ARTICLE COVERSHEET

LWW_CONDENSED(8.125X10.875)

SERVER-BASED

Article : PSM104182
Creator : jkinkito
Date : Saturday February 7th 2015
Time : 19:36:54
Number of Pages (including this page) : 11

ORIGINAL ARTICLE

Longitudinal Associations Between Depression, Anxiety, Pain, and Pain-Related Disability in Chronic Pain Patients

Sheera F. Lerman, PhD, Zvia Rudich, MD, Silviu Brill, MD, Hadar Shalev, MD, and Golan Shahar, PhD

ABSTRACT

Objective: The current study sets out to examine the longitudinal relationship between pain, pain-related disability, and symptoms of depression and anxiety. The latter symptoms are highly prevalent in chronic pain and seriously impede functioning and quality of life. Nevertheless, the direction of the relationship involving these variables among individuals with chronic pain is still unclear.

Methods: Four-hundred twenty-eight individuals with chronic pain (238 women, mean age = 54.84 years, mean pain duration =85.21 months) treated at two pain clinics completed questionnaires regarding their pain (Short-Form McGill Pain Questionnaire), depression (Center for Epidemiological Studies–Depression Scale), state anxiety (State-Trait Anxiety Inventory), and pain-related disability (Pain Disability Index) at four time points, with an average of 5 months between measurements. Cross-lagged, structural equation modeling analyses were performed, enabling the examination of longitudinal associations between the variables.

Results: Significant symptoms of both depression and anxiety were reported by more than half of the sample on all waves. A latent depression/anxiety variable longitudinally predicted pain ($\beta = .27$, $p < .001$) and pain-related disability ($\beta = .38$, $p < .001$). However, neither pain ($\beta = .10$, $p = .126$) nor pain-related disability ($\beta = -.01$, $p = .790$) predicted depression/anxiety.

Conclusions: Among adult patients with chronic pain treated at specialty pain clinics, high levels of depression and anxiety may worsen pain and pain-related disability.

Key words: chronic pain, depression, anxiety, pain-related disability.

INTRODUCTION

Depression and anxiety are highly prevalent among individuals with chronic pain (ICPs), derailing functioning and quality of life (1–5), treatment outcome (6), and increased health care costs (7). Although most research in ICP has focused on depression (4,8,9), mounting evidence indicates the high comorbidity of pain and anxiety and the significant contribution of anxiety to pain (10,11).

Most research in the field has focused on *the general population*, finding that depression increases the risk for developing chronic back and neck pain in the general population (12,13), in older adults (14), and in a sample of asymptomatic Veterans Affairs outpatients (15). In contrast, pain was the strongest predictor of depression after controlling for other variables (12,16), and other studies demonstrated a reciprocal relationship between pain on the one hand, and depression or anxiety on the other hand (17–23).

Unfortunately, these findings have little bearing on the depression and anxiety experienced by ICP. These patients are usually treated at specialty pain clinics, commonly arriving for treatment already suffering from significant emotional distress. The few studies that exist suggest that depression and anxiety predict a worsening in pain over time (24–26). Other studies, however, indicate that the longitudinal relationship between pain and depression was strong and similar in both directions (18,27).

ICP = individuals with chronic pain, **CES-D** = Center for Epidemiological Studies–Depression Scale, **STAI** = State Anxiety Inventory, **SF-MPQ** = Short-Form McGill Pain Questionnaire, **PDI** = Pain Disability Index, **SEM** = structural equation modeling

AQ1

SDC Supplemental Content

From the Department of Psychology (Lerman, Shahar), Ben-Gurion University of the Negev, Beer-Sheva, Israel; Pain Specialty Clinic (Rudich, Shalev), Soroka University Medical Center, Beer-Sheva, Israel; Chaim Sheba Medical Center (Lerman), Tel Hashomer, Israel; and Pain Specialty Clinic (Brill), Sourasky Medical Center, Tel-Aviv, Israel.

Address correspondence and reprint requests to Sheera F. Lerman, PhD, The Stress, Self & Health (STREALTH) Lab, Department of Psychology, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel. E-mail: sheera@post.bgu.ac.il

Received for publication April 8, 2014; revision received October 21, 2014.

DOI: 10.1097/PSY.0000000000000158

ICPs often experience a reduction in their participation in daily activities and in their ability to work due to their pain, costing millions in direct and indirect costs (28). Pain, depression, and anxiety are known to be associated with significant disability (29,30), and here too, extant findings are consistent with a reciprocal relationship (24,31,32). Arguably, these variables are strongly related through a number of possible mechanisms; however, the pattern of this relationship in individuals who experience significant and highly chronic pain is still unclear.

The aim of the current study was to understand the longitudinal associations between depression, anxiety, pain, and pain-related disability using a multiwave design. ICPs treated at specialty pain clinics completed questionnaires at four time points. We used a cross-lagged, structural equation modeling (SEM) analytic strategy in an attempt to examine the direction of the relationships between the variables. The present study also examined the unique role of depression versus anxiety in the relationship with pain and related disability. As noted above, depression and anxiety are highly comorbid (10,33,34), and it is important to determine whether the shared variance of the two construct is longitudinally associated with pain versus the unique features of each.

METHODS

Participants

The sample included 428 ICPs treated at two outpatient pain specialty pain clinics: Sourasky Medical Center (n = 239) and Soroka T1 University Medical Center (n = 189). As seen in Table 1, the sample included 238 women (56%) with an average (standard deviation [SD]) age of 54.84 (16.54) years (range, 18-90 years). Average (SD) education was 12.52 (3.36) years (range, 3-30 years). The average (SD) pain duration was 85.21 (102.73) months (range, 3-816 months). Diagnoses included low back and cervical radiculopathy (54%), widespread musculoskeletal pain (22%), neuropathic pain (16%), and other diagnosis (8%). The inclusion criterion was continuous pain for at least 3 months. The exclusion criterion was an insufficient understanding of Hebrew.

The study protocol was approved by the hospitals' Helsinki Committee for Ethics in Human Subjects. No adverse events were documented. Data were collected between the years 2007 and 2012. Nonoverlapping findings from the first two waves of measurement have been previously reported (35–37).

Procedure

At Time 1, patients were approached at the pain clinic during a scheduled appointment and were requested to participate in a study on psychological adjustment to chronic pain. Those signing an informed consent form completed questionnaires on sociodemographic variables, pain, depression, anxiety, and pain-related disability. Upon completion, patients were thanked and debriefed and were given a nominal gift. At Times 2, 3, and 4, participants were approached either when they came to the clinic for a prescheduled follow-up visit or by telephone when no follow-up visit was scheduled. Medical information was collected from patients' medical files.

TABLE 1. Participant Characteristics and Assessments During Follow-Up

Variable		Mean	SD	Range
Time 1 (n = 428)	Age, y	54.84	16.54	18–90
	Education, y	12.52	3.36	3–30
	Sex, females	n = 238 (56%)		
	CES-D	25.95	13.88	0–59
	STAI	48.48	15.46	20–80
	Affective MPQ	7.25	3.47	0–12
	Sensory MPQ	20.59	7.34	2–33
	PDI	36.15	17.70	0–70
Time 2 (n = 278)	CES-D	26.30	13.89	0–56
	STAI	48.67	15.31	20–80
	Affective MPQ	7.18	3.36	0–12
	Sensory MPQ	20.61	7.78	0–33
	PDI	34.99	16.87	0–70
Time 3 (n = 195)	CES-D	26.21	13.08	0–53
	STAI	49.53	15.01	20–79
	Affective MPQ	7.24	3.53	0–12
	Sensory MPQ	20.75	7.92	0–33
	PDI	34.83	15.02	0–70
Time 4 (n = 135)	CES-D	25.59	13.65	2–58
	STAI	48.79	15.82	20–77
	Affective MPQ	7.12	3.59	0–12
	Sensory MPQ	21.13	7.67	0–33
	PDI	32.44	17.92	0–70

SD = standard deviation; CES-D = Center for Epidemiological Studies–Depression Scale; STAI = State Anxiety Inventory; MPQ = Short-form McGill Pain Questionnaire; PDI = Pain Disability Index.

The average (SD) interval between Time 1 and Time 2 was 7.11 (4.7) months; Time 2 and Time 3, 7.9 (4.7) months; and Time 3 and Time 4, 5.16 (2.09) months. Of the 428 participants who completed Time 1 questionnaires, 278 completed Time 2 questionnaires, 195 completed Time 3 questionnaires, and 135 completed Time 4 questionnaires.

MEASURES

Pain

The Short-Form McGill Pain Questionnaire (SF-MPQ) (38) was used to measure the multidimensional experience of pain. Participants rate the extent their pain corresponds to 15 pain adjectives on a 4-point Likert scale. This scale has a sensory subscale (11 items) and an affective subscale (4 items). Internal consistency values of the sensory scale for Times 1, 2, 3, and 4 were α = .79, .83, .87, and .88, respectively, and those for the affective scale for Times 1, 2, 3, and 4 were Cronbach α = .68, .75, .79, and .78, respectively.

Depressive Symptoms

The 20-item Center for Epidemiological Studies–Depression Scale (CES-D) (39) was used to measure depressive symptoms severity. Participants indicate how often they experienced depressive symptoms in the past 2 weeks using a 4-point scale. The CES-D seems to discriminate well between pain patients with and without major depression (40). Internal consistency values for Times 1, 2, 3, and 4 were Cronbach α = .91, .92, .91, .and 92, respectively.

Anxiety

The 20-item state subscale of the State-Trait Anxiety Inventory (STAI) (41) was used to measure symptoms of anxiety. Participants rate how often they experienced certain feelings in the past week using a 4-point scale. Internal consistency values for Times 1, 2, 3, and 4 were Cronbach α = .94, .93, .94, .and 95, respectively.

Pain-Related Disability

The Pain Disability Index (PDI) (42) was used to assess the degree participants see themselves as disabled due to their pain in seven different areas of daily living (home, social, recreational, occupational, sexual, self-care, life support). For each life domain, participants provide perceived disability ratings on 11-point scales, with the end points being "0 = no disability" and "10 = total disability." Internal consistency for Times 1, 2, 3, and 4 were Cronbach α = .90, .88, .88, and .91, respectively.

Data Analysis

The longitudinal data were analyzed through two cross-lagged panel analysis using SEM. SEMs were conducted using the AMOS 21.0 statistical program. Missing data were estimated using maximum likelihood estimation (43). Three latent factors were created: a depression/anxiety latent factor was derived from CES-D depression and STAI anxiety, a pain latent factor was derived from the affective and sensory subscales of the SF-MPQ and a pain-related disability latent factor was derived from two parcels created randomly from Items 1, 3, 5, and 7 and Items 2, 4, and 6 of the PDI. Random parceling was used because the PDI was found to be a one-factor scale (44,45). Latent factors are preferable to manifest variables because the former are free from measurement error; hence, they yield more reliable findings. Also, the use of latent factors enables separating shared and unique variances (46), and this is particularly pertinent to our aim of examining whether the shared variance of depression and anxiety, as opposed to the unique variance of each psychological state, is involved in the pain process.

Because of the high attrition evinced in Waves 2 to 4, in our principal SEM analysis we averaged scores of the study variables at Waves 2 to 4 and used these composite score as an enhanced Wave 2 in the SEM models. Thus, the cross-lagged SEM consisted of Wave 1, and the enhanced Wave 2 (which collapses across the original waves). However, we also repeated the analysis focusing on the original four waves.

A cross-lagged SEM analysis includes a number of effects. *Synchronous relations* pertain to the associations between depression/anxiety, pain, and pain-related disability at each time point. *Autoregressive effects* include the influence of depression/anxiety at one time point on a subsequent time point, as is the case for pain and pain-related disability. This effect indicated the temporal stability of the latent constructs. Most importantly, *cross-lagged effects* represent the reciprocal effects between the variables throughout the time points, while controlling for the autoregressive effects.

The following indices were used to evaluate model fit: the *comparative fit index* (CFI) (47): values higher than 0.90 represents acceptable model fit; *Bentler-Bonett's nonnormed fit index* (NNFI) (48): values higher than 0.90 represent acceptable model fit; and *root-mean-square error of approximation* (RMSEA) (49): values of 0.08 and lower represent acceptable model fit. The commonly used χ^2 index was not used because of its sensitivity to sample sizes. For sample sizes of 200 and more, even models that fit the data well might yield statistically significant χ^2 values (indicating a poor model fit; see Hu and Bentler (50). When running the models, we arrived at the most parsimonious models by eliminating nonsignificant pathways (51).

Because of the longitudinal nature of this study, all mentions of a predictive relationship between the study variables refer to a variable at one time point predicting a variable at a later time point.

RESULTS

Attrition Analysis

An attrition analysis comparing participants in the study with those who dropped out after Time 1 in terms of depression, anxiety, sensory and affective pain, pain-related disability, sex, pain duration, and education showed no statistically significant differences. The groups differed in terms of age: those who participated in the second wave were older than those who did not (means = 54.9 and 54.6, respectively; $t(df = 426) = 6.35$, $p = .013$).

Preliminary Analyses

Mean, SDs, and range of the manifest variables are presented in Table 1. Zero-order correlations between the manifest variables and relevant demographic variables are presented in Table 2 and in Table S1 (Supplemental Digital Content 1, http://links.lww.com/PSYMED/A189). The variables presented high stability effects throughout the four time points (r values ranging from 0.44 to 0.83). Depression and anxiety were very highly correlated across time points,

TABLE 2. Zero-Order Correlations Between the Manifest and Demographic Study Variables at Time 1 (n = 428)

	Variable	1	2	3	4	5	6	7	8	9
1	Sex	1.00								
2	Age	0.18**	1.00							
3	P-duration	0.02	0.19**	1.00						
4	Education	−0.06	−0.14**	−0.07	1.00					
5	T1CES-D	0.12*	−0.07	0.05	−0.24**	1.00				
6	T1STAI	0.13*	−0.01	0.06	−0.19**	0.85**	1.00			
7	T1A-MPQ	0.17**	0.06	0.05	−0.29**	0.56**	0.52**	1.00		
8	T1S-MPQ	0.14**	−0.02	0.12*	−0.22**	0.41**	0.34**	0.64**	1.00	
9	T1PDI	0.07	0.02	0.02	−0.23**	0.58**	0.49**	0.52**	0.47**	1.00

P-duration = pain duration; T1 = Time 1; CES-D = Center for Epidemiological Studies–Depression Scale; STAI = State Anxiety Inventory; A-MPQ = Affective subscale of Short-Form McGill Pain Questionnaire; S-MPQ = Sensory subscale of Short-Form McGill Pain Questionnaire; PDI = Pain Disability Index.

* $p < .05$, ** $p < .01$.

supporting our decision to treat the two syndromes as manifest indicators of a single latent factor. Affective pain and sensory pain were moderately correlated with depression and anxiety and pain-related disability. Education was significantly negatively correlated with all the manifest variables at all four time points. Women demonstrated higher levels of depression, anxiety, and pain in almost all time points. There was no difference between men and women in the level of pain-related disability.

Turk and Okifuji (52) recommended the use of the cutoff of 19 on the CES-D for significant depressive symptoms in ICP. In our sample, 66% were above this cutoff at Time 1, 69% at Time 2, 66% at Time 3, and 68% at Time 4. Geisser and colleagues (40) recommend the use of the cutoff of 27. In our sample, 50% were above this cutoff at Time 1, 47% at Time 2, 51% at Time 3, and 51% at Time 4.

A cutoff of 39 to 40 has been suggested for the state STAI to detect clinically significant symptoms of anxiety in the general population (53). In our sample, 69% were above this cutoff at Time 1, 68% at Time 2, 75% at Time 3, and 73% at Time 4. To the best of our knowledge, there is no recommended cutoff for chronic pain populations.

A large percent of the sample was above both the cutoff of 27 for depression and the cutoff of 39 for anxiety. At Time 1 and Time 2, 45% of the sample scored above both of these cutoffs, 47% at Time 3, and 48% at Time 4. These findings provide additional support for our treatment of depression and anxiety as a manifest indicator of a single latent factor.

SEM Analysis—Two-Wave Model

The two-wave model created by averaging Waves 2 to 4 into one wave evinced an adequate fit (χ^2 = 122.53, df = 39, $p < .001$; NNFI = 0.97, CFI = 0.98, RMSEA = 0.07). Omitting nonsignificant parameters, we have arrived at the most parsimonious model, which also evinced an adequate fit (χ^2 = 128.05, df = 43, $p < .001$; NNFI = 0.97, CFI = 0.98, RMSEA = 0.07). As shown in Figure 1, statistically F1 significant cross-lagged effects demonstrated the longitudinal effect of latent depression/anxiety on both latent pain and latent pain-related disability; Time 1 depression/anxiety predicted Time 2-4 pain (b = 0.11, standard error [SE] = 0.03, β = .27, CR = 3.90, $p < .001$), and AQ2 depression/anxiety predicted Time 2-4 pain-related disability (b = 0.06, SE = 0.01, β = .38, CR = 6.16, $p < .001$). No other statistically significant cross-lagged effects were found in this model. Specifically, neither pain (β = .10, p = .126) nor pain-related disability (β = −.01, p = .790) predicted depression/anxiety.

Of particular interest are the standardized values of the cross-lagged coefficients (β values) representing the fraction of an SD change in the outcome variable produced by a 1-SD change in the predictor variable. Because these are standardized estimates, their magnitude might be compared with the magnitude found in other studies assessing similar cross-lagged associations (35) and in cross-lagged studies involving depression (54). The magnitude of the obtained estimates might be situated within Cohen's guidelines for standardized associations (correlations) found in social sciences. Cohen suggests that r = 0.1-0.23 pertains to small effect sizes, r = 0.24-0.36 pertains to medium effect sizes, and r = 0.37 or larger pertains to large effect sizes. Our standardized confidents fall within Cohen's large effect category (55,56).

Synchronous associations in Time 1 were high (depression/anxiety-pain: r = 0.64; depression/anxiety–pain-related disability: r = 0.62; pain–pain-related disability: r = 0.63), as well as in the collapsed Time 2 (depression/anxiety-pain: r = 0.51; depression/anxiety–pain-related disability: r = 0.58; pain–pain-related disability: r =

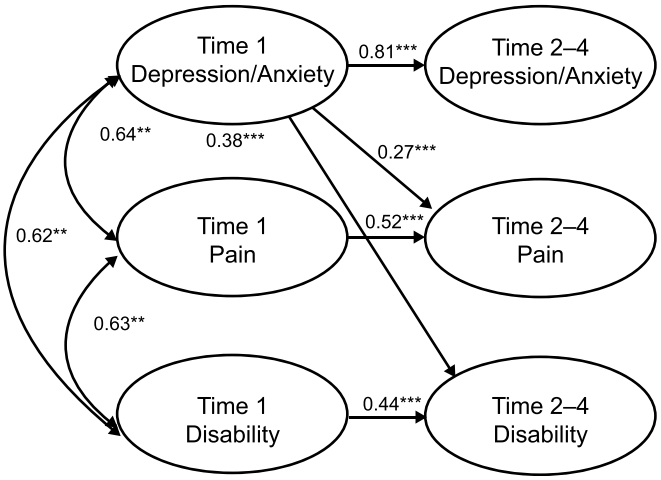

FIGURE 1. Two-wave structure equation model of the most parsimonious model of the relationship between latent depression/anxiety, pain, and pain-related disability using standardized parameters. * $p < .05$, ** $p < .01$, *** $p < .001$.

0.60). In addition, high stability effects were found for depression/anxiety ($b = 0.77$, SE = 0.04, $\beta = .81$, CR = 19.34, $p < .001$), pain ($b = 0.52$, SE = 0.07, $\beta = .52$, CR = 7.39, $p < .001$), and pain-related disability ($b = 0.38$, SE = 0.05, $\beta = .44$, CR = 3.90, $p < .001$).

Four-Wave Model

The cross-lagged model evinced an adequate fit ($\chi^2 = 421.38$, $df = 177$, $p < .001$; NNFI = 0.93, CFI = 0.96, RMSEA = 0.06). Omitting nonsignificant parameters, we have arrived at the most parsimonious mode (see Figure S1, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A190), which also evinced an adequate fit ($\chi^2 = 488.65$, $df = 211$, $p < .001$; NNFI = 0.92, CFI = 0.95, RMSEA = 0.06).

Similar to the two-wave model, depression/anxiety predicted pain between the Time 1 and Time 2 period ($b = 0.07$, SE = 0.02, $\beta = .31$, CR = 4.10, $p < .001$), Time 2 and Time 3 period ($b = 0.05$, SE = 0.02, $\beta = .19$, CR = 2.20, $p = .28$), and Time 2 and Time 4 period ($b = 0.05$, SE = 0.02, $\beta = .21$, CR = 2.26, $p = .24$). Depression/Anxiety also predicted pain-related disability between the Time 1 and Time 2 period ($b = 0.05$, SE = 0.01, $\beta = .32$, CR = 4.74, $p < .001$). A reciprocal relationship was found between pain and pain-related disability; pain predicts pain-related disability during the Time 1 and Time 2 period ($b = 0.16$, SE = 0.06, $\beta = .21$, CR = 2.75, $p = .006$) and the Time 2 and Time 3 period ($b = 0.13$, SE = 0.04, $\beta = .21$, CR = 2.80, $p = .005$). Pain-related disability predicted pain between the Time 3 and Time 4 period ($b = 0.43$, SE = 0.18, $\beta = .26$, CR = 2.45, $p = .014$) and Time 2 and Time 4 period ($b = -0.45$, SE = 0.18, $\beta = -.30$, CR = −2.51, $p = .012$). Importantly, the correlations between pain and pain-related disability are in the positive direction. This implies that this negative value of the β coefficient is due to a statistical suppression effect (57).

Multigroup SEM analyses testing the moderating role of sex in the aforementioned associations yielded null findings.

Unique Effects of Anxiety and Depression

In both models, we examined whether depression and anxiety exert unique effects on pain over and above the aforementioned effect of latent depression/anxiety on pain and pain-related disability. This was done by specifying unidirectional parameters leading from the unique variances of CES-D depression and STAI anxiety on subsequent latent pain and pain-related disability variables at each time point when the latent depression/anxiety variable was shown to be predictive. No unique effects of depression and anxiety were found.

DISCUSSION

In this sample of ICPs treated at specialty pain clinics, depression and anxiety were highly prevalent, with more than half reporting significant symptoms of depression and anxiety. A latent factor combining symptoms of depression and anxiety prospectively predicted levels of pain and pain-related disability. Conversely, neither pain nor pain-related disability predicted depression/anxiety.

Most studies examining the longitudinal relationship between pain, depression, and anxiety are based on the general population rather than ICPs. Large community-based prospective studies found depression to be a risk factor for developing pain (13–15,58,59) and for the development of other inflammatory and autonomic medical conditions such as heart disease and asthma (60). Only few studies addressed chronic pain populations, and these, similar to the present study, found depressive symptoms to predict a worsening in pain over time in individuals with knee osteoarthritis (24) and baseline anxiety to predict pain severity after 12 months in primary care patients with pain

and depression (25). Moreover, even short-term changes in emotional distress seem to have an effect on pain levels. In a weekly diary study in women with arthritis, depression and anxiety predicted pain a week later. Depression was related to pain through positive affect, whereas anxiety was related through negative affect, pointing to a possibly different mechanism effecting pain (26). In the present study, however, depression and anxiety had no differential effects on pain and related disability, suggesting that the determination of the role of unique versus specific effects of depression and anxiety on pain awaits future research.

A number of mechanisms may explain why depression and anxiety predicted pain. One possibility can be found in cognitive mechanisms. The combination of pain and depression, but not the sole presence of pain, was found to be associated with a negative health cognitive bias (61), leading patients to be more aware and focused on their pain and disability. Also, both depression and anxiety bring about a negative future appraisal in the form of pessimism and worry, which in turn impedes patients' ability to cope with pain (62). Linton and Bergbom (63) propose an emotion regulation model in which an inability to regulate negative emotions causes flare ups in pain and depression which activates catastrophic worry.

Second, as noted, our results point to the unique effect of the shared features of depression and anxiety. Comorbidity of anxiety and depression is highly prevalent in the general population (33), among ICPs (10,34) as well as in our study population. This anxious-depressive state has been recently conceptualized as a form of chronic inflammation (64), which may cause an increase in chronic pain, with itself considered to be an inflammation-based physical condition (65,66). Importantly, the issue of the role of inflammation in pain has yet to be resolved (67–70). Correspondingly, from the neurobiological perspective, depression, anxiety, and pain share common cortical regions, neurobiological networks, and neurochemical compounds such as serotonin and neuroadrenalin (71–73). Elevated depression or anxiety was found to cause changes in these common networks effecting the modulation of pain and may increase sensitivity to pain (74,75). In addition, the physiological reaction to anxiety may cause a reduced threshold to pain (76,77). This is further supported by evidence that individuals with mixed anxious-depressive symptoms who may not qualify for diagnosis of either of the conditions alone tend to have many unexplained somatic medical symptoms (78).

An additional possibility can be found in the process of *somatization*, the expression of emotional distress through physical symptoms (79). Individuals with a high tendency for somatization were found to be at higher risk for developing chronic widespread pain (80,81). It is possible that the positive relationship between depression/anxiety and pain was mediated by a number of factors including a general somaticizing tendency.

Finally, the specific characteristics of our sample might contribute to the results. Contrary to our results, there are many studies that show that pain contributes to the development of emotional distress (9,12,16) and others that point to a reciprocal relationship (17–21,27). The relationship between pain, depression, and anxiety may change throughout the life span (16,21,82) and may be affected by pain duration. ICPs treated at specialty pain clinics may differ from those treated by general practitioners or those who do not seek treatment. The present study focused on individuals treated at pain clinics who, on average, experienced pain for prolonged periods. In the initial stages of their pain episode, pain might be more likely to increase emotional distress and not vice versa because of the suffering, physical impairment, and disability brought on by pain (83). However, when pain continues and is treatment resistant, emotional distress becomes more prominent in its influence on pain through a psychological reaction to increased physical impairment and diminished social functioning (84).

Notably, not all ICPs have depression or anxiety. This raises the question of factors that contribute to vulnerability in the population and factors that may mediate this relationship. Cognitive coping styles such as catastrophizing have a profound effect on pain, distress, and disability (85,86), and there is evidence that personality traits (87) and adult attachment styles (88) are involved in adaptation to pain. These factors were not the focus of this study but will be addressed in future research.

An additional finding was that depression/anxiety predicted subsequent pain-related disability. This is consistent with a number of studies finding a similar pattern (24,31,32), because emotional distress may impair patients' motivation to participate in rehabilitation and adhere to treatments, which demand energy and resources (89).

Our four-wave model demonstrated a reciprocal relationship between pain and pain-related disability. This relationship is more complex than would be intuitively imagined. Studies show that although there is a significant correlation between the two, it is usually small and influenced by other psychosocial factors (90,91). It is believed that high levels of pain can result in fear of movement, which, according to the Fear-Avoidance Model (92), is part of the negative cycle causing significant disability and preventing recovery, in turn causing more pain. As seen in both study models, a significant relationship was not present in all time points, possibly because the relationship between pain and disability may change across diagnoses (93) and be mediated by different variables not assessed in this study.

Our study's strengths include a longitudinal design with a large sample size, enabling adequate statistical power and the ability to examine the bidirectional relationship. In addition, both depression and anxiety were measured,

allowing to test their specific and combined roles. Moreover, this is one of the few studies to explore these relationships through a longitudinal design in a population of ICPs rather than in the general population.

The study's limitations include our exclusive reliance on self-report measures, which, although reliable and valid, are susceptible to response bias and may inflate shared method variance. Also, measurement of depression and anxiety was done by symptom severity and not by specific diagnostic criteria. That said, a study assessing psychiatric pathologies in ICPs using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders found similar results (94). Furthermore, the high attrition rate might have prevented the detection of additional effects. Importantly, however, there was no difference found between participants who dropped out of the study and those who remained, on any of the study variables, and the collapsed two-wave model showed the same pattern of results. Another caveat pertains to causality. Despite the study's longitudinal design, causal inference should still be made with great caution given the nonexperimental nature of the study. Finally, our focus on adults who experience chronic pain and are treated at pain specialty clinics limits generalization of our findings to other populations.

To conclude, the obtained effect of depression/anxiety on pain and related disability in ICPs treated at specialty pain clinics contributes to the understanding of the complex link between mood, pain, and disability and can serve as the basis for psychological and pharmacological interventions addressing affective symptoms in chronic pain.

This report is based, in part, on Sheera F. Lerman's doctoral and postdoctoral work, supervised by Golan Shahar.

Source of Funding and Conflicts of Interest: Support for this work was received by the Goldman Fund of the Health Science Faculty, Ben-Gurion University of the Negev, Beer-Sheva, Israel, to Zvia Rudich (Principal Investigator) and Golan Shahar (Co–Principal Investigator) and by The Israel Science Foundation (Grant No. 751/08) to Golan Shahar. The authors declare that they have no conflicts of interest.

REFERENCES

1. Gureje O, Von Korff M, Kola L, Demyttenaere K, He Y, Posada-Villa J, Lepine JP, Angermeyer MC, Levinson D, de Girolamo G, Iwata N, Karam A, Guimaraes Borges GL, de Graaf R, Browne MO, Stein DJ, Haro JM, Bromet EJ, Kessler RC, Alonso J. The relation between multiple pains and mental disorders: results from the World Mental Health Surveys. Pain 2008;135:82–91.
2. Demyttenaere K, Bruffaerts R, Lee S, Posada-Villa J, Kovess V, Angermeyer MC, Levinson D, de Girolamo G, Nakane H, Mneimneh Z, Lara C, de Graaf R, Scott KM, Gureje O, Stein DJ, Haro JM, Bromet EJ, Kessler RC, Alonso J, Von Korff M. Mental disorders among persons with chronic back or neck pain: results from the World Mental Health Surveys. Pain 2007;129:332–42.
3. Arnow BA, Hunkeler EM, Blasey CM, Lee J, Constantino MJ, Fireman B, Kraemer HC, Dea R, Robinson R, Hayward C. Comorbid depression, chronic pain, and disability in primary care. Psychosom Med 2006;68:262–8.
4. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003; 163:2433–45.
5. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. Psychosom Med 2002;64:773–86.
6. Celestin J, Edwards RR, Jamison RN. Pretreatment psychosocial variables as predictors of outcomes following lumbar surgery and spinal cord stimulation: a systematic review and literature synthesis. Pain Med 2009;10:639–53.
7. Engel CC, von Korff M, Katon WJ. Back pain in primary care: predictors of high health-care costs. Pain 1996;65:197–204.
8. Banks SM, Kerns RD. Explaining high rates of depression in chronic pain: a diathesis-stress framework. Psychol Bull 1996; 119:95–110.
9. Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. Clin J Pain 1997;13:116–37.
10. Gureje O. Psychiatric aspects of pain. Curr Opin Psychiatry 2007;20:42–6.
11. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: results from a nationally representative sample. Pain 2004;111:77–83.
12. Currie SR, Wang J. Chronic back pain and major depression in the general Canadian population. Pain 2004;107:54–60.
13. Carroll LJ, Cassidy JD, Cote P. Depression as a risk factor for onset of an episode of troublesome neck and low back pain. Pain 2004;107:134–9.
14. Reid MC, Williams CS, Concato J, Tinetti ME, Gill TM. Depressive symptoms as a risk factor for disabling back pain in community-dwelling older persons. J Am Geriatr Soc 2003; 51:1710–7.
15. Jarvik JG, Hollingworth W, Heagerty PJ, Haynor DR, Boyko EJ, Deyo RA. Three-year incidence of low back pain in an initially asymptomatic cohort: clinical and imaging risk factors. Spine (Phila Pa 1976) 2005;30:1541–8; discussion 9.
16. Hilderink PH, Burger H, Deeg DJ, Beekman AT, Oude Voshaar RC. The temporal relation between pain and depression: results from the longitudinal aging study Amsterdam. Psychosom Med 2012;74:945–51.
17. Tunks ER, Crook J, Weir R. Epidemiology of chronic pain with psychological comorbidity: prevalence, risk, course, and prognosis. Can J Psychiatry 2008;53:224–34.
18. Kroenke K, Wu J, Bair MJ, Krebs EE, Damush TM, Tu W. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. J Pain 2011; 12:964–73.
19. Arola HM, Nicholls E, Mallen C, Thomas E. Self-reported pain interference and symptoms of anxiety and depression in community-dwelling older adults: can a temporal relationship be determined? Eur J Pain 2010;14:966–71.
20. Chou KL. Reciprocal relationship between pain and depression in older adults: evidence from the English Longitudinal Study of Ageing. J Affect Disord 2007;102:115–23.
21. Meyer T, Cooper J, Raspe H. Disabling low back pain and depressive symptoms in the community-dwelling elderly: a prospective study. Spine (Phila Pa 1976) 2007;32:2380–6.

22. Gureje O, Simon GE, Von Korff M. A cross-national study of the course of persistent pain in primary care. Pain 2001;92: 195–200.
23. Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain 1994;56:289–97.
24. Riddle DL, Kong X, Fitzgerald GK. Psychological health impact on 2-year changes in pain and function in persons with knee pain: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2011;19:1095–101.
25. Bair MJ, Poleshuck EL, Wu J, Krebs EK, Damush TM, Tu W, Kroenke K. Anxiety but not social stressors predict 12-month depression and pain severity. Clin J Pain 2013;29:95–101.
26. Smith BW, Zautra AJ. The effects of anxiety and depression on weekly pain in women with arthritis. Pain 2008;138: 354–61.
27. Williams LS, Jones WJ, Shen J, Robinson RL, Kroenke K. Outcomes of newly referred neurology outpatients with depression and pain. Neurology 2004;63:674–7.
28. Maniadakis N, Gray A. The economic burden of back pain in the UK. Pain 2000;84:95–103.
29. Borsbo B, Peolsson M, Gerdle B. The complex interplay between pain intensity, depression, anxiety and catastrophising with respect to quality of life and disability. Disabil Rehabil 2009;31:1605–13.
30. Pincus T, Burton AK, Vogel S, Field AP. A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. Spine (Phila Pa 1976) 2002;27:E109–20.
31. Hurwitz EL, Morgenstern H, Yu F. Cross-sectional and longitudinal associations of low-back pain and related disability with psychological distress among patients enrolled in the UCLA Low-Back Pain Study. J Clin Epidemiol 2003;56: 463–71.
32. Brage S, Sandanger I, Nygard JF. Emotional distress as a predictor for low back disability: a prospective 12-year population-based study. Spine (Phila Pa 1976) 2007;32: 269–74.
33. Rush AJ, Zimmerman M, Wisniewski SR, Fava M, Hollon SD, Warden D, Biggs MM, Shores-Wilson K, Shelton RC, Luther JF, Thomas B, Trivedi MH. Comorbid psychiatric disorders in depressed outpatients: demographic and clinical features. J Affect Disord 2005;87:43–55.
34. Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. Psychosom Med 2008;70:890–7.
35. Lerman SF, Shahar G, Rudich Z. Self-criticism interacts with the affective component of pain to predict depressive symptoms in female patients. Eur J Pain 2012;16:115–22.
36. Lerman SF, Rudich Z, Shahar G. Distinguishing affective and somatic dimensions of pain and depression: a confirmatory factor analytic study. J Clin Psychol 2010;66:456–65.
37. Lerman SF, Rudich Z, Shahar G. Does war hurt? Effects of media exposure after missile attacks on chronic pain. J Clin Psychol Med Settings 2013;20:56–63.
38. Melzack R. The Short-Form McGill Pain Questionnaire. Pain 1987;30:191–7.
39. Radloff LS. A self-reported depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
40. Geisser ME, Roth RS, Robinson ME. Assessing depression among persons with chronic pain using the Center for Epidemiological Studies–Depression Scale and the Beck Depression Inventory: a comparative analysis. Clin J Pain 1997;13: 163–70.
41. Spielberger CD, Gorsuch RL, Luschene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press; 1983.
42. Tait RC, Chibnall JT, Krause S. The Pain Disability Index: psychometric properties. Pain 1990;40:171–82.
43. Enders CK, Bandalos DL. The relative performance of full information maximum likelihood estimation for missing data in structural equation models. Struct Equ Modeling 2001;8:430–57.
44. Chibnall JT, Tait RC. The Pain Disability Index: factor structure and normative data. Arch Phys Med Rehabil 1994;75:1082–6.
45. Little TD, Cunningham WA, Shahar G, Widaman KF. To parcel or not to parcel: exploring the question, weighing the merits. Struct Equ Modeling 2002;9:151–73.
46. Bentler PM. Multivariate analysis with latent variables: causal modeling. Ann Rev Psychol 1980;31:419–56.
47. Bentler PM. Comparative fit indices in structural equation models. Psychol Bull 1990;107:238–46.
48. Bentler PM, Bonett DG. Significance tests and goodness of fit in the analysis of covariance structure. Psychol Bull 1980;88: 588–606.
49. Steiger JH. Test for comparing elements of a correlation matrix. Psychol Bull 1980;87:245–51.
50. Hu L, Bentler PM. Fit indices in covariance structure modeling: sensitivity to underparameterized model misspecification. Psychol Methods 1998;3:424–53.
51. Bentler PM, Mooijaart A. Choice of structural model via parsimony: a rationale based on precision. Psychol Bull 1989; 106:315–7.
52. Turk DC, Okifuji A. Detecting depression in chronic pain patients: adequacy of self-reports. Behav Res Ther 1994;32:9–16.
53. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken) 2011;63(suppl 11):S467–72.
54. Shahar G, Davidson L. Depressive symptoms erode self-esteem in severe mental illness: a three-wave, cross-lagged study. J Consult Clin Psychol 2003;71:890–900.
55. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
56. Cohen J. A power primer. Psychol Bull 1992;112:155–9.
57. Tzelgov J, Henik A. Suppression situations in psychological research: definitions, implications, and applications. Psychol Bull 1991;109:524–36.
58. Linton SJ. Do psychological factors increase the risk for back pain in the general population in both a cross-sectional and prospective analysis? Eur J Pain 2005;9:355–61.
59. Larson SL, Clark MR, Eaton WW. Depressive disorder as a long-term antecedent risk factor for incident back pain: a 13-year follow-up study from the Baltimore Epidemiological Catchment Area sample. Psychol Med 2004;34:211–9.
60. Patten SB, Williams JV, Lavorato DH, Modgill G, Jette N, Eliasziw M. Major depression as a risk factor for chronic disease incidence: longitudinal analyses in a general population cohort. Gen Hosp Psychiatry 2008;30:407–13.
61. Rusu AC, Pincus T, Morley S. Depressed pain patients differ from other depressed groups: examination of cognitive content in a sentence completion task. Pain 2012;153:1898–904.
62. Von Korff M, Simon G. The relationship between pain and depression. Br J Psychiatry Suppl 1996;101–8.
63. Linton SJ, Bergbom S. Understanding the link between depression and pain. Scand J Pain 2011;2:47–54.
64. Camacho A. Is anxious-depression an inflammatory state? Med Hypotheses 2013;81:577–81.

65. Woolf CJ, Doubell TP. The pathophysiology of chronic pain—increased sensitivity to low threshold A beta-fibre inputs. Curr Opin Neurobiol 1994;4:525–34.
66. Xu Q, Yaksh TL. A brief comparison of the pathophysiology of inflammatory versus neuropathic pain. Curr Opin Anaesthesiol 2011;24:400–7.
67. Wang H, Schiltenwolf M, Buchner M. The role of TNF-alpha in patients with chronic low back pain—a prospective comparative longitudinal study. Clin J Pain 2008;24:273–8.
68. Wang H, Moser M, Schiltenwolf M, Buchner M. Circulating cytokine levels compared to pain in patients with fibromyalgia—a prospective longitudinal study over 6 months. J Rheumatol 2008; 35:1366–70.
69. Wang H, Buchner M, Moser MT, Daniel V, Schiltenwolf M. The role of IL-8 in patients with fibromyalgia: a prospective longitudinal study of 6 months. Clin J Pain 2009;25:1–4.
70. Wang H, Ahrens C, Rief W, Gantz S, Schiltenwolf M, Richter W. Influence of depression symptoms on serum tumor necrosis factor-alpha of patients with chronic low back pain. Arthritis Res Ther 2010;12:R186.
71. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002; 34:13–25.
72. Porro CA. Functional imaging and pain: behavior, perception, and modulation. Neuroscientist 2003;9:354–69.
73. Blackburn-Munro G, Blackburn-Munro RE. Chronic pain, chronic stress and depression: coincidence or consequence? J Neuroendocrinol 2001;13:1009–23.
74. Strigo IA, Simmons AN, Matthews SC, Craig AD, Paulus MP. Association of major depressive disorder with altered functional brain response during anticipation and processing of heat pain. Arch Gen Psychiatry 2008;65:1275–84.
75. Thibodeau MA, Welch PG, Katz J, Asmundson GJ. Pain-related anxiety influences pain perception differently in men and women: a quantitative sensory test across thermal pain modalities. Pain 2013;154:419–26.
76. Schmidt NB, Cook JH. Effects of anxiety sensitivity on anxiety and pain during a cold pressor challenge in patients with panic disorder. Behav Res Ther 1999;37:313–23.
77. Keogh E, Mansoor L. Investigating the effects of anxiety sensitivity and coping on the perception of cold pressor pain in healthy women. Eur J Pain 2001;5:11–22.
78. Katon W, Roy-Byrne PP. Mixed anxiety and depression. J Abnorm Psychol 1991;100:337–45.
79. Lipowski ZJ. Somatization: the concept and its clinical application. Am J Psychiatry 1988;145:1358–68.
80. McBeth J, Macfarlane GJ, Benjamin S, Silman AJ. Features of somatization predict the onset of chronic widespread pain: results of a large population-based study. Arthritis Rheum 2001;44:940–6.
81. Gupta A, Silman AJ, Ray D, Morriss R, Dickens C, MacFarlane GJ, Chiu YH, Nicholl B, McBeth J. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. Rheumatology (Oxford) 2007;46:666–71.
82. Iliffe S, Kharicha K, Carmaciu C, Harari D, Swift C, Gillman G, Stuck AE. The relationship between pain intensity and severity and depression in older people: exploratory study. BMC Fam Pract 2009;10:54.
83. Chapman CR, Gavrin J. Suffering: the contributions of persistent pain. Lancet 1999;353:2233–7.
84. Tjakkes GH, Reinders JJ, Tenvergert EM, Stegenga B. TMD pain: the effect on health related quality of life and the influence of pain duration. Health Qual Life Outcomes 2010;8:46.
85. Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, Lefebvre JC. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain 2001;17:52–64.
86. Richardson EJ, Ness TJ, Doleys DM, Banos JH, Cianfrini L, Richards JS. Depressive symptoms and pain evaluations among persons with chronic pain: catastrophizing, but not pain acceptance, shows significant effects. Pain 2009;147: 147–52.
87. Harkins SW, Price DD, Braith J. Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. Pain 1989;36:209–18.
88. Meredith P, Ownsworth T, Strong J. A review of the evidence linking adult attachment theory and chronic pain: presenting a conceptual model. Clin Psychol Rev 2008;28:407–29.
89. Hill JC, Fritz JM. Psychosocial influences on low back pain, disability, and response to treatment. Phys Ther 2011;91:712–21.
90. Kovacs FM, Abraira V, Zamora J, Teresa Gil del Real M, Llobera J, Fernandez C, Bauza JR, Bauza K, Coll J, Cuadri M, Duro E, Gili J, Gestoso M, Gomez M, Gonzalez J, Ibanez P, Jover A, Lazaro P, Llinas M, Mateu C, Mufraggi N, Muriel A, Nicolau C, Olivera MA, Pascual P, Perello L, Pozo F, Revuelta T, Reyes V, Ribot S, Ripoll J, Rodriguez E. Correlation between pain, disability, and quality of life in patients with common low back pain. Spine (Phila Pa 1976) 2004; 29:206–10.
91. Gronblad M, Hupli M, Wennerstrand P, Jarvinen E, Lukinmaa A, Kouri JP, Karaharju EO. Intercorrelation and test-retest reliability of the Pain Disability Index (PDI) and the Oswestry Disability Questionnaire (ODQ) and their correlation with pain intensity in low back pain patients. Clin J Pain 1993;9: 189–95.
92. Lethem J, Slade PD, Troup JD, Bentley G. Outline of a Fear-Avoidance Model of exaggerated pain perception—I. Behav Res Ther 1983;21:401–8.
93. Hawley DJ, Wolfe F. Pain, disability, and pain/disability relationships in seven rheumatic disorders: a study of 1,522 patients. J Rheumatol 1991;18:1552–7.
94. Knaster P, Karlsson H, Estlander AM, Kalso E. Psychiatric disorders as assessed with SCID in chronic pain patients: the anxiety disorders precede the onset of pain. Gen Hosp Psychiatry 2012;34:46–52.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

AQ1 = DSM, T, P-duration, A-MPQ, and S-MPQ were deleted from the list as a result of deleting these abbreviations from the actual text in accordance with AMA rules. Please check.

AQ2 = Please define CR.

END OF AUTHOR QUERIES