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Relationship of Depression and Catastrophizing to Pain, Disability, and Medication Adherence in Patients with HIV-Associated Sensory Neuropathy

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Abstract

Few studies have examined how patients with chronic HIV infection cope with pain and how pain relates to medication adherence. Pain coping strategies such as catastrophizing are often associated with increased pain and disability and may also influence adherence to medications. The goal of our study is to assess the relationship of catastrophizing and depression to pain, disability, and medication adherence through questionnaires administered to a cross-section of patients with HIV-associated sensory neuropathy. In our study, 46 HIV-seropositive subjects completed questionnaires evaluating neuropathic pain severity, pain catastrophizing, pain-related disability, depressive symptoms, severity of antiretroviral therapy (ART) side effects, and common reasons for medication non-adherence. Hierarchical regression analysis indicated that pain catastrophizing correlated with severity of neuropathic pain independent of depressive symptoms. Furthermore, depressive symptoms were not associated with multiple factors independent of pain catastrophizing, such as severity of neuropathic pain and pain-related disability. Pain catastrophizing, but not depressive symptoms, correlated with increased pain disability even after controlling for the effects of age and neuropathic pain. We also found that poor adherence attributed to fear of side effects or forgetfulness was associated with increased severity of neuropathic pain, while depressive symptoms but not catastrophizing correlated with ART side effects. These findings suggest that both catastrophizing and depressive symptoms are important factors to consider in the management of pain from HIV neuropathy and adherence to ART.

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Keywords

HIV; neuropathy; depression; catastrophizing; medication adherence

Introduction

Neuropathic pain may be caused by either central (e.g. stroke, multiple sclerosis) or peripheral (e.g. diabetic neuropathy, herpes zoster) nervous system disease or injury (Jensen, Chodroff, & Dworkin, 2007). Peripheral neuropathy is a frequent neurologic complication in HIV-seropositive patients (Verma, 2001), and distal sensory polyneuropathy (DSP) is the most common peripheral neuropathy in this population, afflicting approximately one-third of patients (Keswani, Pardo, Cherry, Hoke, & McArthur, 2002). The pathogenesis of HIV-associated sensory neuropathy (HIV-SN) is unclear, but both chronic HIV infection and anti-retroviral therapy (ART) toxicity have been implicated as etiologies (Luciano, Pardo, & McArthur, 2003). HIV-SN may be associated with spontaneous and evoked neuropathic pain regardless of etiology, such as burning paresthesias, numbness, tingling, and severe shooting pains (Simpson & Tagliata, 1995). When chronic, these symptoms may account for significant morbidity in this population (Singer et al 1993). Despite prior studies investigating the epidemiology of HIV peripheral neuropathy, as well as risk factors, mechanisms, and potential interactions with other coexistent conditions, few studies have explored how patients with HIV cope with chronic pain.

Since medical treatment of chronic neuropathic pain is often limited due to medication side effects and/or symptom intractability, there has been an interest in the psychological effects of neuropathic pain and the development of non-medicinal interventions. Pain catastrophizing has received a great deal of attention in the pain literature and is characterized as a negative emotional and cognitive response to pain comprised of magnification, rumination, and helplessness (Sullivan et al. 2001). For persistent pain in general, there is an association between catastrophizing, helplessness, and pain-related anxiety/fear with increased pain, psychological distress, and physical disability (Keefe, Rumble, Scipio, Giordano, Perri, 2004). Self-efficacy, pain-coping strategies, acceptance, and readiness to change were also associated with reduced pain, distress, and disability. Catastrophizing has been recognized as an important determinant of pain and pain-related disability in patients with many chronically painful conditions, including neuropathic pain (Sullivan, Lynch, & Clark, 2005), and has also been reported as a risk factor for suicidal ideation in patients with chronic pain (Edwards, Smith, Kudel, & Haythornthwaite, 2006). These associations belie the importance of therapies directed at catastrophizing--pain-coping strategies--that could provide relief for patients with chronic pain, including pain from HIV-SN.

In patients with HIV, chronic pain has been associated with depression. For example, a study of HIV-positive men demonstrated that patients with greater pain had greater depressive symptoms and that the increased depression was accounted for by the somatic complaints (Evans et al. 1998). Catastrophizing, however, was not measured in this study. Subsequent research among individuals specifically suffering from HIV peripheral

neuropathy showed that catastrophizing was an important predictor of increased depression and pain interference; these results were not correlated with a neuropathic pain scale, however (Griswold, Evans, Spielman, & Fishman, 2005). In the same study, catastrophizing predicted distress and interference with function, while depressive symptoms predicted pain intensity and interference. Coping strategies that address catastrophizing were also noted to differ in this study depending on age, gender, and ethnic background.

Treating catastrophizing may have effects beyond ameliorating chronic pain. A recent review has speculated that catastrophizing might influence long-term outcomes via numerous pathways, including effects on various health behaviors such as medication adherence (Edwards, Bingham, Bathon, & Haythornthwaite, 2006). At this time, however, evidence regarding the relationship between chronic pain, pain-related coping strategies, and medication adherence to ART, particularly in the setting of known and frequent side effects to some of these medications (e.g. neuropathy), is sparse. Negative thoughts about pain, including helplessness and thoughts similar to catastrophizing, have been associated with interference in daily functional activities, overall distress, and affective symptoms in HIV patients reporting neuropathic pain (Evans, Weinberg, Spielman, & Fishman, 2003). While medication adherence has been investigated in both HIV-infected and chronic pain patients (Ingersoll, & Cohen, 2008), the complex inter-relationships between pain, impairment, psychological function, and coping strategies have not been fully investigated, and to our knowledge no studies have evaluated how patients' emotional and cognitive responses to chronic pain correlate with medication adherence in the HIV-SN patient population.

In this study, we examined the inter-relationships among neuropathic pain, depression, catastrophizing, and medication adherence. Determining the associations between these factors is an important step in formulating the appropriate treatment of the psychological effects of chronic pain in HIV-positive patients. Our investigation was a cross-sectional study examining clinic populations with chronic HIV infections and HIV-SN in order to quantify the effect of this combination of medical problems in terms of the patient's psychosocial functioning. We hypothesized that: 1) higher levels of depressive symptoms and pain catastrophizing would be associated with the report of more severe neuropathic pain and greater disability; 2) patient self-report of neuropathic pain symptoms as a medication side effect would be associated with decreased ART adherence; 3) increased patient catastrophizing and depression would predict more medication side effects and poor adherence.

Materials and Methods

Patient Selection

From 2002–2005, 46 HIV-seropositive subjects followed in two HIV neurology specialty clinics were identified either during routine clinic visits, after review of medical records, or recruited from the North East AIDS Dementia (NEAD) patient cohort (Sevigny et al. 2007). None of the patients (16/46) recruited from the NEAD cohort had cognitive impairment. However, patients were not controlled for similar CD4 counts. Approval for this study was granted by the Institutional Review Boards of the participating facilities. All patients enrolled in this study were diagnosed with HIV-SN by an HIV neurology specialist. There

were no exclusion criteria. Each subject was initially approached about the study by his or her physician, and if the patient agreed to participate, then informed consent was obtained. No subject declined to participate. Each subject completed a battery of questionnaires (see below), either in the clinic or via telephone. Each questionnaire was de-identified, and the patient's medical history beyond diagnoses of HIV and DSP were not included in the analysis.

Measures

Study subjects completed questionnaires evaluating neuropathic pain, pain catastrophizing, pain-related disability, depressive symptoms, quality of life, severity of ART side effects, and several common reasons for medication non-adherence. All of these questionnaires were previously published and validated except for the questionnaire regarding severity of ART side effects.

- a. *Neuropathic pain.* To measure the severity of each subject's neuropathic pain symptoms, the Neuropathic Pain Scale (Galer & Jensen, 1997) was administered. This scale asks respondents to rate the quality (burning, cold, sharp, dull, etc.) and intensity of their pain on a 0-to-10 point scale in which 0 = no pain and 10 = the most intense, sharp, hot, etc. pain imaginable.
- b. *Pain catastrophizing.* The Pain Catastrophizing Scale (Sullivan, Bishop, & Pivik, 1995) consists of 13 items describing different thoughts and feelings that respondents might experience when having pain in the lower extremities. Items are rated on a 0-to-4 scale and factor into 3 dimensions: helplessness, rumination, and magnification. On this scale, for instance, patients rated the degree to which they experienced certain thoughts/feelings: 0 = not at all; 1 = slight degree; 2 = moderate degree; 3 = great degree; 4 = all the time.
- c. *Pain severity.* The pain severity scale from the Brief Pain Inventory (Anderson, Syrjala, & Cleeland, 2001) asks patients to rate their current pain and the pain intensity at its worst, least, and average for the past week on a 0-to-10 point scale.
- d. *ART Side Effects.* This questionnaire was developed for the purpose of evaluating ART side effects in this specific population. First, subjects were asked what anti-retroviral medications they were currently taking. Second, they rated a list of signs and symptoms known to be attributable to antiretroviral medications as being absent or "None," "Mild," "Moderate," or "Severe." Included among the signs and symptoms were: "low blood count (anemia)," "nausea/vomiting/gastrointestinal upset," "bloated/pain," "diarrhea," "pain in lower extremities," "weight loss," "memory problems," "rash," "cough/sore throat," "fever," "bad/abnormal dreams," "numbness/tingling/pain in feet," "impaired concentration," "sugar in blood (diabetes)," and "fat redistribution/ lipodystrophy." Each side effect was ranked by the percentage of subjects reporting to have it at least mildly.
- e. *Pain-related disability.* The Pain Disability Index (Tait, Pollard, Margolis, Duckro, & Krause, 1987) assesses the degree to which subjects perceive themselves to be disabled in seven different areas of daily living: home, social, recreational, occupational, sexual, self-care, and life support. Disability ratings are made on a 0-

to-10 scale based on level of impairment from 0 = no disability to 10 = total disability due to pain.

- f. *Depressive symptoms.* The Beck Depression Inventory (Beck, Steer, & Garbin, 1988) is a 21 item measure designed to assess severity of depressive symptoms. Each symptom is rated on a 0-to-3 scale and scores range in total from 0–63, with higher scores indicating increased depressive symptoms. For instance, a score from 10–18 indicates mild-moderate depression, 19–29 indicates moderate-severe depression, and 30–63 indicates severe depression.
- g. *Health-Related Quality of life.* A quality of life measure, SF-36[®] Health Survey (Ware & Sherbourne, 1992), measures a subject's rating of his or her ability to perform activities of daily living, how much assistance is required, and how much his or her symptoms affect functioning. The SF-36[®] Health Survey has been shown to be as effective at measuring quality of life in the HIV population as the MOS-HIV Survey (Shahriar, Delate, Hays, & Coons, 2003).
- h. *Medication adherence.* The AIDS Clinical Trial Group (ACTG) Adherence Questionnaire I and II (Chesney et al. 2000) is a measure of individual self-report that has been validated by the ACTG to measure factors such as forgetfulness and concern for medication side effects that may affect adherence.

Statistical Analysis

Statistical analyses examined the simple and multivariate correlations between pain, depressive symptoms, catastrophizing, pain-related disability, ART side effects, and medication adherence. Two-tailed T tests and Pearson correlations were performed using SPSS v. 11.0. All patient questionnaires were included in the analysis. Missing responses on the questionnaires were scored as the appropriate response for normal or negative in the given measure and included in the final analysis except where otherwise specified.

A series of hierarchical regression models were used to test the effects of catastrophizing on pain, pain-related disability, and ART side effects. For pain, the first step included age, the second step included depressive symptoms, and the third step included catastrophizing. For pain-related disability, step one included age and pain severity, step two included depressive symptoms, and step three tested the effect of catastrophizing. For ART side effects, pain severity was entered first, depressive symptoms second, and catastrophizing third. Results are reported in terms of R^2 and were evaluated using the F test.

Results

Patient Characteristics

Forty-six study subjects were enrolled and their demographic characteristics are depicted in Table 1. In general, our population was nearly evenly divided between Caucasians (50%) and African Americans (48%). African Americans were over-represented relative to their proportion of the US population. There was only one Hispanic patient. Our subjects ranged in age from 31 to 66 years old and were well-educated with a majority (89%) reporting at

least some college education. 65% of patients reported being HIV-seropositive for greater than 10 years.

Analyses of neuropathic pain, pain disability, catastrophizing, and depression

The average neuropathic pain scale score was 45.5/100 (range 0–85, sd 20.7); the average pain catastrophizing scale score was 19.6 (range 0–49, sd 13.7); the average BDI score was 15.5 (range 0–49, sd 9.4). As shown in Table 2, there was a significant correlation between severity of neuropathic pain and pain catastrophizing ($p<0.01$), pain-related disability ($p<0.01$), and depressive symptoms ($p<0.05$). Depressive symptoms were also associated with pain-related disability ($p<0.01$) and catastrophizing ($p<0.01$). However, the brief pain inventory did not correlate significantly with depressive symptoms, although this measure did significantly correlate to disability ($p<0.01$) and catastrophizing ($p<0.01$). Pain-related disability was also strongly associated with pain catastrophizing ($p<0.01$).

Hierarchical regression analyses of pain catastrophizing, neuropathic pain, and pain-related disability independent of depressive symptoms

Hierarchical regression analyses were conducted to assess the relationship of: 1) catastrophizing to pain severity independent of age and depressive symptoms; 2) catastrophizing to pain-related disability independent of pain severity and depressive symptoms (Table 3). Depressive symptoms correlated with pain severity independent of age ($R^2 = 0.16$, $p<0.05$), but less significantly than catastrophizing, controlling for both age and depressive symptoms ($R^2 = 0.22$, $p<0.01$). Catastrophizing also correlated with disability after controlling for pain severity and depressive symptoms ($R^2 = 0.08$, $p<0.05$), although pain severity more significantly correlated with disability ($R^2 = 0.54$, $p<0.01$). Interestingly, depressive symptoms did not correlate with disability independent of pain severity ($R^2 = 0.03$, $p>0.05$).

Adverse effects and medication adherence

Patients were taking a full range of ART medications, the most common being tenofovir, stavudine, and ritonavir often in combination with lopinavir, as well as lamivudine/zidovudine alone or in combination with abacavir. Neurotoxic ARTs are no longer widely used in the United States, but stavudine is still a commonly prescribed component of fixed dose regimens in the developing world. Table 4 displays percentage of patients reporting each of the possible antiretroviral medication side effects, distinguishing between non-painful side effects and painful side effects (e.g. pain in the lower extremity, numbness in the feet, headaches). As shown in Table 2, we found during bivariate analysis that the sum of adverse medication effects correlated with neuropathic pain ($p<0.05$), depressive symptoms ($p<0.01$), pain disability ($p<0.01$), and catastrophizing ($p<0.01$). Using hierarchical regression analysis, we established that neuropathic pain score ($R^2 = 0.18$, $p<0.01$) and depressive symptoms ($R^2 = 0.19$, $p<0.01$) were significantly associated with more frequent ART side effects (Table 3), whereas catastrophizing showed no relationship to the frequency of ART side effects.

Four patients did not respond to any questions on adherence. Of the 42 patients who completed the medication adherence section, 38% reported full adherence with ART

medication use during the past month, whereas 62% reported some degree (rarely/sometimes/often) of non-adherence for various reasons. The most common reasons acknowledged for non-adherence were the following: simply forgetting (46%), sleeping through a dose (43%), changes in routine (31%), feeling too sick or ill to take medications (31%), having too many pills (26%), and avoiding side effects (26%). Comparisons of the patients who reported full adherence (N=16) with the group that reported some degree of non-adherence (N=26) yielded no group differences in neuropathic pain severity, pain-related disability, depressive symptoms, or pain catastrophizing.

Discussion

In our study, pain catastrophizing strongly correlated with the reported severity of neuropathic pain and pain-related disability in patients with HIV-SN. Previous research in HIV-positive men showed an association between increased depressive symptoms and greater pain, although the study did not include pain catastrophizing in its investigation (Evans et al. 1998). As our results show, the effect of catastrophizing on neuropathic pain was independent of depressive symptoms. Depressive symptoms were related to pain but not disability in our analyses. As we previously stated, pain-related disability has been correlated with catastrophizing in patients with neuropathic conditions (Sullivan, 2005), although this is the first study that we are aware of to specifically focus on patients with HIV-SN.

These findings could have significant implications for pain management in patients suffering from painful HIV-SN. One possible conclusion from our study is that therapies directed at a patient's depressive symptoms would not be expected to significantly improve reported pain or disability unless it was coupled to interventions that targeted catastrophizing. However, we propose that this supposition underestimates the relevance of antidepressants as they are frequently used to modulate pain perception. Current research suggests that inhibition of both serotonin and norepinephrine reuptake independent of depression leads to increased inhibition of descending pain pathways, modulating pain perception (Marks et al. 2009). Therefore in this patient population, treatment of catastrophizing in addition to antidepressant therapy may be most beneficial even in the absence of clinical depression.

Catastrophizing is considered a passive coping mechanism. Therapy for catastrophizing usually involves training in alternative coping strategies and cognitive interventions to reduce maladaptive catastrophizing thoughts. An example of a coping strategy includes praying-hoping. Prior studies have found that coping strategies are highly individualized in patients with painful HIV neuropathy (Griswold, 2005; Ownby & Dune, 2007).

Catastrophizing has also been found to be predictive of depressive symptoms, but neither were assessed in relation to a neuropathic pain scale (Griswold, 2005). Our study extends this research by demonstrating a relationship between catastrophizing, depression, and disability to neuropathic pain intensity in the HIV-SN population. Further research is needed to determine if the reported severity of neuropathic pain in this population can be used as a marker to follow the effectiveness of individualized coping strategies at reducing these symptoms.

Adherence to ART is of vital importance to patients with HIV. Failure to follow prescribed dosing regimens can lead to increased HIV replication, increased viral mutations, and antiretroviral drug resistance. Our study shows that neither self-report of neuropathic pain side effects (e.g. pain in lower extremities, numbness in feet), depressive symptoms, nor catastrophizing correlates with decreased adherence. Poor medication adherence due to fear of side effects or forgetfulness was associated with pain; depressive symptoms and catastrophizing were not. However, depressive symptoms did correlate with adverse effects overall. Depressive symptoms have been previously reported to predict an increased incidence of neuropsychiatric side effects in HIV-seropositive patients taking Efavirenz, although adherence was not included in the analysis (Boly, Cafaro, & Dyer, 2006). Furthermore, decreased adherence in patients with HIV has been shown to be partially accounted for by depressive symptoms (Cha, Erlen, Kim, Sereika, & Caruthers, 2008). Despite these findings, additional research is needed to further elucidate the interaction between medication adherence, ART side effects, and psychological co-morbidities in this population.

There are several reasons that have been identified in HIV patients that contribute to poor medication adherence, including patients misunderstanding dosing regimens (Stone et al. 2001). Furthermore, patients infected with HIV via drug injection self-reported more side effects than those who were not infected through drug injection (Carrieri et al. 2007). We did not record patient data on mode of HIV infection. Study subjects' complete medical history was also not recorded, a factor that limits the interpretation of our results as other medical problems may have affected medication adherence or ability to cope with pain.

Improved treatment of chronic pain in patients with HIV-SN is clearly important both psychologically and therapeutically. Identifying the relationships of the psychological effects of chronic pain like catastrophizing and depressive symptoms in this population is essential to designing effective therapeutic interventions. Pain catastrophizing, pain-related disability, and depressive symptoms were all correlated to the severity of neuropathic pain. Hierarchical regression analysis showed that a patient's experience of neuropathic pain secondary to painful HIV-SN is mediated by pain catastrophizing independent of depressive symptoms. The reverse, however, was not shown: depressive symptoms did not correlate with the severity of neuropathic pain independent of catastrophizing. These findings suggest that the effect of depressive symptoms on neuropathic pain is mediated by pain catastrophizing and that successful treatment may involve coping strategies aimed at catastrophizing. Further research is necessary to define the parameters of a successful treatment algorithm for these patients.

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TABLE 1**PATIENT DEMOGRAPHICS (N = 46)**

Age, mean (sd)	48 (7.4)
Age, range	31–66
Male (%)	85%
Female (%)	15%
Ethnicity	
<i>Caucasian</i>	50%
<i>African-American</i>	48%
<i>Hispanic</i>	2%
Education	
<i>Less than high school</i>	6.5%
<i>High school or equivalent</i>	4.3%
<i>Some College</i>	89%
Duration of HIV Infection	
<i>Less than 5 years</i>	8.7%
<i>5–10 years</i>	26.1%
<i>Greater than 10 years</i>	65.2%

TABLE 2

BIVARIATE CORRELATIONS AMONG STUDY MEASURES

Measure	Pain	BDI	PDI	CAT	SE	Fears
BDI	0.40*					
PDI	0.75**	0.45**				
CAT	0.59**	0.52**	0.67**			
BPI	0.75**	0.22	0.65**	0.46**		
SE	0.43*	0.60**	0.52**	0.54**		
Fears	0.43*	0.14		0.29	0.21	
Forgetfulness	0.40*	0.16		0.09	0.26	0.77**

* p<0.05
** p<0.01

Neuropathic pain (pain), Beck Depression Index (BDI), Pain Disability Index (PDI), Pain Catastrophizing Scale (CAT), BPI (Brief Pain Inventory), SE (ART side effects), noncompliance due to Forgetfulness and Fear of antiretroviral side effects.

TABLE 3
HIERARCHICAL REGRESSION ANALYSES OF PAIN, PAIN-RELATED DISABILITY, AND SIDE EFFECTS

Step	Variable	B	SE	Beta	R ²	R ²
DV = Pain Severity						
1. Age		0.02	0.05	0.07	0.00	0.00
2. Depressive Symptoms		0.09	0.04	0.04	0.16	0.16*
3. Catastrophizing		1.24	0.36	0.36	0.39	0.22**
DV = Pain Disability Index						
1. Age		0.00	0.03	0.01		
Pain Severity		0.70	0.11	0.73	0.54	0.54**
2. Depressive Symptoms		0.04	0.03	0.21	0.57	0.03
3. Catastrophizing		0.83	0.31	0.21	0.65	0.08*
DV = ART Side Effects						
1. Pain Severity		0.63	0.20	0.43	0.18	0.18**
2. Depressive Symptoms		0.15	0.04	0.46	0.38	0.19**
3. Catastrophizing		0.32	0.45	0.11	0.38	0.00

* P < 0.05
** P < 0.01

DV = Dependent variable; B = unstandardized coefficients; SE = standard error; Beta = standardized coefficients; R² = coefficient of variation; R² = R² change.

TABLE 4**ANTIRETROVIRAL SIDE EFFECTS**

Non-painful side effects	% reporting at least mild symptom
Fatigue	76%
Nausea/vomiting	40%
Light headedness	50%
Diarrhea	62%
Weight loss	29%
Kidney stones	6%
Cough/sore throat	35%
Abnormal dreams	28%
Trouble concentrating	65%
Mood changes	50%
Painful side effects¹	% reporting at least mild symptom
Pain in the lower extremities	79%
Numbness in the feet	82%
Headache	41%

¹ Other side effects were not included in computation of total side effects