levels toward the end of taking the NAC medication was observed (Figure 29). There was a general downward trend in depression symptoms (PHQ-9) which continued after discontinuation of the study medication (Figure 30)

The participants subjective responses to the NAC medication were positive. She reported "possible" improvements in her pain after the first week. After the second and third weeks of taking the medication she reported that she thinks the "medication is helping ". No side effects were reported by the participant while taking the NAC medication. The participant did not report taking the medication after it was no longer provided for her study participation and no reason for not taking the NAC medication was given by the participant.

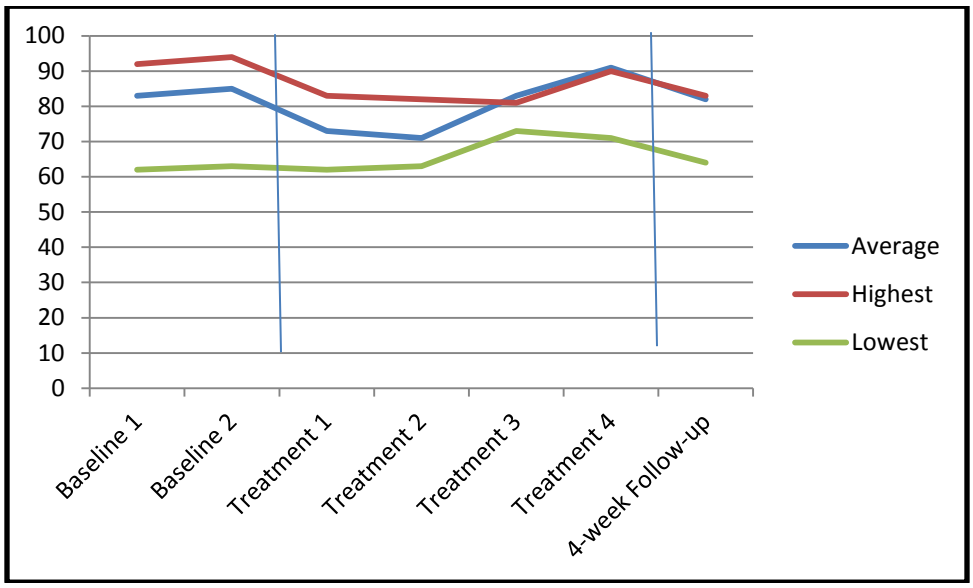


Figure 26. VAS ratings provided by participant #007.

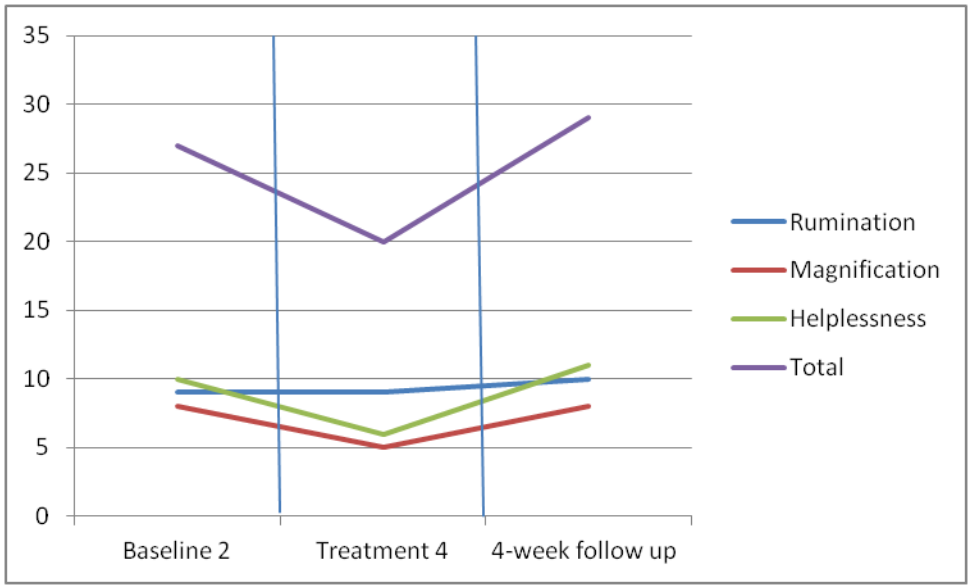


Figure 27. Pain catastrophizing scores for participant #007.

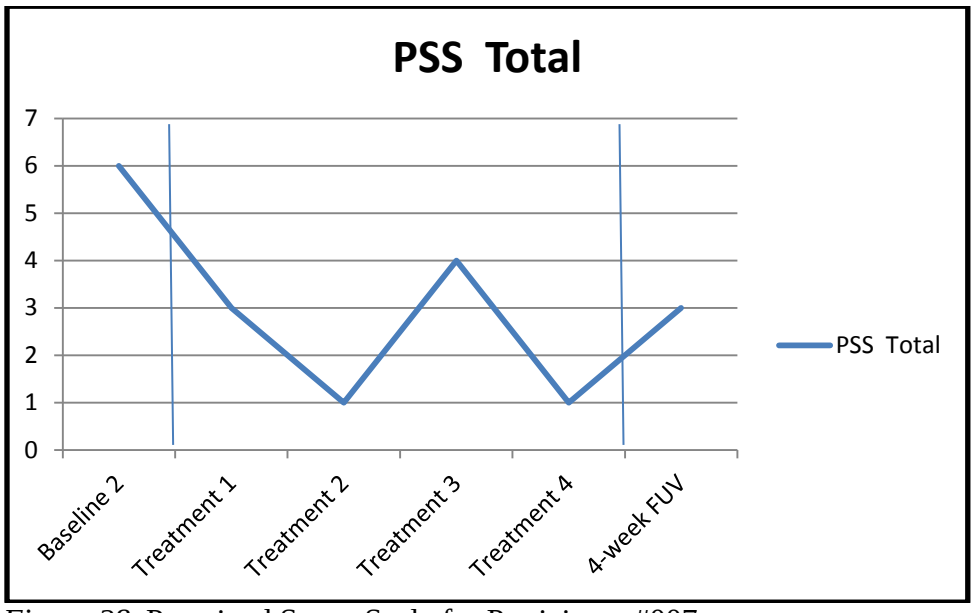


Figure 28. Perceived Stress Scale for Participant #007.

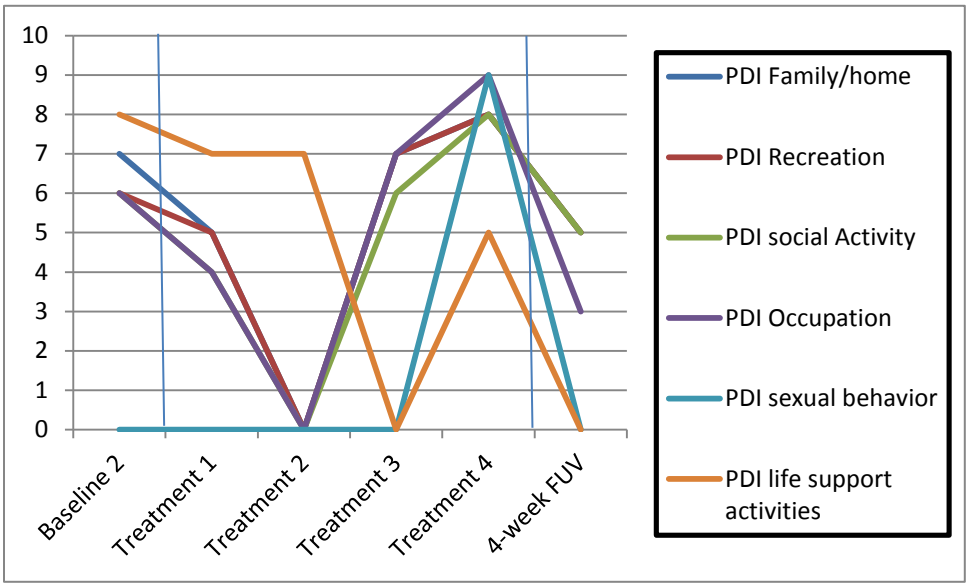


Figure 29. Pain disability for participant #007.

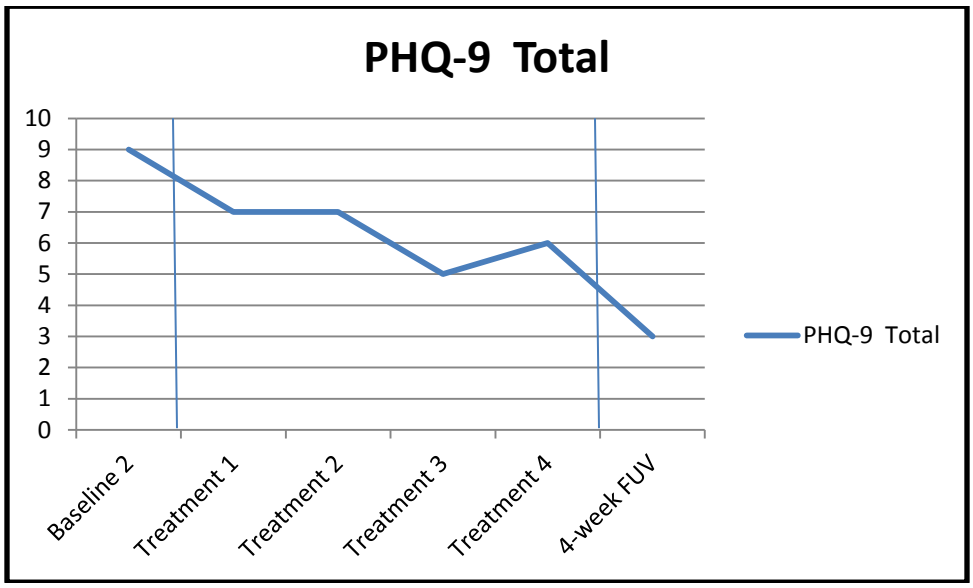


Figure 30. PHQ-9 scores of depression for participant #007.

Participant 024. Participant 024 (GF) was a 43 year old Caucasian male. He was single and did not smoke. He had a disability case (physical) pending and was unemployed. Medical problems included: critical monopathy, nerve pain, chronic pain, shoulder pain, diabetes, diabetic neuropathy, congestive heart failure, coronary artery disease, asthenia, hyperlipidemia, burst blood vessel in eye, seasonal allergies. He was prescribed Tramadol as a PRN (as-needed) opioid medication and Gabapentin for his neuropathic pain. He reported being prescribed the same dose of Tramadol (50 mg every 6 hours as needed) and Gabapentin (300 mg three times a day) for 6 months prior to entering the study. In addition, he was prescribed the following for non-pain related conditions: atorvastatin, lipitor, warfarin, clopidogrel, furosemide, insulin isophane, insulin lispro, losartan, metoprolol, nitroglycerine, trazodone, rivaroxaban, lasix, and spironolactone. All medications were confirmed through chart review. His Gabapentin was increased (600 mg three times per day) 4 days before the final study visit (4 week follow up) and his Warfarin was discontinued at the same time. He scored a 4 on the ID-PAIN scale (-1 to 5) and endorsed that his pain felt "like pins and needles", "numb", "electric shocks", and that is it "made worse with the touch of clothing or bed sheets".

His self-report VAS scores (Figure 31) shows that his Highest and Lowest pain ratings remained stable or with a slight upward trend. His Average pain rating shows a decrease after he

starts taking the NAC medication. A slight return to pre-NAC VAS ratings are observable at his 4-week post treatment visit. His responses on the PCS show (Figure 32) increases in 'Rumination', 'Magnification' and 'Helplessness' from baseline to the Treatment 4 visit and then the same or increasing catastrophizing at the 4-week follow up. An overall decrease in perceived stress (Figure 33) is after starting the study medication and an increase after he discontinued taking the NAC medication, though it did not return to baseline, was observed. A slight improvement in 'life support activities' and 'sexual behavior' is seen while taking the study medication with a worsening after discontinuing NAC (Figure 34). An increase in disability is observed for 'recreation' and 'social activity' after starting the study medication. There was a general decrease in depressive symptoms while taking the study medication which were maintained at the 4-week follow up visit (Figure 35). Study measures show a mixed response with decreases in perceived stress and depression symptoms while showing increases in catastrophizing, pain related disability and no appreciable changes in pain ratings.

The participant reported his subjective impressions of the effect of the study medication at several of his follow up appointments. He reported that he did not observe any changes in his pain or functioning while taking the study medication but did not have any adverse reactions to the NAC. At his final treatment visit he reported no changes in his pain as a result of the study medication and that he "isn't sure it is helping". The participant did not report taking the medication after it was no longer provided for his study participation reports that he "did not take any NAC since last" because he "didn't feel it was helpful". No Adverse Events were reported by the participant.

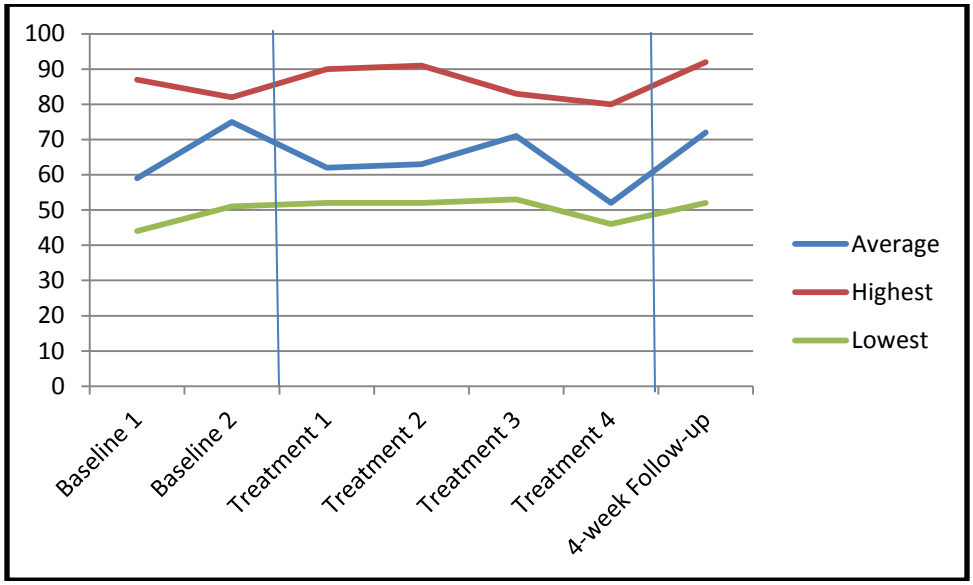


Figure 31. VAS ratings provided by participant #024.

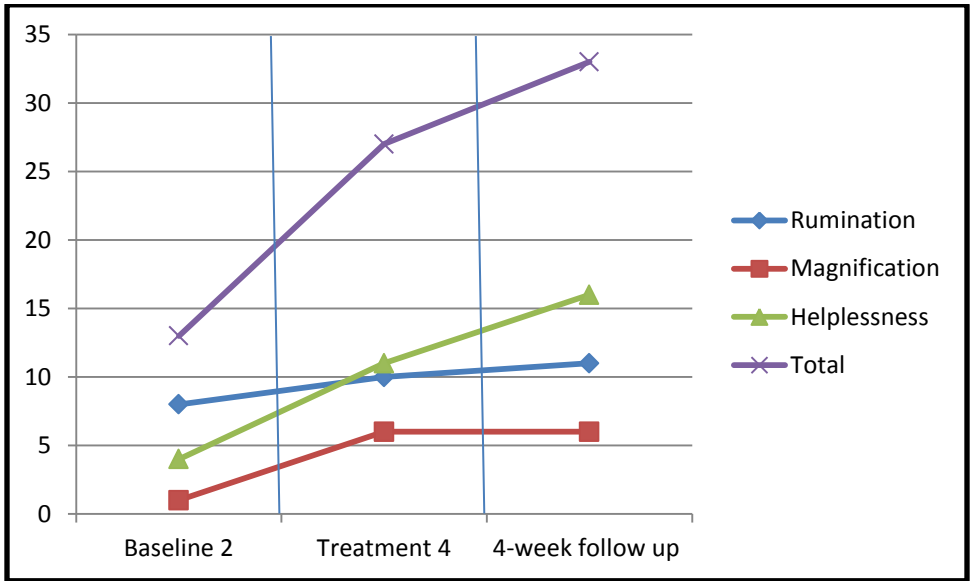


Figure 32. Pain catastrophizing scores for participant #024.

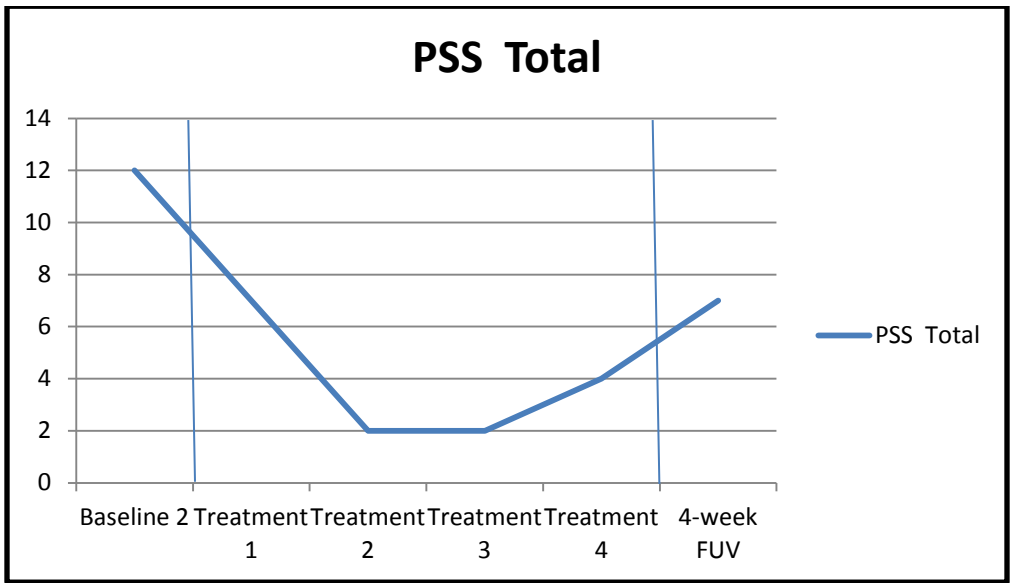


Figure 33. Perceived Stress Scale for Participant #024.

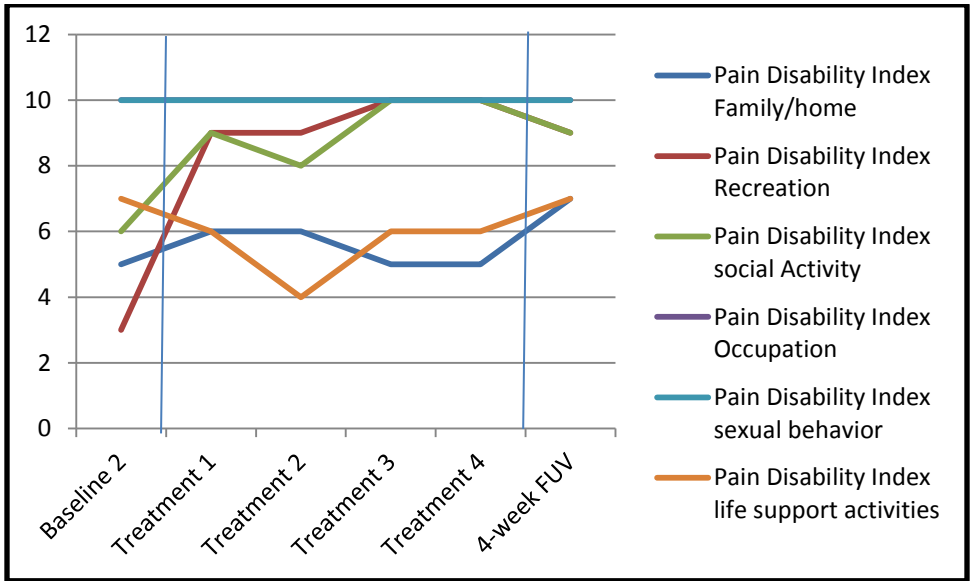


Figure 34. Pain disability for participant #024.

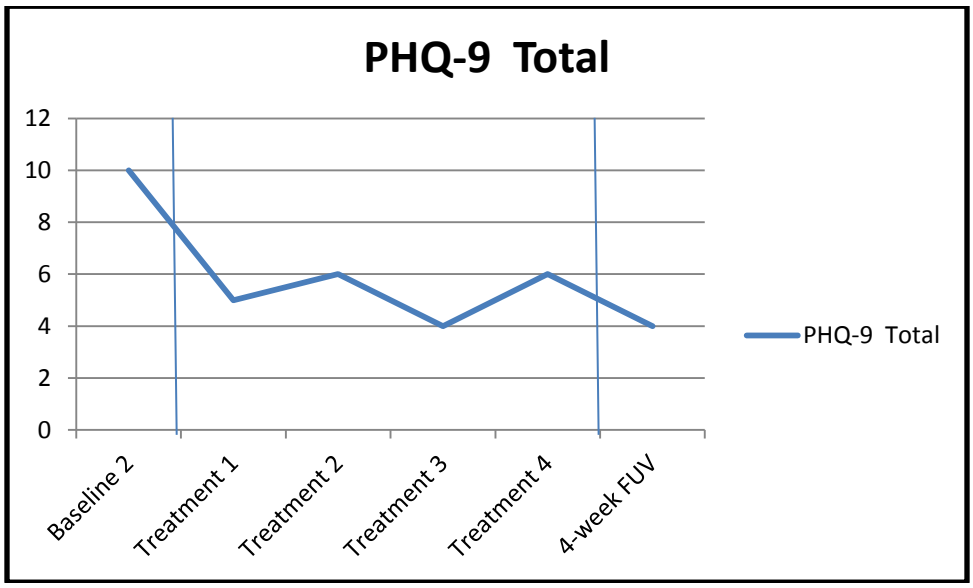


Figure 35. PHQ-9 scores of depression for participant #024.

Discussion

The present study was an open label medication trial focused on changes in pain ratings, medication use, and quality of life associated with an over-the-counter pharmaceutical drug and nutritional supplement, N-acetyl-L-cysteine (NAC). Study participants were VCUHS patients being treated with PRN opioid medication and prescribed a stable dose of opioid medication, or gabapentin for neuropathic pain. The primary outcome variables included Visual Analogue Scale pain ratings and morphine equivalent doses of opioid medications. The study tested hypotheses that addition of the study medication would be associated with a decline in pain ratings (VAS scores), reductions in PRN opioid pain medication use, and improvements in physical and mental health-related quality of life scores. Further, it was hypothesized that participants with a more positive appraisal of their pain (Low catastrophizers) would report lower pain ratings while taking study medication than participants with more negative appraisals of their pain (High catastrophizers).

A total of N = 28 participants were recruited but only N = 11 completed baseline and began the active medication phase of the study. Of these, N = 10 completed the 4 week medication trial and follow up visit. While the smaller than anticipated sample size limited testing and interpretation of formal study hypotheses, the rich dataset for the N = 10 participants who completed the study afforded an excellent opportunity for qualitative evaluation of study findings. This is timely, given increased recognition that small-scale pilot studies represent an important, and often essential, step in the development and evaluation of novel interventions (Moore, Carter, Nietert & Stewart, 2011; Leon, Davis & Kraemer, 2011). Specifically, the present study provides valuable data on the feasibility and acceptance of recruitment, retention, and assessment procedures that were integral to study design. As such, these data will likely contribute not only from a scientific, but also a practical perspective, to future research with NAC. In addition, lessons learned through the conduct of this study will be invaluable to the design and conduct of future pharmacological as well as psychosocial interventions for this important population of chronic neuropathic pain patients.

NAC and use of PRN opioid medication.

For the sample as a whole, when baseline was compared to the medication trial and 4-week post-trial follow-up, no change was observed in self-administration of MED across the 3 phases. At the individual level, however, 4 of 10 participants (30%) showed a 10% or greater decrease in daily MEDs from baseline to treatment, with the other participant values remaining approximately stable. None of the participants reported increases of their MED during NAC. Changes in the MEDs for the whole sample were quite small from Pre-NAC to NAC (3.1% more MEDs while taking NAC).

Similarly, while there was no change overall at 4-Week follow-up, 4 of the participants showed a 10% or greater increase in their daily MEDs from treatment to 4-week follow-up while one participant showed a decrease of at least 10%. This observation is complicated by the fact that total MEDs for the whole sample from decreased by 15.81% from NAC to Post-NAC. Given that no participants reported continuing NAC after the study medication was no longer provided, this drop is not attributable to the study medication. Likely, the resulting drop in MEDs is attributable to prescription changes for PRN opioid and stable pain medication reported by 4 of the participants.

Several factors may have contributed to the lack of change in MEDs during the NAC trial period. First, NAC may not be a promising adjuvant in the treatment of chronic neuropathic pain. Second, NAC may have had an effect, but only in a subgroup of study participants, and small sample size clouded this effect. This possibility warrants further study, to determine if participants with some reduction in MED administered during the trial differ in some way from those who did not. For example, were participants prescribed Gabapentin as their stable dose medication for neuropathic pain more or less likely to show a change than those with a stable dose opioid medication?

Another contributing factor may be the way in which chronic pain patients used their PRN medications. This approach to pain management is designed to provide flexible and safe dosing and

meet the individual's unique needs. However, it was apparent during the conduct of the study that a number of study participants, rather than taking PRN medications in response to breakthrough pain, were instead taking them primarily in a time-dependent manner similar to that of their stable dose medication schedule. Pasero and colleagues (1999) report that pain is often undertreated because physicians under prescribe opioid analgesics (order inappropriately low doses or prolonged dosing intervals). This under prescribing could prompt the patient to utilize their PRN medications in the stable manner we observed to bridge the gap in their pain management regimen.

Another possibility for understanding this stable use of opioid is through the findings of Kwon and colleagues (2015), that PRN opioid medications were sometimes used not only in response to acute elevations in pain, but also as a means of chemically coping with stress. A potential stress among the current population is likely to be the fear of breakthrough pain and as such, the opioid medication may be used prophylactically to avoid the experience of breakthrough pain. This pattern, motivated by avoidance of pain, would make a reduction in MED taken during NAC unlikely, as the PRN medication was taken in advance of experiencing the pain.

The use of PRN medications to avoid break through pain could also impact pain severity ratings, limiting the range of pain severity experienced by some participants. That is, if PRN medications are taken in anticipation of impending pain, to avoid experiencing the pain, then the range of pain experienced may be more circumscribed. A possible interpretation of the lack of significant or consistent changes in MED in the current study is found when we consider these results in the context of a fear-avoidance (FA) model of chronic pain. According to this model, a cycle is initiated when pain is catastrophically interpreted and this interpretation gives rise to pain-related fear, avoidance/escape behaviors and hyper vigilance. In chronic pain, this maladaptive process serves to further entrench fear and avoidance of new behaviors (or a return to previous behaviors) and hypervigilance to pain experiences even when pain may be lessened (Turk & Wilson, 2011).

In the context of the current study, the lack of consistency to the reported changes in MED might be related in part, to a fear avoidance approach that chronic pain participants sometimes have toward their pain. Research supports the validity of the FA model for chronic pain (Crombez, Eccleston, Van Damme, Valaeyen, & Karoly , 2012), and suggests the effectiveness of exposure-based pain treatment. For instance, results from a recent study in a primary care setting found that a brief (one session) exposure-based intervention produced measureable changes in fear avoidance beliefs and functioning for patients with chronic pain (Guck, Burke, Rainville, Hill-Taylor, & Wallace). A behavioral intervention, such as the one utilized by Guck and colleagues (2015), could help to challenge the entrenched fear and avoidance found among chronic pain patients that might be preventing them from recognizing changes in their pain as a result of a novel medication.

Alternatively, it is also possible that some participants did not change their opioid medication use because of a well-learned pattern of behavior. Chronic pain patients, at the individual level have learned how their pain manifests itself and what the progression or escalation of pain symptoms will be like. In an attempt to manage this cycle, some may take pain medications regularly in concert with pain fluctuations they have learned over time. With such individuals, we might see a decrease in pain severity ratings but we are less likely to see a change in MEDs. That is, they could continue to take their usual doses of medication while also reporting a reduction in pain symptom severity. This warrants further study, looking first at MED data in concert with the Average and Highest pain ratings reported by patients for the same period of time.

NAC and pain severity ratings.

Average pain ratings while taking NAC, for nearly 2/3rds (60%) of the sample, did not change significantly from those collected at Baseline, with 80% of participants showing this same pattern for worst (most severe) pain ratings. This was not seen for lowest level of pain, with nearly half of participants reporting an increase during NAC administration, with further increase at 1

month follow-up. McCraken (1997) found that people who report greater attention to pain also report higher pain intensity. It is possible that the frequent tracking of their pain ratings throughout the week resulted in an increased attention to lower intensity pain and a resulting increase in the perception of pain.

A point to consider is the differences in retrospective recall of pain ratings versus daily tracking of pain ratings. The current study measures focused on 1-week recall of pain. One study showed a high correlation between 1-week recall of average pain intensity and estimates of average pain intensity from a daily diary (Jensen et al., 1996). Another study showed that alternative measures of retrospective recall (e.g. least pain, average pain, worst pain) were highly correlated with daily recordings, however average pain ratings tended to be most highly correlated (r=0.78) (Jensen et al., 1998). While retrospective pain recall is relatively stable it could be beneficial in future studies to compare both the daily pain ratings with the retrospective recall pain ratings to assess stability.

NAC and Quality of Life.

When quality of life measures were examined, physical ratings were unchanged and remained relatively stable throughout the study. Mental health ratings, however, showed a downward trend suggesting improvements in mental health functioning while on the study medication and continuing through 4-Week Follow-up.

There was not a large enough sample size to power the proposed analyses, however effect sizes could be measured. Effect size measures the magnitude of a treatment effect, and unlike significance tests these indices are independent of sample size (Dattalo, 2007). As such, the effect sizes are interpretable. While the majority of the effect sizes suggest that there was a small or, in some cases, negligible treatment effect there are a few instances worth noting. Effect sizes observed suggest that the medication may have beneficially impacted the participants' responses on the

Mental Component Summary (MCS). This effect size was small from Baseline 2 to Treatment 4 (Cohen's *d* = .261) and from Treatment 4 to 4-Week Follow-up (Cohen's *d* = .145), however it was approaching a medium effect size (Rice & Harris, 2005) from Baseline 2 to 4-Week Follow-up (Cohen's d = .421). Additionally, small effects were observed for Average and Worst pain. The effect sizes observed suggest a real, but difficult to detect effect of NAC on improved mental health functioning. This finding is bolstered by individual level findings that showed half of the participants reporting mild improvements in mood while on NAC and decrements in mood when no longer taking NAC.

The study participants had a large number of other medical problems in addition to their chronic neuropathic pain (discussed more fully below). Given the scope of medical problems participants were experiencing and the minimum duration of their pain it seems that the goal of seeing changes in health related quality of life was overly ambitious. Any changes in health related quality of life were likely dwarfed by the overwhelming duration and complexity of their presentation (Kazis, Miller, Clark, Skinner, Lee et al., 1998). It is unreasonable to hope that simply through the addition of the study medication that the entrenched and chronic response to their pain would be impacted.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) suggest that the impact of a study medication on aspects of well-being and functioning also be assessed (Turk et al., 2003). Following this recommendation, the current study assessed HRQoL, to evaluate changes in functioning that may, or may not, accompany changes in pain experience. As a result of the inclusion of these measures, improvements in mental health functioning as a result of the study medication were seen. This lends support to the importance of recognizing the multifaceted nature of chronic pain.

Catastrophizing and response to NAC.

When data were compared for the Low Catastrophizer and High Catastrophizer groups, findings were mixed. During the active medication phase, improvements as well as declines were observed for both Low and High catastrophizers in mental health and physical functioning. Similarly, mixed findings were also observed when looking at the these two groups at the 4-Week Follow-up.

With N = 5 per group there was not a large enough sample size to interpret the proposed analyses, and as such, the findings are limited to observations of the data and individual participant ratings. An initial review of the data shows that average pain ratings were lower for the Low catastrophizers than for High catastrophizers. This finding was expected but worth noting because higher pain catastrophizing scores have been found to be predictive of higher pre-treatment and post-treatment pain ratings, even when controlling for baseline pain (Edwards, Bingham, Bathon & Haythornthwaite, 2006). Additionally, high levels of catastrophizing predict poorer response to pharmacological interventions for neuropathic pain (Sullivan et al., 2001). This finding provides important context for interpreting the observations about the two groups.

A 20 point reduction was observed in Average VAS pain ratings at the Treatment 4 visit and, to a lesser degree, at 4-Week Follow-up, for Low catastrophizers. Interestingly, a similar drop was observed for Worst pain ratings but not for least pain ratings (potentially due to floor effects of the VAS). Upon closer examination of the data, the drop appears to be mostly attributable to one participant who showed significant decreases in both Average and Worst pain after initiating the NAC medication. The decreases from Baseline for Average and Worst pain ratings were maintained at the 4-Week Follow-up. This finding suggests that NAC may have had an impact on reported average and worst pain ratings in 1 of 5, or 20% of, Low catastrophizers. While it is possible that this decrease in pain ratings is attributable to other factors, it is worth paying special attention to Low catastrophizers responses to the NAC medication in future trials.

No clear patterns were evident in support of the beneficial effects of NAC, however there were some interesting observations that could warrant further study. In future studies of NAC and chronic pain it will be important to consider the role that catastorphizing approach has on pain ratings and response to the medication as well as ways to counteract months or years of disability related to their chronic pain. Identifying potential groupings of patients who will be more, or less, responsive for NAC could be essential in assessing the impact of the medication.

Lessons Learned: Informing Future Research

While the smaller than anticipated sample size limited testing and interpretation of formal study hypotheses, the development, launch and conduct of the study yielded additional information. Data are available not only for the 10 primary study participants, but also the larger group of patients that contributed to other study components which culminated in the open-label NAC trial. The present study is timely, as there is increased recognition of the important role pilot studies play in the development and testing of novel interventions (Moore, Carter, Nietert & Stewart, 2011; Leon, Davis & Kraemer, 2011).

The following section presents methodological issues germane to the design and conduct of the open label NAC trial, highlighting lessons learned and how the data can inform future studies; not only those focused on NAC, but also more broadly, the research that seeks to expand and improve treatment options for chronic pain. The discussion is organized temporally, beginning with early study design and participant identification issues and ending with study follow-up concerns. The discussion is intended to inform the field from not only a scientific, but also a practical perspective.

Case identification. The present study planned to use the VCUHS primary care clinic as the primary site for identification and recruitment of study participants. While it was initially estimated that approximately 1,500 primary care clinic patients would present with a diagnosis of neuropathic

pain and that 600 (40%) of these patients would be receiving opioid pain medication, case identification proved challenging. As previously described, the patient chart review for the 6 month period (April to November, 2014) was conducted prior to, and through the start of, study enrollment. Three findings of particular importance, emerged from this review: 1) only 10% of patients had a diagnosis of neuropathic pain, 2) 13.9% of patients, regardless of diagnosis, were prescribed a stable opioid, and 3) less than one-third (29.8%) of all patients were prescribed PRN opioid medication. The chart review affirmed that despite projections for a large pool of potential neuropathic pain patients who were prescribed opioid medications, far fewer patients were eligible for the study which significantly hampered recruitment. In the 15 months of active study recruitment, only N = 187 unique and potentially eligible patients were identified through a variety of sources (e.g., chart review, provider referral).

Neuropathic pain. A diagnosis of neuropathic pain was found in only 10% of patient records. While this rate was commensurate with national prevalence rates in the range of 1-8% in the general adult population (e.g., Dworkin et al., 2007; Torrance, Smith, Bennett & Lee, 2006; Bouhassira, Lantéri-Minet, Attal, Laurent & Touboul, 2008), they were markedly lower than expected in the target medical clinic. Factors contributing to these lower rates include: under diagnosing of neuropathic pain and/or cases where neuropathy is viewed as a secondary diagnostic concern, and therefore not listed, with primary attention given to the disease or condition which lead to neuropathic pain.

Other studies have found under diagnosis of neuropathic pain to be of concern. Ziegler and colleagues (2015), for example, in their national educational initiative focused on prevalence of diagnosed and previously undiagnosed polyneuropathy in primary care settings, found that in their sample of N = 1017 patients, more than half of those who screened positive for polyneuropathy through medical history, physical examination and/or clinical testing were previously undiagnosed. Similarly, Bongaerts and colleagues (2013) found that 91% of patients diagnosed with distal

sensorimotor polyneuropathy were previously unaware of their diagnosis. These studies affirm that underdiagnosis can be a serious concern in studies of chronic neuropathic pain.

Another form of underdiagnosis is suggested by Pollack and colleagues (2013), who found many neuropathic pain diagnoses might be subsumed under the diagnostic label of the associated condition. This could occur because neuropathic pain is not a single diagnosis but rather a type of pain that arises as a "direct consequence of a lesion or disease affecting the somatosensory system" (Treede et al., 2008). For instance, diabetic neuropathy is the result of nerve damage secondary to vascular problems that occur with diabetes (Pinzur, 2011). While the majority of non-cancer cases of neuropathic pain can be traced to either diabetes (approximately one-third) or some type of autoimmune disorder (another one-third), the remaining third are classified as idiopathic, with unknown pathogenesis or spontaneous origin (Loeser, 2001).

The lower than anticipated rates of chronic neuropathy and the potential for underdiagnosis suggest that broader, more liberal criteria should be the standard practice for identify cases when utilizing chart review. In fact, it may be beneficial to focus on other, more consistently identifiable criteria such as any diagnosis of "any pain" and/or "opioid pain medications" as a preliminary screening for chart reviews. Such a broad screening approach could then be followed by an assessment tool such as the ID-Pain questionnaire, a standardized measure that provides specific cut-off scores to identify individuals with neuropathic pain. Future studies should continue this practice.

Stable opioid. Fewer patients were prescribed a stable opioid (13.9%), regardless of diagnosis, than expected. A stable opioid medication, defined as the same dose and dosing schedule for at least 6 months, was one of the initial inclusion criteria. Throughout the course of the study several challenges were identified with the requirement of a stable does of opioid medication for at least six months before study enrollment; 1) tolerance to opioid medications, 2) reclassification of tramadol and hydrocodone-based medications, and 3) new prescribing requirements.

The first challenge for requiring a stable opioid medication in the prior 6 months was related to tolerance. The inherent nature of opioid medications is that the analgesic efficacy may not be maintained over time and a level of tolerance can be achieved for patients (Mercadante & Bruera, 2006; Ballantyne & Shin, 2008). With a diagnosis of chronic neuropathic pain, the opioid medication is acting to mask the pain symptoms, however by its very nature; the cause of the chronic pain will remain. Given time, the chronic pain patient will receive less analgesic relief from pain as their body becomes tolerant to the opioid medication. This tolerance to the opioid medication results in a reemergence of pain symptoms. One approach taken by physicians in response to increased pain is to increase the dose of the patient's opioid medication dosage or change the medication to achieve analgesic efficacy (Ballantyne & Shin, 2008). Either option would result in participant exclusion.

The second and third challenges were the result of an unforeseen change in the classification of both stable and PRN opioid medications by the U.S. Drug Enforcement Agency (DEA) (Pergolizzi, 2015). Effective August 18, 2014, the DEA reclassified Tramadol, a previously unscheduled synthetic opioid analgesic, as a Schedule IV drug. Minor restrictions were placed on frequency of prescriptions and limits were placed on number of available refills. More significantly, effective October 6, 2014, The DEA also rescheduled hydrocodone combination products (i.e. hydrocodone-acetaminophen) from a Schedule III to the more restrictive Schedule II. The restrictions resulting from this change were significant; written prescriptions must be provided (no fax or phone prescriptions), and a new written prescriptions must be provided for any refills. The change only allows physicians to prescribe these medications for intervals of 30 days or less. Patients requiring refills were required to visit their physician for a new prescription. Anecdotally, several patients approached for study enrollment reported recent changes to their pain medication when they had previously been on a stable dose, thus making them ineligible for the current study.

These changes were part of an effort to curb prescription drug abuse and highlight the recognition that some providers were not closely monitoring their patients opioid medications. The risks of iatrogenic addiction are a significant safety concern that was, in part, addressed by the DEA changes. The reclassification of these medications also likely drew attention to prescribing practices and could have resulted in a more conservative approach toward opioid pain management. While every effort was made to keep study inclusion and exclusion criteria consistent throughout the clinical trial, the consistently lower rate at which patients were prescribed stable dose opioids for the management of chronic neuropathic pain, likely in part due to the above, the decision was made 5 months after study launch to broaden study criteria to include gabapentin.

PRN opioid medication. Finally, fewer patients were prescribed PRN opioid (29.8%), regardless of diagnosis, than expected. While the percentage approached what we expected to see they were still low. In addition to sharing many of the same challenges as identified for stable opioid medications, PRN opioid medication also has the potential to be used as a stable opioid as discussed previously.

Screening for eligibility. To determine study eligibility, potential participants were screened to review inclusion/exclusion criteria. For the present study, over 60% of potential participants were determined ineligible because they did not meet study inclusion/exclusion criteria. Three criteria are worth discussing more fully: stable dosing, average pain ratings, and exclusion for medical conditions.

Stable dosing. Another factor that contributed to patient ineligibility came from changes in medication type or dose. A stable pain medication (opioid or gabapentin) was required for participation and recent changes in the dose or a switch in medication would make the patient ineligible for participation. According to Dowell and colleagues (2016), the benefits and harms of continued opioid therapy should be evaluated every 3 months. A common result of this re-

evaluation can be a switch in medication or change in medication dosages (increase or decrease as is clinically warranted). This practice along with new scheduling guidelines for some common opioid medications accounted for a large portion of participant exclusion. While some participant exclusion was expected because of changes in stable medications the frequency of this occurrence was surprising.

Pain Rating. Participants were eligible if they reported an average pain rating of ≥ 5 for the prior week. A cut-off score for pain ratings is necessary for the measurement of the efficacy of a medication for pain and if no cut-off score had been used a floor effect might have been present (Vermeersch, Lambert, & Burlingame, 2000). Specifically, the intent of this required pain rating was twofold; first was to capture patients with significant unmanaged neuropathic pain, and second to have a moderate pre-treatment pain level which would allow for observable changes in pain ratings while taking the study medication. Still, it is possible that a balance could be struck between a lower cut-off score which would allow for the identification of additional eligible participants while also allowing for the ability to monitor and measure potential changes in pain as a result of study participation. For instance, one study of neuropathic pain required a ≥ 4 VAS pain rating for study inclusion (Backonja, Beydoun, Edwards, Schwartz, Fonseca, Hes et al., 1998), while another required ≥ 3 VAS pain rating (Van de Vusse, Stomp-van den Berg, Kessels & Weber, 2004). While setting a lower average pain rating for inclusion would not have dramatically changed the recruitment levels it has the potential for expanding the number of potentially eligible patients.

Additionally, the challenge of the chosen pain rating cut-off is that it requires a participant to report an Average pain state from moderate to severe. This presents a difficult position for patients and doctors. A participant with higher pain ratings for the past week might be seeking a change in their pain medication, excluding them from the study. Alternatively, a patient with a pain rating below 5 may have recently received a change in their pain medications (e.g. dose escalation, new medication) to better control their pain, excluding them from the study.

Exclusions for medical conditions. Another exclusion criterion found for 16% of patients who were unable to enroll in the study was diagnosis of asthma. Asthma was an exclusion criteria for study participation because NAC may worsen asthma symptoms and should be used with caution. For safety reasons, clearly asthma must remain as an exclusion criterion. However, safety related exclusion criteria can also pose challenges to recruitment that need to be taken into account for future recruitment. The characteristics of recruitment sites should be thoroughly understood prior to study launch to help mitigate the impact that these factors may play on recruitment.

Among minority, urban, and low-socioeconomic patients, asthma rates are 11.2% (Akinbami et al., 2012). In the Ambulatory Care Clinic, where the patient population was majority African American, urban, and low-socioeconomic status we should expect to see comparable rates. We saw slightly higher rates for exclusion because of asthma than might have been expected, and double the rates seen in a general population sample (7.7%) (Cloutier, Wakefield, & Bailit, 2005). This awareness of the general base rates of necessary exclusion criteria will help to identify an appropriately sized recruitment pool from which the recruitment goals can realistically be realized.

Asthma was an important exclusion criteria for maintaining the safety of the participants as it is contraindicated for patients with asthma to take NAC. However, this exclusion criteria will also pose a limit to the generalizability of findings should NAC prove to be an effective adjuvant for inadequately managed chronic pain in future studies. The challenges of asthma as an exclusion criteria were not fully understood when recruitment began and will be important considerations when planning further study of NAC in this population.

Medical Complexity. The number of medical diagnoses among participants screened for this study affirmed the complexity of health problems often found co-occurring in inadequately managed chronic neuropathic pain patients. Of the participants (N = 28) who enrolled in the study, the range of medical diagnoses identified was 4 to 19 with a mean of 9.3 (SD=4.24). A review of these diagnoses supports the fact that participants who enrolled in the study presented with serious medical

conditions (i.e. hepatitis B, hepatitis C, lupus, irritable bowel syndrome, cervical disk disease, diabetes, atrial fibrillation, chronic pancreatitis), in addition to their chronic pain neuropathic pain. The exclusion criteria were limited to those conditions that would compromise patient safety (e.g. asthma) with the goal of offering the study to as many patients as possible.

However, such broad inclusion criteria for the current study allows for the possibility of a greater variety and complexity of co-morbid medical conditions. The sample was representative of a "real world" population which allows for greater generalizability, however this poses the obvious challenge of a complex presentation of medical and psychological diagnoses impacting and obscuring potential findings.

Provided informed consent. Another time point for participant attrition was after participants provided informed consent, completing study enrollment, but prior to medication initiation. Almost two-thirds (60%) of enrolled participants were withdrawn prior to initiating study medication. This attrition prior to medication initiation was higher than observed in several medication trials for neuropathic pain, which generally ranged from 16-36% (Rowbotham et al., 1998; Eisenberg, McNicol & Carr, 2005; Simpson et al., 2010; Campbell et al., 2012; Van Seventer et al., 2010). None of the studies reviewed reported rates as high as 60%. There were three distinct groupings for withdrawal observed in the current study: participant initiated, physician prompted, and change in eligibility. Participants initiated their withdrawal through both active (e.g. requesting to be withdrawn) and passive (e.g. not responding to study phone calls or attending study appointments) means. Physician prompted withdrawal was as a result of identification of a contraindication for study participation, either by the study doctor or at the recommendation of the participants physician. Finally, participants were withdrawn from the study if their eligibility status changed prior to medication initiation (i.e. illicit substance use, >5 pain rating).

There are several possible reasons for the high rate of drop out. One possible reason could be related, in part, to the limited availability of study staff. While every attempt was made to accommodate participants scheduling needs the study coordinator and RAs were only able to be in the clinic part time. It is also possible that the study compensation for enrollment of $5 was enticing for the indigent care population and that a portion of participants had no intention to continue in the study after enrollment. Another possibility is the frequency of study visits was overly burdensome on the participants.

There was one finding of particular interest related to the ID-PAIN measure, completed at study enrollment. Specifically, 23.5% of participants who did not initiate the medication endorsed 5 symptoms associated with neuropathic pain while only 9.7% of participants who initiated the medication endorsed the same number. Participants who did not initiate NAC are reporting more neuropathic pain symptoms than the participants who did initiate the medication. This raises the question as to whether greater responses on the ID-PAIN are predictive of study withdrawal. Further, the participants endorsing more items on the ID-Pain may experience greater difficulty in following through with study procedures (e.g. weekly visits, daily medication and pain tracking), thus necessitating their withdrawal. This could impact future neuropathic pain studies and should be monitored closely.

Length of medication trial. Identifying an appropriate length for the medication trial and dosage of the medication to allow for changes in the underlying symptomotology is also a challenge. The current study utilized a 4-week period of active study medication, however there is wide variability within the literature on the duration of active medication within trials, even for the same medications. The length of duration for taking an active medication in studies varies based on a number of factors. Medication will reach therapeutic levels depending on the dose, length of time, and frequency of use. The length of medication trials cannot be compared across different medications because of their different make up and mechanism of action. However, trials of the

same medications (i.e. gabapentin) often have variations in the length of the trial and dosage administered. This is a common step in assessing the appropriate dosage and length of time until optimum therapeutic effect is reached. This process can be observed for several prominent medications currently utilized for neuropathic pain. For instance, in a randomized controlled trials of gabapentin for the treatment of neuropathy, several different durations and titration approaches are reported in the literature, including: 4-week dose titration immediately followed by a 4 week stable dose period (Backonja, Beydoun, Edwards, Schwartz, Fonseca et al., 1998; Serpell, 2002), 1 week titration followed by a 12 week stable dose period(Zhang, Rainka, Freeman, Harden, Bell et al., 2013) and 2 day titration followed by 6 week stable dose period (Morello, Leckband, Stoner, Moorhouse, & Sahagian, 1999). Variations were also observed in studies examining pregablin, including: 1 titration week followed by 11 weeks of stable dose period (Freynhagen, Strojek, Griesing, Whalen & Balkenohl, 2005), 1 week titration and 6 weeks of stable dose period (Richter, Portenoy, Sharma, Lamoreaux, Bockbrader, & Knapp, 2005). The dosage and length of medication trial should not be compared for NAC, however these studies show that variations in length of a medication trial are a common practice.

Variations in dosage and duration were also observed across the available NAC trials (Deepmala, 2015). One study, looking at depressive symptoms in bipolar disorder, provided 2000 mg NAC over a 24 week period as an adjunctive to usual medication (Berk et al., 2008). Another study looking at Tricholtillomania provided 1200 mg daily of NAC for 6 weeks and then increased the dose to 2400 mg daily for the remaining 6 weeks (Grant, Odlaug, & Kim, 2009). Still others provided 2400 mg of NAC as study medication daily for 16 days (Amen, Piacentine, Ahmad, Li, Mantsch et al., 2011), 2400 mg daily for 4 weeks (Roten, Baker & Gray, 2013), 1,200 or 2400 mg daily for 8 weeks (LaRowe, Kalivas, Nicholas, Randall, Mardikian, Malcolm, 2013), 600 to 900 mg daily for 10 weeks (Nikoo, Radnia, Farokhnia, Mohammadi, Akhondzadeh, 2015), 2400 or 4800 mg daily for 12 weeks (Garcia, Francis, Dawood, Lai, Faraone, & Perl, 2013; McClure, Baker & Gray,

2014), 450 to 1200 mg daily for 12 weeks (Miller & Angulo, 2014) and 1000 to 2000 mg daily for 24 weeks (Bernardo, Dodd, Gama, Copolov, Dean et al., 2009).

Among NAC studies, initial therapeutic effect has been observed at variable time points. A review of NAC for OCD and OCD-related disorders found that doses of 2400 to 3000 mg over an 8 week period were adequate for exerting an initial therapeutic effect (Oliver et al., 2015). A randomized, double blind, placebo controlled trial prescribed 2400 mg of NAC daily and found a significant effect from week 9 to the end of the 12 week trial (Grant, Odlaug, & Kim, 2009). Another study used a 16 week medication period, however the results suggest that a non-significant trend was observable over the first 12 weeks of the study in support of NAC (Sarris, Oliver, Camfield, Dean, Dowling et al., 2015). In a study looking at the effect of NAC on cocaine dependence which looked at both 1200 and 2400 mg dosing over an 8 week period did not find reductions in cocaine dependence (LaRowe, et al, 2013). Results for the efficacy of NAC after 4 weeks of medication are promising across two addiction studies. One study of NAC on methamphetamine addiction provided 4 weeks of NAC medication at 1,200 mg and observed significant reductions in methamphetamine cravings (Mousavi et al., 2015), while another study of cannabis dependence found that 4 weeks of 2,400 mg of NAC resulted in decreases in self reported use and cravings but no observable changes cannabis use (Gray et al., 2010).

The variations in both dose and duration are important to consider when investigating the efficacy of the medication with a new population. After further review of the dose, duration and when efficacy was observed in other studies, changes in the duration of the medication trial should be considered. Additionally, the long standing nature of participant pain and medical complexity may support a longer trial for the identification of potential efficacy of NAC for neuropathic pain patients.

Medication initiated. While rates of attrition were high prior to beginning the 4-week trial of NAC, rates of attrition thereafter were low. Only one participant was withdrawn from the study due to an adverse reaction (discussed in greater detail below). All of the remaining 10 participants completed the study. A review of several medication trials for neuropathic pain revealed that attrition rates after medication initiation, excluding withdrawals due to adverse events, ranged from 4% to 22% (Rowbotham et al., 1998; Eisenberg, McNicol & Carr, 2005; Simpson et al., 2010; Campbell et al., 2012; Van Seventer et al., 2010). Additionally, adherence was high; all 10 participants completed 100% of their study visits. The rates of completion and adherence were particularly high after medication initiation in the current study and this is very encouraging for future medication trials.

Adverse Events. In the current study we saw one participant (9%) withdraw because of an adverse event. Adverse events to medications are specific to the medication (e.g. dosage, duration, frequency) and cannot be compared across medication classes. A review of NAC studies that used 2400mg of NAC, and reported withdrawal because of adverse events, showed 0% and 7% experienced adverse events resulting in study withdrawal (Gray, Watson, Carpenter & LaRowe, 2010; Bloch, Panza, Grant, Pittenger & Leckman, 2013).

NAC was well tolerated with less than half (45%) of participants reporting any adverse reaction to the study medication. One participant was withdrawn after reporting a potential allergic reaction, itching, after taking a single dose of the medication. While it is possible that the itching was a result of the NAC medication, as it is an identified side effect, it is also possible that it was unrelated to the study medication. Of the remaining participants, only 4 reported any side effects while taking NAC, and those reported were consistent with the NAC literature which reported between 43% and 63% of patients having side effects that were either probably or possibly related to the study medication (McClure et al., 2015; Gray, Watson, Carpenter & LaRowe, 2010; Bloch, Panza, Grant, Pittenger & Leckman, 2013). The most common side effects in the present study

were nausea (N =3), diarrhea (N = 2), and reflux/heartburn (N = 2). These same side effects were commonly reported in other studies of NAC as well (Sarris et al., 2015; LaRowe et al., 2006; McClure et al., 2015; Gray, Watson, Carpenter & LaRowe, 2010; Bloch, Panza, Grant, Pittenger & Leckman, 2013). Participants generally reported these symptoms as mild and that the nausea and reflux improved when taking the medication with food. Overall, the limited and mild nature of side effects is in line with existing literature and suggests that the study medication was well tolerated at the current dose.

4-Week Follow-up. The original study design did not include a follow up period and in fact was very informative. Upon suggestion of the dissertation committee a 4-week follow-up was added to the current study and allowed for the assessment of pain ratings, PRN opioid pain medication use, and physical and mental health related quality of life scores after the active medication had been discontinued.

There were two particularly interesting findings from the 4-week follow-up. First, all participants who completed the medication trial also completed this follow up visit. The follow through by the study participants was particularly surprising. As was discussed previously, the rates of follow through in the current study were well above the rates commonly observed in chronic pain research. This suggests a level of investment in their care, and through that, in the study.

Secondly, at 4-Week Follow-up, all participants reported discontinuing NAC at the end of the study and none of the participants reported seeking out the NAC medication after it was no longer provided for their use. Several of the participants provided subjective reports that the NAC medication was helpful, yet despite this, none of the participants sought to continue the medication. Possible reasons for this lack continuation of NAC include; cost, difficulty in obtaining NAC, or belief that NAC did not impact their pain despite subjective reports of changes in pain experience. NAC is a relatively easy to procure over the counter supplement available in most pharmacies (i.e.

CVS, Walgreens, Kroger) suggesting that availability was likely not a problem. The cost of NAC can be variable depending on quantity and brand. A brief search of a national pharmacy chain found that the least expensive NAC available would cost approximately $30 for a one month supply at the dosage used in the study (1200 mg twice a day). Given the indigent nature of much of the recruitment pool, it is very plausible that this was a factor choosing not to continue taking NAC. Finally, it is possible that participants did not continue the medication because they did not feel it was helpful for their neuropathic pain. Further qualitative investigation in future studies would be beneficial in understanding reasons participants did not continue with the supplement.

Study Limitations

The present study had a number of limitations. First, small sample size. We experienced particularly high rates of attrition prior to medication initiation. These rates of attrition are possibly related to the time commitment for participation. For example, participants were required to be present 8 times in a 10 week period. Perhaps the compensation was not adequate for further participation. participants were responsible for transportation to and from their study appointments as well associated costs (i.e. parking, bus pass, gas money). Within the indigent care population that participants were primarily recruited, this might have been overly burdensome. Every attempt was made to be flexible in scheduling appointments and pairing study visits with other appointments, however this may not have been sufficient. Additionally, there was a time and effort commitment necessary for coming to appointments as well as tracking medications and pain ratings throughout the day for the length of the study. Small sample size limited analyses and interpretation of study findings to effect sizes and observed differences at the individual participant level. While some of this was the result of the inclusion/exclusion criteria, the number that did not continue once ascertained warrants further attention. It is possible that additional efforts to encourage and facilitate patient engagement prior to medication initiation would bolster retention rates.

Complicating the challenges of participant burden is that current study only looked at the effects of 2400mg of NAC daily on chronic neuropathic pain for 4 weeks. A 4-week active medication period may be an insufficient length of time see and impact on long held beliefs about pain, avoidance activities, and learned behaviors associated with long term chronic pain. Additionally, a 4-week trial may not be long enough to impact a pattern of taking medication prior to experiencing higher pain, as a means of prophylaxis.

Another limitation of the current study was the lack of a control group. The study was open labeled, not controlled, and not randomized. In an open label study that has no control group, participants are recruited to a known intervention with no risk of receiving placebo. Efficacy and retention information is based on those receiving unblinded treatment. Findings thus far could be significantly impacted by the addition of randomization and a placebo control.

Finally, the current study included participants with multiple concomitant medication, including prescription, non-prescription, and medical/nutritional supplements. Use of concomitant medications makes it impossible to determine whether treatment response was due to NAC alone or its combination with other medications. Attempts to address this for the pain medication were made by requiring a stable prescription of pain medication (opioid or gabapentin) and consistent PRN prescription prior to study enrollment. Unfortunately, it was not feasible to require that participants have stable medication regimens for medication unrelated to their pain. This raises the possibility that changes in concomitant medications, used for unrelated medical or mental health conditions, could be masking the treatment effects of NAC.

Study Strengths

Despite these limitations, the present study also has a number of strengths. This study adds to a small, but growing, body of literature looking at the potential benefits of NAC. It is also one of the only trials to date that has explored NAC as an adjuvant to traditional treatment for chronic

neuropathic pain. The exploration of NAC as a nonopioid medication for chronic neuropathic pain is timely given the recent recommendations from the CDC for the use of nonopioid therapy as the preferred treatment for chronic pain (Dowell, Haegerich & Chou, 2016).

Another strength of this study was the focus on multiple domains associated with chronic pain, including; medication usage, pain intensity, and physical and emotional functioning. Collection of multiple measures allows for the multiple avenues to measure changes in pain related to the novel medication. This approach allowed for observations in improvements of mental health functioning even when the MED and pain ratings were nonspecific.

Another strength of the current study was the use of case studies to illustrate the range of participant responses to the NAC medication. Case studies provided a comprehensive view of the complex, real-life, experiences of patients with chronic neuropathic pain. Additionally, these case studies allowed for an exploration of individual participant response to NAC across multiple domains allowing for in-depth exploration of data from this small sample.

While difficult to recruit, once NAC was initiated we saw high rates of adherence and retention. There were very few exclusionary criterion applied to patients in the present study, beyond those necessary for safety, allowing for adequate sampling of typical neuropathic pain patients with unmanaged, chronic pain.

A prominent strength of the current study is the role it can play to inform future, large scale, studies through the lessons learned. The current study identified several challenges that future researchers could face with recruitment, retention, and intervention and made suggestions on directions and approaches that future research with NAC and chronic neuropathic pain could explore.

Findings from the current study must be interpreted with caution. Nonetheless, while not overwhelming, findings are promising. Individual report, effect sizes that were small but observable in support of NAC for improving mental health QoL and pain ratings, and acceptability of NAC

support the potential of NAC as a treatment adjuvant for chronic neuropathic pain. Application of the lessons learned from the current study will benefit a larger, randomized control trial, investigating the efficacy of NAC for chronic neuropathic pain. Given the severity of the problems associated with chronic pain, as well as the potential harms associated with opioid pain medications, NAC offers a well tolerated adjuvant to traditional chronic neuropathic pain management approaches worthy of further exploration.

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Appendix

1. Daily Monitoring Form
2. Visual Analogue Scale
3. Pain Catastrophizing Scale
4. Patient Health Questionnaire-9 (PHQ-9)
5. Short Form-12 Health Survey Questionnaire (SF-12)

Daily Monitoring Form

Medication Inventory Form

Participant ID #:_____ Initials:_____ Dates:__/__/__-__/__/__

Date Taken	Time Taken	Medication (Percocet, Oxycodone, Gabapentin, NAC etc.)	Dosage (milligrams)	Amount of Medication (# of pills)	Breakout pain? (Was this taken as-needed?)	Average Pain	Highest Pain
/ /					Y/N		
/ /					Y/N		
/ /					Y/N		
/ /					Y/N		
/ /					Y/N		
/ /					Y/N		
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The following are prescriptions we are interested in having you track:

Visual Analogue Scale

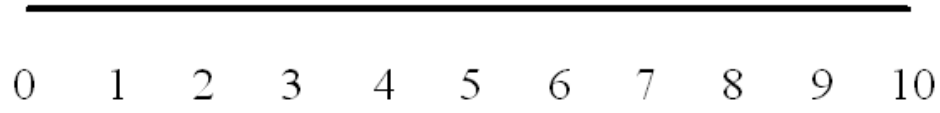
Patient ID #:_____ Date:__/__/__

Visual Analogue Scale

We would like you to indicate on this scale the **AVERAGE** pain that you felt **TODAY**.

Please draw an line at whichever point on the scale indicates your **AVERAGE** pain for **TODAY**.

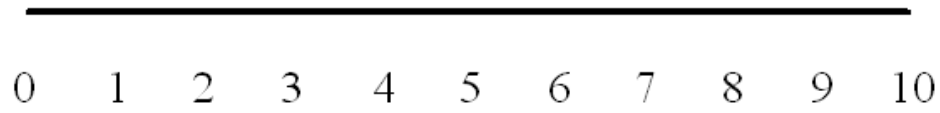
No Pain Worst pain



Now we would like you to indicate on this scale the **WORST** pain that you have felt **TODAY**.

Please draw an line at whichever point on the scale indicates your **WORST** pain for **TODAY**.

No Pain Worst pain



Pain Catastrophizing Scale

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feeling that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4

I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

PHQ-9

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "X" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? (PLEASE CIRCLE)

Not difficult at all Somewhat difficult Very difficult Extremely difficult

SF-12®	**Patient Questionnaire**				Page 1 of 3
Study ID:					**Date:**
Examination Period: ____	Baseline		____	Follow up	

SF-12®:

This information will help your doctors keep track of how you feel and how well you are able to do your usual activities. Answer every question by placing a check mark on the line in front of the appropriate answer. It is not specific for arthritis. If you are unsure about how to answer a question, please give the best answer you can and make a written comment beside your answer.

1. In general, would you say your health is:
   _____ Excellent (1)
   _____ Very Good (2)
   _____ Good (3)
   _____ Fair (4)
   _____ Poor (5)

The following two questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?

2. MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:
   _____ Yes, Limited A Lot (1)
   _____ Yes, Limited A Little (2)
   _____ No, Not Limited At All (3)

3. Climbing SEVERAL flights of stairs:
   _____ Yes, Limited A Lot (1)
   _____ Yes, Limited A Little (2)
   _____ No, Not Limited At All (3)

During the PAST 4 WEEKS have you had any of the following problems with your work or other regular activities AS A RESULT OF YOUR PHYSICAL HEALTH?

4. ACCOMPLISHED LESS than you would like:
   _____ Yes (1)
   _____ No (2)

5. Were limited in the KIND of work or other activities:
   _____ Yes (1)
   _____ No (2)

SF-12® Cont'd:

During the PAST 4 WEEKS, were you limited in the kind of work you do or other regular activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

6. ACCOMPLISHED LESS than you would like:
   _____ Yes (1)
   _____ No (2)

7. Didn't do work or other activities as CAREFULLY as usual:
   _____ Yes (1)
   _____ No (2)

8. During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?
   _____ Not At All (1)
   _____ A Little Bit (2)
   _____ Moderately (3)
   _____ Quite A Bit (4)
   _____ Extremely (5)

The next three questions are about how you feel and how things have been DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS –

9. Have you felt calm and peaceful?
   _____ All of the Time (1)
   _____ Most of the Time (2)
   _____ A Good Bit of the Time (3)
   _____ Some of the Time (4)
   _____ A Little of the Time (5)
   _____ None of the Time (6)

10. Did you have a lot of energy?
    _____ All of the Time (1)
    _____ Most of the Time (2)
    _____ A Good Bit of the Time (3)
    _____ Some of the Time (4)
    _____ A Little of the Time (5)
    _____ None of the Time (6)

SF-12® Cont'd:

11. Have you felt downhearted and blue?
    _____ All of the Time (1)
    _____ Most of the Time (2)
    _____ A Good Bit of the Time (3)
    _____ Some of the Time (4)
    _____ A Little of the Time (5)
    _____ None of the Time (6)

12. During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?
    _____ All of the Time (1)
    _____ Most of the Time (2)
    _____ A Good Bit of the Time (3)
    _____ Some of the Time (4)
    _____ A Little of the Time (5)
    _____ None of the Time (6)

Signature_____ **Date**_____

Vita

Thomas Burton Moore was born on July 14, 1980, in Arlington Virginia, and is an American citizen. He graduated from Yorktown High School, Arlington, Virginia in 1998. He received his Bachelor of the Arts in Psychology from the Evergreen State College, Olympia, Washington in 2003 and subsequently worked as a substance abuse counselor at St. Peters Hospital, Lacey, Washington. He received his Master of Science in Counseling Psychology from Northeastern University, Boston, Massachusetts in 2007 and subsequently worked as a Clinical Liaison and Research Assistant for the Adolescent Substance Abuse Program at Boston Children's Hospital, Boston, Massachusetts. He enrolled in the clinical psychology doctoral program at Virginia Commonwealth University in Richmond, Virginia in 2009 and in 2012 received his Master of Science in Clinical Psychology.