

PAIN IN CHRONIC MEDICAL ILLNESS

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Pain in Chronic Medical Illness

Pain Research and Treatment

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Guest Editors: Jeffrey J. Borckardt, Jarred Younger,
Alok Madan, and Justin Brown



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Editorial

Pain in Chronic Medical Illness

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It has recently been reported that chronic pain affects 43% of American, approximately 100 million adults in 2012 (Tsang and colleagues, *The Journal of Pain* 9(10): 883–891, 2008); accordingly, it remains essential that research continue to advance the current ability to assess and manage pain. Here, in this special issue, we highlight the impact of pain in chronic medical illness and present a body of research that addresses areas where data are currently lacking. Specifically, we present articles that characterize pain in cardiovascular disease, pulmonary disease, breast cancer, gastric bypass surgery, neurofibromatosis, low back pain, and postherpetic neuralgia. Importantly, these studies characterize pain in underrepresented populations including adolescents and surgical patients, and in diverse populations that include individuals from the United States, Iran, and France. Several commonalities arise involving an association between obesity and pain, a call for increased patient education, and a call for continuing education in pain for health care professionals.

Included, you will find the following ten articles: (1) “Prevalence of chest pain, depression, somatization, anxiety, global distress, and substance use among cardiac and pulmonary rehabilitation patients” by E. Serber and colleagues, (2) “Pain narratives in breast cancer survivors” by P. Peretti-Watel and colleagues, (3) “Presurgical weight is associated with pain, functional impairment, and anxiety among gastric bypass surgery patients” by S. Wedin and colleagues, (4) “Physical, cognitive, and psychosocial predictors of functional disability and health-related quality of life in adolescents with neurofibromatosis-1” by M. Garwood and colleagues, (5) “The pain crisis: what it is and what can be done” by B. Sessle, (6) “Low back pain prevalence and associated factors in Iranian

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As a whole, this body of research highlights the impact, incidence, and characteristics of pain in chronic medical illness, as well as opportunities to improve care and assessment.

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Review Article

Sarcoidosis and Pain Caused by Small-Fiber Neuropathy

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Sarcoidosis is a chronic inflammatory illness and small-fiber neuropathy (SFN) is one of the disabling and often chronic manifestations of the disease. SFN presents with peripheral pain and symptoms of autonomic dysfunction. The character of the pain can be burning or shooting. Besides, allodynia and hyperesthesia can exist. Diagnosis is usually made on the basis of clinical features, in combination with abnormal specialized tests. The aim of treatment is often to reduce pain; however, total pain relieve is seldom achieved. The role of TNF- α in the pathogenesis of SFN in sarcoidosis appears interesting to explore. Novel therapeutic agents such as ARA 290, a nonhematopoietic erythropoietin analogue with potent anti-inflammatory and tissue protective properties, are interesting to explore in the treatment of SFN in sarcoidosis.

1. Sarcoidosis

Sarcoidosis has been known for more than 100 years and has been first described by the dermatologist Hutchinson and several years later by two other dermatologists, Besnier and Boeck. It is a multiorgan inflammatory disorder that is characterized by noncaseating granuloma (Figure 1). The exact etiology remains unknown. It is suspected that exposure to one or more extrinsic antigens in a genetically susceptible individual leads to the overactivation of inflammatory pathways that promote the formation of sarcoid granuloma [1]. Granuloma formation is regulated by a complex interaction between T-helper lymphocytes and macrophages, in which cytokines such as tumor necrosis factor (TNF)- α play an important role.

The clinical course of sarcoidosis is highly variable and depends on ethnicity, duration of illness, site and extension of organ involvement, and activity of the granulomatous process, which shows a tendency to wax and wane. Mode of presentation varies from asymptomatic, to an “acute onset” presenting as Lofgren’s syndrome and to a chronic course, frequently accompanied with pain and fatigue. Practically every organ can be involved. However, most commonly (>90%) the lungs are affected [2, 3]. Often patients suffer from symptoms a long time before the diagnosis sarcoidosis is confirmed. Due to the manifold presentation of the

disease, it is a challenge to recognize in an early phase. The acute stage of disease usually presents itself with erythema nodosum, arthritis, fever, and fatigue with a good prognosis. Spontaneous remission usually occurs within two years, while chronic sarcoidosis mostly has an insidious onset with often relapses, resolution being less likely. In some of the cases, the disease is progressive. Development of lung fibrosis, cardiac sarcoidosis, and neurosarcoidosis is related to worse prognosis. Factors that trigger the formation of fibrosis in sarcoidosis are poorly understood. Up to 5% will eventually die from sarcoidosis.

In chronic sarcoidosis, pain and fatigue are important symptoms, even when sarcoidosis is clinically in remission fatigue and pain may persist and become a chronic complaint. These complaints often result in a severe reduction in quality of life. Although a lot of research has been done, the exact mechanism behind this “postsarcoidosis chronic fatigue syndrome” remains unsolved.

Recently, it has been shown that pain in patients with sarcoidosis is often related to neuropathy of small fibers of the peripheral nervous system [4–7].

2. Small Fiber Neuropathy

Small-fiber neuropathy (SFN) is a peripheral nerve disorder that selectively affects thinly myelinated A δ fibers

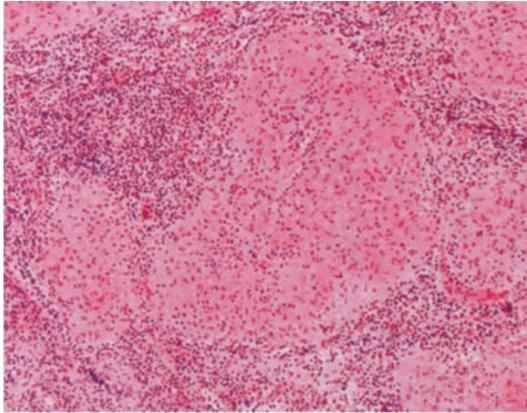


FIGURE 1: A microscopical section of mediastinal lymph node with HE stain, $\times 40$. Multiple granulomas with various sizes from 0,2 to 0,8 mm in diameter are observed in the lymph node. These granulomas consist of histiocytes, which have large cytoplasm and partly connect to each other but lack a necrotic region.

and unmyelinated C fibers. Small nerve fibers are involved in both somatic and autonomic function [8]. As a result, patients with SFN may present with symptoms of neuropathic pain (NP) and autonomic dysfunction [5].

Damage to or loss of small somatic nerve fibers results in burning pain, tingling, or numbness that typically affects the limbs in a distal to proximal gradient. Symptoms are usually worse at night and often affect sleep. People sometimes sleep with the feet uncovered because they can not bear the touch of the sheets. Besides, walking may be difficult due to pain by the pressure on the floor. When autonomic fibers are affected, patients may experience dry eyes, dry mouth, orthostatic dizziness, constipation, bladder incontinence, sexual dysfunction, hyperhidrosis or hypohidrosis, or red or white skin discoloration. Finally restless legs syndrome may be present, characterized by disagreeable leg sensations that usually occur prior to sleep onset and cause an almost irresistible urge to move (Table 1).

Most patients suffer from length-dependent small-fiber neuropathy (LD-SFSN): symptoms and signs start to develop in the toes and feet, symptoms gradually progress to involve distal legs, fingertips, and hands. Non-length-dependent small-fiber neuropathy (NLD-SFSN) is not as common as LD-SFSN and patients develop complaints in a patchy distribution. This can include face, upper limbs, or trunk before the lower limbs are affected. The NLD-SFSN is more seen in women and presents at a younger age [9, 10].

2.1. Diagnosis of Small Fiber Neuropathy. Nerve conduction studies, which are the key in evaluation of other (large fiber) neuropathies, are generally normal in SFN. Therefore, the syndrome of SFN has been an enigma to practitioners because of the unexplained contrast between severe pain and a paucity of neurological and electrophysiological findings. Recent advantages in diagnostic techniques facilitate objective confirmation of clinical diagnosis and characterization of fiber involvement. However, a golden standard for the diagnosis of SFN is not available yet. Diagnosis is usually

TABLE 1: Symptoms of small fiber neuropathy.

Sensory symptoms	Pain*
	Paraesthesias
	Sheet intolerance
	Restless legs syndrome**
Symptoms of autonomic dysfunction	Hypo- or hyperhidrosis
	Diarrhoea or constipation
	Urinary incontinence or -retention
	Gastroparesis
	Sicca syndrome
	Blurry vision
	Facial flushes
	Orthostatic intolerance
	Sexual dysfunction

* Pain in small fiber neuropathy is often burning, tingling, shooting, or prickling in character.

** Restless legs syndrome is a disorder characterized by disagreeable leg sensations that usually occur prior to sleep onset and that cause an almost irresistible urge to move.

made on the basis of clinical features, in combination with abnormal specialized tests, which include among others, assessment of intraepidermal nerve fiber density (IENFD) in skin biopsy, temperature sensation tests, and sudomotor and cardiovagal testing for autonomic fibers [4, 6, 11]. However, all tests have their limitations.

Quantitative sensory testing (QST) includes temperature threshold testing. Thermal (cold and warm) and mechanical (tactile and vibration) detection thresholds assess small-fiber function (including the central pathways). The cold detection threshold (CDT) examines the A-delta-fiber function, while assessment of C-fiber function is examined by the warm detection threshold (WDT). The major limitation of QST is its psychophysical character. As a consequence, malingering and other nonorganic factors can influence test results [12].

To objectively test small nerve fibers, laser-evoked potentials (LEP) and contact heat-evoked potentials (CHEPs), have been developed. It is well established that both laser and contact heat stimulation activate thermo-nociceptive cutaneous nerves. Even though attention and other cognitive processes influence the amplitude of Laser Evoked Potentials (LEPs) and Contact Heat Evoked Potentials (CHEPs) these tests carry up relevant information on the functional state of nociceptive terminals.

For the CHEPs, a thermofoil thermode stimulator is used to reach a temperature of 53°C at a rate of 70°C/s . It has been shown that patients with sensory neuropathy have lower-amplitude CHEPs, which correlates with other SFN tests [13].

Multiple studies have emphasized the importance of intraepidermal nerve fiber density (IENFD) assessment using PGP-9.5 immunofluorescent staining in skin biopsy in the evaluation SFN [14]. Epidermal nerves are the distal terminals of small dorsal root ganglia neurons that pierce

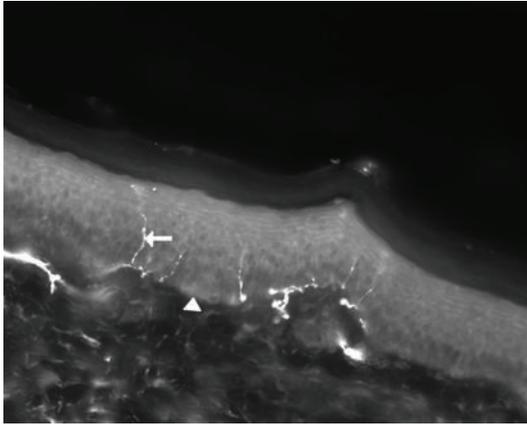


FIGURE 2: Magnification 200x. Punch skin biopsy from a healthy control showing intraepidermal nerve fibers. Arrow: intraepidermal nerve fiber. Arrowhead: basal membrane (above the basal membrane the epidermis is shown, under the basal membrane the dermis is shown).

the dermal-epidermal basement membrane and penetrate the epidermis. The discovery of the antibody to the neuropeptide protein gene product (PGP) 9.5 made it possible to effectively stain nerve fibers (Figure 2). PGP 9.5 is a ubiquitin C-terminal hydrolase and is enriched in epidermal nerve fibers [14]. A punch biopsy is performed following established procedures, mostly 10 cm above the lateral malleolus after local anesthesia with 1% lidocaine. A limitation of skin biopsies is that they are available in only a few academic centers. The histological technique is moderately complicated and time consuming, and before implementing it, a relatively large subset of healthy controls should be studied as the normative range is wide. Finally skin biopsy appears to have a high specificity but low sensitivity in sarcoidosis: Bakkers in 2009 showed that 32,8% of sarcoidosis patients with symptoms of SFN had a reduced IENFD score in the skin biopsy, and 14,3% in patients without SFN symptoms had a reduced IENFD [4]. The rule “physicians, not tests make diagnosis” appears especially applicable for SFN. Examination often reveals allodynia, hyperalgesia, or reduced pinprick and thermal sensation in the affected area. Motor strength and proprioception, however, are (as functions of the large fibers) preserved.

2.2. Etiology of Small Fiber Neuropathy. In 50% of the cases presenting with SFN no underlying disease is found: “idiopathic SFN” [15]. Recent studies have shown gain of function mutations in sodium channel Na(V)1.7 in a subset (28.6%) of those patients with idiopathic SFN [16]. The exact role of these mutations is unresolved yet.

In 50% of the cases presenting with SFN, an underlying disease is present, including diabetes, sarcoidosis, and amyloidosis among others (Table 2) [6]. It is remarkable that SFN appears frequent in several immune-mediated diseases. This leads to the hypothesis that there might be a common pathway in immune-mediated diseases resulting in SFN. The idea of an immune-mediated mechanism as the cause of SFN has also been reported by others [17–19].

TABLE 2: Causes of small fiber neuropathy [6].

Idiopathic	Familial amyloidosis
	Autosomal recessive hereditary neuropathy
	Hereditary sensory and autonomic neuropathy
Inherited	Fabry’s disease
	Ross syndrome
	Friedreich’s ataxia
	Tangier disease
Acquired	Diabetes mellitus
	Impaired glucose tolerance
	Alcoholism
	Systemic amyloidosis
	Vasculitis
	Sarcoidosis
	Sjögren’s disease
	Systemic lupus erythematosus
	Guillain-Barre syndrome
	Antecedent viral infection
	HIV
	Antisulfatide antibodies
	Hyperlipidemia
Complex regional pain syndrome	
Paraneoplastic syndrome	
Neurotoxic medication	

The pathogenetic role of oxidative stress, inflammatory cytokines such as TNF- α , and neuropeptides such as substance P (SP) are interesting to explore as a common final pathway in SFN in several immune-mediated inflammatory diseases. We described a patient with severe SFN who showed spectacular improvement after treatment with anti-TNF- α therapy [20]. This case supports the idea that TNF- α may be a crucial cytokine in the pathogenesis of SFN related to sarcoidosis and presumably in SFN related to other immune-mediated inflammatory diseases as well. Theoretical support for the effect of anti-TNF- α therapy on SFN may be found in the following. First, TNF- α plays an important role in immune-mediated neuropathies such as Guillain-Barré syndrome, in which small nerve fibers are also involved. Elevated serum concentration of TNF- α shows a positive correlation with neuropathy severity in patients with Guillain-Barré syndrome. Furthermore, the decrease in serum TNF- α and increase in serum soluble TNF receptors show a positive correlation with neuropathy recovery in those patients. Second, pharmacological and physiological studies report that proinflammatory cytokines such as TNF- α are strongly involved in the generation and maintenance of neuropathic pain [21–25].

TABLE 3: Drugs for pain control in small fiber neuropathy.

Drug	Dosage (per day)	Common side effects
Antidepressants		
Amitriptyline (Elavil)	20–150 mg	Sedation, weight gain, anticholinergic effects, sexual dysfunction, arrhythmia (side effects most prominent)
Nortriptyline (Aventyl)	20–150 mg	Sedation, weight gain, anticholinergic effects, sexual dysfunction, arrhythmia (side effects most prominent)
Desipramine (Norpramin)	20–200 mg	(side effects most prominent with amitriptyline)
Duloxetine (Cymbalta)	60–120 mg	
Anticonvulsants		
Gabapentin (Neurontin)	600–3,600 mg	Sedation, dizziness, peripheral edema, weight gain
Pregabalin (Lyrica)	150–600 mg	Similar to gabapentin
Topiramate (Topamax)	25–400 mg	Weight loss, sedation, cognitive slowing, renal stones, paresthesias
Lamotrigine (Lamictal)	25–400 mg	Stevens-Johnson syndrome, rash, dizziness, nausea, sedation
Carbamazepine (Tegretol)	200–1,200 mg	Dizziness, sedation, ataxia, aplastic anemia, liver enzyme elevation
Oxcarbazepine (Trileptal)	600–2,400 mg	Dizziness, nausea, fatigue, leukopenia
Topical anesthetics		
5% Lidocaine patch (Lidoderm)	Every 12 hours	Local edema, burning, erythema
0.075% Capsaicin patch	Three or four times a day	Burning
Opioids, opioid agonists		
Tramadol (Ultram)	100–400 mg	Sedation, dizziness, seizures, nausea, constipation
Oxycodone (Oxycontin)	10–100 mg	Sedation, constipation, nausea; potential for addiction and abuse

3. Treatment

Although alternatives to corticosteroids have been frequently administered in this disease, corticosteroids remain the mainstay of treatment in sarcoidosis. Immunosuppressive agents (chlorambucil, cyclophosphamide, methotrexate, cyclosporine, azathioprine), anticytokine agents (thalidomide, pentoxifylline), antimalarials (chloroquine, hydroxychloroquine), melatonin, and monoclonal antibody (infliximab) have been used in chronic resistant sarcoidosis [26].

Usual treatments in sarcoidosis such as prednisone and methotrexate do not appear beneficial in sarcoidosis-related SFN (personal experience). SFN is disabling for patients and the pain is often difficult to treat. SFN has a high impact on the quality of life and often invalidates the patient. Case reports mention beneficial effects of intravenous immunoglobulin [19] and anti-TNF- α therapy [20]. The exact potency of these drugs needs further study, however.

Symptomatic neuropathic pain treatment in sarcoidosis patients is not different from treatment of neuropathic pain from other causes and consists of antidepressants, anticonvulsants and prolonged-release opioids (Table 3). However, in common with their effects in other neuropathic pain states, these agents provide limited pain relief in just 30–60% of patients, at the cost of considerable side effects. These data indicate that there is an imminent need for analgesic agents with high efficacy in neuropathic pain patients without causing debilitating side effects.

4. Directions for Future Studies

As the role of TNF- α in the pathogenesis of SFN in sarcoidosis appears interesting to explore, anti-TNF therapy might be beneficial in the treatment of SFN in sarcoidosis. A recent therapeutic development has been the availability of agents that directly inactivate the proinflammatory cytokine TNF- α . Those are expensive drugs with possible severe side effects including opportunistic infection.

Recently, we initiated a program aimed at the treatment of neuropathic pain in patients with sarcoidosis with a novel therapeutic agent, ARA 290. ARA 290 is a nonhematopoietic erythropoietin analogue with potent anti-inflammatory and tissue protective properties, acting at the innate repair receptor [27–29]. In recent years, an endogenous system has been identified that antagonizes the production and action of proinflammatory cytokines that are involved in promoting tissue injury, while simultaneously activating repair processes. The primary mediator of this system is hypoglycosylated erythropoietin (EPO) that acts through a unique receptor isoform, the innate repair receptor (IRR), which is a combination of EPO and beta common receptor subunits. Many diverse preclinical models of tissue injury have demonstrated the efficacy of EPO as an effective cytoprotectant and activator of healing and repair. For example, EPO acting through the IRR has been shown to improve recovery and function from nerve injury in a variety of preclinical models, including the small-fiber neuropathy caused by uncontrolled

diabetes [28]. Because the IRR has a lower affinity for EPO than the receptor utilized in hematopoiesis ($\sim 2 \cdot 0$ – $20 \cdot 0$ nM versus $0 \cdot 2$ nM resp.), larger doses of erythropoietin must be administered to activate the IRR. Since EPO interacts with both of these receptors, translation of this knowledge into clinical use has been hindered by the presence of unavoidable hematopoietic side effects triggered by the hematopoietic receptor. For example, clinical studies evaluating use of EPO for tissue protection have consistently revealed increased rates of serious thrombosis [28]. To circumvent this problem, a number of IRR-specific ligands have been engineered.

One novel approach is pyroglutamate helix B surface peptide (ARA 290). This peptide mimics the spatial configuration of EPO that is believed to interact with the IRR. In spite of having a plasma half life of less than 2 minutes, ARA 290 is as efficacious as EPO in a wide variety of models of tissue injury. Additionally, preclinical toxicology studies of ARA 290 and single- and multiple-ascending repeated dosing of human volunteers and patients with kidney disease, diabetes mellitus, or sarcoidosis have raised no safety issues (unpublished data, Araim Pharmaceuticals).

First studies in animals (with nerve-damage induced neuropathic pain) and in patients with chronic neuropathic pain from sarcoidosis and diabetes mellitus indicated that ARA 290 is highly effective in causing pain relief in these neuropathic pain states. This compound appears potential for this chronic inflammatory disease and further investigation has been started.

Abbreviations

SFN:	Small-fiber neuropathy
TNF- α :	Tumor necrosis factor- α
NP:	Neuropathic pain
LD-SFSN:	length dependent small-fiber neuropathy
NLD-SFSN:	Non-length-dependent small-fiber neuropathy
IENFD:	Intra-epidermal nerve fiber density
QST:	Quantitative sensory testing
CDT:	Cold detection threshold
WDT:	Warm detection threshold
PHS:	Paradoxical heat sensation
MDT:	Mechanical detection threshold
VDT:	Vibration detection threshold
CPT:	Cold pain threshold
HPT:	Heat pain threshold
PPT:	Pain pressure threshold
MPT:	Mechanical pain threshold
LEP:	Laser evoked potential
CHEPs:	Contact heat evoked potentials.

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Research Article

Depressive Symptoms, Pain, and Quality of Life among Patients with Nonalcohol-Related Chronic Pancreatitis

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Objective. The present study was conducted to determine if depressive symptoms were associated with variability in pain perception and quality of life among patients with nonalcohol-related chronic pancreatitis. **Methods.** The research design was cross-sectional, and self-report data was collected from 692 patients with nonalcohol-related, intractable pancreatitis. The mean age of the sample was 52.6 (SD = 14.7); 41% of the sample were male. Participants completed the MOS SF12 Quality of Life Measure, the Center for Epidemiological Studies 10-item Depression Scale (CESD), and a numeric rating scale measure of “pain on average” from the Brief Pain Inventory. **Results.** Depressive symptoms were significantly related to participants’ reports of increased pain and decreased quality of life. The mean CESD score of the sample was 10.6 (SD = 6.5) and 52% of the sample scored above the clinical cutoff for the presence of significant depressive symptomology. Patients scoring above the clinical cutoff on the depression screening measure rated their pain as significantly higher than those below the cutoff ($P < 0.0001$) and had significantly lower physical quality of life ($P < 0.0001$) and lower mental quality of life ($P < 0.0001$). **Conclusion.** Although causality cannot be determined based on cross-sectional, correlational data, findings suggest that among patients with nonalcoholic pancreatitis, the presence of depressive symptoms is common and may be a risk factor associated with increased pain and decreased quality of life. Thus, routine screening for depressive symptomology among patients with nonalcoholic pancreatitis may be warranted.

1. Introduction

Chronic pancreatitis (CP) is a long-term, often debilitating medical condition that drastically impacts the health and quality of life of affected patients. The disease involves persistent inflammation of the pancreas, causing the hallmark symptom of severe abdominal pain in 80–90 percent of patients [1, 2]. Initial symptoms are often described as pancreatitis “attacks” characterized by episodes of extreme acute pain. Progression of the disease is marked by increased incidence and severity of pain attacks, culminating in chronic pain, nausea, and vomiting, which significantly impairs physical and psychosocial functioning. In addition

to debilitating pain symptoms, CP patients frequently report an array of distressing gastrointestinal symptoms, including malabsorption, fat intolerance, anorexia, diarrhea, jaundice, and progressive impairment of pancreatic enzyme output. Insufficient enzyme production often leads to additional complications, such as endocrine insufficiency and insulin dependence [3–5]. Untreated chronic pancreatitis is associated with high morbidity and mortality rates; long-term improvement of pain symptoms without surgical intervention is uncommon [5, 6].

Importantly, in addition to multiple distressing physical symptoms, individuals with chronic pancreatitis report significant difficulties in social and emotional functioning.

The unique interplay between physical and psychosocial symptoms of CP is not well-understood. Higher rates of clinically significant depression and anxiety amongst CP patients (in which the etiology is frequently due to alcohol use) are documented in the literature, and various social and physical variables associated with CP likely interact to create distressing symptoms and reports of reduced quality of life [7–14]. For instance, chronic pain has been documented as the most important factor in causing distress in CP patients [15, 16]. Untreated social, emotional, and behavioral symptoms may also lead to disease progression and exacerbate pain and gastrointestinal symptoms in CP patients.

Further, the etiology of patient's CP may contribute to reported emotional, social, and physical symptoms. Alcoholism is the most common cause for nonobstructive pancreatitis and is thought to account for 70% of cases of CP [17]. Treatment of alcohol-related pancreatitis is often challenging, due to multiple problems associated with alcohol misuse, including dependency, psychosocial difficulties, mood symptoms, and physical complications of malnutrition and hepatic insufficiency [18, 19]. More specifically, comorbid psychosocial symptoms associated with alcohol misuse and CP make accurate identification of the etiology and treatment of distressing symptoms very complex. For example, high levels of emotional distress reported by CP patients may be attributable to coping with a chronic painful medical condition (CP), a current or past history of alcohol misuse, or a combination of the two. Research has also documented a relationship between alcohol use and pain; ongoing use has the potential to exacerbate a CP patient's pain experience [20]. However, very little research exists that examines patients with nonalcohol-related CP and associated psychosocial distress. Additional research that explores the presentation and association of psychosocial variables unique to nonalcoholic-related CP is needed.

A better understanding of the relationship between depressive symptoms, pain, and quality of life in patients with nonalcohol-related CP holds promise for improving pain management and the quality of life of this unique patient population. The present study explores the frequency with which participants with nonalcohol-related CP endorse depressive symptoms and examines the relationship between depressive symptoms, pain experience, and quality of life among participants. Consistent with previous research on the relationships between depression, pain, and quality of life among patients with other chronic medical conditions, it was hypothesized that individuals with nonalcoholic intractable CP who met criteria for significant depressive symptomatology would report higher pain ratings and lower quality of life scores compared to those who did not meet criteria.

2. Methods

2.1. Ethics. All data were collected with full approval from the Institutional Review Board at the Medical University of

South Carolina. Participants' personal health information was handled ethically and in accordance with Health and Human Services regulations.

2.2. Subjects. The participants in this study consisted of 692 patients with nonalcohol-related, intractable pancreatitis. Participants had been diagnosed with pancreatitis for at least 6 months. The sample on average was middle age ($M = 52.6$, $SD = 14.7$), and 59% of the sample were female.

2.3. Procedure. Data were collected as part of routine clinical care with patients who were being consecutively medically treated. Participants used a web-based computer psychosocial screening system to complete the measures at their initial visit to a tertiary care specialty clinic (Digestive Disease Center) at a large southeastern medical university. The participants completed the measures in a private physician office while they waited for their consultation with their physician. Nursing staff was available to help participants log-in to the system and to assist with completion of the online questionnaires if necessary.

2.4. Measures. The following measures were completed by all participants.

- (1) *The Medical Outcomes Trust Short Form 12 (SF-12)*. Health-related quality of life was assessed by administering the SF-12 [21]. The SF-12 is an abbreviated form of the SF-36 health status questionnaire [22], and it is a quality of life instrument that assesses mental (MCS) and physical (PCS) health and functioning over the past 4 weeks. The reliability and validity of the SF-12 have been well established [21], and the instrument has been validated for use in patients with chronic pain [19, 23–25]. The physical and mental quality of life scales are computed using the 12-items and range from 0 to 100 with a score of 0 indicating the lowest quality of life and a score of 100 indicating the highest quality of life.
- (2) *The Center for Epidemiologic Studies 10-Item Depression Scale (CESD-10)*. The CESD-10 was used to assess self-reported depressive symptoms. This is a 10-item self-report measure with a 4-point rating scale (0–3) and has been demonstrated to be as effective as the full version of the CESD in identifying significant depressive symptoms [26–28]. Scores on the CESD-10 range from 0–30, with a score of 10 or greater indicating the presence of depressive symptoms.
- (3) *The Brief Pain Inventory (BPI)*. The Brief Pain Inventory Short Form (BPI) is a 17-item self-report, multidimensional pain questionnaire that provides information about pain history, location, and intensity [29]. Participants are asked to rate the intensity of their pain experience on a scale of 0 (*no pain*) to 10 (*pain as bad as you can imagine*) at several time points: at its worst and its least over the past 24 hours, on average, and at the time of the assessment.

For the purpose of the present study, participants only rated their pain on average. Although the BPI was first designed to evaluate cancer pain, it has since been validated in a chronic noncancer pain patient population [30].

2.5. Statistical Analyses. All study analyses were conducted with SPSS, version 12. Statistical significance was set at $P = 0.05$. Descriptive analyses were conducted, and Pearson correlations were run among the group as a whole examining the association between depression, quality of life, and pain on average. In addition, to further explore the relationship among variables, participants were divided into two groups: those that met criteria for the presence of depressive symptoms (score of 10 or higher on CESD 10) and those who did not meet criteria for presence of depressive symptoms. Independent sample t -tests were used to explore the differences between groups in quality of life (SF-12) and their rating of pain on average. If participants skipped any items they were excluded pairwise from each relevant analysis.

3. Results

The mean age of all participants was 52.6 (SD = 14.7); 41% of the sample were men. Demographic variables were not significantly related to depressive symptoms, pain, or quality of life. Correlation data for variables analyzed are summarized in Table 1. As predicted, participants' reports of depressive symptoms were significantly and positively related to ratings of pain on average ($r = 0.46, P < 0.0001$).

Similarly, participants' reports of depressive symptoms were significantly and inversely related to ratings of physical quality of life ($r = -.22, P < 0.0001$) and mental quality of life ($r = -0.37, P < 0.0001$).

The mean CESD-10 score of the sample was 10.6 (SD = 6.5) with 52% of participants scoring above the cutoff for clinical depressive symptomatology. The average CESD-10 score for participants who scored above the clinical cutoff for depressive symptoms was 15.76 (SD = 4.34) compared to a mean of 4.96 (SD = 2.68) among the group scoring below the cutoff for depressive symptoms. Participants who scored above the clinical depression cutoff endorsed significantly more pain on average compared to those who did not meet the criteria for depressive symptoms. Specifically, participants above the depressive symptomatology cutoff rated their pain on average as 5.5 (out of 10; SD = 2.5), whereas those below the cutoff rated their pain on average as 3.4 (SD = 2.9; $t(691) = 9.9, P < 0.0001$). Moreover, participants above the cutoff on the CESD-10 rated their quality of life as significantly lower compared to participants below the cutoff. The mean physical quality of life norm-based t -score for those above the depressive symptomatology cutoff was 34.2 (SD = 7.6) on the physical quality of life subscale of the SF-12, and for those below the cutoff the mean physical quality of life was 37.6 (SD = 8.2; $t(634) = 5.3, P < 0.0001$). Similarly, the mean mental quality of life norm-based t -score for participants who scored above the

TABLE 1: Correlations among variables tested in hypotheses.

	1	2	3
(1) Center for Epidemiological Studies Depression Scale-10	—		
(2) Pain on average	0.46 **	—	
(3) Physical quality of life (SF-12)	-0.22 **	-0.17 **	—
(4) Mental quality of life (BPI)	-0.38 **	-0.18 **	-0.40 **

** $P < 0.0001$.

TABLE 2: Independent t -tests between participants who met cutoff criteria for depressive symptoms and those who did not meet symptoms criteria and quality of life and pain on average.

	Depressive symptoms	No depressive symptoms	t	P
Physical QOL ^a	34.2 ± 7.6	37.6 ± 8.2	5.3	0.0001
Mental QOL ^b	44.9 ± 8.2	49.0 ± 7.3	5.3	0.0001
Pain ^c	5.5 ± 2.5	3.4 ± 2.9	9.9	0.0001

$N = 691$. However, the sample size for some of the variables is smaller due to missing data. ^a $n = 610$. ^b $n = 610$. ^c $n = 666$.

cutoff was 44.9 (SD = 8.2), and for those below the cutoff, it was 49.0 (SD = 7.3; $t(634) = 5.3, P < 0.0001$). Results are summarized in Table 2.

4. Discussion

Chronic pancreatitis is a debilitating disease characterized by severe pain that negatively affects quality of life. While the etiology of the pain associated with chronic pancreatitis is not well-understood, alcoholism is the presumed cause in 55–80% of patients [31]. Assessing, treating, and managing patient's with alcohol-associated CP is difficult as a result of the myriad of psychosocial problems related to alcohol dependency, such as depression. A unique contribution of the current study is the large sample size comprised of patients with nonalcohol-related intractable CP, as this removes the confounding variable of alcohol dependency.

Results from the current study suggest that individuals who endorse more depressive symptoms also report more pain on average and lower physical and psychological quality of life. Further, findings from the present study indicate that many patients with nonalcoholic chronic pancreatitis (52%) experience depressive symptoms. Importantly, participants who endorsed significant depressive symptoms tended to also report worse pain and lower physical and psychological quality of life compared to those who did not acknowledge significant depressive symptoms.

Findings lend support for the importance of assessing and treating CP patients using a biopsychosocial model. This treatment approach posits that biological, psychological, and social factors all significantly impact individuals' level of functioning within the context of chronic illness. This model has received increasing attention and support in the literature for understanding the etiology, course, and treatment planning for medical illness [31].

Current findings highlight the importance of the treatment of depressive symptoms in improving pain experience and physical and mental quality of life. A biopsychosocial model of treatment that targets symptoms of depression may include use of antidepressants and cognitive-behavioral interventions of activity-pacing, cognitive restructuring, and relaxation strategies. Environmental interventions may focus on increased communication, utilization of social resources, and physical rehabilitation. This comprehensive approach to treatment addresses the physiological, psychiatric, and social variables that are associated with increased distress in patients with CP.

The present study also highlights the potential value of early intervention and ongoing assessment of psychosocial variables in reducing depressive symptoms and improving pain and the general well-being of CP patients who are not alcohol dependent. The use of clinical interviews and self-report measures can provide valuable information to the treatment team related to the unique challenges that individual CP patients face and treatment can be tailored accordingly. Importantly, initial and ongoing psychosocial assessment provides physicians with information related to patients' needs for referrals to other specialists, such as mental health providers.

There are several limitations to the present study. The current analysis was of retrospective data, limiting variables to the confines of prior data collection. Further, as this is a cross-sectional study, findings identify an association between depression, pain level, and quality of life; the direction of this relationship is unknown. Future prospective research that includes a theoretical design, experimental methods including healthy controls and participants with alcohol-related pancreatitis, and longitudinal designs are likely to further delineate the role of depression in the course of CP. The current study is also somewhat limited by the lack of examination of other psychosocial variables. It is possible that variables such as level of social support, coping style, substance use, and treatment history also play a role in patients' report of depressive symptoms, pain experience, and quality of life. Additional research that explores the possible mitigating role of these variables will provide valuable information related to the complexity of the relationship between depression, pain, and quality of life in CP patients. Further, more comprehensive measurement of the frequency, intensity, and quality of pain will offer a more nuanced picture of CP patients' experience.

In conclusion, findings suggest that among patients with nonalcohol-related CP depression is common and may be a risk factor associated with increased pain and decreased quality of life. Thus, routine screening and intervention for depression among patients with nonalcohol-related chronic pancreatitis may be warranted.

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Research Article

Depression and Anxiety Symptoms Relate to Distinct Components of Pain Experience among Patients with Breast Cancer

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Breast cancer is a leading cancer diagnosis among women worldwide, with more than 210,000 new cases and 40,000 deaths per year in the United States. Pain, anxiety, and depression can be significant factors during the course of breast cancer. Pain is a complex experience with sensory, affective, and cognitive dimensions. While depression and anxiety symptoms are relatively common among breast cancer patients, little is known about the relation between these psychiatric factors and distinct components of the pain experience. In the present study 60 females presenting to an NCI-designated Cancer Center with newly diagnosed breast cancer completed the Center for Epidemiological Studies 10-item Depression Scale, the State Instrument of the Spielberger State-Trait Anxiety Inventory, and the McGill Pain Questionnaire. Findings indicate that anxiety and depression are common among newly diagnosed breast cancer patients; furthermore, patients experience an appreciable amount of pain even before oncologic treatment starts. State anxiety serves as a predictor of the sensory dimension of the pain experience, whereas depression serves as a predictor of the affective dimension of the pain experience.

1. Introduction

Breast cancer is a leading cancer diagnosis among women worldwide, with more than 210,000 new cases and 40,000 deaths per year in the United States [1]. Pain can be a complex and significant factor during the course of breast cancer and is often related to the underlying malignancy and tumor burden, surgeries, chemotherapies, radiation, and hormonal therapies used to treat the malignancy. Notably, pain is usually not a symptom of tumor burden in less advanced disease and is only experienced in 5–15% of breast cancer patients prior to diagnosis [2].

Contemporary models have expanded pain to involve more than just a nociceptive experience. Melzack and Casey

[3] describe a multidimensional model of pain processing with sensory, affective, and cognitive components. Sensory aspects help to identify the location, size, and intensity associated with the noxious stimuli, whereas affective components of pain refer to the unpleasantness or distress associated with the physical sensation of pain. Lastly, cognitive components include evaluation and interpretation of the meaning of the pain experience.

Pain, anxiety, and depression often co-occur [4]. Research indicated that individuals with pain endorse significantly elevated rates of depression and anxiety when compared to those without pain. More specifically, results of epidemiological studies across 17 different countries suggest that anxiety disorders are 2-3 times more prevalent in

chronic pain populations [5]. Results from a nationally representative sample indicate that both depression and anxiety are 1.5 times to 4 times more likely in individuals with pain conditions compared to those with no pain condition [6].

Anxiety and depression commonly occur in cancer patients who are facing multiple biological and psychosocial stressors. Biologic stressors impacting an individual's function include the tumor burden, treatment morbidity, neurobiological changes, pain, and physical sensations. Psychosocial stressors impacting an individual's functioning include themes of uncertainty, loss of control, changes in life trajectory, and increased dependency, as well as changes in role functioning, appearance, and identity [7]. Anxiety and depression can develop at different points on the treatment continuum from the point of abnormal finding to diagnosis, initiation or completion of treatment, progression of disease, survivorship, and throughout palliative care [8].

When compared to the general population, cancer patients are at higher risk for experiencing depression and anxiety. Within the general population, the 12-month and lifetime prevalence rates for major depressive disorder are 6.6% and 16.5% [8, 9], whereas the prevalence rates for major depressive disorder within the cancer population are 0–38% [10]. The prevalence rate increases up to 58% of the cancer population when considering other depressive disorders [10]. Within the general population, the 12-month prevalence rate of anxiety is 8%. As with depression, anxiety is more prevalent in the cancer population with epidemiologic studies estimating rates at 10–30% [11]. Burgess et al. [12] found in their study with early-stage breast cancer patients that 33% of their sample was diagnosed with depression and anxiety at cancer diagnosis, 15% at 1 year after cancer diagnosis, and 45% at cancer recurrence. Similarly, Vahdaninia et al. [13] found in their recent prospective study of breast cancer patients that 47.4% of patients experienced severe anxiety, and 18.0% experienced clinically significant symptoms of depression at a prebreast cancer diagnostic assessment. Interestingly, at 18-month followup mean levels of anxiety and depression had decreased, but 38.4% of patients still experienced severe anxiety, and 22.2% experienced clinically significant depression.

Specifically within the breast cancer population, Vahdaninia et al. [13] examined the relation between anxiety, pain, and depression at baseline prediagnosis, 3-month follow-up, and 18-month follow-up. Researchers did not find a significant relation between anxiety and depression and pain at 3-month follow-up, but at the 18-month follow-up pain was significantly related to both anxiety and depression. Moreover, pain was the most significant variable related to anxiety at 18-month followup over and above disease state.

In their systematic review of cancer pain and depression, Laird et al. [14] found that pain and depression were highly prevalent. They additionally found that certain pain characteristics were related to depression. First, pain intensity [15–17] and pain duration [16, 18] were associated with increased levels and risk of depression respectively. Next, when responding to the McGill Pain Questionnaire, depressed patients had higher affective pain intensity scores and used a greater number of affective pain descriptors

when compared to the nondepressed patients in the sample [17].

The current study seeks to describe the pain experience of women recently diagnosed with cancer who have not yet undergone cancer-related treatment. We focus on the prevalence of anxiety and depression and their relation to multiple dimensions of pain. In addition to describing anxiety, depression, and pain within this unique sample, we strive to build on the existing literature by examining whether anxiety and depression differentially predict components of the pain experience.

2. Methods and Materials

2.1. Participants and Procedure. In the present study 60 females presenting to a southeastern NCI-designated Cancer Center with newly diagnosed breast cancer (prior to treatment) completed paper-and-pencil measures in the waiting room. Hospital staff then entered the scores from the measures into a computer system. The data were collected as part of routine clinical practice, and IRB approval was attained in order to permit publication of the data in aggregate for the present study. A chart review provided participants' demographic information.

2.2. Measures

2.2.1. Depression. The Center for Epidemiological Studies 10-Depression Scale (CESD-10) [19] is a ten item self-report scale measuring somatic, affective, cognitive, and interpersonal components of depression. Respondents report on the intensity that they experienced symptoms over the past two weeks using a 4-point scale (1 = rarely or none of the time; 4 = all of the time). Sample items include: "I felt depressed" and "I felt that everything I did was an effort."

2.2.2. Anxiety. The State-Trait Anxiety Inventory-State Scale (STAI-S) [20] is a 20-item self-report scale measuring worry, tension, and apprehension that the respondent experiences in his or her current circumstances (state anxiety). Respondents report on the frequency that they experience symptoms on a 4-point scale (1 = not at all; 4 = very much so). Sample items include: "I feel nervous and restless" and "I feel that difficulties are piling up so that I cannot overcome them."

2.2.3. Pain. The McGill Pain Questionnaire-Short Form (SF-MPQ) [21] is a self-report scale measuring qualitative and quantitative components of pain. The scale consists of 15-descriptor items with 1–11 describing sensory pain dimension and 12–15 describing affective pain dimensions. Items are then ranked on a 4-point scale (0 = no pain to 4 = severe pain). Descriptor items include: "throbbing," "shooting," and "stabbing."

2.3. Data Analyses. Descriptive statistics were calculated for all study variables. Simple regression was utilized to address the predictive relationships between anxiety, depression,

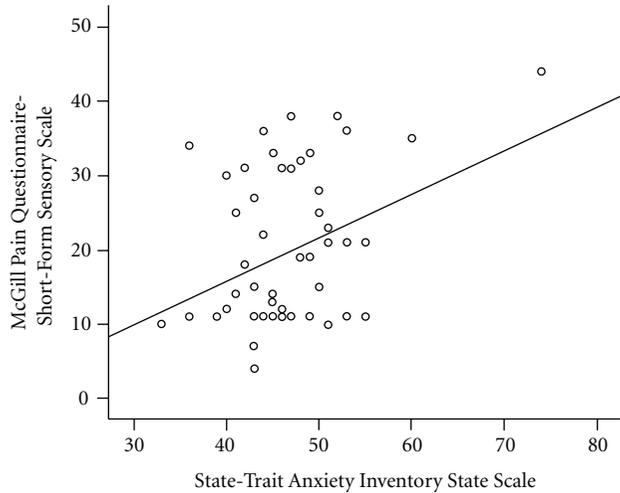


FIGURE 1: Scatterplot representing the relation between state anxiety and sensory pain.

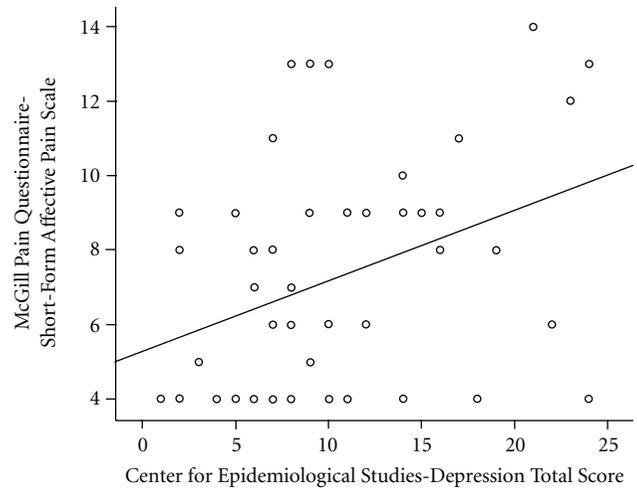


FIGURE 2: Scatterplot representing the relation between depression and affective pain.

and components of pain. Pairwise deletion was utilized to account for missing data.

3. Results

Six percent of the sample was between the ages of 20 and 29, 11% was in the 30–39 age-range, 12% was in the 40–49 age range, 24% was in the 50–59 age range, 29% was in the 60–69 age range, and 18% of the sample was 70 or older. 72% of the sample was Caucasian, 27% was African American, and 1% was of Asian descent. 1% of the sample identified themselves as being of Hispanic ethnicity.

Seventy-two percent of participants exceeded the cutoff for clinically significant anxiety symptoms on the STAI (mean score = 46.75, SD = 6.14), and 48% exceeded the cut-off for clinically significant depression on the CESD (mean score = 10.25, SD = 5.83). Mean percent of total possible sensory and affective pain scores from the MPQ were 44% and 45%, respectively, suggesting a moderate amount of reported pain by respondents despite not yet starting cancer treatment.

Anxiety scores were positively predictive of the sensory component of the pain experience ($r(58) = .36, P = .006$) but not the affective component of the pain experience ($r(58) = .12, P = .36$), whereas depression scores were predictive of the affective component of the pain experience ($r(58) = .36, P = .005$) but not the sensory component ($r(58) = -.04, P = .73$). Figure 1 represents the relation between anxiety and sensory pain, and Figure 2 represents the relation between depression and affective pain. Anxiety scores and depression were not related ($r(58) = -.004, P = .97$).

4. Discussion

This study examined the prevalence and relation between anxiety, depression, and pain among newly diagnosed breast

cancer patients. We found that 72% of participants exceeded the clinical cut-off for anxiety, and 48% exceeded the clinical cut-off for depression. Additionally, although participants had not yet started oncologic treatment, they reported experiencing moderate amount of pain. Interestingly, the relation between psychiatric factors and components of pain differed. Increased levels of state anxiety were significantly related to increased levels of the sensory pain component but were not related to the affective pain component. On the other hand, increased levels of depression were significantly related to increased levels of the affective pain component, but were not related to the sensory pain component.

Findings from this preliminary study suggest that anxiety and depression may be common among newly diagnosed breast cancer patients, and that these patients may be experiencing an appreciable amount of pain even before oncologic treatment starts. In the current study, increased levels of pain experienced by women could be related to recent biopsy, primary tumor burden, and metastatic disease. Furthermore, findings suggest that state anxiety may be a predictor of the sensory dimension of the pain experience, whereas depression may be a predictor of the affective dimension.

Results from the current study are consistent with previous research finding that clinically significant anxiety and depression are common within the newly diagnosed cancer population. More specifically, rates of depression were similar to previous research given our use of the CES-D to identify depressive symptomatology. The CES-D is a screening device for symptoms rather than a diagnostic tool; consequently, prevalence rates of clinically significant depression are reflective of depressive diagnoses across the continuum-adjustment disorders with depressed mood to major depressive episodes. Rates of anxiety were significantly higher in our study than in previous research and could be reflective of our methodology in measuring anxiety prior to participant's first meeting with their oncologist. Anxiety related to cancer is typically experienced at high rates and

intensity until a treatment plan has been established. Once a treatment plan has been developed, some women experience a decline in state levels of anxiety.

As per the relation between psychiatric factors and components of pain, this study validates previous findings on a strong relationship between depression, anxiety, and pain within a cancer population. Furthermore, our study replicates findings from Sist et al. [17] indicating that depression is related to the affective dimension of pain within the cancer population. The current study findings expand on previous studies within the cancer population to demonstrate that anxiety and depression are differentially related to the affective and sensory components of pain.

As the current study did not assess for underlying medical conditions outside of cancer contributing to the pain experience, we cannot attribute pain solely to tumor burden or biopsy. Staging and cancer-related information is additionally necessary for helping to establish an etiology to the sensation component of the pain experience. Our correlational study provides preliminary findings to the relationship between different psychiatric conditions and different components of the pain experience. Although we cannot extrapolate to the underlying causality of the relation between psychiatric factors and cancer patients' pain experience, our study provides evidence for future longitudinal studies to examine the temporal course of pain, depression, and anxiety and coregulation of these factors across the continuum of cancer diagnosis, treatment, and survivorship. Future epidemiological, neuroimaging, and interventional research may be warranted to better understand these patterns and to determine optimal strategies to tailor interventions targeting anxiety, depression, and pain among breast cancer patients. Current study findings have implications for the treatment of pain within the breast cancer population. Clinicians should attend to the multidimensional nature of the pain experience and the high comorbidity between pain and anxiety and depression. Furthermore, in order to fully address and treat pain, clinicians should take a multidisciplinary and integrative approach attuned to sensory and affective components.

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Clinical Study

Prevalence of Chest Pain, Depression, Somatization, Anxiety, Global Distress, and Substance Use among Cardiac and Pulmonary Rehabilitation Patients

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Psychosocial factors of cardiovascular disease receive a preponderance of attention. Little attention is paid to psychosocial factors of pulmonary disease. This paper sought to describe psychosocial characteristics and to identify differences between cardiac and pulmonary patients entering a phase II rehabilitation program. Parametric and nonparametric analyses were conducted to examine scores on the Brief Symptom Inventory-18 (BSI-18) and the CAGE-D, administered at entry as standard clinical care. Participants were 163 cardiac and 63 pulmonary patients. Scores on the BSI-18 “chest pain” item indicated that more cardiac patients report chest pain than pulmonary patients. Among all subjects, chest pain ratings were positively related to anxiety, depression, and global distress. There were equivocal proportions of anxiety and somatization in patient groups. Pulmonary patients were more likely to endorse clinically significant levels of depression and global psychological distress than cardiac patients. Cardiac patients were significantly more likely to screen positively on the CAGE-D than pulmonary patients. Findings show a relationship between symptoms of chest pain and psychological distress. Despite equivalent proportions of anxiety and somatization between groups, a greater proportion of pulmonary patients reported symptoms of depression and global psychological distress, while more cardiac patients reported chest pain. Further research is needed to examine this paradigm.

1. Introduction

Cardiovascular disease (CVD) continues to be the most frequent cause of death worldwide, and close behind, chronic obstructive pulmonary disease (COPD) is estimated as the future third leading cause of death worldwide by 2030 [1]. A great deal of research exists related to behavioral and psychosocial variables in the pathogenesis and expression of CVD, as well as precipitating cardiac events [2, 3]; however, little information is available related to these variables in pulmonary disease.

Cardiac rehabilitation is a well-known, comprehensive, secondary prevention program that has been proven to

reduce morbidity and mortality and improve quality of life in patients with CVD [4–7]. Studies have also shown an even greater reduction in mortality in patients with high psychosocial stress or depression who have improved their physical fitness and/or completed a cardiac rehabilitation program, while also reducing psychosocial stress and depression prevalence [6, 8]. Participation in cardiac rehabilitation consistently yields improved lipid profiles, exercise capacity, physical fitness, health behaviors, and psychological outcomes in both younger and older cardiac patients [5, 6, 9–12].

The multidisciplinary secondary prevention program of cardiac rehabilitation, a model of integrative care, is applied

to other populations, including pulmonary patients, demonstrating to be an equally effective treatment. Cardiac and pulmonary diseases have several similar physical complaints (i.e., dyspnea, exercise intolerance, fluid retention, chest tightness, and heart palpitations), as well as psychosocial variables (i.e., depression, anxiety, substance use, somatization, social support, dietary choices, and level of patient education) that play a significant role in the etiology and course of both disease processes. However, pulmonary rehabilitation appears to be even more underutilized than cardiac rehabilitation [13, 14]. The research is also significantly less extensive, but demonstrates that pulmonary rehabilitation provides multiple benefits such as improving quality of life and exercise capacity and reducing dyspnea and symptoms of depression and anxiety [15–17].

Pulmonary patients who are referred to rehabilitative treatment are often provided with similar treatment and are often housed within or alongside a cardiac rehabilitation program. To our knowledge, there is no research that has explored similarities and differences of psychosocial variables in cardiac compared to pulmonary rehabilitation patients. Increased understanding of the different psychosocial strengths and challenges that cardiac and pulmonary patients face holds promise for identifying the unique needs of these patient populations and for the development of individualized treatment plans.

The current study sought to examine the psychosocial and behavioral characteristics in patients participating in cardiac and pulmonary rehabilitation programs. Given the similarities between cardiac and pulmonary patients, it was hypothesized that there would be no significant difference between self-reported symptoms of depression, anxiety, somatization, global distress, or substance abuse among cardiac and pulmonary patients.

2. Methods

In the present study, participants were patients initiating cardiac rehabilitation or pulmonary rehabilitation at a large academic medical center. As part of standard clinical care, patients were given various questionnaires regarding medical, psychosocial, and health behavior history. Patients complete their intake forms in a private waiting area while waiting for their initial consultation with a rehabilitation specialist. All patients used a web-based computer psychosocial screening system to complete the measures on-site at the facility. Rehabilitation staff was available to help patients log-in to the system and to assist with completion of the online questionnaires if necessary.

In this paper, we examined data obtained from the Brief Symptom Inventory-18 and the CAGE-D. IRB approval was obtained in order to report the data in aggregate for the purpose of this study.

2.1. The Brief Symptom Inventory-18 (BSI-18) [18]. The BSI-18 includes 18 symptoms; participants rate how much their level of distress over the past seven days using a five-point Likert scale (0 “not at all” to 4 “extremely”). It includes three subscales (depression, anxiety, somatic; range 0–24) and

a total score (range 0–72). Item number 4 (chest pain) loads on the somatic subscale. Higher scores indicate more distress. This measure has been validated with various community and medical samples [18].

2.2. CAGE Questionnaire [6]. CAGE is a mnemonic for assessing: cutting down, annoyance by criticism, guilty feeling, and eye-openers. The CAGE questionnaire was used to screen for substance use (CAGE-D) [6].

2.3. Planned Analyses. Descriptive statistics were used to describe the sociodemographic and psychosocial characteristics of the sample. Independent sample *t* tests or Pearson *r* chi-squared (χ^2) tests were conducted, depending on continuous or categorical variables, to examine whether there were differences between cardiac and pulmonary patients. For all analyses, significance was set at $\alpha = .05$.

3. Results

Completing the two screening questionnaires (BSI-18 and CAGE-D) were a total of 226 patients. There were 163 cardiac (M age = 61 ± 11 , 62% male and married) and 63 pulmonary (M age = 67 ± 12 , 59% male and 67% married) patients. There were significant differences between cardiac and pulmonary patients on sociodemographic variables. Cardiac patients were more likely to be male compared to pulmonary patients (61.8% versus 41.2%, $P = .04$), whereas pulmonary patients were more likely to be older than cardiac patients (M age = 61 ± 11 versus M age = 67 ± 12 , $P < .001$).

Examination of the endorsement of the “chest pain” item (Item number 4) on the BSI-18, demonstrated that 22.2% of cardiac patients reported moderate to severe pain compared to 14.6% of pulmonary patients. However, there was no significant difference in mean chest pain ratings between groups ($t(224) = 1.57$, $P = .12$). Among all subjects, chest pain intensity ratings were positively related to anxiety ($r(226) = .29$, $P < .001$), depression ($r(226) = .21$, $P = .002$), and global distress ($r(226) = .44$, $P < .0001$). Correlation was expected and does not exceed the collinearity cutoff of $r = .70$ [19].

No difference was found in the incidence of somatization between cardiac (19.7%) and pulmonary (21.1%) rehabilitation patients ($\chi^2 P = .08$), nor in the incidence of clinically significant anxiety (6.4% for cardiac patients; 8.9% for pulmonary patients; $\chi^2 P = .61$). However, pulmonary rehabilitation patients were significantly more likely to exceed the cut-off for clinically significant depression (15.6%) than cardiac patients (7.7%; $\chi^2 = 4.46$, $P = .03$), and for global psychological distress (17.8% for pulmonary patients; 9.4% for cardiac patients; $\chi^2 = 4.41$, $P = .03$). However, cardiac patients were significantly more likely to screen positively on the CAGE-D (13.8%) than pulmonary patients (5.4%; $\chi^2 = 4.62$, $P = .02$) for substance abuse.

4. Discussion

In the current sample of cardiac and pulmonary patients initiating a phase II rehabilitation program, symptoms of chest

pain were commonly reported. Ratings of pain as moderate to severe were more commonly endorsed by cardiac patients compared to pulmonary patients. There were not significant differences between cardiac and pulmonary patients on incidence of somatization or anxiety. This is notable in that chest pain is a commonly reported somatization and anxiety symptom. Also seen in these cardiac patients at entry into rehabilitation program, was a higher probability of substance abuse, as measured by the CAGE-D questionnaire compared to pulmonary patients. Pulmonary patients, however, were more likely to have clinically significant depression and global psychological distress than were cardiac patients.

Both patient populations reported similar amounts of physical complaints (somatization). Interestingly, many of the medical symptoms associated with chest pain in cardiac and pulmonary patients (e.g., shortness of breath, fatigue) are physiological symptoms that overlap with anxiety and depression. Given that both patient groups in this study reported similar levels of somatization, higher reports of physical pain by cardiac patients compared to pulmonary patients may reflect differences in how psychological distress manifest within these different patient samples. Increased report of chest pain in cardiac patients with anxiety is commonly seen as patients who become hypervigilant to their somatic symptoms, particularly those that may be construed as cardiac in origin [20, 21]. Current findings may also suggest that these cardiac patients are more likely to misuse substances as a means of coping with and reducing distressing physiological responses, such as cardiac and noncardiac chest pain.

Compared to the cardiac patients, these pulmonary patients, on the other hand, indicate that the distress symptoms they are experiencing are less related to physiological pain compared to cardiac patients. Given the higher probability of pulmonary patients endorsing depression and global psychological distress, it is critical to identify the specific psychosocial and somatic symptoms pulmonary patients express when experiencing psychological difficulties. Particularly highlighted in the current sample, patients' report of distress symptomatology is missed, under-recognized and -appreciated; and therefore, not treated adequately.

5. Limitations

The findings need to take into account several limitations, including the minimal number of data variables available for examination, and the cross-sectional, observational nature of the study, as the data was obtained as part of clinical care and not a formal research study. It would be advantageous for a future study to examine the comprehensive intake and exit data, as well as change in outcomes over time. The current sample was relatively homogenous, characterized largely by Caucasian, middle-aged and married patients. Accordingly, generalizability of findings may be somewhat limited.

6. Conclusion

Findings from the current study offer valuable insight into ways in which rehabilitative treatment can be tailored to

meet the unique needs of cardiac and pulmonary patients. While more is known about cardiac patients presenting to phase II rehabilitation programs, a considerable proportion of both cardiac and pulmonary patients present with an array of psychosocial, health behavior, and physical concerns such as depression, anxiety, pain, and substance use and misuse [22–24]. Differences between patient groups have both assessment and treatment implications.

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Research Article

Pain Narratives in Breast Cancer Survivors

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In-depth interviews were conducted with French breast cancer survivors 24 month after cancer diagnosis ($N = 21$ women). We documented their experience of chronic pain, compared their pain narratives with their answers to the WHOQOL-BREF questionnaire, and studied both the meaning they gave to their pain and how they dealt with it in their daily lives. Half of participants reported are suffering from iatrogenic chronic pain. Most of the time, this pain was not captured by the WHOQOL questionnaire and was not medically treated. Patients “normalized” their pain in various ways: they considered it either as a necessary step on the road to recovery, as the proof of treatment efficacy, or as a permanent condition one must learn to live with. They learned to deal with pain by taking precautions, giving up certain activities, and changing the way they performed others. Participants were also prone to compare themselves with other patients suffering worse pain. Breast cancer survivors should be better informed about chronic pain and how to alleviate it. Physicians should contribute to fighting pain-related beliefs which lead patients to conceal their pain. Techniques used by patients to cope with chronic pain in their daily lives should also be promoted.

1. Introduction

With about one million new cases in the world each year, breast cancer is the most common malignancy in women and comprises 18% of all female cancers [1]. In France, it accounts for 36% of all female cancers and its incidence is increasing sharply (+60% during the past 20 years), particularly among women aged 50–64 and probably because of improved breast cancer screening in this age group [2]. Moreover, progress in terms of screening, treatment, and care has contributed to improving the relative survival rate for this cancer (the 5 year survival rate after diagnosis is 82% in France) [3, 4]. In other words, in France as in other developed countries, an increasing number of women develop breast cancer, and among them an increasing proportion survive their cancer [5]. As a consequence, it is crucial to develop patient-based outcome measures for these women, such as quality of life (QoL). To our knowledge, most studies to date examining QoL in cancer survivors

have relied on psychometric instruments, and especially tools measuring general health-related QoL, such as the WHOQOL or SF36 [6–8].

Experiencing chronic pain provokes distress and fatigue; it also impairs appetite, sleep, mood, and the ability to perform many daily living tasks [9, 10]. Thus, chronic pain is a major determinant of QoL, especially among breast cancer patients [11–13], and psychometric scales measuring QoL routinely comprise pain assessment items. Pain is also one of the most common and most feared symptoms of cancer. Cancer pain may occur at any stage of the disease, generally depending on the type of tumor, the presence, and location of metastases and less frequently on cancer treatment [14, 15]. However, in the case of breast cancer, pain is almost always iatrogenic, due to postoperative complications, radiotherapy, or chemotherapy [16]. This specificity could be of some importance regarding breast cancer survivors' understanding of and attitudes toward the chronic pain many of them endure. For example, breast

cancer survivors' could be more likely to consider pain as a normal aspect of the recovery process, and giving such a meaning to their pain may affect the way they report it to either health professionals or professional interviewers.

The present paper used in-depth interviews conducted with breast cancer survivors participating in a cohort study. Its aims were two-fold. First, we documented patients' experience of chronic pain and how it affected their everyday lives. To do so, we compared in-depth interviews with results from the WHOQOL-BREF questionnaire regarding chronic pain and its impact on everyday activities. Second, in order to better understand the discrepancies revealed by this comparison, we focused on respondents' attitudes toward pain, especially in terms of how they gave meaning to it and how they dealt with it in their daily lives.

2. Materials and Methods

2.1. Participants. Participants were recruited among patients already enrolled in the cohort study ELLIPSE whose purpose was to investigate how breast cancer patients deal with posttreatment daily life. This cohort study focused on younger (aged 18–40) and older (aged 65 and over) women ($N = 1,200$; patients recruited in southeastern France). All cohort respondents completed the WHOQOL-BREF questionnaire 24 months after diagnosis.

The World Health Organization Quality of Life (WHOQOL) questionnaire is an international cross-culturally comparable quality of life assessment instrument [17, 18]. It assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards and concerns. This instrument has been widely field-tested. The WHOQOL-BREF is a shorter version of the original questionnaire. It comprises 26 items measuring physical health, psychological health, social relationships, and environment. We used it to compute summary scores for physical health (PHY) and psychological health (PSY) (for both scales, a higher score is an indication of better health). Questions related to physical health deal with activities of daily living, dependence on medication or medical aid, energy and fatigue, mobility, pain and discomfort, sleep, and rest, as well as work capacity. Questions related to psychological health deal with bodily image and appearance, negative/positive feelings, self-esteem, spirituality, thinking, learning, memory, and concentration.

Participants were not randomly selected. Instead, we used available data related to women already enrolled in the ELLIPSE cohort to select 21 women with contrasting ages (13 were aged between 26 and 43 and 8 were aged between 66 and 83) and contrasting PHY and PSY scores: 8 had scores significantly below the group average, 10 had scores well above the average, and 7 had average scores. A letter of information was sent to selected women asking them whether they would consider participating. A few days later, women were contacted by phone to introduce ourselves and to give further information about the study.

2.2. Data Collection. All contacted women agreed to participate. In-depth semistructured interviews were conducted in participants' homes. A short interview guide helped direct the conversation and interaction with the participants towards the discovery of the meaning they gave to their pain. The interview guide included the following themes: disease and treatment history, current health, experience of pain during the treatment phase, and in current daily life, relationship with health professionals. Interviews lasted between 1 and 4 hours. Interviews were tape-recorded with the patient's consent, transcribed verbatim, and observation notes were added. Any information which would identify a participant was removed to preserve anonymity and confidentiality (first names have been changed in quotations, *infra*). We used an inductive approach based on grounded theory [19, 20].

2.3. Data Analysis. Data were analyzed concurrently with data collection: the themes emerging from the first interviews helped to refine the interview guide used for the next set of interviews, these latter interviews in turn informing the next set and so on. The study's authors coded the transcripts independently and met to compare and discuss their codes. Finally, we undertook a second round of coding to condense our set of initial thematic codes into more abstract, second-line codes.

Regarding comparison with the WHOQOL-BREF questionnaire, we focused on the following items: QoL patient self-rating (how would you rate your quality of life? Very poor, poor, neither poor nor good, good, very good); activity limitation due to pain (how much do you feel that pain prevents you from doing what you need to do? Not at all, a little, a moderate amount, very much, a great deal); satisfaction in everyday activities (how satisfied are you with your ability to perform daily living activities? Very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied, very satisfied).

3. Results

3.1. Description of Participants. Table 1 provides some basic sociodemographic and medical characteristics of the 21 breast cancer survivors interviewed. Average PHY scores were higher among participants aged 26–43, although average PSY scores were similar for both younger and older women. Most women aged 26–43 were married (versus half of those aged 66–83) and working at the time of the survey (all the older women were retired). Concerning previous and current medical treatment, all participants had received chemotherapy (and only some of the younger women received taxane chemotherapy). All participants also received surgery: 15 had a partial mastectomy (lumpectomy), 6 had a total mastectomy, and 13 had axillary surgery. Breast reconstruction was more frequent among younger participants (9 out of 13 received it, versus 4 out of 8 among the older ones). At the time of the study, almost all women (18 out of 21) were on hormonal therapy (usually, aromatase inhibitors are

TABLE 1: Sociodemographic and medical characteristics of the 21 breast cancer survivors interviewed.

	Age	PHY	PSY	Marital status	Employment situation	Mastectomy	Reconstruction	Axillary surgery	On hormonotherapy at the time of the study
Stella	26	28	15	Single	Working	Partial	No	Yes	Yes
Cindy	26	24	16	Single	Working	Partial	No	No	Yes
Hannah	30	29	23	Married	Working	Partial	No	No	Yes
Emmy	31	31	24	Married	Sick leave	Partial	No	Yes	No
Megan	32	32	20	Married	Working	Partial	No	No	Yes
Helen	32	30	25	Married	Working	Partial	No	No	No
Nancy	33	21	8	Married	Working	Partial	Yes	Yes	Yes
Sue	40	34	29	Married	Working	Total	Yes	Yes	Yes
Silvia	41	27	22	Married	Working	Total	Yes	Yes	Yes
Kate	42	26	23	Married	Housewife	Total	Yes	Yes	Yes
Hillary	42	35	29	Married	Working	Partial	Yes	Yes	Yes
Laura	42	23	20	Married	Working	Total	Yes	Yes	Yes
Rachel	43	15	12	Single	Sick leave	Partial	No	Yes	No
Bree	66	29	23	Widow	Retired	Partial	No	No	Yes
Eva	68	21	11	Widow	Retired	Partial	Yes	No	Yes
Linda	68	26	23	Married	Retired	Partial	No	Yes	Yes
Mary	72	35	27	Married	Retired	Partial	No	No	Yes
Clara	75	15	17	Divorced	Retired	Total	No	Yes	Yes
Ella	75	26	23	Married	Retired	Partial	No	No	Yes
Sharon	78	24	20	Single	Retired	Partial	No	Yes	Yes
Susan	83	27	22	Married	Retired	Total	No	Yes	Yes

prescribed to old patients, while the younger ones receive tamoxifen).

3.2. Chronic Pain in the WHOQOL-BREF and In-Depth Interviews. Ten of the 21 participants reported daily chronic pain at the time of the survey (see Table 2). Reported chronic pain was breast cancer treatment-related, mainly due to post-operative complications (scar pain, arm lymphoedema) and hormone therapy side-effects (muscular and bone pain). In one case (Nancy), the pain resulted from the combination of treatment side-effects (when a tight scar became painful due to weight gain induced by hormonal therapy). Among these 10 participants reporting pain, only 5 were taking painkillers at the time of the interview (paracetamol, diclofenac—which is a nonsteroidal anti-inflammatory drug, and in one case trinitrin for chest pain). Pain hindered several participants from performing ordinary daily activities, such as lifting a pack of milk, holding a handbag, or going upstairs.

Despite their daily chronic pain, only 3 of the 10 women stated that their quality of life was “poor” or “very poor”. Only two felt “very much” that pain prevented them from doing what they need to do and only one was “not satisfied at all” with her ability to perform daily living activities. The case of Emily illustrated the typical discrepancy between responses to the WHOQOL-BREF items and discussions about one’s pain during in-depth interviews. She rated her QoL as “very good”, she felt only “a little” activity limitation due to pain, and she stated being satisfied with her ability to perform daily living activities. But during the in-depth interview, she reported always being out of breath since the completion of chemotherapy, and also being unable to ride a scooter, to raise her arms, or even to lift a pack of milk, because of her arm pain.

3.3. The Various Meanings of Pain. Participants reported contrasting experiences and attitudes toward pain, depending on how they perceived it. For some women who reported chronic arm and muscular pain, bearing this pain was considered as a necessary step in fighting their disease experience. They viewed pain as an ordeal they must go through to get cured. This meaning justified the absence of painkillers:

It was a battle between me and the pain. I wanted to win without cheating. It is an on-going fight, make no mistake! That’s why there are people who escape and others who cannot. (Nancy)

Conversely, other women reported that they did not have to suffer since they already felt cured of their cancer:

I consider that I am healed; so I do not need to feel pain... (...). . .To be down-to-earth about it, I am sick, I am operated on, I am healed and it’s over. And if I am cured I do not really have any reason to feel pain. (Hillary)

Participants’ attitudes toward pain and pain management also depended on whether they believed pain was transitory and destined to disappear, or whether they considered it as

a new and permanent condition. In the latter case, it was found that some women refused painkillers because they did not want to take them for the rest of their lives:

[Do you feel pain all the time?] Oh yes, it’s a pain that doesn’t go away! We must learn to live with it. Then it becomes almost normal. I feel pain, it’s that simple. That doesn’t change. (Emmy)

[Is the pain going to disappear?] No, I don’t know, I don’t think so. I was operated on two years ago. If it was going to disappear, I think it would already be gone, the pain. [And your doctor, what did he say to you about your pain?] He prescribed me physical therapy. Anyway, I won’t take drugs. [But he proposed them to you?] Yes, certainly, I don’t know. He probably gave me a prescription but I didn’t get the drugs. I don’t need medication. I must learn to live with pain. Because I don’t want to take drugs forever. (Bree)

[Do you take drugs for relief?] No. I’ve had enough of drugs. No, I don’t take anything. Nothing at all. [Not even to relieve the pain in your arm?] No, do-not-want-anything-at-all. I do not want drugs. [You’ve taken too much?] Yes. Yes. But I mean... otherwise, I would always be in the process of swallowing drugs. Because pain is permanent, so drugs are useless. (Sharon)

Pain was often perceived as a normal phenomenon even after the end of breast cancer treatment. For some women, pain meant that the healing process was running its course. In that case, pain indicated that the treatment was working well, although some women remained cautious since they believed that pain could also indicate a relapse.

There was nothing we could do, the pain was so intense... Because the cells in my spinal cord are reactivating... So I’ve got pain in my back, in my pelvis, in places where the cells are being renewed... [Do you feel that pain was a good sign?] Yes it was proof that everything was reactivated, it was being renewed. (Stella)

In some cases, the normalization of pain was also fuelled by talks with physicians:

[The last time you saw the doctors, did you tell them that you feel pain?] Oh yes, yes, they told me it was normal. They said this was normal. They told me: this is not a small operation you had. [Do you think it’s normal to feel pain in your case?] If I am told that it’s normal, I believe what I’m told. (Eva)

[Does your breast hurt you?] Yes it hurts me. It hurts me a lot. [And to relieve the pain, what can you do?] Nothing. [Have you told your doctor?] Sure, he said it’s normal. In the end I wonder, as I have pain everywhere, maybe breast

TABLE 2: WHOQOL-BREF items, pain management, and pain narratives.

	QoL self-rating	Feeling activity limitation due to pain	Satisfaction in everyday activities	Pain management	Pain-related quotations from in-depth interviews
Clara	Neither... ¹	Very much	Neither... ²	Paracetamol	My scar hurts ... I have also shooting pains in the arm, I can't lift it.
Ella	Good	A little	Neither... ²	Diclofenac	I'm dripping with sweat ... I've lost my appetite ... and the pain starts every morning at 7 A.M.
Nancy	Very poor	A little	Neither... ²	None	My scar hurts all the time, especially when the weather is hot ... The scar was done too tight and it hurts a lot because I put on weight due to my pills.
Eva	Poor	Not at all	Satisfied	Diclofenac, paracetamol	I have a hematoma since breast reconstruction ... it has been hurting for six months now ... I'm tired as soon as I wake up and I feel aching in my entire body, especially the bones.
Linda	Good	Not at all	Neither... ²	Trinitrin	My breastbone hurts a lot ... sometimes my chest feels like it has a huge weight on it and I suffocate ... I can't sleep.
Emmy	Very good	A little	Satisfied	None	I'm always out of breath because of the chemotherapy, it's weakened my heart ... I'm 31 and I can't ride a scooter, I can't raise my arms ... I can't lift a pack of milk, it's too painful.
Stella	Good	Moderate	Satisfied	None	My arm has been hurting since the surgery ... especially in the morning ... and sometimes my breast also hurts. Before my cancer I used to blow dry 20 clients' hair every day, but now after 4 or 5 I must stop because my arm hurts too much ... today I can't even hold my handbag ... sometimes I've got shooting pains in my breast, like a stab from a knife.
Cindy	Poor	Moderate	Satisfied	None	
Rachel	Neither... ¹	Very much	Not satisfied at all	Paracetamol	I can't go upstairs, my ankles swell ... If I lift something my arm starts hurting and swelling the day after.
Silvia	Good	Moderate	Satisfied	None	Because of the pills I take I have muscular pain, like cramps, especially in the back and the arm.

1: Neither poor nor good.

2: Neither satisfied nor dissatisfied.

pain is normal? Given that I feel pain in my hands, because I have osteoarthritis... It must be part of a more generalized pain. (Linda)

Some participants reported having told their physicians that they were suffering pain and they were sent to a psychiatrist because pain was viewed as a kind of depressive symptoms.

[Did you consult a physician for pain?] Oh yes, I saw an algo... [An algologist?] Yes. Very nice indeed. They sent me to a psychiatrist because they said that it was all in my head, that it was my mind that wasn't working. But for six months I was in terrible, terrible, terrible pain. Here and here, look. So I quickly phoned my doctor. He said "no", you know, "you should not have pain there". And even now, occasionally, I feel such pain. (Eva)

Such "psychiatrization" of pain made women feel impotent and guilty because it implied that their pain was not "real". Moreover, some participants clearly lacked information about pain. For example, one of them suffered from phantom pain but was never told about such a condition, or at least did not remember being told about it:

I had the feeling of having a breast for quite some time, like when one loses a member, I felt pain when I had nothing. And it is psychological, is not it? I felt it was still there and it was hurting me. [Yes, it is called "phantom pain", the doctors did not mention it?] No. (Nancy)

3.4. *Dealing with Pain in Daily Life.* Before considering behavioral adaptation to chronic pain, it is important to mention that women's psychological adaptation was based on "relativization". All participants were prone to compare their medical condition, and their pain in particular, with other patients' medical conditions and pains. Some women compared themselves with other patients who had been severely burned by radiotherapy and suffered more than them. Others compared themselves with a relative or a friend suffering from a more painful cancer. Older women also tended to compare their then current chronic pain with other pains endured during their lives, for example, childbirth pain. Sometimes physicians encouraged such "relativization", for example, by invoking the case of leukemic children.

When I saw myself in this state I thought: there are some people who are worse off. So then I told myself: I have no right to complain. Even now it is one of the principles that govern my life. There is always someone worse off than yourself. There are those who do not have the chance to live. (Stella)

I prefer to be like this rather than in a wheelchair. There are some who are more unfortunate than me. Not thinking only about myself comforts me. (Mary)

My boyfriend's situation is worse than mine, he had mouth cancer. They ripped out all his teeth and now he has a special apparatus because he cannot eat, he can't chew, he must suffer a lot. (Eva)

How was the radiotherapy? Oh it was... I wasn't burned too much, I had severe rubeosis, I peeled a little but, well... compared to others I feel very happy. (Linda)

Yes, there are difficult moments. But you see, I had two small pupils who had leukemia. We went to visit them at the hospital with my husband, and then unfortunately, one passed away. She was 9 years old. And seeing all these little children, with these large perfusions... You know, when I start to complain about my pain, I think about her... And I feel I have no right to complain. (Linda)

There is a doctor who told me "you know, if you feel pain, madam, take a short tour of accident and emergency and you'll see, you will immediately get better". He said "go and see a few kids at A&E, you'll stop complaining all the time"... I was so shocked that I never returned to that hospital. (Nancy)

Women get used to suffering when they give birth, all these things, right? I think a woman is more tolerant of pain than a man. This has been proved. Because more than once my husband said to me: what you've been through, I couldn't have ever borne. (Nancy)

But daily adaptation to chronic pain was also very concrete. Many women gave up some domestic or leisure activities because they could no longer perform them. They also learned to take some precautions, or to carry out some actions differently in less painful ways. In all, daily adaptation to chronic pain was seen as a painful, self-taught, and learning-by-doing process.

[What kind of domestic activities did you stop doing because of pain?] Cleaning, ironing, washing the windows of course, and I can't drive on long trips. I have to put a ball on the steering wheel so I don't force my muscles. (Nancy)

When I do a little unusual movement that doesn't go in the direction of the muscle, I get blocked, it's a pain that paralyzes me. So sometimes I'm stuck, and I must wait until the muscle relaxes and then I feel better. (Cindy)

With my arms I cannot do anything, I can do absolutely nothing. I always have a small paper in my purse that says that if I have an accident, nothing should be done to this arm. (Eva)

You know, I learned to change some of my movements. I learned movements that relieve. Instead of wringing the kitchen glove like that, now I wring it like this, against the side of the sink. (Linda)

Trying to avoid feeling pain is really important in every day movements. In my case it is primarily the hands, it's really a problem. At first I tried to forget the pain, but it quickly brought me back to reality. So pain forced me to think. Especially about some very ordinary movements. For example, now, I've got used to holding my cup with both hands. (Linda)

4. Discussion

Before discussing our results, some limitations of the present study must be acknowledged. First, we only interviewed a small sample of women, in two specific age ranges, 24 months after diagnosis, and within a region-based cohort of breast cancer survivors. As a consequence, our results, and especially the prevalence of posttreatment chronic pain, should not be generalized to the wider population, or to other cancers. Secondly, we only interviewed patients, not their physicians: pain narratives should be compared with what physicians' have to say, especially concerning the therapeutic relationship. Third, the aim of the study was not to call the validity of the WHOQOL-BREF questionnaire into question. This psychometric tool is not designed to assess cancer pain, unlike other cancer-specific questionnaires. Our aim was rather to illustrate the relative invisibility of chronic pain when a routinely QoL assessment tool is used.

Iatrogenic pain endured by cancer survivors used to be viewed as a relatively unimportant and unavoidable side-effect of necessary life-saving treatments [21]. Even though this perception is changing, our results were in line with previous findings that pointed out that such pain is still frequently underestimated since it remains frequently hidden by patients and is neglected by healthcare professionals [22–24]. Of course, it is difficult to share one's pain experience, especially using a closed-ended questionnaire: respondents answering questions in pain surveys frequently write unsolicited comments on the margins of questionnaires [25].

Previous studies showed that cancer patients tend to believe that pain is inevitable [24, 26], and to equate chemotherapy toxicity with its efficacy [27, 28]. Our results broaden these conclusions to other treatments side-effects, and to patients who had undergone surgery and had completed chemotherapy and/or radiotherapy. For example, a previous qualitative study conducted in the early 1990s in the Netherlands among surgical breast cancer patients found that many of them concealed their postoperative pain and did not ask for pain medication [29]. Such inhibition in reporting pain was due to several factors related to both patients and nurses: many patients believed that postoperative pain was inevitable, they did not want to become used to taking painkillers, and nurses fuelled their belief by suggesting that such pain was normal and did not require alleviation. Nearly two decades later, we find similar

results in France. But our results suggest that physicians, and not only nurses, are also involved in the “normalization” of pain. More importantly, we found that this process of pain “normalization” and the resulting under-treatment of pain continue long after hospitalization.

In addition, this process of pain normalization appeared to be fuelled by very contrasting ways in which patients give meaning to their pain: pain could be considered as a transient condition, a necessary step toward recovery, a proof that the treatment is effective, or on the contrary it can be viewed as a permanent condition people have to get accustomed to. Moreover, our results suggest that physicians did not provide enough information concerning pain, and sometimes might even fuel inadequate pain-related beliefs, instead of fighting them. This is of great significance especially in view of the importance of the doctor-patient relationship in shaping patient beliefs toward pain and pain management [26].

5. Conclusions

During in-depth interviews, half the participants reported significant chronic pain remaining 24 months after breast cancer diagnosis. Most of the time, this pain was not captured by the WHOQOL questionnaire, and it continued without medical care. Pain was “normalized” in various ways which contributed to preventing such care being given: it was considered either as a necessary step on the road to recovery, as a permanent condition one must learn to live with, as the sign that completed medical treatments are working or as a depressive symptom. All participants had the tendency to put their pain into perspective, comparing themselves with other patients suffering worse pain. They also learned to deal with pain in their daily lives, by taking precautions, giving up some activities, and changing the way they performed certain normal physical movements.

Breast cancer survivors should be better informed about chronic pain and the ways to alleviate it. Physicians should be involved in this process, and they should also contribute to fighting pain-related beliefs which lead some patients to hide their pain. Finally, apart from pharmacological pain management, techniques to cope with chronic pain in daily lives should be promoted.

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Research Article

Presurgical Weight Is Associated with Pain, Functional Impairment, and Anxiety among Gastric Bypass Surgery Patients

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Chronic pain and obesity are significant public health concerns in the United States associated with significant levels of health-care expenses and lost productivity. Previous research suggests that obesity is a risk factor for chronic pain, mainly due to excessive weight placed on the joints. However, the obesity-pain relationship appears to be complex and reciprocal. Little work to date has focused on the relationship between weight and pain among patients undergoing gastric bypass surgery for weight loss. Patients scheduled to undergo bariatric surgery for weight loss at a large southeastern academic medical center ($N = 115$) completed the Brief Pain Inventory (BPI), the Center for Epidemiological Studies 10-item Depression scale (CESD-10), and the Beck Anxiety Inventory (BAI). Higher presurgical weight was associated with higher pain-on-average ratings, higher functional impairment due to pain across the domains of physical activity, mood, walking ability, relationships, and enjoyment of life. Higher presurgical weight was associated with higher BAI scores, but weight was not related to depression. Findings suggest that bariatric surgery candidates report a moderate amount of pain prior to surgery and that presurgical weight is associated with higher pain, increased functional impairment due to pain, and increased anxiety. Anxiety was found to mediate the relationship between increased weight and pain.

1. Introduction

Chronic pain and obesity are significant public health concerns in the United States, with costs related to obesity estimated to be at \$118 billion annually, and chronic pain is associated with \$70 billion a year in health-care expenses and lost productivity. While an obesity-pain relationship would seem quite apparent, only recently has the obesity-pain association been confirmed in a large-scale population based study [1].

Previous research suggests that obesity is a risk factor for chronic pain, mainly due to excessive weight placed on the joints. One such study examined the relationship between body mass index (BMI) and reports of significant knee, hip, and back pain in a large sample of older adults. They found that reported pain increased with higher BMIs for all types of pain measured [2]. However, the pain-obesity relationship extends beyond the lower extremity joints. In another large-scale study using Southern Pain Prevalence

Study data a linear relationship between higher weight and reported severe pain occurring at least monthly was found [3]. While pain was more frequently reported in the lower limbs, moderate to severe pain was also more frequently reported in other parts of the body. They found that as BMI increased, there was a significant increase in the total number of locations of pain reported. These authors suggest a reciprocal relation between pain and obesity.

Rai and Sandell [4] reviewed the relationship between osteoarthritis and obesity, particularly in nonweight-bearing joints. Their review highlights that adipose tissues are a major source of cytokines, chemokines, and metabolically active mediators associated with inflammation. These metabolic factors seem related to both the initiation and progression of osteoarthritis thus, both biomechanical and biochemical factors contribute to pain.

Behavioral and emotional factors may also play a role in obesity and pain. Depressed people are often sedentary, which is associated with obesity and may exacerbate chronic

pain. In a recent longitudinal study, a reciprocal link between depression and obesity was found [5] with obesity increasing the risk of depression and depression predicting the development of obesity. Anxiety is often characterized by avoidance behaviors, including restricting life activities. A recent meta-analysis by Garipey et al. [6] found a positive association between obesity and anxiety in adults. The association was stronger between severe obesity (BMI ≥ 35) and anxiety than for moderate obesity (BMI = 30–35).

Increasingly, bariatric surgery is being considered as a treatment option for severe obesity. Little work to date has focused on the relationship between weight and pain among patients undergoing gastric bypass surgery for weight loss. Three studies have looked at musculoskeletal pain located in the lower extremities and lumbar spine in bariatric surgery populations. They have all found improvement in reported pain following weight loss [7–9]. One study evaluated pain at both weight-bearing and nonweight-bearing musculoskeletal sites both before and then 6–12 months post weight loss surgery [10]. These results were then compared to historical controls. Findings indicated significant improvement of symptoms across all sites with change in BMI the primary factor impacting reported pain. However, these studies have not addressed the larger impact of pain on emotional and physical functioning including functional impairments. It is well established that pain consists of sensory, affective, and cognitive components. These components interact to contribute to emotional and functional impairments.

The present study sought to investigate relations between weight, pain, functional impairment, depression, and anxiety in patients undergoing consideration for bariatric surgery. The primary aim was to better characterize the psychosocial impact of pain on this specific population.

2. Methods

One hundred and fifteen patients scheduled to undergo weight loss surgery at a large southeastern academic medical center completed the Brief Pain Inventory (BPI), the Center for Epidemiological Studies 10-item Depression scale (CESD-10), and the Beck Anxiety Inventory (BAI) at the time of their presurgical psychosocial evaluation. Participants were weighed at their clinic visit by the bariatric surgery team prior to surgery.

Data were collected as part of routine clinical care and IRB approval was attained in order to report the data in aggregate for the purposes of this study.

2.1. Measures. The BPI is a 15-item self-report questionnaire, which assesses pain severity and the impact of pain on daily functioning [11]. Each item is ranked from 0–10. The three dimensions of pain severity assessed during the last 24 hours are the worst pain, average pain, and current pain (0 = no pain to 10 = pain as bad as you can imagine). Pain interference items include sleep, work, walking ability, and enjoyment of life (0 = does not interfere to 10 = completely interferes). The BPI has been widely used to assess chronic pain across a variety of conditions, including low back pain [12, 13], arthritis [13], neuropathy

[14], and fibromyalgia [15]. Good reliability (coefficient $\alpha > 0.70$) and validity have been demonstrated across multiple pain conditions [13].

The CESD-10 is a 10-item self-report questionnaire, ranging from 0–30, which assesses symptoms of depression, including depressed mood, happiness, and lethargy [16]. Any score ≥ 10 is considered clinically significant. The CESD-10 demonstrates good convergent validity (e.g., negative correlation with positive affect and positive correlation with poor health) and test-retest reliability. It has previously been used in a number of studies that looked at the relationship between obesity and depression [17, 18]. In this study the CESD-10 was found to be a highly reliable measure ($\alpha = .75$).

The BAI is a 21-item self-report questionnaire used for measuring the severity of an individual's anxiety. It assesses common symptoms of anxiety experienced over the past week, including numbness and tingling, shortness of breath, and fear of the worst happening. Items are ranked on a 4-point scale for a maximum total score of 63. Scores are grouped into minimal (0–7), mild (8–15), moderate (16–25), and severe (26–63) levels of anxiety. Symptoms can be grouped into two groups of somatic and cognitive complaints. The BAI is widely used for assessing clinical anxiety with demonstrated robust psychometric properties [19]. In this study it was found to be a highly reliable measure ($\alpha = .89$).

2.2. Data Analyses. Descriptive statistics were calculated for all study variables. Correlational analyses were utilized to examine relations between main study variables of weight and pain, physical activity, mood, walking ability, relationship impairment, enjoyment of life, anxiety, and depression. Theoretically, anxiety and depression are highly related constructs. As such, separate analyses examined the relation between mental health variables, weight, and pain using simultaneous multiple regression models. These models were utilized to examine the predictive relationship between weight, anxiety, depression, and pain on average after accounting for covariates of age and gender. Last, post hoc analyses utilizing Baron and Kenny's [20] four-step approach tested anxiety as a mediator of the relation between weight and pain.

3. Results

Eighty percent of the sample was female, 63% was Caucasian (37% African American) with a mean age of 46.6 (SD = 12.7). The mean of the pain-on-average ratings from the BPI was 4.7 (SD = 2.7), the mean of the CESD-10 scores was 7.0 (SD = 4.7) and the mean of the BAI scores was 7.6 (SD = 8.1). The average BMI of the sample was 50.7 (SD = 11.6) and the mean presurgical weight was 310.2 (SD = 76) pounds. Table 1 presents means, standard deviations, and ranges of the main study variables.

One item from the pain severity dimension on the BPI was selected (pain on average) along with five pain interference items thought to be most relevant to the multidimensional experience of pain. Correlational analyses were run between weight and the selected items (see Table 2).

TABLE 1: Means, standard deviations, and ranges of main study variables.

	M (SD)	Range
Age	46.6 (12.7)	16–71
Weight (lbs)	310.2 (76)	187–608
Pain on average	4.7 (2.7)	0–10
Interference general activity	4.4 (3.5)	0–10
Interference mood	3.7 (3.4)	0–10
Interference walking ability	5.0 (3.5)	0–10
Interference relationships	2.7 (3.0)	0–10
Interference enjoyment of life	4.5 (3.6)	0–10
Depression	7.0 (4.7)	0–21
Anxiety	7.6 (8.1)	0–45

TABLE 2: Relation between presurgical weight and pain and psychosocial factors.

	β value	<i>P</i> value
Pain on average	.23	0.02
Physical activity	.19	0.04
Mood	.19	0.05
Walking ability	.26	0.005
Relationship impairment	.23	0.02
Enjoyment of life	.29	0.002
BAI	.22	0.05
CESD-10	-.09	0.39

Higher presurgical weight was associated with higher pain-on-average ratings ($r(108) = .23, P = 0.02$), higher functional impairment due to pain across the domains of physical activity ($r(114) = .19, P = 0.04$), mood ($r(113) = .19, P = 0.05$), walking ability ($r(114) = .26, P = 0.005$), relationships ($r(115) = .23, P = 0.02$), and enjoyment of life ($r(115) = .29, P = 0.002$). Higher presurgical weight was associated with higher BAI scores ($r(82) = .22, P = 0.05$), but weight was not related to depression ($r(87) = -.09, P = 0.39$).

Simultaneous multiple regressions were then used to evaluate the relation between pain, weight, depression, and anxiety. First the relation between the independent variables weight and the dependent variable pain was examined. Age and gender served as covariates. The independent variable and covariates were entered into the regression at the same time in order to examine the unique predictive variance above all other variables. Table 3 displays the results for the simultaneous regression for weight predicting pain on average after accounting for covariates age and gender. Increased weight was related to higher levels of pain even after accounting for variance explained by age and gender.

Second, the relation between the independent variables weight and depression and the dependent variable pain was examined. Age and gender served as covariates. Table 4 displays the results for the simultaneous regression for weight and depression predicting variance in average pain after accounting for gender and age. Both weight and depression were independently significant predictors of pain

TABLE 3: Weight predicting pain. Model: simultaneous regression predicting brief pain inventory average pain.

	β	<i>b</i>	SE	<i>P</i> value
Age	.26	.05	.02	0.008
Gender	.10	.69	.69	0.32
Weight	.33	.01	.00	0.002

Model $R^2 = .12$.

TABLE 4: Weight and depression predicting pain. Model: simultaneous regression predicting brief pain inventory average pain.

	β	<i>b</i>	SE	<i>P</i> value
Age	.23	.05	.02	0.05
Gender	.09	.78	.96	0.42
Weight	.32	.01	.00	0.007
CESD-10	.41	.24	.07	0.000

Model $R^2 = .25$.

TABLE 5: Weight and anxiety predicting pain. Model: simultaneous regression predicting brief pain inventory average pain.

	β	<i>b</i>	SE	<i>P</i> value
Age	.19	.04	.03	0.14
Gender	.01	.08	.99	0.94
Weight	.19	.00	.00	0.16
BAI	.33	.11	.04	0.01

Model $R^2 = .20$.

after accounting for gender and age such that increased levels of depression and weight were related to increased pain.

Finally, the relation between the independent variables weight and anxiety and the dependent variable pain was examined. Age and gender served as covariates. Table 5 displays the results for the simultaneous regression for weight and anxiety predicting variance in average pain after accounting for gender and age. Anxiety was a significant predictor of pain after accounting for gender and age such that increased levels of anxiety were related to increased pain. Weight no longer significantly predicted pain on average after accounting for the relation between anxiety and pain; consequently, anxiety serves as a full mediator of the relation between weight and pain (note: all conditions of mediation were met as weight was a significant predictor of pain).

As Figure 1 illustrates, the standardized regression coefficient between weight and pain was nonsignificant when controlling for anxiety.

4. Discussion

This study examined the roles of psychosocial factors in the association between weight and pain. Similarly to previously published findings, higher presurgical weight was associated with higher pain-on-average ratings in this sample of bariatric surgery candidates. In addition, higher presurgical weight was associated with increased functional impairment due to pain across multiple domains including physical activity, mood, walking ability, relationships, and enjoyment of life. Of interest, the strongest associations were

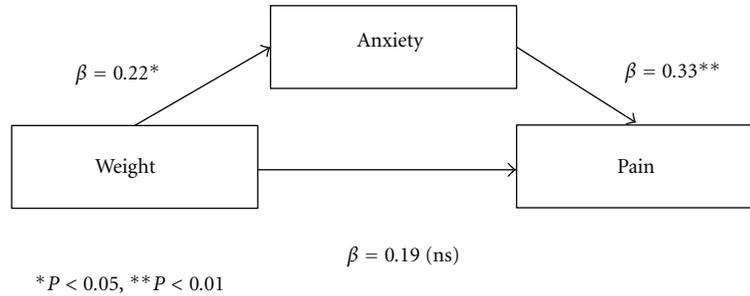


FIGURE 1: Path diagram with anxiety as mediator of weight and pain.

found between higher presurgical weight and difficulties in walking ability and enjoyment of life suggesting functional limitations affect both physical and emotional functioning. Bariatric patients often cite functional limitations as a motivating factor in seeking surgery.

This raises some important clinical implications. Impairment in walking ability may directly impact lifestyle recommendations commonly provided patients including increasing activity levels and regular exercise. This is an area that may require special attention from health care providers who assist patients with behavioral changes as pain while walking may present a specific barrier to increasing activity levels.

Further, health care providers may want to more specifically target increasing enjoyable life activities in this patient population as there may be benefits for both pain and the psychosocial concomitants of pain. As previously stated, emotional and behavioral factors play a key role in the chronic conditions of both pain and obesity.

Little research to date has been done exploring functional impairment due to pain before and after weight loss surgery. Future studies are needed to better determine the most common etiologies of presurgical pain and to determine whether postsurgical weight loss is associated with significant improvement in pain and functional impairment.

A number of studies have explored the relation between obesity and depression. This study found that both increased weight and depression independently predicted pain. This finding supports the direct effect of both weight and depression on the experience of pain. An unexpected finding from the current study was the association of higher weight with anxiety, but not with depression. This is surprising as depression is a common comorbidity in patients seeking weight loss surgery [21]. However, this population was already restricted to an obese population and thus there may have not been enough weight variation in the sample to see an effect.

Anxiety in obesity has been much less studied and reported in the literature. A recent study evaluated bariatric patients for depression and anxiety prior to surgery as well as 6–12 months and 24–36 months postoperatively. They found a significant decrease in point prevalence of depressive disorders but not for anxiety disorders after surgery [22]. This suggests that anxiety plays a unique role in lives of an obese population that may persist even after weight loss.

This study found that anxiety was predictive of pain. In fact, unlike depression and weight, which were found

to be independent predictors of pain, weight no longer predicted pain after accounting for the relation between anxiety and pain. Findings indicate that anxiety serves as a full mediator of the relation between weight and pain. This suggests that anxiety has a unique contribution to the obesity and pain relationship in that it exerts a significant indirect effect between weight and pain. As previously noted, anxiety is often accompanied by avoidance behaviors. In addition, pain frequently interferes with life activities. Further studies are needed to explore this unique relation and the effects of anxiety on functioning in obese patients. Findings also suggest that clinicians may want to more carefully evaluate anxiety in presurgical patients, particularly as it relates to pain and functioning.

Anxiety in an obese population presents some unique implications. Obesity is associated with a variety of somatic complaints including shortness of breath, heart palpitations, and sweating which are similarly present in anxiety. In addition, obese individuals often complain of social discomfort and associated anxiety related to perceived negative judgment from others. The BAI was designed to measure both somatic and cognitive symptoms of anxiety. Further studies are needed to more clearly characterize the nature of anxiety in an obese population and more specifically in bariatric surgery candidates.

One limitation of this study is that the etiology of pain was unknown as was whether the pain was present before obesity or vice versa. Previous studies have indicated a bidirectional influence between obesity and pain [3]. Further, no postsurgical data is yet available to evaluate the impact of weight loss on pain and functioning. Pain and obesity commonly cooccur and as yet remain a relatively little studied area. More studies are needed in order to understand and treat these common and significant health concerns to include the impact on functioning and psychosocial factors.

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Research Article

Physical, Cognitive, and Psychosocial Predictors of Functional Disability and Health-Related Quality of Life in Adolescents with Neurofibromatosis-1

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Objective. To examine physical, cognitive, and social-emotional predictors of quality of life (HRQOL) and functional disability (FD) in adolescents diagnosed with Neurofibromatosis-1. *Methods.* Participants were twenty-seven adolescents with a diagnosis of NF-1 who were recruited through an NF-1 specialty clinic at a large Midwestern children's hospital. Measurements of the adolescents' cognitive functioning, pain, FD, HRQOL, and social and emotional functioning were obtained with corresponding parent measures. *Results.* Emotional functioning significantly predicted youth-reported and parent-reported HRQOL, whereas days of pain significantly predicted youth-reported FD. *Conclusions.* NF-1 is a complex disease. Measurements of the overall impact of the disease tap into different aspects of the effects of NF-1 on daily life. Global outcomes such as HRQOL appear to be influenced especially by emotional functioning, whereas outcomes such as FD appear to be influenced by the physical/organic aspects of NF-1.

1. Introduction

Neurofibromatosis-1 (NF-1) is one of the most common autosomal dominant disorders affecting the nervous system [1] and occurs in approximately 1 in 4000 individuals [2]. NF-1 occurs equally in all racial and ethnic groups and is best characterized by the presence of skin-pigment abnormalities called café-au-lait spots and the development of benign tumors on or underneath the skin [1]. NF-1 is the result of a mutation on chromosome 17 that is either inherited by an affected parent or occurs as a random genetic mutation during development [1]. While the genetic origin is known, NF-1 is generally diagnosed based on the presence of physical symptoms rather than genetic testing [3].

The physical symptoms of NF-1 can greatly alter quality of life. For example, plexiform neurofibromas may impact movement and focal scoliosis often requires corrective

surgery. Pain has been examined as a possible consequence of NF-1 and has been linked with impaired quality of life in this population. Chrusciel and colleagues [4] reported that pain was common in children with NF-1, with 77% of their sample reporting pain associated with lower self-reported quality of life. In adults with NF-1, the literature suggests that headache pain is the predominant form of pain experienced by youth with NF-1; however, the prevalence rates are mixed. Créange and colleagues [5] found that headaches were reported by 18% of patients and it was the predominant complaint in 11%. Clementi et al. [6] reported rates of headaches around 30%, while DiMario and Langshur [7] reported significantly higher rates of 61% that interfered with daily activities.

In addition to physical limitations, individuals with NF-1 experience difficulties cognitively, socially, and emotionally. Cognitive impairment is considered the most common

neurologic complication of NF-1 in childhood [8]. Intellectual functioning is significantly lower in patients with NF-1 than in typically developing children; however, the degree of impairment is generally mild [9–11]. Additionally, previous research has shown incidence rates of learning disabilities (LDs) in children with NF-1 to range from 30% to 65% and incidence rates of attention deficit hyperactivity disorder (ADHD) to be as high as 50% [8, 11]. Difficulties in visuospatial skills, attention, executive functioning, and expressive and receptive language are also more common in youth with NF-1 [11, 12].

Children with NF-1 may also experience difficulties in their social and emotional functioning. Parent, teacher, peer, and self-reports of social functioning indicate that children with NF-1 experience significantly poorer social and emotional outcomes than their unaffected siblings and other normative comparison groups [13–15]. Children with NF-1 with greater attention difficulties also tend to show more social difficulties [13].

With such wide-ranging symptoms, it is reasonable to expect that adolescents with NF-1 may experience significant difficulties across life domains. Two common measures for the impact of disease on functioning are health-related quality of life (HRQOL) and functional disability (FD). Although related, these distinct constructs have disparate functions related to diagnosis, treatment, and the overall impact of disease [16]. HRQOL is defined as the impact of a disease or condition on physical health status, psychological and social functioning, and emotional well-being [17, 18]. In contrast, FD is the degree of impairment someone experiences due to an illness or medical condition [19]. The importance of examining these constructs independently has been demonstrated in the field of pediatric chronic pain [20, 21], with researchers stating that each adds unique outcome information.

Research about the general impact of NF-1 has been limited. French adults with NF-1 reported impaired HRQOL in both emotional and physical functioning [22]. Youth with NF-1 and their parents have reported significantly lower rates of motor, social, cognitive, and emotional functioning compared to healthy youth [23–28]. These parents also reported higher rates of internalizing and externalizing behavioral problems in their children compared to parents of healthy youth. Currently, no published studies have been reported on FD in youth with NF-1. In one study with adults with NF-1 [5], life-threatening complications were categorized according to their related FD, but degree of impairment was not specifically assessed. It is critical that we better understand factors related to functioning in youth with NF-1.

The goal of the current study is to independently examine the constructs of quality of life and functional disability in youth with NF-1. This research will provide a thorough description of the impact of NF-1 on physical, cognitive, and psychosocial functioning and seek to identify factors of this illness that predict difficulties in functioning that warrant further examination and intervention. With this information, healthcare professionals will be able to target

specific domains when working with families having a child with NF-1 to help improve their overall functioning.

At the descriptive level, it is hypothesized that the adolescents with NF-1 in this sample will display a large degree of symptom variability and will report higher FD and lower HRQOL than expected based on a healthy normative sample. It is anticipated that aspects of physical, cognitive, and socioemotional functioning will significantly predict HRQOL and FD but that the specific predictors of HRQOL and FD will differ. It is expected that the more specific measure of FD will be predicted by cognitive and physical variables (i.e., cognitive functioning, days of pain), whereas the more global measure of HRQOL will be primarily influenced by social and emotional factors.

In summary, NF-1 is a disorder with a large degree of variability in clinical presentation and severity. Lower FD, physical symptoms, cognitive difficulties, and social and emotional difficulties are all sequelae of NF-1. Understanding the different ways to measure the overall impact of the NF-1 will allow for a fuller picture of the impact of disease on adolescents.

2. Methods

2.1. Participants. After getting approval from the hospital internal review board, adolescents with NF-1 and their families were recruited from a specialty clinic at a large Midwestern children's hospital. Adolescents all had a diagnosis of NF-1 made by a physician expert in the field, were between the ages of 12–18 years, lived within 120 miles of the hospital, and were English speakers. Thirty-seven families met these criteria and were approached to participate in the study during their annual appointment at the neurofibromatosis clinic. Two families refused participation and 10 families later cancelled their appointments due to scheduling problems. The final sample consisted of twenty-seven adolescents from twenty-five families.

2.2. Procedure. Families who expressed interest and met the eligibility criteria met with either a graduate or upper-level undergraduate student research assistant who described the research study and details of participation. If eligible and interested, parental consent and child assent were obtained. At this initial meeting, a pain diary was given for the adolescent to complete over the next 2 weeks and an appointment was scheduled for the assessment portion of the study. These assessments were completed in families' homes. Clinical psychology graduate students administered measures of cognitive functioning, functional disability, HRQOL, and social and emotional functioning. Parents were also asked to complete measures of their child's social and emotional functioning, HRQOL, and FD. If participants had questions while completing the measures (e.g., the meaning of a term or an item), assistance was provided (e.g., by explaining the item). All family members were given a \$15 gift card to thank them for their participation.

2.3. Measures. The current study uses a portion of the assessment measures collected as part of a larger study

examining psychosocial and neuropsychological functioning in youth with NF-1.

2.3.1. Background Information. A background questionnaire was created for this study that asks parents to provide information about their child's school, medical, and mental health history, as well as sibling health; parents' ages, occupations, and education level; extended family medical history. This questionnaire included items asking parents to report whether or not they themselves had a diagnosis of NF-1.

2.3.2. Medical Severity. Severity of disease was measured using a scale previously used by Reiter-Purtil et al. [29] in their study of parental distress and family functioning in children with NF-1. These authors created their scale by combining three previous scales of NF-1 severity including a scale of overall medical severity [30], a scale of the degree of visibility of NF-1 features [31], and a scale of neurological impairment [32]. For the current study, this combined scale was used and participants received a severity rating 1 (minimal) to 4 (severe) on three separate scales (i.e., general, appearance, and neurological). These ratings were completed by a clinical geneticist or physician in the NF-1 specialty clinic using medical chart review. An average severity score was calculated for use in the following analyses.

2.3.3. Cognitive Functioning. The Kaufman Brief Intelligence Test-2nd Edition (KBIT-2) [33] was administered to evaluate cognitive functioning. The KBIT-2 is a screening measure of intelligence that assesses both verbal and nonverbal abilities. The KBIT-2 includes three subtests: verbal knowledge, riddles, and matrices used to calculate an IQ composite score ($M = 100$, $SD = 15$). While not a comprehensive measure of cognitive functioning, the KBIT-2 has demonstrated excellent reliability and internal consistency. This measure has also shown strong validity as a measure that is correlated with other intelligence tests as well as academic achievement measures [33].

2.3.4. Social and Emotional Functioning. To assess social and emotional functioning, the adolescent Behavior Assessment System for Children—Second Edition (BASC-2) [34] was completed by both the child and at least one parent. This measure's multidimensional design and the use of multiple informants provide a comprehensive screen of children's behaviors. The Parent Rating Scale (PRS) assesses adaptive and problem behaviors in the home and community setting and the Self-Report-Adolescent (SRP-A) form provides information about the child's thoughts, feelings, and behavior. As a measure of overall social and emotional functioning, the BASC-2 self-report Emotional Symptoms Index and the parent-report Behavioral Symptoms Index were examined. These scales provide t -scores with a mean of 50 and standard deviation of 10. Scores of 60–69 indicate that the individual is "At Risk" of developing clinically significant problem and scores greater than 70 indicate "Clinically Significant" problems. Although these summary scales have different

labels, the Emotional Symptoms Index and the Behavioral Symptoms Index both measure the construct of emotional functioning. These index scores will be used throughout the remainder of the paper to reflect youth self-reported and parent proxy-reported emotional functioning.

2.3.5. Pain. Frequency and intensity of pain were assessed using daily pain diaries with a Visual Analog Scale (VAS) [35]. Pain diaries were completed at 3 time points (morning, midday, and before bed) each day, over a two-week period. Participants rated their *average pain* (0: "no pain," 10: "worst pain possible"). This scale yielded a measure of how many days, over a 2-week period, the adolescent reported having pain. Previous research in youth with NF-1 has targeted the occurrence of headaches [4–7]. In the current study, the goal was to assess the frequency with which youth with NF-1 experience daily generalized pain and how this may be related to their current functioning.

2.3.6. Health-Related Quality of Life. HRQOL was measured using the Pediatric Quality of Life Inventory [36]. The PedsQL is a 23-item multidimensional measure assessing children's and adolescent's perceptions of their quality of life during the past month. The child self-report form (8–12 years) and adolescent self-report form (13–18 years) were used. The PedsQL has demonstrated good reliability and validity across age groups [36]. Scores range from 0 to 100 with higher scores reflecting greater HRQOL. This measure has been shown to distinguish between healthy youth and youth with acute or chronic medical conditions and to be associated with morbidity and illness burden [36]. In one large study, healthy youth were shown to have average self-report total scores of 83.00 ($SD = 14.79$) compared to chronically ill youth ($M = 77.19$; $SD = 15.53$) and acutely ill youth ($M = 78.70$; $SD = 14.04$) [36]. This measure also distinguished between parent-reported quality of life in healthy youth ($M = 87.61$; $SD = 12.33$) compared to chronically ill youth ($M = 74.22$; $SD = 18.40$) and acutely ill youth ($M = 80.42$; $SD = 15.26$) [36].

2.3.7. Functional Disability. Functional limitations for youth were assessed with the Functional Disability Inventory (FDI) [19]. The FDI is a one-dimensional scale rating perceptions of activity limitations because of physical health during the past two weeks. The FDI is a self-report inventory for children that measures perceived difficulty in performing a number of activities in the domains of school, home, recreation, and social interactions. It consists of 15 items rated on a 5-point scale (0 = no trouble to 4 = impossible) and yields total scores that can range from 0 to 60, with higher scores reflecting greater functional disability [37]. In addition to a child self-report form, a parent-proxy version exists and was also used in this study. In a sample of youth 5–17 years with chronic abdominal pain, average FDI scores were 11.25, with a range of 0–53 [19].

TABLE 1: Descriptive information.

Scale	Minimum	Maximum	Mean	SD
Child HRQOL total score	38.04	96.74	78.34	13.98
Parent HRQOL total score	30.43	100.00	70.78	17.88
Child HRQOL physical score	46.88	100.00	82.74	13.92
Parent HRQOL physical score	34.38	100.00	80.29	16.93
Child HRQOL psychosocial score	23.33	95.00	75.99	17.63
Parent HRWOL psychosocial score	25.00	100.00	65.71	21.06
Functional disability child total score	0.00	26.00	4.62	5.30
Functional disability parent total score	0.00	25.00	3.42	6.56
BASC Child Emotional Symptoms Index	35.00	71.00	47.50	9.88
BASC parent Behavioral Symptoms Index	39.00	96.00	57.23	15.95
KBIT IQ composite	69.00	122.00	97.62	14.39
Total days of pain	0	14	4.13	3.83

3. Results

3.1. Demographic and Background Characteristics. Twenty-six adolescents ages 12 to 18 years (54% female, M age = 13.65, SD = 1.88) were included in these analyses. One additional participant was recruited for this study but was dropped from the current analyses due to the fact that she was a significant outlier in terms of her level of cognitive functioning (IQ = 47). Twenty-five mothers and 13 fathers completed questionnaires. As not all youth had both parents' complete questionnaires, data from each adolescent's primary caregiver were used (25 mothers, 1 father). Eleven of the adolescents (42%) had a parent with NF-1 (seven mothers and four fathers) and six had an affected sibling (23%). Three youth (12%) were reported to have been held back a grade during their school career; 13 (50%) were reported to have an individualized education plan (IEP) or 504 plan; 11 (42%) were enrolled in special education classes. Seventy-five percent of parents reported attending postsecondary education. Participants were predominately Caucasian (88%), 8% identified themselves as African American, and 4% reported belonging to more than one racial group.

Adolescents with NF-1 fell within the minimal to moderate range for disease severity. Fifty percent fell in the minimal severity range indicating that they had few NF-1 features and experienced no health complications. Twenty-seven percent fell in the mild severity range indicating they had symptoms such as mild hypertension or asymptomatic tumors. The remainder of the sample, 23%, fell in the moderate severity range. They presented with symptoms such as orthopedic complications or large or symptomatic plexiforms. Days of pain ranged from 0 to 14, with youth reporting on average 4.13 days of pain in the last two weeks. Scores on the KBIT ranged from 69 to 122 with a mean intelligence quotient (IQ) of 97.62. Sixty-two percent scored within the average range with 19% falling below average and 19% above average. On average, youth's ratings of quality of life were closer to youth with acute and chronic illnesses than healthy youth (see Table 1 for measure descriptives) [36]. Parents' ratings of their child's quality of

life were lower than previously published parents' ratings of their chronically and acutely ill children. Overall, youth and parents reported low levels of functional disability although there was a considerable range with some reports of moderate impairment. On the BASC-2, both youth and parents reported emotional functioning scores within the average range. Twenty-three percent of parents rated their children as having emotional functioning scores within the "At Risk" range, and 19% within the "Clinically Significant" range. Eleven percent of youth reported symptoms falling within the "At Risk" range and one participant had a self-report score in the "Clinically Significant" range.

Kendall's tau bivariate correlations were used to examine the relationship between the primary variables (Table 2). This nonparametric statistic was used due to the small sample size. Disease severity was not significantly correlated with total days of pain, participant- and parent-reported HRQOL, FD, or emotional functioning. Significant correlations were observed between disease severity and cognitive functioning ($\tau = -.45, P < .01$).

Gender and age differences were examined for HRQOL, FD, cognitive functioning, and emotional functioning. None of these variables were found to differ significantly by gender. Age was found to be significantly correlated with self-reported emotional functioning ($\tau = .40, P < .01$) and parent-reported emotional functioning ($\tau = .39, P < .05$).

3.2. Prediction of Health-Related Quality of Life and Functional Disability

3.2.1. Health-Related Quality of Life. Hierarchical multiple regressions were used to examine the effects of age, pain, and emotional and cognitive functioning on child- and parent-reported HRQOL (see Table 3). Due to significant bivariate relations, age was entered as the first step in the regression analyses.

As shown in Table 3, 38% of the variance in child-reported HRQOL was explained by the model ($F(4, 19) = 2.89, P = .05$). The first step of the analysis was not significant, with age accounting for only 14% of the

TABLE 2: Bivariate correlations.

	1	2	3	4	5	6	7	8	9	10	11
(1) Gender		.06	.14	-.11	-.04	.13	-.07	-.02	.09	-.03	.17
(2) Age			.07	.12	-.29	-.02	.17	-.20	-.26	.39*	.40**
(3) Disease severity				-.28	-.45**	.14	.07	-.11	-.06	.11	.30
(4) Days of pain					.09	.31*	.16	-.17	-.33*	.21	.23
(5) IQ						0.00	-.14	-.07	.12	-.13	-.16
(6) Child FDI							.10	-.32*	.04	-.08	.22
(7) Parent FDI								-.10	-.47**	.43**	.20
(8) Child total HRQOL									.17	-.17	-.39**
(9) Parent total HRQOL										-.64**	-.26
(10) Parent BASC											.34*
(11) Child BASC											

* $P < .05$, ** $P < .01$.

TABLE 3: Hierarchical multiple regressions predicting health-related quality of life.

Variable	Cumulative R^2	F	β	R^2 increment
Child HRQOL				
Step 1	.138	3.53		.138
Child age			-.37	
Step 2	.378	2.89		.240
Child BASC			-.47*	
IQ			-.10	
Days of pain			-.21	
Parent HRQOL				
Step 1	.075	1.78		.075
Child age			-.27	
Step 2	.625	7.93**		.551**
Parent BASC			-.75**	
IQ			-.13	
Days of pain			.04	

* $P < .05$, ** $P < .01$.

variance. The second step, which incorporated pain and cognitive and emotional functioning, accounted for an additional 24% of the variance ($P = .05$). Emotional functioning was a significant individual predictor ($\beta = -.47$, $P = .04$), with higher scores on the BASC-2 (i.e., more clinically significant emotional symptoms) correlated with lower HRQOL.

The parent-report model was also significant ($F(4, 19) = 7.93$, $P < .01$) predicting 63% of the variance in HRQOL. Age, entered again as the first step, was not a significant predictor, accounting for only 8% of the variance. The second step, incorporating pain and cognitive and emotional functioning, was significant, accounting for an additional 55% of the variance ($P < .01$). Emotional functioning was again a significant individual predictor ($\beta = -.75$, $P < .001$), with higher scores on the BASC correlated with lower HRQOL.

3.2.2. *Functional Disability.* Hierarchical multiple regressions were used to examine the effects of age, pain, and

emotional and cognitive functioning on child- and parent-reported FD (see Table 4). Due to significant bivariate relations with age, age was entered as the first step in the regression analyses.

The child-report model was significant ($F(4, 19) = 5.69$, $P < .01$) predicting 55% of the variance in child-reported FD. Age, entered in the first step, was not a significant predictor of child-reported FD, accounting for only 2% of the variance. The second step which incorporated pain and emotional and cognitive functioning was significant, accounting for an additional 52% of the variance ($P < .01$). Total days of pain was a significant unique predictor ($\beta = .61$, $P < .01$), with greater days of pain correlated with greater FD. The parent-report model was not significant ($F(4, 19) = 0.44$, $P = .78$), accounting for only 9% of the variance in parent-reported FD.

4. Discussion

This study examined the effects of physical, cognitive, and emotional factors on the quality of life and functioning of

TABLE 4: Hierarchical multiple regressions predicting functional disability.

Variable	Cumulative R^2	F	β	R^2 increment
Child FD				
Step 1	.023	.52		.023
Child age			.15	
Step 2	.545	5.69**		.522**
Child BASC			.12	
IQ			-.32	
Days of pain			.61**	
Parent FD				
Step 1	.005	.10		.005
Child age			-.07	
Step 2	.085	.44		.080
Parent BASC			.16	
IQ			.21	
Days of pain			.13	

* $P < .05$, ** $P < .01$.

adolescents with NF-1. A broad exploration of functioning was utilized due to the fact that NF-1 is a complex disease, with the potential to impact the lives of adolescents in myriad ways. To better understand the impact of NF-1, this study focused on two main outcomes: health-related quality of life (HRQOL) and functional disability (FD).

Consistent with study predictions, participants showed varied levels of functioning. Emotional functioning was found to be a significant predictor of HRQOL for both youth and parents but did not predict FD. Clinicians would do well to be aware that even children who do not exhibit decreased physical functioning could still be experiencing emotional difficulties that impact their quality of life. Measures of HRQOL in patients with NF1 can supplement measures of clinical severity and physical limitations to comprehensively assess the status of the patient and suggest treatment directions.

Also as expected, days of pain was a significant predictor of self-reported FD. It was not found to be a significant predictor of parent-reported FD. Consistent with findings from studies involving youth with chronic pain (see [19]), these results suggest that pain is an important indicator of functioning for adolescents with NF-1. It is possible that greater attention to pain management may mitigate pain intrusiveness and improve physical functioning. The findings should be taken with caution, however, as there were fewer self-reported days of pain in our sample than may have been expected from past literature that focused specifically on headache pain. It is possible that our measurement of pain was met with resistance from the adolescents who may have underreported their pain. Future research may consider adding parental report of youth pain or a shorter time-frame for pain reporting.

In contrast with our hypothesis and previous research findings, cognitive functioning did not predict either HRQOL or FD. Earlier studies have shown a relationship between aspects of cognitive functioning and neurological severity on social and emotional functioning [32, 38, 39].

Although the youth in our sample had similar IQ scores as reported by Martin et al. (2012), participants in the current study were much less likely to be in special education classes, which may reflect a discrepancy in the degree of impairment between these samples [39]. Barton and North (2004) also reported that attention deficit hyperactivity disorder (ADHD) was an important risk factor for difficulties in social and emotional functioning [13]. Rates of attention deficits were not obtained in the current study. It is possible that attentional difficulties were not as prevalent in the current study, contributing to a reduced relationship between emotional and cognitive functioning. Support for the need to assess a wider array of cognitive skills was demonstrated by Huijbregts and De Sonnevle [38]. Cognitive ability was assessed using a composite of processing speed, social information processing, and cognitive control. This composite was found to significantly explain emotional difficulties [38]. Future studies should obtain assessments of a wide variety of cognitive constructs (e.g., attention, executive functioning, processing speed, IQ) to further determine what skills within the cognitive deficits seen in NF-1 are the most strongly related to social and emotional difficulties. Identification of specific cognitive deficits associated with social and emotional deficits can then lead to targeted interventions.

Interestingly, cognitive functioning was correlated with disease severity, indicating that lower IQ scores were found for children with symptoms of more severe disease. Perhaps the impact of cognitive functioning found in previous studies is directly related to physical disease and only indirectly related to quality of life and functional disability. Future research should examine the complexities of these potential relationships.

Historically, research on global outcomes in pediatrics has focused predominantly on HRQOL. However, recent work [21, 40] has called for the addition of a specific FD measure in conjunction with assessing global quality of life. Our findings bolster this recommendation by showing that while HRQOL was predicted by emotional functioning, it

was a measure of FD that showed the effects of physical symptoms. NF-1 is a complex disease with the potential to impact myriad domains of functioning. The results of this study reflect the importance of assessing a wide variety of potential disease effects and their impact on adolescent physical functioning and quality of life.

5. Limitations

There are several limitations in the current study. This study did not employ an experimental design or a comparison group, which limits our ability to make causal inferences. However, the results do add to the growing literature of HRQOL research and fill a need for more research on functional disability in youth with NF-1.

Youth in this sample were predominately Caucasian. Although NF-1 usually presents equally in all racial and ethnic groups [1], this distribution is characteristic of the sample typically seen in the specialty clinic where recruiting occurred. The current sample was also restricted in terms of disease severity. The majority of participants were within the minimal to mild range. This is not representative of the range of impairment typically seen in adolescents with NF-1, and this restricted variability may have affected study results. Although the sample was limited in terms of disease severity, the sample was found to be representative of youth with NF-1 with regard to their need for educational services [41]. Half of youth received accommodations from IEP or 504 plans and 42% were in special education classes. Recruitment in future research should aim for a wider range of symptom and severity presentations to allow for greater exploration of the relationship between severity and functioning. Future studies would also be strengthened by having a larger sample size which would improve the power of the study and the range of hypotheses that could be examined.

6. Conclusions and Future Directions

NF-1 is a disease that can vary considerably in its medical complications and severity expression and thus might be expected to show variability in its functional impact. The findings from the current study support the need for a broad approach to the study and treatment of the sequelae of this disease. Because NF-1 can impact physical, emotional, and cognitive functioning, it is important to assess all areas when making inferences about well-being. Relying only on HRQOL to describe the functioning of adolescents with NF-1 would miss important factors such as the impact of pain on ability to perform tasks. Emotional aspects of NF-1 may be best understood by examining a global outcome such as quality of life, but to fully understand the impact of this disease the incorporation of FD is necessary. Future work can build upon these findings by examining how difficulties in physical, emotional, and cognitive domains interact to impact well-being and disability. Predictors of well-being and FD should also be examined across developmental stages and severity levels for individuals with NF-1. Finally, we hope that this work will help professionals working

with children having NF-1 to understand the implications this complicated disease may have on both well-being and physical functioning to continue to improve the quality of care and support they can provide.

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Review Article

The Pain Crisis: What It Is and What Can Be Done

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Chronic pain is present in epidemic proportions in most countries, is often unrelieved, and has a huge socioeconomic impact. It is not just a “medical” illness but indeed is a problem that faces all healthcare professional fields. Several steps are identified to address this crisis. These include approaches to enhance pain awareness and access to timely and effective care for pain, and educational and research approaches to improve the knowledge base of healthcare professionals and students and diagnostic and management procedures for pain. Several opportunities to enhance pain understanding, access, and management are also identified.

1. Introduction

Despite recent advances in our understanding, diagnosis, and management of pain, several problems confront the pain field, especially in the case of chronic pain which remains a public health problem of epidemic proportion in most countries. This is largely due to the limited levels of (a) awareness of pain, particularly its socioeconomic impact and burden, and access to timely and appropriate care, (b) pain education, especially of health professionals, and (c) research into pain mechanisms and into ways to improve diagnostic and management approaches and healthcare delivery. This pain crisis has been highlighted over the past 2 decades by several authors and again recently by the recent report in the USA by the Institute of Medicine (IOM) [1–7]. This article will focus on these areas and provide for each some possible means to address the current crisis of chronic pain.

2. Awareness of Pain and Its Impact

Pain is a subjective individual experience encompassing sensory, cognitive, emotional, and social dimensions. One person may report a moderate level of pain following an injury while another person with a similar injury may report a much higher, or lower, pain level. This individual-by-individual experience of pain depends on numerous features that include each person’s unique genetic features and cognitive, motivational, emotional, and psychological

state as well as environmental factors stemming from their gender, past experiences and memories of pain, cultural and social influences, plus their general health condition.

Pain does serve an important vital function as a warning signal of tissue damage, resulting from an accidental trauma, infection, or inflammation, for example. It usually disappears after the injured tissue has healed. In contrast to such acute pain episodes, chronic pain is usually considered as having no biological role but is associated with changes in the peripheral and central nervous systems that contribute to its persistence. Because of these changes that involve alterations in brain morphology, physiology, and neurochemistry [8–10], chronic pain is now often viewed as a neurological disorder akin to other chronic medical illnesses and conditions involving analogous alterations in the nervous system (e.g., epilepsy, Parkinson’s disease); in other words, chronic pain is a disease or illness in its own right. Furthermore, chronic pain may be a pain disorder per se (e.g., fibromyalgia, trigeminal neuralgia, temporomandibular disorders, migraine) although affecting other functions (e.g., mobility, cognitive function), or be an accompaniment of many chronic diseases and disorders (e.g., arthritis, diabetes, cancer, HIV/AIDS). It can also result from acute pain since approximately 20% of acute pain conditions can transition into chronic pain, especially if the acute pain is not appropriately managed [11].

Chronic pain is very prevalent, with estimates ranging from 12–30% depending on the country surveyed

[1, 4, 12–14]. Yet, it is a “silent epidemic” as several studies have noted, since there is little awareness of its prevalence and social and economic costs for the patient and society as a whole [2, 4, 6, 7, 15–18]. These socioeconomic consequences include reduced quality of life, negative impact on relationships, job loss or reduced job responsibilities, ineffective management of pain, and increased rates of depression. In addition to the personal social and psychological “costs” for the person suffering with chronic pain, there are also considerable economic costs to the patient and to society as a whole. For example, in Canada, the personal financial costs for pain patients is close to \$1,500 per month and the direct and indirect costs to the Canadian economy have been estimated to be >\$30 B/year. The recent IOM report places this cost at >\$500 B/year in the USA; this economic burden is higher than the healthcare costs for heart disease, cancer and diabetes combined, and stems from the costs of healthcare services, insurance, welfare benefits, lost productivity, and lost tax revenues, among others [2, 5, 16, 18].

A pain crisis exists, and it is relatively unrecognized by the public and policy makers. Plus, it is not going to get any better unless concerted efforts are made to enhance awareness of pain and its huge socioeconomic impact since demographic research suggests that chronic pain conditions will become even more of a health problem and socioeconomic burden [18–21]. Over the coming years, changing demographics will result in a higher proportion of the population of most countries being middle-aged and elderly, the age cohorts where most chronic pain conditions are particularly evident and usage of the healthcare system is particularly high.

The pain crisis is compounded, even in so-called developed countries, by the difficulty that many patients in pain, especially chronic pain, have in gaining timely access to appropriate pain care in spite of such access being a basic human right recognized by the United Nations, World Health Organization, and IASP [11, 22–25]. Timely access is essential since chronic pain patients experience considerable deterioration in their psychological well-being and health-related quality of life while they wait until treatment can be instituted; the longer they have to wait for relief of their pain, the more severe the impact, the greater the degree of chronicity, and the larger the cost to the healthcare system [11].

Because of the cognitive, emotional, and psychological effects that may be associated with pain, a biopsychosocial concept of pain has emerged over the past 2-3 decades along with considerable evidence supporting management approaches addressing the psychosocial aspects of a patient with chronic pain [2, 3, 5, 22]. Yet such approaches, and even management strategies based on pharmacological, surgical or other interventions, are difficult for many patients to access. This is because of several barriers that reflect the nature of organizational, structural, educational, and reimbursement features of current healthcare systems in most countries. For example, most patients in pain first try to seek care from primary healthcare professionals, and indeed pain complaints may account for 40% or more of patient visits to physicians, for example [2, 26–28]. However,

as pointed out in the recent IOM Report [2], primary care in the USA usually is organized and reimbursed in such a manner that precludes comprehensive patient assessment, to the pain patient’s detriment. Insurance coverage may favour some procedures (e.g., drug interventions, surgery) over behavioural or physical therapies that in many cases may be more beneficial to the patient.

Access to appropriate care in a timely fashion is a problem particularly in most developing countries. For example, access to opiate drugs is very limited because of factors such as costs, opiate phobia, government restrictions, inability to access prescribing clinicians, and in some countries the infrastructure of the healthcare system is insufficient for pain patients to obtain care, even for those with horrific injuries [3, 22, 29, 30]. And even in developed countries, some of these features are also evident, compounded by limited evidence-based data on treatment outcomes and by abuse or misuse by a minor segment of society of some drugs used for pain patients. The possibility of such abuse or misuse runs the risk of legislation being put in place that negatively affects access by legitimate pain patients to appropriate analgesic medications. It could also compromise chronic pain management, resulting in undertreatment and even pseudo-addiction.

Several steps can, and should, be taken to address the pain crisis, especially from the point of view of awareness and access to care. As the recent IOM report [2] has noted, it necessitates a “cultural” shift in the way clinicians and the public view pain and its treatment. Policy makers should also be included in this cultural realignment. There needs to be increased efforts to

- (a) inform the public, and government and policy makers about pain and its socioeconomic impact and problems with access to timely, appropriate pain management,
- (b) develop integrated, comprehensive strategies for pain prevention, management, education, and research that will result in enhanced levels of access and care for pain patients,
- (c) develop and widely distribute pain information sheets and articles for patients, healthcare professionals, government/policy makers, and so forth,
- (d) inform and collaborate with other stakeholders in these initiatives, such as patient advocacy groups which would include educational material on pain self-management and prevention so that pain patients play a more active role in dealing with their pain,
- (e) ensure a sufficient number of accessible pain clinics are available so that timely and appropriate multidisciplinary care is available to all citizens,
- (f) enhance collaborative activities between primary healthcare providers and pain specialists that include referrals to such multidisciplinary pain management clinics,
- (g) ensure pain management/medicine becomes a recognized and popular healthcare specialty,

- (h) advocate to government/policy makers, insurance companies, and so forth, so that evidence-based management approaches are widely available, and
- (i) develop guidelines for appropriate wait times for access to pain care.

In recent years, several steps have taken to address these points. They include the establishment by the International Association for the Study of Pain (IASP) of the Global Year Against Pain, an initiative linked to national and regional awareness initiatives in IASP chapters around the world. Another IASP initiative has been the international Pain Summit (held in Montreal following the IASP World Congress on Pain in September 2010) and this has been complemented by national pain summits. Another analogous approach is the recent European-Union-sponsored Symposium [31] calling on all European governments to take action to address the huge societal impact of pain. Pain advocacy groups have also held events for policy makers both locally and nationally to raise their pain awareness. Linked to some of these initiatives have been steps to encourage policy makers to develop and put in place a comprehensive pain strategy to address the many facets of the pain crisis. In the case of access to care, initiatives already taken here include a recent IASP international Task Force, cochaired by Mary Lynch and myself, which developed guidelines to address the timely and appropriate management of chronic pain on a global basis. These guidelines are based on the principle that all people have the right for timely access to appropriate care for chronic pain and that each nation should take steps to ensure that the principle is applied to all its citizens. Other steps taken in some countries have been the establishment of procedures for accreditation of hospitals and other healthcare organizations that has taken into account enhancement of access to appropriate pain management as well as of the quality of that care. In Canada, steps have been taken in some provinces to improve access at the community level and to advocate successfully for the establishment of a pain specialty [32–34].

3. Education of Health Professionals and Students

In addition to the public and policy makers being an advocacy target in order to “educate” them about pain and its socioeconomic burden, another target must be healthcare professionals and students in health professional programmes. Several recent reports have noted the inadequate knowledge of most healthcare professionals about pain and its diagnosis and management and how this impacts on their decision making [2, 3, 5, 6, 35–39]. As a result, costly or inappropriate or inadequate procedures are often carried out when other approaches could be more appropriate (e.g., counseling, prevention, self-management). There is still variability amongst clinicians in applying new and even existing knowledge about pain and its management. This is reflected in the documentation of inappropriate or indeed lack of treatment for patients with cancer, HIV/AIDS,

neonatal, and postoperative pain, among others [35, 40–44]. This stems from inadequate knowledge or outdated attitudes about pain diagnosis or management. However, it may be compounded by several factors including the limited availability of effective analgesics and other pain-relieving approaches in many countries, limited access to pain treatment (as noted above), and use of management approaches that have not been validated or fully tested for their sensitivity and specificity. The variability in applying new knowledge and standards of practice and management of pain may be particularly evident in regions with economic and infrastructure limitations [29].

Major factors contributing to the misunderstanding and limited knowledge of pain by many healthcare professionals include the difficulty of treating most chronic pain conditions and the numerous other “competing” diseases and illnesses that most practicing clinicians have to be aware of and competent to manage. Another factor is their relatively poor understanding of chronic pain mechanisms because of the limited pain education that the vast majority of clinicians receive in their undergraduate and postgraduate professional programmes. At most health professional programmes, the topic of pain occupies only a minor component of the curriculum. This is evident in surveys carried out in North America [39] and Europe [45] where, for example, dental and medical students receive on average only 15–16 hours of formal education about pain throughout their multiyear programme; yet veterinary medicine is far ahead of the other professional programmes. Such neglect of pain in the vast majority of health professional programmes is incongruous given (i) the current high prevalence of pain and its socioeconomic costs, (ii) the changing demographics that suggest future increases in the incidence of chronic pain, (iii) that pain is an integral component of practice in medicine, dentistry, nursing, pharmacy, and other health disciplines, and (iv) that pain is indeed one of the major reasons for patients visiting physicians, dentists, and other healthcare professionals. The relative neglect of pain in the curriculum is also evident from the competency and accreditation requirements of graduating healthcare professionals and their educational programmes. For example, my own discipline (dentistry), only 2 of 47 and 2 of 39 competency requirements, respectively, in Canadian and U.S. dental schools (Association of Canadian Faculties of Dentistry; American Dental Education Association) relate to pain and its diagnosis and management; competency requirements in medicine also pay little attention to pain.

Several steps are needed to address this imbalance and improve the understanding of pain and its management by clinicians, for the benefit of the patient in pain. They include

- (a) increase pain curricular time in all health professional programmes,
- (b) utilize current pain curricula developed by national and international pain-related organizations,
- (c) ensure pain is taught within a biopsychosocial framework and in an integrated interdisciplinary manner that reflects its multidimensional nature,

TABLE 1: Recent advances in pain research and management.

-
- (i) Identification of peripheral and central nociceptive processes involving nonneural as well as neural mechanisms
 - (ii) Discovery of several endogenous neurochemicals and intrinsic pathways in the brain and their influences on nociceptive transmission and behaviour
 - (iii) Development of concepts and insights of the neuroplasticity of pain processing that can lead to chronic pain
 - (iv) Rapid advances in the fields of brain imaging, biomarkers, genetics, and molecular biology as well as their applicability to the pain field
 - (v) Recognition of the multidimensionality of pain and importance of biopsychosocial factors in pain expression and behaviour
 - (vi) Improvements in surgical, pharmacological, and behavioural management of pain:
 - (a) more effective and varied drug-delivery systems
 - (b) broader range of analgesics and other drugs for management of pain and related conditions
 - (c) spinal cord and brain stimulation, transcutaneous electrical nerve stimulation
 - (d) physical/rehabilitative medicine
 - (e) new or improved surgical approaches
 - (f) cognitive behavioural therapy
-

- (d) ensure there is sufficient coverage of pain in accreditation requirements of health professional programmes and in practice standards for healthcare professionals, hospitals, and other healthcare facilities,
- (e) synthesize new pain-related information for widespread readership by healthcare professionals, and
- (f) ensure effective knowledge transfer and application about pain and its management.

These various approaches are essential to improve the healthcare professional's knowledge about pain, although it is recognized that local academic constraints and school "politics" likely will make it difficult to increase curricular content on pain in many healthcare professional programmes. But they can be accomplished, as evidenced by an initiative at my own university, the University of Toronto, where the shortcomings in the curricula for medical, dental, nursing, pharmacy, and other health professional students were recognized. As a result, an interfaculty pain curriculum dealing with the many facets of pain, from basic science to clinical management to patient issues, was put in place 10 years ago for these students; it has continued to have successful outcomes [38, 46, 47]. Steps are being taken to address this problem in other countries, including the USA [48, 49].

4. Pain Research

There have been significant advances in our understanding of pain and improvements in pain management approaches (see Table 1), and more exciting advances can be expected in the coming decades as research developments in brain imaging, biomarkers, genetics, behavioural strategies, and so forth, are applied to pain diagnosis and management. Nonetheless, the evidence base for some of these approaches is limited, and in addition further research is needed to

clarify the mechanisms, aetiology, and pathogenesis of most chronic pain conditions. This includes research directed at the mechanisms accounting for the differences between individuals in their pain experience, at the mechanisms and factors involved in the transition from acute to chronic pain, at more clinically applicable animal models of pain, and at translational approaches linking experimental pain findings with improved pain management in clinical settings. Also needed is more research addressing the basic science and clinical utility of recent technologies utilizing brain imaging, biomarkers, genotyping, and so forth, so as to identify those patients who will most benefit from newly developed therapeutic approaches for pain. There also needs to be an increased research focus on the multitude of current approaches used to manage pain which for many lack an appropriate evidence basis [2, 3, 5, 20, 50].

A critical factor essential for underpinning such multifaceted research is more research funding directed at studies into pain mechanisms, diagnosis, and management. Pain research funding has always been hugely out of proportion to the prevalence and socioeconomic impact of pain, compared to other less common conditions (e.g., cancer, HIV/AIDS, heart disease, arthritis, epilepsy). Recent surveys in the USA and Canada, for example, reveal the stark reality that funding for pain research is <1% of the research budgets of the US National Institutes of Health and the Canadian Institutes of Health Research [51, 52]. Such limited funding not only hampers the timely advancement of the understanding of pain and improvements in diagnostic and management approaches but also limits the number of scientists and clinicians attracted to pain research.

To address this aspect of the pain crisis, a number of steps should be taken. These include

- (a) raising awareness of policy makers and funding agencies of the need to place much more emphasis on pain research by increasing opportunities for training basic science and clinical pain researchers and by increasing pain research funding,

- (b) ensuring established and potential pain researchers are aware that the pain field can be more rapidly advanced by utilizing recently developed and emerging technologies (e.g., in molecular biology, genetics, brain imaging),
- (c) increasing emphasis on inter-/multidisciplinary and translational research,
- (d) developing more expeditious approaches to assess and apply new therapies for pain,
- (e) applying new basic science knowledge and evidence-based principles in clinical pain research, and
- (f) developing more substantive clinical data bases and placing greater emphasis placed on epidemiological studies and randomized clinical trials.

5. Conclusion

Chronic pain is in epidemic proportions in most countries. It carries with it huge socioeconomic burdens and it is often unrelieved. The last 4 decades have seen some remarkable advances in our understanding of pain mechanisms and improvements in pain diagnosis and management, and healthcare delivery in general. Nonetheless, considerable gaps in knowledge and approaches still exist. There is need to enhance pain awareness and education and ensure timely access to appropriate pain care, and to enhance pain research activity and resources. Several approaches have been identified to address this pain crisis. Since there is considerable variability between countries in their healthcare policies, programmes, resources, and educational programmes, many of the approaches and strategies outlined above will have to be customized to each country's socioeconomic, educational, healthcare delivery, and research infrastructures.

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Research Article

Low Back Pain Prevalence and Associated Factors in Iranian Population: Findings from the National Health Survey

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Background. There are very few studies that had a sample size sufficient to explore the association between factors related to low back pain in a representative sample of the Iranian population. **Objective.** To examine the relationship between sociodemographic factors, smoking, obesity, and low back pain in Iranian people. **Methods.** We used Iranian adults respondents ($n = 25307$) from the National Health Survey. Adjusted odds ratios and 95% confidence intervals were estimated by using logistic regression. **Results.** The prevalence of low back pain was found in 29.3% of the studied sample. High age, female sex, being married, obesity, low-economic index, being smoker, in a rural residence, and low educational attainment, all increased the odds of low back pain. **Conclusions.** Our findings add to the evidence on the importance of obesity in relation to low back pain. These results can be used as a basis to reinforce health programs to prevent obesity.

1. Introduction

Low back pain (LBP) is a common medical problem [1, 2] that has many outcomes including disability [3] and taking time off from work [3, 4]. LBP is a major public health problem in the USA because more than 34 million (17%) adults reported LBP only, and 19 million (9%) reported LBP and neck pain in a 3 months duration [1]. One study in Canada estimated that 84% of adults have had LBP during their lifetime [5]. Average prevalences were 59% in UK [6], 70% in Denmark [7], and 75% in Finland [8]. In the general population, the prevalence of low back pain in a 1-month and annual duration ranges from 30% to 40% and 25% to 60%, respectively [9–11].

Overweight and obesity are also public health problems, due to their rapid growth in recent decades and their related health disorders, such as cardiovascular diseases, diabetes,

some cancers, and other diseases [12]. In recent years, the statistics about obesity were appalling. In 2010, almost 43 million children (35 million in developing countries and 8 million in developed countries) were estimated to be overweight or obese [13]. It has been estimated that by 2020, type 2 diabetes and cardiovascular disease will account for almost 75% of all deaths worldwide [14].

Because of multifactorial nature of LBP, researchers have focused on both medical and nonmedical factors such as sociodemographic factors [15–18]. One potential predictor could be age. The positive association between age and LBP has been found in some studies [19, 20]. Another predictor is sex which has shown that LBP is more common in female than in male [2, 10, 21–24]. Bener et al. found a statistically significant association between place of residence and LBP among patients attending primary health care [19]. Some studies have shown that smoking is consistently associated

with LBP [7, 25–28]. Findings from some studies showed that people with low levels of educational and low income have had the higher prevalence of LBP [3, 26–29].

Although obesity is a significant factor that is frequently associated with the presence of LBP [1, 30–32], but this association has not been confirmed by other studies [33, 34]. In a meta-analysis, Shiri et al. [24]. reported that obesity increases the risk of LBP [24]. Their findings showed that this association is stronger women than men.

Until now very few studies of the association between factors related to LBP have been carried out in a representative sample of Iranian population. Therefore, it is clear that there is a need to determine the factors related to LBP of people in this country. The present study was designed to assess relationships between age, sex, education level, place of residence, smoking, marital status, obesity, economic index, and active workforce and LBP among Iranian men and women.

2. Materials and Methods

2.1. Data Set Examined. The National Health Survey in Iran (NHSI) is a survey designed to gain comprehensive knowledge and information about health care problems and difficulties in Iran. All necessary information for the conduct of this study was obtained from the NHSI database. These data were collected by the National Research Center of Medical Sciences and are presented partially at the Department of Biostatistics and Epidemiology, Tehran University of Medical Sciences for research. For the present study, pregnant women were excluded from the analyses, and the analyzed data included 25307 women and men aged 20–65 years. This study was approved by the Ethic Committee of the University of Social Welfare and Rehabilitation Sciences.

2.2. Study Outcome. Low back pain was defined as a binary variable with “yes” if a respondent has had low back trouble during the past 30 days.

2.3. Personal Status Covariates

Obesity. Height was measured in centimeters to the nearest 5 mm in a standing position, with shoes removed, using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg with the subject in light indoor clothes, with shoes removed and emptied pockets. BMI (body mass index) was calculated as weight in kilograms divided by height in meters squared, and subjects were stratified into obese (BMI ≥ 30 kg/m²) and nonobese (BMI < 30 kg/m²).

Education Level. The respondents were categorized into three groups: those with low (0–8 years), moderate (9–12 years), or high (more than 12 years) education.

Smoking. Smoking status was dichotomized into smoker versus nonsmoker.

Economic Index. Due to ethical considerations, we did not ask respondents about their income, because they were afraid

of paying their taxes. We surrogated economic index for their household income. Economic index was defined as square meter of living place divided by number of household.

Demographic Variables. Information about the respondent's age was based on their self-reported birth year (age); females versus males based on (sex); married versus single based on (marital status); rural versus urban based on (place of residence).

2.4. Data Analysis. Descriptive statistics were presented in terms of prevalence of each covariate between subjects with and without LBP. We used χ^2 tests to test significance of associations of each covariate with LBP. We applied logistic regressions to assess the association between obesity and LBP controlling for other covariates. In doing so, we first assessed a “crude” association between obesity and LBP without controlling for any variable. We then assessed the obesity-LBP relationship after controlling for all other covariates. No statistical interactions between different covariates were detected. The results are presented as odds ratios and their 95% confidence intervals (CI). The Hosmer-Lemeshow test was used in this model to evaluate the significance of improved port with introduction of additional variables. All analyses were carried out by using the SPSS software package, version 15.

3. Results

Our data included 25307 women and men aged 20–65 years with a mean age of 36.19 year. The presence of LBP was found in 29.3% of the respondents. The mean economic index was 23.62 m². Of the respondents, 12.6% were obese, 56.2% were women and 34.4% were rural. Altogether, 14.1% and 80.6% were smoker and married, respectively. Overall, 25.5% and 8.2% of respondents were classified as moderate and high educational levels, respectively.

The prevalence of each covariate across the LBP categories is presented in Table 1. Results of χ^2 tests showed that LBP was significantly associated with each of the covariates.

We started by fitting a preliminary logistic model including only obesity and LBP to observe the influence of the potential confounders on LBP. This model showed that unadjusted LBP odds ratio was 1.62 (95% CI: 1.50–1.75).

In logistic model controlling for age, sex, economic index, education level, marital status, place of residence, and smoking status, adjusted LBP odds ratio was 1.15 (95% CI: 1.06–1.24) for obesity. Comparing two models, we found that the LBP odds ratio decreased after adjustment for confounding variables, reducing by 47% from that of primary model. The results of the multivariate logistic model are shown in Table 2.

In the multivariate analysis, the presence of LBP was associated with the female gender. The LBP odds ratio was 3.05 (95% CI: 2.84–3.27).

An association was observed between place of residence and LBP. The LBP odds ratio was 1.24 (95% CI: 1.17–1.32) for rural participants.

TABLE 1: Descriptive prevalence of low back pain across study variable levels.

Variable	Low back pain		P value
	No.	%	
Obesity			
Nonobese	5209	28.0	
Obese	1234	38.6	<0.001
Sex			
Men	2162	18.3	
Women	5409	37.5	<0.001
Place of residence			
Urban	4609	26.8	
Rural	2962	32.6	<0.001
Smoking			
Smoker	958	25.3	
Nonsmoker	6611	29.4	<0.001
Marital status			
Single	990	19.1	
Married	6581	31.2	<0.001
Education level			
Basic	5898	33.9	
Moderate	1342	20.2	<0.001
High	324	15.0	

We found a statistically significant association between smoking and LBP. For smoker participants, the adjusted odds ratio was 1.40 (95% CI: 1.27–1.53).

An association observed between marital status and LBP. The LBP odds ratio was 1.51 (95% CI: 1.39–1.64) for married.

Overall, subjects with higher education appeared as an associated factors with OR less than 1. Using basic education as the reference group, LBP odds ratios were 0.79 (95% CI: 0.73–0.85) and 0.65 (95% CI: 0.57–0.74) for the moderate and high groups, respectively.

The Odds ratio of presence of LBP was inversely associated with the economic index. The LBP odds ratio was 0.996 (95 percent CI: 0.994–0.998). A 1-m² increase in economic index has 1% decrease in the odds of LBP.

The odds of presence of LBP increased with age. The LBP odds ratio was 1.03 (95 percent CI: 1.029–1.034). We infer that a 1-year increase in age has 3% increase in the odds of LBP.

4. Discussion

In this cross-sectional study, we assessed associations between the some factors and presence of LBP in men and women. In the first model (without confounders), unadjusted LBP ratio was 1.62 (95% CI: 1.50–1.75). Furthermore, we adjusted the odds ratio for common known covariates for LBP, for example, smoking and sociodemographic factors. After adjustment for confounding variables, obesity is positively associated with presence of LBP in adults.

TABLE 2: Adjusted^a odds ratios for low back pain among 25307 Iranian adults, National Health Survey in Iran, in the logistic analysis.

variable	OR ^b	95% CI ^c
Obesity		
Nonobese	1.00	
Obese	1.15	1.06–1.24
Sex		
Men	1.00	
Women	3.05	2.84–3.27
Place of residence		
Urban	1.00	
Rural	1.24	1.17–1.32
Smoking		
Nonsmoker	1.00	
Smoker	1.40	1.27–1.53
Marital status		
Single	1.00	
Married	1.51	1.39–1.64
Education level		
Basic	1.00	
Moderate	0.79	0.73–0.85
High	0.65	0.57–0.74
Economy index	0.996	0.994–0.998
Age	1.03	1.029–1.034

^aAdjusted for all other variables in the table.

^bOdds ratio.

^cConfidence interval.

Obesity behaved as an important predictor in two models, in agreement with the findings in the literature [30–32, 1, 24]. Shiri et al. have reported that obesity is a risk factor for LBP in both cross-sectional and cohort studies [24]. Biomechanic and metabolic factors have been suggested to explain this relation. Obesity may cause LBP through metabolic syndrome. it is also possible that obesity and low back pain would be linked more directly via inflammatory mechanisms [35]. One study showed that people with high BMI increased risk of injury as well as higher injury-related expenditure [36]. Obesity has been shown as a risk factor for disc degeneration [37] and may increase the prevalence of LBP from this way. Because of a worldwide increase in the prevalence of obesity [14], it is reasonable to assume that the prevalence of back pain will continue to increase.

Studies have shown that the prevalence of LBP in the general population was higher in women than in men, and these findings are in agreement with the results of the present sample [2, 10, 21–24]. The sex difference could be related to gonadal steroid hormones such as estradiol and testosterone modulate sensitivity to pain and analgesia [38]. It is possible that LBP would have more influence on the life style habits in females than in males. Other variables such as diet, parity, and use of contraceptives may be relevant.

Rural people had higher prevalence of LBP than urban people. We conclude that the geographical variation in

prevalence of LBP in Iran is largely due to differences in propensity to consult a doctor once a symptom is present, and patient behaviour once symptoms have developed. Our results are consistent with some studies that reported the regional differences in the prevalence of LBP [29, 39].

In agreement with earlier findings [7, 25, 26, 28], our results showed that smoking, consistently associated with LBP. The association between smoking and LBP may be explained by the analgesic properties of nicotine [40]. Smokers might have stopped smoking on doctors' orders due to some disease that could be related to pain [41]. Smoking can effect on disc height [42]. Some biologically plausible explanations could be related to the effect of smoking on nutrition of the disc [43]. A positive correlation between severe disk degeneration and LBP was found in some studies [44].

Compared with unmarried, significantly increased odds of LBP were seen in married participants. Our results are consistent with some studies [45]. It is possible that the presence of a spouse may operate as a social factor on lack of LBP. It may include physiological mechanisms after their marriage.

According to the literature, people with lower educational attainment and economic index have an increased prevalence of LBP [3, 26–29]. These findings were also apparent among our participants.

There are likely to be other aspects of environments and lifestyle which influence the presence of LBP.

It is possible that LBP is more likely to be reported by those with lower economic index and lower educational qualification. Higher education and economy may provide knowledge or resource that influences on the lack of LBP.

Our findings suggest that age was an important associated factor revealing that prevalence of LBP increases with the increase of age. Age has also been a strong predictor for LBP in some previous studies [19, 20], possibly due to increasing degeneration of the tendons resulting from aging.

There are several limitations in this study. The analysis is cross-sectional and therefore unable to infer causation. We did not examine all potentially important variables. Marital status could be categorized into legally married and non-married only. Nonmarried people are a very heterogeneous group and should be more closely examined in further studies. The lack of approach to the functional impairment is a limitation to this study. The chronic pain is also not included in our investigation. Although we cannot be certain of the temporal relationship between these variables and LBP, any of these can influence and limit the inferences about factors associated with LBP in this sample.

Despite these limitations, the NHS sampling design permits the representative sampling of households in Iran. The adult respondents included in this paper are therefore a valid representative sample of the Iranian population ages 20 years and older. Height and weight were actually measured rather than self-reported. It is well known that self-reports underestimate the prevalence of obesity.

5. Conclusion

Our findings add to the evidence on the importance of obesity in relation to low back pain. If confirmed in other studies, these findings will have implications with respect to attempts in preventing obesity in the population.

Conflict of Interests

The authors have no conflict of interests.

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Clinical Study

Validation of the Self-Assessment of Treatment Questionnaire among Patients with Postherpetic Neuralgia

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Introduction. A five-item Self-Assessment of Treatment (SAT) was developed to assess improvement and satisfaction with treatment associated with the application of a novel high concentration 8% capsaicin topical patch in clinical trials in patients with postherpetic neuralgia (PHN). This study evaluated the item performance and psychometric properties of the SAT. **Methods.** The SAT, Brief Pain Inventory, SF-36v2, Short-Form McGill Pain Questionnaire, and Patient and Clinician Global Impression of Change (PGIC; CGIC) scores were measured in two 12-week Phase 3 clinical trials. Factor analysis assessed the underlying factor structure, followed by examination of the reliability and validity of the multi-item domain. **Results.** Pooled data from 698 patients completing SAT after 12 weeks of treatment were analyzed. A one-factor model combining three of the five items emerged as the optimal solution. Internal consistency reliability of this treatment efficacy factor was high (Cronbach's alpha = 0.89). Construct validity was demonstrated by moderate to high correlations with change in other study endpoints. SAT mean scores consistently discriminated between patient change groups defined by PGIC and CGIC. **Conclusions.** The measurement properties of the three-item version of SAT are valid and reliable for assessment of treatment with a high concentration capsaicin patch among patients with PHN.

1. Introduction

Postherpetic neuralgia (PHN) is a rare and debilitating complication of an acute herpes zoster (shingles) episode and is defined as pain that persists more than three months after the zoster skin lesions (rash) have healed [1]. Typically, individuals with PHN develop severe pain in the area of the body, usually the trunk, where shingles occurred. This debilitating pain, described as burning, sharp, jabbing, deep, and aching, can persist for months or years and is often not responsive to oral analgesics [2]. Recently, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved the use of a high concentration capsaicin topical patch 8% (QUTENZA) for the treatment of peripheral neuropathic pain in nondiabetic

adults, either alone or in combination with other medicinal products for pain (EU label), and the management of neuropathic pain associated with postherpetic neuralgia (US label), based on the results from two Phase 3 randomized, double-blind, dose-controlled trials in subjects with PHN [3, 4]. Most commonly known as the pungent component of hot chili pepper, capsaicin in high concentrations like the 8% topical patch is a transient receptor potential vanilloid 1 (TRPV1) agonist that is useful in relieving pain. In the body, the TRPV1 receptors are expressed in sensory neurons that detect noxious painful stimuli. Therefore, the agonist effect of capsaicin at VR1 receptors results in the defunctionalization of sensory nerve endings [4].

For the past decade, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)

have developed consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain. At their first meeting in November 2002, agreement was reached on the core outcome domains that should be considered by investigators conducting clinical trials of the efficacy and effectiveness of treatment for chronic pain. The six recommended core domains were: (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of improvement and satisfaction with treatment, (5) symptoms and adverse events, and (6) participant disposition [5].

Pain relief and patient satisfaction are distinct concepts identified by IMMPACT as central to evaluating treatment of chronic pain. Pain relief measures are used to determine whether the patient has actually benefited from an intervention and provide valuable information on how effectively pain is being managed. In contrast, patient satisfaction measures capture the personal evaluation of the intervention provided [6]. The American Pain Society (APS) Satisfaction Survey was tested to evaluate the relationships among the survey items, and whether the items are related to satisfaction [7]. The APS survey demonstrated a weak relationship between pain intensity and satisfaction, and satisfaction was influenced largely by effectiveness of medication, independent of pain intensity [7]. These results highlight that a satisfaction survey related to the effectiveness of a pain medication is an important measurement tool.

In planning the clinical trials for this novel pain treatment, satisfaction surveys in pain were reviewed to evaluate whether an existing instrument could be used in clinical trials to measure the IMMPACT core domain of patient satisfaction. The APS Satisfaction Survey focuses on pain management in general practice, but is not directly related to satisfaction with medication. Another existing survey examined was the Pain Treatment Satisfaction Scale (PTSS) [8], which measures satisfaction in patients receiving treatment for either acute or chronic pain. However, it was not designed for use in clinical trials, as it evaluates satisfaction with medical care received as well as pain medication. A third instrument that was considered for measuring patient satisfaction was the Patient's Global Impression of Change (PGIC) [9]. However, PGIC asks the patient to rate change in their overall status, which relates to multiple domains of health, rather than only assessing satisfaction with the pain treatment. Therefore, this instrument is too generic to fully describe which domains are impacted most by this novel treatment for pain. Although there were a variety of instruments capturing patient satisfaction, no existing measures were identified as appropriate for assessing patient satisfaction with medication used to treat chronic pain in the context of a clinical trial.

This lack of a suitable pain satisfaction instrument for use in trials that measure multiple domains of importance to patients supported the development of a new instrument. A recent IMMPACT survey [10] also identified 19 relevant domains of patient-reported outcomes from the perspective of people who experience pain. In addition to pain relief, aspects of daily life related to functioning and wellbeing were identified as key areas affected by symptoms that should

be targeted by treatment. The IMMPACT results stress the importance of including these domains when measuring treatment efficacy and pain relief, and they should also be taken into consideration in measuring satisfaction.

Therefore, to measure the IMMPACT-recommended domains of participant-reported improvement and satisfaction with treatment and incorporate aspects of daily life, the five-item Self-Assessment of Treatment (SAT) questionnaire was developed for use in the clinical trials evaluating a high concentration 8% capsaicin topical patch (Table 1). The SAT was developed based on this need for a clinically meaningful instrument meeting the properties of QUTENZA and the specific symptoms of PHN patients to be used in the clinical development program for QUTENZA, given that no existing treatment satisfaction instrument was identified that was deemed suitable for this work. This study examined the item performance and psychometric properties of the SAT to validate this instrument and enhance the future use of the SAT questionnaire. Standard quantitative methods were conducted using data from both of the Phase 3 registration trials to explore the factor structure, reliability, and validity of the SAT multi-item scales.

2. Methods

2.1. Study Objective. The primary objective of this study was to evaluate the psychometric properties of the SAT questionnaire as part of the validation of this instrument in patients with moderate to severe neuropathic pain secondary to PHN.

2.2. Study Design. This analysis used data collected as part of Studies C116 and C117, two Phase 3 randomized, double-blind, controlled, multicenter clinical trials conducted by NeurogesX to evaluate the efficacy, safety, and tolerability of a high-concentration 8% capsaicin topical patch (640 mcg/cm²), for the treatment of PHN (clinical trial identifiers: NCT00115310, NCT00300222).

Subjects eligible for inclusion in the two studies were adults in good health with a diagnosis of PHN and at least six months since shingles vesicle crusting, with an average Numeric Pain Rating Scale (NPRS) score for PHN-associated pain of 3 to 9, inclusive, on a scale of 0 = no pain and 10 = worst possible pain, during the screening period (usually 14 days before Study Patch Application Visit). Exclusion criteria included subjects with other pain conditions (e.g., compression-related neuropathies, fibromyalgia, arthritis) or cognitive impairment that might interfere with judging PHN-related pain or completing pain assessments.

Patients received either the study medication or low-concentration capsaicin (3.2 mcg/cm²) patches for 12 weeks. Low-concentration capsaicin control patches were used in place of placebo patches to allow for effective blinding of the study, since topical capsaicin can produce a local erythema and a burning sensation. Study C116 included 52 centers in the US, and Study C117 was comprised of 61 study sites in the US and Canada.

TABLE 1: Self-Assessment of Treatment (SAT).

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- (1) How do you assess your pain relief after treatment in this study?
- I feel my pain is much worse (-2)
 - I feel my pain is somewhat worse (-1)
 - I feel my pain is no better and no worse (0)
 - I feel my pain is somewhat better (1)
 - I feel my pain is much better (2)
- (2) How do you assess your activity level after treatment in this study?
- I feel much less active (-2)
 - I feel somewhat less active (-1)
 - I feel no more and no less active (0)
 - I feel somewhat more active (1)
 - I feel much more active (2)
- (3) How has your quality of life changed after treatment in this study?
- I feel my quality of life is much worse (-2)
 - I feel my quality of life is somewhat worse (-1)
 - I feel my quality of life is no better and no worse (0)
 - I feel my quality of life is somewhat better (1)
 - I feel my quality of life is much better (2)
- (4) Would you undergo this treatment again?*
- No, definitely not (-2)
 - No, probably not (-1)
 - Unsure (0)
 - Yes, probably (1)
 - Yes, definitely (2)
- (5) How do you compare the treatment you received in this study to previous medication or therapies for your pain?
- Very much prefer my previous treatments to this treatment (-2)
 - Somewhat prefer my previous treatments (-1)
 - No preference (0)
 - Somewhat prefer this treatment to my previous treatment (1)
 - Very much prefer this treatment to my previous treatments (2)
-

*In Study C116, SAT Item 4 was administered with 3 response options: “No, absolutely not” (-2), “Unsure” (0), and “Yes, definitely” (2). The item was administered in Study C117 with 5 response levels as shown above.

The primary objective of the two PHN studies (C116 and C117) were assessment of capsaicin patch efficacy over 12 weeks. The primary efficacy variable in each clinical trial was the percent change in “average pain for the past 24 hours” NPRS scores from Baseline to Weeks 2–8. The NPRS item is one of many other pain items in the Brief Pain Inventory (BPI). Percent change and proportion of subjects with 30% and 50% decreases in NPRS scores from Baseline to Weeks 2–8 and Weeks 2–12 were key secondary efficacy measures. Other efficacy measures included change in other BPI items, Short-Form McGill Pain Questionnaire (SF-MPQ) pain intensity rating, Medical Outcomes Study Short Form-36 Health Survey, version 2 (SF-36v2), Patient Global Impression of Change (PGIC), and Clinical Global Impression of Change (CGIC) scores from Baseline to Weeks

4, 8, and/or 12 (when measured at followup) and SAT at Week 12 (end of study).

2.3. Study Measures

2.3.1. Patient-Reported Outcome (PRO) Measures

Brief Pain Inventory (BPI). The BPI [11] provides an index of pain severity, pain relief, and the effects of pain on the subject’s ability to function. The standard BPI questionnaire includes nine items, but a modified version of the BPI (Short Form [12, 13]) was used in Studies C116 and C117. The BPI was completed at Screening, Week 8, and Termination Visit (Week 12).

The BPI administered included four questions on pain levels, where subjects were asked to rate their pain on a scale

of 0 (no pain) to 10 (worst possible pain) in response to (1) pain at its *worst* in the last 24 hours; (2) pain at its *least* in the last 24 hours; (3) pain *on average* in the last 24 hours (NPRS item); (4) pain *right now*. An additional question asked subjects to rate the level on interference of their pain with general activity, mood, and other activities of daily living on a scale of 0 (does not interfere) to 10 (completely interferes). Pain interference was assessed in seven areas: (1) general activity; (2) mood; (3) walking ability; (4) normal work (includes both work outside the home and housework); (5) relations with other people; (6) sleep; (7) enjoyment of life.

Data on the “pain now” item was collected at all study visits (Screening, Baseline (Week 0), Week 4, Week 8, and Termination Visit (Week 12)). Subjects also recorded NPRS scores for “average pain for the past 24 hours” daily in a take-home diary beginning on the evening of the Study Patch Application Visit (Day 0) through the evening before the Week 12 visit.

Short-Form McGill Pain Questionnaire (SF-MPQ). The SF-MPQ [14] asks subjects to identify their Present Pain Intensity (PPI) on a scale of 0 (no pain) to 5 (excruciating). The SF-MPQ also includes sensory and affective pain descriptors. The SF-MPQ was administered at Screening, Week 8, and Termination Visit (Week 12).

Medical Outcomes Study Short Form-36 Health Survey, Version 2 (SF-36v2). The SF-36v2 is an assessment of overall health and wellbeing rated in eight areas, including overall health, ability to perform various physical activities, emotional problems, social functioning, vitality, and pain in the previous 4 weeks [15, 16]. Scores range from 0–100, with higher scores indicating better health status. The SF-36v2 was administered at Screening and Week 8.

2.3.2. Subjective-Rated Measures of Treatment Effectiveness

Patient Global Impression of Change (PGIC) and Global Impression of Change (CGIC). The PGIC and CGIC addressed change in the severity of a patient’s illness over a particular time interval. In the C116 and C117 clinical trials, the reference time period was “after receiving study treatment.”

The PGIC was patient-reported, and asked the subject to “indicate how you feel now, compared to how you felt before receiving treatment in this study” on a 7-point scale of –3 (very much worse), 0 (no change), to +3 (very much improved). This rating scale permitted a global evaluation of the *patient’s* impression of change in their condition since admission to the study. The PGIC was completed at all three visits (Weeks 4, 8, and 12) in Studies C116 and C117, following the Study Patch Application Visit.

The CGIC was completed by the study investigator, who was asked to compare “how the subject appears to you now, compared to how they appeared to you before receiving treatment in this study” on a 7-point scale of –3 (subject very much worse), 0 (no change), to +3 (subject very much

improved). This rating scale permitted a global evaluation of the *clinician’s* impression of change in the patient’s condition since admission to the study. In Study C117, the CGIC was collected at all study visits after Baseline (Weeks 4, 8, and 12); the CGIC was not completed in Study C116.

SAT Questionnaire. Subjects were asked to assess capsaicin patch treatment using the SAT questionnaire at the Termination Visit (Week 12). The SAT evaluation form included five questions with three- or five-point response options (Table 1). The items included assessments after treatment in the study for three areas (pain relief; activity level; quality of life) and two additional items regarding (1) whether the patient would undergo the treatment again, and (2) a comparison of the study treatment to previous treatments for pain.

For each question, the subject checked a box on a five-point scale, where the middle option (0) indicated a neutral response and the lower (–2) and higher (+2) options indicated a negative or positive response, respectively. For example, SAT Item 1 asked the patient “How do you assess your pain relief after treatment in this study?” with the response options of “I feel my pain is much worse” (–2), “somewhat worse” (–1), “no better and no worse” (0), “somewhat better” (1), and “much better” (2). In Study C116, Question 4 “Would you undergo this treatment again?” was administered to subjects with only three response options: “No, absolutely not” (–2), “Unsure” (0), and “Yes, definitely” (2).

2.4. Statistical Analyses. Post hoc analyses of the SAT and other PROs were performed on the intent-to-treat (ITT) population, which included all subjects enrolled in the C116 or C117 studies who were randomized, received the study drug, and had at least three days of nonmissing “average pain for the past 24 hours” NPRS scores for the calculation of the Baseline NPRS score. The analyses incorporated the patient population for whom Termination Visit (Week 12) data were available, as this was the only time in both studies that SAT data were collected. The schedule of visits and study measures used in this analysis are summarized in Table 2.

The psychometric analyses focused on the factor structure, reliability, and validity of the SAT in the C116 and C117 datasets. Psychometric properties of the SAT were first assessed using data from Study C116; replicability of the results for SAT psychometric properties was investigated using data from Study C117. Results from analyses using the pooled samples are presented herein, given the representativeness of this larger dataset and the replicated psychometric properties demonstrated by each individual study. SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA) and MPlus version 5.21 (Muthén & Muthén, Los Angeles, CA, USA) were used to conduct the analyses. All statistical tests were two-sided and used a significance level of 0.05 unless otherwise noted.

2.4.1. Missing Values and Scoring Algorithms. For the SF-MPQ and SF-36v2, missing data were handled per the

TABLE 2: Schedule of Study Visits and Measures.

	Screening (14+ days)	Baseline (Week 0)	Visit 1 (Week 4)	Visit 2 (Week 8)	Termination Visit (Week 12)
Numeric Pain Rating Scale (NPRS)	x	x	x	x	x
Brief Pain Inventory (BPI)	x			x	x
Short-Form McGill Pain Questionnaire (SF-MPQ)	x			x	x
Short Form-36 Health Survey version 2 (SF-36v2)	x			x	
Patient's Global Impression of Change (PGIC)			x	x	x
Clinician Global Impression of Change (CGIC)*			x	x	x
Self-Assessment of Treatment (SAT)					x

*CGIC was collected in Study C117 only.

instrument developer's scoring instructions. NPRS scores for average pain in the last 24 hours were based on a daily take-home diary; baseline and Week 12 scores were computed as the average NPRS pain rating for 7 days prior to the visit. Observed data were used for analyses, with no additional imputations for missing data unless otherwise specified. As part of the exploratory nature of the analyses of the SAT's measurement properties, individual SAT items were analyzed separately, and composite subscale scores were generated. Two subscales informed by the confirmatory factor analysis (CFA) results were evaluated, reflecting items relating to treatment success (SAT Items 1, 2, and 3) and treatment satisfaction (SAT Items 4 and 5) computed as the arithmetic average of respective items' responses scores (Table 1).

2.4.2. Descriptive Statistics

Sociodemographic and PRO Measures. Descriptive statistics (mean, median, standard deviation (SD), minimum, and maximum for continuous variables and frequencies for categorical variables) for patients in the pooled sample were reported. Age, gender, race/ethnicity, height, and weight were evaluated at screening. Descriptive statistics (mean, SD, median, minimum, and maximum) for PRO subscale and component scores were examined for the overall sample. PRO measures included NPRS "pain now" and "average pain in the last 24 hours" ratings at screening and baseline (Week 0), average scores for the subscales of the SF-36v2 and SF-MPQ pain intensity at screening, BPI pain scores and composite pain interference scores at screening, SAT items and subscales, PGIC for Studies C116 and C117, and CGIC for Study C117 at Week 12.

SAT Factor (Scale) Structure. After examining the Spearman inter-item correlations to assess the extent to which the five SAT items correlated with each other, an exploratory factor analysis (EFA) and a CFA using a structural equation modeling (SEM) approach was conducted to evaluate the factor (scale) structure of the SAT and fit of the items within the hypothesized scale. The EFA and CFA were performed using the five items comprising the SAT at Week 12. In the SEM approach, parameter estimates were generated based on analysis of the actual covariance matrices representing the

relationships among SAT items and the estimated covariance matrices of the measurement model. Measurement models for one and two domains were developed, with each item loading on its respective scale. In addition, factor solutions with eigenvalues near or greater than 1.0 were examined, as well as the amount of variance accounted for by the resulting factor structure. The overall fit of each model was assessed, as well as the magnitude of the item factor loadings.

In the CFA analyses, several fit statistics were used to provide information about the adequacy of the model to explain the data. In general, the model was considered to explain the data well if the comparative fit index (CFI) was ≥ 0.90 . The standardized root mean residual (SRMR) measures the mean absolute difference between the observed and model-implied correlations; values < 0.1 were considered acceptable [17]. Finally, the root mean square error of approximation (RMSEA) is a measure of fit assessing the discrepancy between the predicted and observed data per degree of freedom; values < 0.08 were considered acceptable [18] and the 90% CI for the RMSEA should be narrow, thereby giving additional confidence in the estimate. Adequacy of item fit was also assessed through the examination of modification indices, item residual correlations, and item factor loadings.

Internal Consistency Reliability. Internal consistency reliability is a measure of the consistency of results across individual items on the same instrument. Internal consistency reliability of the SAT was evaluated using Cronbach's alpha [19] to calculate coefficients for the total instrument using data for the Termination Visit (Week 12), with a value greater than 0.70 denoting a more homogeneous instrument, offering acceptable reliability [20].

Construct Validity. Construct validity refers to the extent to which the instrument measures what it is intended to measure [20]. Construct validity of the SAT items and subscales were evaluated through the examination of the relationships between the SAT, subscales, and component scores of conceptually-related outcome measures using Spearman correlation coefficients. It was expected that patients reporting higher improvements on the PGIC and CGIC at Week 12 would also score better in the SAT items and subscale scores. In addition, correlations between the

SAT item and subscale scores and pain at the moment of responding were also explored, using the different pain questions available at Week 12: NPRS pain now and the last 24-hour average; BPI pain at worst and at least, and pain interference assessments; pain dimensions and present pain intensity of the SF-MPQ; three SF-36v2 scores for physical functioning, pain, and vitality domains most closely associated with pain. The latter were not recorded at Week 12, so change from Baseline to Week 8 was used instead. The resulting SF-36v2 subscale mean scores were also compared to the means for the US general population.

Known-Groups/Discriminant Validity. The ability of the SAT items and composite and subscale scores to discriminate between groups of patients according to levels and changes of symptom severity was also evaluated. Discriminant or known-groups validity was assessed using analysis of variance (ANOVA). These analyses provided a test of whether there were significant differences in mean SAT scores for different amounts of change based on other PRO measures. The ANOVAs were performed comparing mean SAT items and composite and subscale scores for the relevant time points and by groups defined by the following variables: (1) patient- and clinician-reported change groups created by PGIC and CGIC using the seven levels of change, and (2) high (NPRS ≥ 7) and lower (NPRS < 7) pain patients at baseline [21].

Concurrent Validity. To evaluate concurrent validity of the SAT, all items and the composite and subscale scores were used. According to the SAT responses, three response levels were created: (1) patients who improved (much better and somewhat better, or probably and definitely would undergo treatment again); (2) patients with no change (no better and no worse, or unsure about undergoing treatment again); (3) patients who worsened (much worse and somewhat worse, or probably and definitely not undergo treatment again). NPRS and other BPI item change scores were compared by SAT response groups using ANOVA models; average change scores from baseline to Week 12 in the pain reported by the NPRS pain now and average 24-hour pain and from screening to Week 12 for BPI worst and least pain items were evaluated.

3. Results

3.1. Patient Characteristics. A total of 698 patients from the ITT populations of Studies C116 ($N = 349$) and C117 ($N = 349$) were included in the current SAT analyses. Patient characteristics (age, sex, and race/ethnicity) for the patient population pooled across the two trials were similar between treatment groups (Table 3). Patients were predominantly white, with slightly more female patients (54.3%), and a mean age of 71 years (range 21–94 years).

PRO scores prior to the start of treatment provide an overall description of patient condition (Table 4). At screening, NPRS “pain now,” BPI pain ratings and pain interference, SF-MPQ pain rating, and SF-36 bodily pain

subscale scores consistently indicated that patients reported noticeable levels of pain prior to study treatment. The mean NPRS “pain now” rating at screening was 4.7 (SD = 2.2) with a median rating of 5 on the 0–10 scale. BPI scores for pain ratings and pain interference on a scale of 0–10 also indicated the presence of pain and interference from pain in most patients. SF-MPQ had a mean present pain intensity rating of 2.1 (SD = 0.9) and a median of 2 on a 0–5 scale at Screening. Average SF-36v2 subscale scores for bodily pain (mean = 44.0, SD = 18.9) were lower than other SF-36 subscales mean scores. Moreover, all mean subscale scores were below the respective US general population averages, indicating worse than average health [16].

3.2. Psychometric Properties of the SAT

3.2.1. Descriptive Statistics. Descriptive statistics for SAT items and composite and subscale scores at Week 12 are reported in Table 5 for the blinded data. Positive SAT scores corresponded to patient assessment of improvement at the completion of the study. Mean scores for SAT items ranged from 0.4 (activity level) to 1.0 (undergo treatment again), relating to an average rating between neutral and somewhat improved. On Items 1 to 3, patients reported pain relief (22.1%) and quality of life (16.3%) as “much better” and feeling “much more active” (12.3%). Over half of the patients responded that they would definitely undergo the treatment again (SAT Item 4; 51.0%). It is important to note that in Study C116, SAT Item 4 was administered to subjects with only three response options rather than a five-level response scale, which may inflate these results. Nearly one quarter responded that they preferred the study treatment to previous treatments they had received (SAT Item 5; 25.6%). Very few patients responded at the lowest possible score on SAT items; the most frequent were 5.9% on SAT Item 4 (undergo treatment again) and 5.6% on Item 5 (compared to previous treatment).

3.2.2. Inter-Item Correlations. Spearman inter-item correlations assessed the extent to which the five items of the SAT correlated with each other and with the composite scores (data not shown). Items 1 (pain relief), 2 (activity level), and 3 (quality of life) were strongly correlated with each other, and moderately correlated with Items 4 (undergo treatment again) and 5 (compared to previous treatment). Correlations among the first three items ranged from 0.67 to 0.77 (all $P < 0.0001$), while their bivariate relationships with Items 4 and 5 were weaker, ranging from 0.35 to 0.60 ($P < 0.0001$). There was a moderate correlation between Items 4 and 5 ($r = 0.51$, $P < 0.0001$).

3.2.3. SAT Factor (Scale) Structure. One- and two-factor measurement models of the SAT were developed using the pooled dataset (Study C116 and C117 combined) to evaluate item loadings and overall model fit (Table 6). Factor solutions that had eigenvalues near or greater than 1.0 and accounted for substantial amounts of the variance were considered.

TABLE 3: Patient demographic characteristics at screening (pooled dataset; $N = 698$)¹.

	<i>N</i>
Age (years)	
Mean (SD)	70.9 (11.7)
Min, Max	21–94
Age group [years; <i>n</i> (%)]	
≤50	44 (6.3%)
51–60	72 (10.3%)
61–70	168 (24.1%)
71–80	275 (39.4%)
>80	139 (19.9%)
Sex, <i>n</i> (%)	
Male	319 (45.7%)
Female	379 (54.3%)
Ethnicity, <i>n</i> (%)	
Hispanic or Latino	25 (3.6%)
Not Hispanic or Latino	673 (96.4%)
Race	
White	648 (92.8%)
African American	21 (3.0%)
Asian	12 (1.7%)
Other	17 (2.4%)

SD: standard deviation.

¹ Pooled dataset included data from two clinical trials, Studies C116 ($N = 349$) and C117 ($N = 349$).

Exploratory Factor Analysis. Exploratory one- and two-factor models were evaluated to determine the factor structure of the SAT (Table 6). The one-factor solution, including all five SAT items, had an eigenvalue of 3.26, and the model explained 65% of the variance in the SAT. Factor loadings ranged from 0.47 to 0.85, suggesting that all five items were related to the overall treatment construct. EFA results showed that factor loadings were largest for SAT Items 1 to 3, with all loadings >0.80; loadings for the other SAT items were acceptable, but slightly lower with a loading of 0.47 for SAT Item 4 and 0.65 for SAT Item 5.

A two-factor exploratory model was also specified to evaluate the tenability of extracting a second factor (Table 6). Eigenvalues in the two-factor model were 3.26 for the first factor and 0.79 for the second factor. The proportion of variance explained by the first factor was 65%, and total variance explained by the model was 81%; the addition of a second factor in the model accounted for an additional 16% of variance in SAT items. Factor loadings showed a clear demarcation between factors, with SAT Items 1, 2, and 3 loading on the first factor (treatment effects), and SAT Items 4 and 5 loading of a second factor (treatment satisfaction).

Confirmatory Factor Analysis. Based on the EFA results, confirmatory models were performed to formally test the one- and two-factor structures (Table 6). In the single factor

model, the five SAT items were specified to load onto the first factor. General results for the CFA model were the same as reported previously for the one-factor EFA model. The chi-square test for model fit was highly significant ($\chi^2(df = 5) = 92.83, P < 0.0001$). Model fit statistics showed good fit (CFI = 0.95) and relatively low residuals (SRMR = 0.048); RMSEA suggested a slightly worse fit (RMSEA = 0.16, 90% CI = 0.13–0.19).

In the second model, SAT Items 1, 2, and 3 were specified as loading on the first factor, and SAT Items 4 and 5 as loading on the second factor. The chi-square test of model fit for the two-factor CFA was significant ($\chi^2(df = 4) = 29.19, P < 0.0001$). Model fit was very good (CFI = 0.99) with small residuals (SRMR = 0.024; RMSEA = 0.10, 90% CI = 0.07–0.13), indicating that the model adequately explained the data; RMSEA suggested a slightly worse fit than other fit indices. Loadings for the prespecified factor structure were generally large and consistent with the EFA results. Factor loadings for SAT Items 1, 2, and 3 with Factor 1 were 0.82, 0.85, and 0.93, respectively, and 0.59 for SAT Item 4 and 0.84 for SAT Item 5 on the second factor. Although the two factors were strongly correlated ($r = 0.75$), this two-factor solution created the best structure for interpretable SAT composite scale scores.

3.2.4. Internal Consistency Reliability. Cronbach's alpha was used to examine internal consistency reliability for the two SAT subscales using combined patient populations from the two trials at the Termination Visit (Week 12). The SAT subscale comprised only of SAT Items 1 to 3 (pain relief, activity level, and quality of life) evaluating treatment effectiveness had excellent reliability, with an alpha of 0.89. A separate subscale made up of SAT Items 4 and 5 (undergo treatment again, compared to previous treatment) evaluating treatment satisfaction had an alpha of 0.66.

3.2.5. Validity

Construct Validity. Construct validity of the SAT was assessed by examining relationships between SAT items and subscale scores with conceptually-related outcome measures using Spearman correlation coefficients (Table 7). Outcome measures included PGIC and CGIC at Week 12, change scores between Baseline (Week 0) and Week 12 for pain now and average 24-hour pain, change scores between Screening and Week 12 for BPI pain and interference and SF-MPQ pain dimensions, and change scores between screening and Week 8 for SF-36v2 physical functioning, bodily pain, and vitality subscales.

Moderate to large positive correlations were observed between SAT items and scores and PGIC and CGIC (Study C117 only) at Week 12 (Table 7). These positive relationships indicated that improvements based on global impressions of change were related to better evaluation of the study treatment at Week 12. All correlations reached statistical significance, and a similar pattern was found with both the patient and clinician assessments. Correlations between SAT items and PGIC in the combined sample ranged from 0.44 to 0.90 (all $P < 0.0001$). In Study C117, correlations with

TABLE 4: Descriptive statistics for PRO measures at screening and baseline (pooled dataset; $N = 698$)¹.

	N	Mean (SD)	Median	Range
NPRS pain now (screening)	698	4.7 (2.2)	5	0.0–10.0
NPRS average pain in last 24 hours ² (baseline)	695	5.8 (1.6)	6	1.6–9.9
BPI (screening)				
Pain at its worst in the last 24 hours	698	6.8 (2.0)	7	0.0–10.0
Pain at its least in the last 24 hours	698	3.1 (2.1)	3	0.0–10.0
Pain on average in the last 24 hours	698	5.1 (1.7)	5	0.0–10.0
Pain right now	698	4.5 (2.3)	4	0.0–10.0
BPI pain interference scores (screening)				
A. General activity	698	3.6 (2.9)	3	0.0–10.0
B. Mood	697	3.7 (2.8)	3	0.0–10.0
C. Walking ability	697	2.5 (2.9)	1	0.0–10.0
D. Normal work	697	3.6 (2.9)	3	0.0–10.0
E. Relation with other people	698	2.5 (2.6)	2	0.0–10.0
F. Sleep	698	4.1 (3.1)	4	0.0–10.0
G. Enjoyment of life	698	4.2 (2.9)	4	0.0–10.0
SF-MPQ (screening)				
Present pain intensity	696	2.1 (0.9)	2	0.0–5.0
SF-36v2 (screening)				
Physical functioning	698	59.5 (27.9)	60	0.0–100.0
Role-physical	698	55.6 (28.0)	56	0.0–100.0
Bodily pain	698	44.0 (18.9)	41	0.0–100.0
General health	698	67.4 (19.3)	67	5.0–100.0
Role-emotional	698	71.9 (27.3)	75	0.0–100.0
Vitality	698	52.0 (20.7)	56	0.0–100.0
Mental health	698	71.8 (18.7)	75	5.0–100.0
Social functioning	698	71.6 (26.2)	75	0.0–100.0
PGIC (Week 12)	697	0.9 (1.2)	1	–3.0–3.0
CGIC ³ (Week 12)	349	1.0 (1.2)	1	–2.0–3.0

BPI: Brief Pain Inventory; CGIC: Clinician Global Impression of Change; NPRS: Numeric Pain Rating Scale; PGIC: Patient Global Impression of Change; SD: standard deviation.

¹Pooled dataset included data from two clinical trials, Studies C116 ($N = 349$) and C117 ($N = 349$).

²Average NPRS pain rating for 7 days prior to visit.

³Study C117 only.

TABLE 5: Descriptive statistics for SAT items at Week 12 (pooled dataset; $N = 698$)¹.

SAT item	N	Mean (SD)	Median	Floor (n, %)	Ceiling (n, %)
(1) How do you assess your pain relief after treatment in this study?	698	0.6 (0.9)	0	8 (1.1%)	154 (22.1%)
(2) How do you assess your activity level after treatment in this study?	698	0.4 (0.8)	0	8 (1.1%)	86 (12.3%)
(3) How has your quality of life changed after treatment in this study?	698	0.5 (0.8)	0	6 (0.9%)	114 (16.3%)
(4) Would you undergo this treatment again?	698	1.0 (1.2)	2	41 (5.9%)	356 (51.0%)
(5) How do you compare the treatment you received in this study to previous medication or therapies for your pain?	698	0.5 (1.1)	0	39 (5.6%)	179 (25.6%)

SAT: Self-Assessment of Treatment; SD: standard deviation.

¹Pooled dataset included data from two clinical trials, Studies C116 ($N = 349$) and C117 ($N = 349$).

CGIC ranged from 0.48 to 0.85 (all $P < 0.0001$). SAT Item 1 (pain relief) was the most strongly related to PGIC ($r = 0.90$, $P < 0.0001$) and CGIC ($r = 0.85$, $P < 0.0001$). Correlations between SAT Item 4 (undergo treatment again) with PGIC ($r = 0.44$, $P < 0.0001$) and CGIC ($r = 0.48$, $P < 0.0001$)

were quite smaller, although moderate in magnitude and statistically significant.

Among SAT composite scale scores, the three-item subscale comprised of pain relief, activity level, and quality of life had the largest correlations with patient ($r = 0.89$,

TABLE 6: Standardized factor loadings for one- and two-factor exploratory and confirmatory SAT models (pooled dataset; $N = 698$)¹.

SAT item	Factor loadings				
	1-factor EFA/CFA	2-factor EFA		2-factor CFA	
		Domain 1	Domain 2	Domain 1	Domain 2
(1) How do you assess your pain relief after treatment in this study?	0.83	0.65	0.24	0.82	
(2) How do you assess your activity level after treatment in this study?	0.85	0.89	-0.05	0.85	
(3) How has your quality of life changed after treatment in this study?	0.92	0.93	0.01	0.93	
(4) Would you undergo this treatment again?	0.47	-0.01	0.66		0.59
(5) How do you compare the treatment you received in this study to previous medication or therapies for your pain?	0.65	0.21	0.62		0.84

EFA: exploratory factor analysis; CFA: confirmatory factor analysis; SAT: Self-Assessment of Treatment.

¹Exploratory and confirmatory factor analyses were conducted to evaluate the factor (scale) structure of the SAT and fit of the 5 items within the hypothesized scale. Pooled dataset included data from two clinical trials, Studies C116 ($N = 349$) and C117 ($N = 349$).

$P < 0.0001$) and clinician ($r = 0.83, P < 0.0001$) assessments. The two-item subscale made up of SAT Items 4 and 5 was more weakly related to PGIC ($r = 0.61, P < 0.0001$) and CGIC ($r = 0.64, P < 0.0001$).

Overall, SAT was moderately correlated with changes in pain-related outcomes (Table 7). Statistically significant negative correlations indicated that better evaluation of study treatment was generally associated with reduction in pain over the study period. Correlations between SAT items and NPRS pain now and average 24-hour pain change scores ranged from -0.30 to -0.69 (all $P < 0.0001$). Changes in BPI pain at worst ($r = -0.28$ to -0.64 , all $P < 0.0001$) and at least ($r = -0.27$ to -0.52 , all $P < 0.0001$) in the last 24 hours and SF-MPQ present pain intensity scores ($r = -0.20$ to -0.45 , all $P < 0.0001$) showed a similar range of correlations with SAT items. As expected, SAT pain relief (Item 1) consistently showed the strongest relationships with pain change scores. Associations between SAT activity level (Item 2) and quality of life (Item 3) with changes in pain were slightly smaller. The weakest relationships were found with SAT items related to treatment satisfaction (Items 4 and 5). Weaker associations were observed between SAT items and changes in BPI pain interference with general activity, mood, and other activities of daily living and SF-MPQ pain intensity ratings for sensory and affective descriptors (data not shown). The majority of these correlations were small, with none larger in magnitude than -0.40 .

Among the SAT composite scale scores, the treatment effect subscale (pain relief, activity level, and quality of life) showed stronger relationships with changes in pain based on NPRS, BPI, and SF-MPQ items than the two-item treatment satisfaction subscale.

SAT items were more related to SF-36v2 bodily pain ($r = 0.27$ to 0.43 , all $P < 0.0001$) than physical functioning ($r = 0.14$ to 0.25 , all $P < 0.001$ or lower) or vitality ($r = 0.09$ to 0.25 , all $P < 0.05$ or lower) subscales. Also, correlations between SAT treatment effect items (pain relief, activity level, and quality of life) and changes in health status were consistently larger than with SAT items related to satisfaction (undergo treatment again, compared to previous treatment).

A similar pattern was obtained for SAT subscale scores with changes in SF-36v2 health status domains.

Discriminant/Known-Groups Validity. Known-groups analyses examined the ability of SAT items and subscale scores at Week 12 to discriminate between patient groups using patient- and clinician-reported change at Week 12 and NPRS pain levels at Baseline. Change groups represented global assessments of change over the study period using the seven response levels for PGIC and CGIC. NPRS pain ratings at Baseline were categorized as high (NPRS ≥ 7) and low (NPRS < 7) pain groups.

Significant differences in mean SAT items and scores between change groups based on PGIC and CGIC were identified. Results demonstrate an overall pattern of average SAT scores that differ as a function of response levels for global assessments of change (Table 8). SAT showed evidence of ability to discriminate between change levels based on patient and clinician global assessments; SAT scores had a pattern of least-squares means very close to zero, corresponding to the “no change” group for PGIC or CGIC, and increasingly positive mean SAT scores for global assessment improvement levels and corresponding negative mean SAT scores for worsening levels. The lowest response levels on the negative end of the PGIC/CGIC response scale had very small sample sizes; the “very much worse” and “much worse” responses were pooled for these analyses. The “slightly worse” global assessment level was still shown to have lower mean SAT scores than the “no change” group, and higher mean SAT scores than the “much worse/very much worse” group, as expected. Mean SAT scores significantly differed between change groups for SAT items and subscale scores (all $P < 0.0001$).

Some SAT scores showed evidence of ability to discriminate between patient pain level groups based on NPRS pain at Baseline (Table 9). Mean SAT scores for patients with high pain at Baseline were slightly lower than scores for lower pain patients. Based on t -test comparisons, patients with less pain at Baseline had significantly higher scores than those with

TABLE 7: Construct validity: correlations between SAT and PRO measures (pooled dataset; $N = 698$)¹.

	Spearman correlations ²						
	SAT 1 (Pain relief)	SAT 2 (Activity level)	SAT 3 (Quality of life)	SAT 4 (Undergo treatment again)	SAT 5 (Compared to previous treatment)	3-Item SAT treatment effect subscale	2-Item SAT treatment satisfaction subscale
PGIC	0.90	0.68	0.77	0.44	0.62	0.89	0.61
CGIC ³	0.85	0.63	0.73	0.48	0.64	0.83	0.64
NPRS change scores							
Pain now	-0.60	-0.47	-0.51	-0.30	-0.37	-0.59	-0.38
Average 24 hour pain	-0.69	-0.53	-0.60	-0.35	-0.45	-0.68	-0.46
BPI change scores							
Pain in last 24 hours—at worst	-0.64	-0.50	-0.53	-0.28	-0.40	-0.63	-0.39
Pain in last 24 hours—at least	-0.52	-0.38	-0.44	-0.27	-0.32	-0.50	-0.34
SF-MPQ present pain intensity change scores	-0.45	-0.41	-0.43	-0.20	-0.29	-0.47	-0.29
SF-36v2 change scores							
Physical functioning	0.20	0.16	0.25	0.14 ⁴	0.15 ⁴	0.23	0.16
Bodily pain	0.43	0.40	0.40	0.27	0.29	0.46	0.33
Vitality	0.25	0.23	0.21	0.09 ⁵	0.14 ⁴	0.25	0.14 ⁴

BPI: Brief Pain Inventory; CGIC: Clinician Global Impression of Change; NPRS: Numeric Pain Rating Scale; PGIC: Patient Global Impression of Change; SAT: Self-Assessment of Treatment.

¹Construct validity of SAT item and subscales were evaluated by examining relationships between SAT items and subscales with component scores of conceptually-related outcome measures using Spearman correlation coefficients. Pooled dataset included data from two clinical trials, Studies C116 ($N = 349$) and C117 ($N = 349$).

²Bivariate correlations were significant at $P < 0.0001$, except where noted otherwise.

³Study C117 only.

⁴ $P < 0.001$.

⁵ $P < 0.05$.

TABLE 8: Known-groups validity: ANOVA models of SAT scores by global assessment levels at Week 12 (pooled dataset; $N = 698$)¹.

		SAT at Week 12							
		n	(1) Pain relief	(2) Activity level	(3) Quality of life	(4) Undergo treatment again	(5) Compared to previous treatment	3-Item SAT treatment effect subscale	2-Item SAT treatment satisfaction subscale
PGIC, LS mean (SE)									
Very much improved		103	1.9 (0.0)	1.4 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	5.0 (0.1)	3.5 (0.2)
Much improved		115	1.4 (0.0)	0.8 (0.1)	1.0 (0.0)	1.6 (0.1)	1.1 (0.1)	3.3 (0.1)	2.7 (0.1)
Slightly improved		159	0.8 (0.0)	0.3 (0.0)	0.5 (0.0)	1.1 (0.1)	0.5 (0.1)	1.6 (0.1)	1.6 (0.1)
No change		275	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.6 (0.1)	0.0 (0.1)	-0.1 (0.1)	0.6 (0.1)
Slightly worse		31	-0.7 (0.1)	-0.3 (0.1)	-0.1 (0.1)	0.0 (0.2)	-0.2 (0.2)	-1.1 (0.2)	-0.2 (0.3)
Much worse ²		14	-1.2 (0.1)	-0.9 (0.2)	-0.9 (0.1)	-0.9 (0.3)	-1.1 (0.2)	-3.0 (0.3)	-2.0 (0.4)
P -value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
CGIC ³ , LS mean (SE)									
Very much improved		63	1.9 (0.1)	1.4 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	5.0 (0.2)	3.5 (0.2)
Much improved		56	1.4 (0.1)	0.7 (0.1)	1.0 (0.1)	1.3 (0.1)	1.1 (0.1)	3.0 (0.2)	2.4 (0.2)
Slightly improved		78	0.7 (0.1)	0.3 (0.1)	0.5 (0.1)	0.9 (0.1)	0.4 (0.1)	1.5 (0.2)	1.3 (0.2)
No change		140	-0.1 (0.0)	-0.1 (0.1)	-0.1 (0.0)	0.3 (0.1)	-0.2 (0.1)	-0.3 (0.1)	0.1 (0.1)
Slightly worse		10	-0.1 (0.2)	0.1 (0.2)	0.2 (0.2)	-0.2 (0.3)	-0.1 (0.3)	0.2 (0.4)	-0.3 (0.5)
Much worse ²		2	-1.5 (0.4)	-0.5 (0.5)	-0.5 (0.4)	-1.5 (0.7)	-0.5 (0.7)	-2.5 (1.0)	-2.0 (1.1)
P -value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

ANOVA: analysis of variance; CGIC: Clinician Global Impression of Change; LS: least-squares; PGIC: Patient Global Impression of Change; SAT: Self-Assessment of Treatment; SE: standard error.

¹Known-groups validity was assessed using ANOVA to evaluate whether SAT items and subscale scores discriminated between patient groups based on different amounts of patient- and clinician-reported change at Week 12. Pooled dataset included data from two clinical trials, Studies C116 ($N = 349$) and C117 ($N = 349$).

²PGIC and CGIC responses of “Very much worse” and “Much worse” were combined due to small sample sizes.

³Study C117 only.

TABLE 9: Known-groups validity: *t*-tests of SAT scores by NPRS pain level at baseline (pooled dataset; *N* = 698)¹.

SAT	Baseline NPRS pain level		<i>P</i> -value
	High pain (<i>n</i> = 172)	Low pain (<i>n</i> = 526)	
	Mean (SD)	Mean (SD)	
(1) Pain relief	0.4 (1.0)	0.7 (0.9)	0.001
(2) Activity level	0.2 (0.8)	0.4 (0.8)	0.013
(3) Quality of life	0.4 (0.8)	0.5 (0.8)	0.015
(4) Undergo treatment again	1.0 (1.2)	1.0 (1.2)	0.841
(5) Compared to previous treatment	0.4 (1.1)	0.5 (1.1)	0.080
SAT treatment effect subscale (Items 1, 2, and 3)	1.0 (2.3)	1.6 (2.3)	0.002
SAT treatment satisfaction subscale (Items 4 and 5)	1.3 (1.9)	1.5 (2.0)	0.275

NPRS: Numeric Pain Rating Scale; SAT: Self-Assessment of Treatment; SD: standard deviation.

¹Known-groups validity was assessed using *t*-tests to evaluate whether SAT items and subscale scores discriminated between patient groups by baseline pain level (high, low pain). Pooled dataset included data from two clinical trials, Studies C116 (*N* = 349) and C117 (*N* = 349).

TABLE 10: Concurrent validity: ANOVA models of NPRS change scores by SAT scores at Week 12 (pooled dataset; *N* = 698)¹.

SAT	NPRS change scores at Week 12						
		Pain now			Average pain in last 24 hours		
		<i>N</i>	LS mean (SE)	<i>P</i> -value	<i>N</i>	LS mean (SE)	<i>P</i> -value
(1) How do you assess your pain level after treatment in this study?	Better	341	-2.5 (0.1)	<0.0001	339	-2.9 (0.1)	<0.0001
	No change	310	-0.3 (0.1)	303	-0.5 (0.1)		
	Worse	47	0.8 (0.3)	46	(0.2)		
(2) How do you assess your activity level after treatment in this study?	Better	210	-2.9 (0.1)	<0.0001	209	-3.2 (0.1)	<0.0001
	No change	453	-0.7 (0.1)	445	-1.0 (0.1)		
	Worse	35	0.4 (0.4)	34	-0.1 (0.3)		
(3) How has your quality of life changed after treatment in this study?	Better	266	-2.6 (0.1)	<0.0001	265	-3.1 (0.1)	<0.0001
	No change	410	-0.6 (0.1)	402	-0.8 (0.1)		
	Worse	22	1.2 (0.4)	21	(0.4)		
(4) Would you undergo this treatment again?	Better	451	-1.8 (0.1)	<0.0001	445	-2.1 (0.1)	<0.0001
	No change	174	-0.4 (0.2)	172	-0.8 (0.1)		
	Worse	73	-0.3 (0.3)	71	-0.5 (0.2)		
(5) How do you compare the treatment you received in this study to previous medication or therapies for your pain?	Better	296	-2.2 (0.1)	<0.0001	294	-2.6 (0.1)	<0.0001
	No change	312	-0.7 (0.1)	306	-0.9 (0.1)		
	Worse	90	-0.4 (0.2)	88	-0.8 (0.2)		
SAT treatment effect subscale (Items 1, 2, and 3)	Better	359	-2.4 (0.1)	<0.0001	357	-2.8 (0.1)	<0.0001
	No change	280	-0.3 (0.1)	273	-0.5 (0.1)		
	Worse	59	0.9 (0.3)	58	0.2 (0.2)		
SAT treatment satisfaction subscale (Items 4 and 5)	Better	448	-1.8 (0.1)	<0.0001	443	-2.1 (0.1)	<0.0001
	No change	141	-0.5 (0.2)	138	-0.9 (0.2)		
	Worse	109	-0.2 (0.2)	107	-0.5 (0.2)		

ANOVA: analysis of variance; LS: least-squares; NPRS: Numeric Pain Rating Scale; SAT: Self-Assessment of Treatment; SE: standard error.

¹Concurrent validity was evaluated using ANOVA to compare NPRS changes in pain by SAT response levels (patients improved; no change; worsened). Pooled dataset included data from two clinical trials, Studies C116 (*N* = 349) and C117 (*N* = 349).

TABLE 11: Concurrent validity: ANOVA models of BPI change scores by SAT scores at Week 12 (pooled dataset; $N = 698$)¹.

SAT		BPI change scores at Week 12					
		Pain at its worst in last 24 hours			Pain at its least in the last 24 hours		
		<i>N</i>	LS mean (SE)	<i>P</i> -value	<i>N</i>	LS mean (SE)	<i>P</i> -value
(1) How do you assess your pain level after treatment in this study?	Better	340	-3.6 (0.1)	<0.0001	340	-1.3 (0.1)	<0.0001
	No change	309	-0.8 (0.1)	309	0.7 (0.1)		
	Worse	47	0.5 (0.3)	47	1.3 (0.3)		
(2) How do you assess your activity level after treatment in this study?	Better	210	-4.1 (0.2)	<0.0001	210	-1.5 (0.1)	<0.0001
	No change	451	-1.3 (0.1)	451	0.3 (0.1)		
	Worse	35	0.2 (0.4)	35	(0.4)		
(3) How has your quality of life changed after treatment in this study?	Better	266	-3.8 (0.1)	<0.0001	266	-1.4 (0.1)	<0.0001
	No change	408	-1.1 (0.1)	408	0.5 (0.1)		
	Worse	22	0.3 (0.5)	22	(0.4)		
(4) Would you undergo this treatment again?	Better	450	-2.6 (0.1)	<0.0001	450	-0.6 (0.1)	<0.0001
	No change	173	-1.1 (0.2)	173	0.5 (0.2)		
	Worse	73	-0.9 (0.3)	73	(0.3)		
(5) How do you compare the treatment you received in this study to previous medication or therapies for your pain?	Better	295	-3.3 (0.1)	<0.0001	295	-1.1 (0.1)	<0.0001
	No change	312	-1.3 (0.1)	312	0.4 (0.1)		
	Worse	89	-1.0 (0.3)	89	0.3 (0.2)		
SAT treatment effect subscale (Items 1, 2, and 3)	Better	358	-3.5 (0.1)	<0.0001	358	-1.2 (0.1)	<0.0001
	No change	279	-0.8 (0.1)	279	0.7 (0.1)		
	Worse	59	0.4 (0.3)	59	1.2 (0.3)		
SAT treatment satisfaction subscale (Items 4 and 5)	Better	447	-2.7 (0.1)	<0.0001	447	-0.6 (0.1)	<0.0001
	No change	141	-1.0 (0.2)	141	0.6 (0.2)		
	Worse	108	-0.9 (0.3)	108	0.5 (0.2)		

ANOVA: analysis of variance; BPI: Brief Pain Inventory; LS: least-squares; SAT: Self-Assessment of Treatment; SE: standard error.

¹Concurrent validity was evaluated using ANOVA to compare BPI changes in pain by SAT response levels (patients improved; no change; worsened). Pooled dataset included data from two clinical trials, Studies C116 ($N = 349$) and C117 ($N = 349$).

high pain on SAT Items 1 (pain level; $P < 0.01$), 2 (activity level; $P < 0.05$), and 3 (quality of life; $P < 0.05$).

Concurrent Validity. Concurrent validity of SAT items and scores was evaluated using ANOVA models comparing average change scores from Baseline to Week 12 in pain reported by the NPRS pain now and average 24-hour pain, and Screening to Week 12 for BPI worst and least pain items by SAT response levels (patients who improved, no change, or worsened).

The degree of change in NPRS scores between Baseline and Week 12 of the study concurred with the classification into change groups based on SAT scores (Table 10). Negative change scores on NPRS pain now and average pain for the last 24 hours indicated decreases in pain over time, and SAT groups for “better,” “no change,” and “worse” were associated with varying amounts of change. Most NPRS change scores at all levels of SAT responses were negative, suggesting that patients overall had experienced a decrease in pain over the

study period. On average, patients in the SAT improvement group had the largest negative change scores (two- to three-point decreases in pain); two-point changes in NPRS can be interpreted as reflecting important change [22]. Patients with no change had smaller change scores, generally less than a one-point mean decrease. Worsening reported on the SAT corresponded to either small negative change scores (small decreases in pain) or positive change scores, indicating more pain. Significant differences in NPRS measures were observed across the three SAT response levels for all items and scores (all $P < 0.0001$).

Change in pain based on BPI pain at its worst and pain at its least also reflected differences based on SAT response levels (Table 11). Magnitude of the change scores tended to be larger for BPI pain at its worst than for pain at its least in the last 24 hours, particularly for “better” and “no change” SAT groups. Similar to the NPRS outcomes, negative change scores corresponded to decreases in pain over time, and varying amounts of mean change on these BPI items were

observed for SAT change groups. Average BPI change scores for the SAT “better” group were the largest, with decreases of up to four points. Both positive and negative mean changes were observed for the “no change” and “worse” groups. Based on the ANOVA models, differences in BPI change scores for pain by SAT groups were statistically significant (all $P < 0.0001$).

4. Discussion

Because the value and importance of therapeutic changes differ greatly among participants, as well as between patients and their clinicians [23], it is essential that chronic pain clinical trials directly measure patient-reported improvement and satisfaction with treatment [5].

The SAT was designed for use in clinical trials to assess the IMMPACT-recommended domain of improvement of patients with PHN and their satisfaction with treatment using a high concentration 8% capsaicin patch. Psychometric properties of the SAT examined in this study demonstrated that the first three items assessing improvement of pain relief, activity level, and quality of life had a strong factor structure, high internal consistency reliability, and moderate to strong construct validity with change in other study endpoints. Moreover, the three-item SAT scores consistently discriminated between patient change groups defined by the PGIC response categories in both studies and the CGIC responses used in Study C117. Two additional SAT items querying whether patients would undergo the treatment again and how the study treatment compares to previous medication or therapies for the patient’s pain did not demonstrate a strong structural relationship with the other three items, although both are key components to understanding satisfaction with this treatment. These two items assess important treatment-related concepts for patients who must determine whether the positive attributes of a treatment outweigh any potential side effects; this determination is key in understanding whether current and future patients will adhere to and continue with treatment [5].

To provide useful and valid information, a satisfaction subscale needs to be reliable and valid, and should capture a meaningful concept. In this case, the measurement properties were weaker for the two-item satisfaction subscale in terms of internal consistency reliability and known-groups validity. The satisfaction subscale had lower construct and concurrent validity, and was also less responsiveness in detecting change. Moreover, although the factor analysis supported a two-factor solution, the magnitude of the second factor’s loading did not support a clear and distinct concept.

Despite the favorable psychometric results displayed by the five SAT items—and specifically the three-item treatment effects scale—there are several limitations to these SAT items. First, the patient’s response to the SAT items requires a 12-week retrospective assessment by the patient, requiring each to somehow remember their condition (pain, activity level, quality of life, etc.) before initiating treatment, and to mentally subtract this assessment from their current state to select the most appropriate response (Table 1). These retrospective assessments are known to be prone to recall

bias [24], with a strong correlation to the current state and a weak relationship with the initial state. Second, the concepts of pain, activities, and quality of life can have broad meaning across a population of patients, and without more detailed terms (e.g., daily, strenuous, social, etc.) for each of these three concepts, it remains unknown what patients considered when making their assessments of change. Third, the response scales used in Item 4 differed between the two studies and could have contributed to this item’s weaker psychometric properties compared to the other SAT items in these analyses. In addition, Item 5 asks patients to compare their treatment to previous medications or therapies for pain, but these comparator treatments remain unknown and may have greatly differed across the patients in these two clinical trials.

Although there is no publication describing the instrument development process for the SAT, these items assess key areas of treatment change (i.e., pain, activities, quality of life) recommended by IMMPACT [5] and are appropriate for use in clinical trial study and research settings to measure participant ratings of improvement and satisfaction with treatment stressed in the IMMPACT recommendations. However, the psychometric performance suggests that the questionnaire items could be further improved with additional patient input for item clarity, response option revision, and the associated recall period to better reflect pain-related treatment benefits. Future research grounded in patient input should examine the use of frequent cross-sectional assessments with a seven-day recall period to assess change in these concepts measured at Baseline and over time at study visits. Moreover, because activity level and quality of life are very broad terms, specific types of activity (e.g., daily, strenuous, social, etc.) may provide more interpretable measures. Similarly, asking about “quality of life” is also quite broad and nonspecific, and improved measurement of specific domains (e.g., emotional wellbeing, physical functioning, and social functioning) may also increase the usefulness of these patient ratings collected over time.

5. Summary

The ability of the SAT questionnaire to measure improvements and satisfaction with treatment in PHN clinical trials was psychometrically evaluated, with recommendations for future use.

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