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Predictors of Change in Pain and Physical Functioning Among Post-Menopausal Women With Recurrent Pain Conditions in the Women's Health Initiative Observational Cohort

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Abstract: Pain complaints are commonly reported symptoms among postmenopausal women and can have significant effects on health-related quality of life. We sought to identify medical and psychosocial factors that predict changes in pain and overall physical functioning over a 3-year period among postmenopausal women with recurrent pain conditions. We examined data from postmenopausal women age 50 to 79 with recurrent pain conditions (low back pain, neck pain, headache or migraines, or joint pain or stiffness) over a 3-year period using the Women's Health Initiative Observational Study Cohort (N = 67,963). Multinomial logistic regression models controlling for demographic and clinical characteristics were used to identify baseline predictors of change in the SF-36 subscales for pain and physical functioning between baseline and 3-year follow-up. Body mass index (BMI) was associated with worsening of pain (OR [95% CI] 1.54 [1.45-1.63] for BMI ≥30) and physical functioning (1.83 [1.71-1.95] for BMI ≥30). A higher reported number of nonpain symptoms, higher medical comorbidity, and a positive screen for depression (1.13 [1.05-1.22] for worsened pain) were also associated with worsening of pain and physical functioning. Baseline prescription opioid use was also associated with lack of improvement in pain (OR .42, 95% CI .36-.49) and with worsened physical functioning (1.25 [1.04-1.51]).

***Perspective:** This study presents prospective data on change in pain and physical functioning in postmenopausal women over a 3-year period. Our results suggest depression, nonpain physical symptoms, obesity, and possibly opioid treatment are associated with worse long-term pain outcomes in this population.*

***Key words:** Pain, obesity, opioid, women, longitudinal, cohort.*

The prevalence of persistent pain complaints is higher among women than among men and increases with age.[7,47,53] Pain complaints are commonly reported symptoms among women in midlife and later[9,20,24,25] and, along with other complaints such as vasomotor symptoms, depression, and sleep disturbance, can have significant effects on health-related quality of life.[3,18,52] For example, approximately half of perimenopausal or postmenopausal women age 45 to 50 in the Australian Longitudinal Study on Women's Health endorsed back pain, headaches, or joint pain.[9] In both the Penn Ovarian Aging Study and the Study of Women's Health Across the Nation (SWAN), approximately three-fourths of women endorsed joint pain or stiffness.[20,24] In the SWAN study, approximately one-quarter of women reported these symptoms as moderate-to-severe intensity. While headaches have been reported to decrease in the transition

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to menopause,[24] joint pain tends to increase.[20,25] This finding is consistent with surveys of older adults (men and women), where about half report experiencing joint pain compared to one-quarter to one-third of younger adults.[7,40]

Psychological symptoms have been associated with persistent pain. Depression has been shown to both precede and follow the development of pain,[19,42] and the co-occurrence of depression and pain is associated with worse physical and emotional functioning in cross-sectional studies.[2,7,8] Depression has been reported to be positively associated with higher subjective levels of pain interference both in the broader pain population[2,8] and in menopausal women specifically.[49] Anger and hostility have been associated with poor pain treatment outcomes, and ambivalence over emotional expression, the tendency to be conflicted about expressing one's emotions, may be linked to increased pain.[11,13,22,36] In a recent study of chronic low back pain patients, patients scoring high on ambivalence over emotional expression were much more likely to report higher pain on the affective and evaluative pain scales of the McGill Pain Questionnaire.[13] In a longitudinal study of 169 continuing care retirement community residents, the percent with any pain increased 6.5% over the 24-month period; the percent with pain without activity limitations remained relatively stable, but the percent with pain with activity limitations increased from 35.5 to 42.2%.[39] Psychiatric comorbidity, poor pain coping behaviors, high baseline functional impairment, and low general health status have been shown to be predictive of persistent disabling back pain 1 year later among those with fewer than 8 weeks of low back pain.[15] Little is known, however, about the longitudinal course and modifiers of pain in the general population or in postmenopausal women specifically.

In this study, we sought to identify psychosocial, demographic, and clinical factors that predict changes in pain and overall physical functioning over a 3-year period among postmenopausal women with recurrent pain conditions, using data from the Women's Health Initiative Observational Cohort. The subpopulation of patients with noncancer pain receiving opioid therapy is of special interest, given the marked increase in use of these drugs for noncancer pain over the past 30 years. Individuals with depression are more likely to be prescribed opioids for noncancer pain than those without depression,[6,21,48] and postmenopausal women may be more likely to receive opioids than younger women for noncancer pain given the health risks associated with COX-2 inhibitors and nonsteroidal anti-inflammatory drugs.[1,12] Hence, we included use of regular prescription opioids as 1 of the clinical factors examined in our study.

Methods

Population

Data are from the Women's Health Initiative Observational Study Cohort. The Women's Health Initiative is a national health study consisting of a set of randomized controlled trials and an observational study. The Observational Study Cohort followed 93,676 postmenopausal women age 50 to 79 for a period of 8 to 12 years starting in 1998. Women were eligible if they were age 50 to 79, postmenopausal, had ability and willingness to provide written informed consent, and intention to reside in the area for at least 3 years. Women were excluded if they had a medical condition with predicted survival of less than 3 years, or mental disorders that might interfere with adherence or retention in the study (assessed by asking potential study participants, "Are there any reasons, like serious emotional problems, mental illness, or too much stress, that would make it hard for you to be in a research study?"). Women screened for participation in the clinical trials but unwilling or ineligible (ie, because of the presence of a health condition that was a competing risk factor or safety concern for trial outcomes) were offered the opportunity to participate in the Observational Study Cohort. Participants completed questionnaires and provided blood specimens and physical measurements at the baseline screening visit and returned for a second visit 3 years later. Informed consent from each participant was obtained, and human subjects review committees at each participating institution approved the study. Analyses for this study were limited to the subset of women in the Observational Study Cohort with "recurrent pain," defined as endorsing low back pain, neck pain, headache or migraines, or joint pain or stiffness in the prior 4 weeks at both the baseline and 3-year follow-up visits (N = 67,963). Details about the design of the WHI can be found elsewhere.[30,43]

Variables

Participants were asked to indicate the presence and severity of 34 symptoms of distress (scale of 0 = symptom did not occur to 3 = severe) in the prior 4 weeks at baseline and follow-up visits. The list of symptoms was obtained from the Postmenopausal Estrogen/Progestin Intervention study and from other national health surveys. Those who responded $\geq$1 for low back pain, neck pain, headache/migraine, or joint pain/stiffness at both baseline and follow-up visits were defined as having recurrent pain. Responses to the other items were summed to create a measure of the number of nonpain symptoms. Pain severity and pain interference in the prior 4 weeks were assessed via a Likert scale (pain severity, 0 = none to 5 = severe; pain interference, 1 = not at all to 5 = extremely) using questions from the Short Form (SF)-36,[55] and averaged to create 1 pain score (ie, the SF-36 pain subscale). Physical functioning was assessed using the physical functioning subscale of the SF-36. Scores were converted to a scale ranging from 0 to 100, with a higher score indicating a more favorable health state. Changes in pain and physical functioning were determined by subtracting the numerical score at baseline from that at year 3 for each respondent. For the sake of clarity, moving to a more favorable health state between baseline and year 3 (ie, decrease in pain, increase in physical functioning) was defined as "improved" and moving to a less favorable health state between baseline

and year 3 (ie, increase in pain, decrease in physical functioning) was defined as "worsened." Medical comorbidity was assessed with the Charlson comorbidity index.[14] Hours per day of sedentary activity was obtained by self-report and defined as hours sleeping, sitting, or lying down. Participants were asked about use of medications for 2 weeks or more, along with duration of use. Opioid use was defined as use of DEA Schedule II-V prescription opioids. Other analgesic use was defined as use of acetaminophen, ibuprofen and other nonsteroidal anti-inflammatories, aspirin, salicylate analgesics, other aspirin like analgesics, lidocaine, and capsaicin creams. Use of hormone replacement therapy (HT) was assessed by a series of questions about use of hormone medications for relief of menopausal symptoms, following hysterectomy with removal of the ovaries, or for prevention of disease such as bone loss. Body mass index (BMI) was calculated from height and weight measurements obtained at the baseline visit (weight in kilograms/height in meters^2). For analysis purposes, BMI was divided into 3 categories to correspond with normal, overweight and obese: <25, 25–<30, ≥30. Demographic characteristics and disability status were obtained by self-report.

Depression was assessed with the Burman scale,[10] a shortened form of the Center for Epidemiologic Studies Depression (CES-D) scale that has been validated in a large study of office-based practices. Respondents with scores ≥.06 were considered to be depressed. Social support was assessed by 9 questions from the Medical Outcomes Study.[45] Possible scores ranged from 9 to 45, with a higher score indicating greater support. The Ambivalence Over Emotional Expression Questionnaire was used to assess the relationship between negative emotion and health outcomes.[35] The questionnaire consists of 3 items (eg, after I express anger at someone, it bothers me for a long time); possible scores range from 1 to 5, with higher scores indicating greater ambivalence in expressing negative emotions. Cynicism was measured using the 13-item cynicism subscale of the Cook-Medley Hostility Questionnaire (example items: no one cares much what happens to you; I think most people would lie to get ahead); possible scores ranged from 0 to 13, with higher scores indicating greater cynicism.[5]

Statistical Analyses

Demographic and clinical variables were analyzed descriptively using frequencies and percents for categorical variables and means with standard deviations for continuous variables, stratified by change in pain between baseline and year 3 (no change, worsened, improved pain). Chi-square tests were performed for categorical variables, and 1-way analysis of variance tests were performed for continuous variables to assess differences among groups. Multinomial logistic regression models were used to identify predictors of change in pain and physical functioning between baseline and 3-year follow-up, while controlling for demographic (age at screening, highest education level, family income, employment status-disabled, race/ethnicity) and clinical characteristics (BMI, Charlson index, number of nonpain symptoms, HT use, baseline pain, or physical functioning) at baseline. Specifically, the models examined the association between the independent variables and: 1) increase in pain (ie, worsening) versus no change in pain; 2) decrease in pain (ie, improvement) versus no change in pain; 3) increase in physical functioning (ie, improvement) versus no change in physical functioning; and 4) decrease in physical functioning (ie, worsening) versus no change in physical functioning between baseline and year 3. Independent variables in the regression models included opioid use, the presence of depression, ambivalence over emotional expressiveness, hostility, social support, and hours of sedentary activity per day. Data from participants with missing values for 1 or more covariates in the models was excluded from the regression analyses, leaving a total of 51,839 participants for the model with outcome change in pain and 50,849 for the model with outcome change in physical functioning.

Results

Of the 93,676 women enrolled in the WHI OS, 67,963 met the criteria for recurrent pain and were included in the analyses for this study. An additional 9,774 reported pain at baseline and were missing the pain measures at year 3, and another 4,584 reported pain at baseline and not at year 3.

Sociodemographic and Clinical Characteristics

Table 1 presents the demographic and clinical characteristics of the cohort with recurrent pain, stratified by whether they experienced a worsening, improvement, or no change in pain between baseline and year 3. In general, the women were primarily white, had at least a high-school diploma, an annual family income >$35,000, a mean age of 63 to 64 years, and a mean BMI in the overweight range. The majority of the women reported at least mild joint pain or stiffness; the next most common pain condition reported was low back pain. Most women (56,017 [82%]) reported more than 1 pain type. Mean baseline scores for pain and physical functioning were higher among those reporting no change or worsened pain between baseline and year 3. Nearly half of the women (43.9%, N = 29,721) reported use of a nonopioid analgesic. Four and one-third percent (2,914) reported prescription opioid use: 2.3% (1,582) at baseline, 2.0% (1,332) at year 3 only, and .9% (615) at baseline and year 3. Most women with baseline opioid use had used for >90 days (83%, N = 1,325). The median duration of those reporting opioid use at baseline was 2 years, and at year 3 was 1.5 years. Approximately 11% of women screened positive for depression on the Burman (shortened CES-D) scale (score ≥.06); average scores for ambivalence over emotional expressiveness and cynicism were low, and for social support were high.

Women with any prescription opioid use at baseline differed from women with no opioid use at baseline on all variables examined. They tended to have worse pain

Table 1. Sociodemographic and Clinical Characteristics at Baseline of Post-Menopausal Women With Recurrent Pain Conditions 3 Years Later

	Change in Pain Baseline to 3-Year Follow-Up			
Characteristics	Improved (N = 20,742)	None (N = 20,163)	Worsened (N = 26,647)	P value
Sociodemographic				
Age at screening, mean (SD)	63 (7.3)	63 (7.2)	64 (7.3)	<.001
Racial/ethnic group, N (%)				
White	17,542 (84.6%)	17,447 (86.5%)	22,749 (85.4%)	<.001
Black	1,524 (7.3%)	1,276 (6.3%)	1,909 (7.2%)	
Hispanic	759 (3.7%)	550 (2.7%)	838 (3.1%)	
American Indian	90 (.4%)	59 (.3%)	112 (.4%)	
Asian/Pacific Islander	538 (2.6%)	578 (2.9%)	671 (2.5%)	
Unknown	289 (1.4%)	253 (1.3%)	368 (1.4%)	
Highest education level				
0–8 years	314 (1.5%)	175 (.9%)	380 (1.4%)	<.001
Some high school	704 (3.4%)	545 (2.7%)	923 (3.5%)	
High school diploma/GED	3,279 (15.8%)	3,183 (15.8%)	4,532 (17.0%)	
School after high school	7,708 (37.2%)	7,213 (35.8%)	9,972 (37.4%)	
College degree or higher	8,569 (41.3%)	8,907 (44.2%)	10,635 (39.9%)	
Total family income*				
<$10,000	781 (3.8%)	617 (3.1%)	1,053 (4.0%)	<.001
$10,000–$19,999	2,229 (10.7%)	1,907 (9.5%)	2,997 (11.2%)	
$20,000–$34,999	4,583 (22.1%)	4,143 (20.5%)	6,113 (22.9%)	
$35,000–$49,999	3,863 (18.6%)	3,866 (19.2%)	5,085 (19.1%)	
$50,000–$74,999	3,962 (19.1%)	4,045 (20.1%)	4,981 (18.7%)	
$75,000+	3,898 (18.8%)	4,266 (21.2%)	4,645 (17.4%)	
Disabled	564 (2.7%)	374 (1.9%)	516 (1.9%)	<.001
Recurrent pain and other medical conditions				
Joint pain or stiffness				
Severe	2,221 (10.7%)	992 (4.9%)	1,286 (4.8%)	<.001
Moderate	6,031 (29.1%)	3,592 (17.8%)	5,773 (21.7%)	
Mild	9,386 (45.3%)	11,345 (56.3%)	14,522 (54.5%)	
Low back pain				
Severe	1,880 (9.1%)	891 (4.4%)	1,094 (4.1%)	<.001
Moderate	4,663 (22.5%)	2,761 (13.7%)	4,566 (17.1%)	
Mild	7,286 (35.1%)	8,293 (41.1%)	10,831 (40.6%)	
Neck pain				
Severe	1,091 (5.3%)	520 (2.6%)	753 (2.8%)	<.001
Moderate	3,380 (16.3%)	2,242 (11.1%)	3,252 (12.2%)	
Mild	6,454 (31.1%)	6,757 (33.5%)	9,118 (34.2%)	
Migraines or headaches				
Severe	773 (3.7%)	435 (2.2%)	565 (2.1%)	<.001
Moderate	2,448 (11.8%)	1,726 (8.6%)	2,576 (9.7%)	
Mild	7,495 (36.1%)	8,062 (40.0%)	10,460 (39.3%)	
Charlson index (mean [SD])	.8 (1.1)	.7 (1.0)	.8 (1.1)	<.001
Number of nonpain medical conditions (mean [SD])	9.2 (4.7)	8.4 (4.5)	9.1 (4.6)	<.001
BMI (mean[SD])	27.5 (5.9)	26.8 (5.6)	27.7 (6)	<.001
Sedentary activity, hours per day (mean [SD])‡	15.2 (4.2)	15.2 (4)	15.1 (4.1)	.153
Pain, mean (SD)§	56 (22.7)	77 (21.3)	79 (19.1)	<.001
Physical functioning, mean (SD)§	76.7 (21.7)	83.2 (19.3)	80.3 (19.4)	<.001
BASELINE medication use				
Opioid use	634 (3.1%)	405 (2.0%)	542 (2.0%)	<.001
Other analgesic use‖	9,675 (46.6%)	8,418 (41.7%)	11,603 (43.5%)	<.001
HT use	9,730 (46.9%)	9,548 (47.4%)	12,504 (46.9%)	.789
Psychosocial				
Depressed† (≥.06 on shortened CES-D scale)	2,677 (12.9%)	1,887 (9.4%)	3,097 (11.6%)	<.001

Table 1. Continued

Characteristics	Change in Pain Baseline to 3-Year Follow-Up: Improved (N = 20,742)	None (N = 20,163)	Worsened (N = 26,647)	P value
Ambivalence over emotional expressiveness,¶ mean (SD)	3.0 (.7)	3.0 (.7)	3.0 (.7)	<.001
Cynicism,** mean (SD)	3.8 (2.8)	3.5 (2.7)	3.8 (2.8)	<.001
Social support,†† mean (SD)	35.8 (7.8)	36.5 (7.5)	35.6 (7.8)	<.001

Abbreviations: BMI, body mass index; HT, hormone replacement therapy; CES-D, Center for Epidemiologic Studies Depression scale.
*6–7% missing.
†1–3% missing.
‡Hours sleeping, sitting or lying down.
§From the SF-36, possible scores range from 0 to 100, higher scores indicate better health/functioning.
‖Use of acetaminophen, ibuprofen and other nonsteroidal anti-inflammatories, aspirin, salicylate analgesics, other aspirin like analgesics, lidocaine, and capsaicin creams.
¶Possible scores range from 1 to 5, higher scores indicating greater ambivalence in expressing negative emotions.
**Possible scores range from 0 to 13, higher scores indicating greater cynicism.
††Possible scores range from 9 to 45, higher scores indicating greater support.

scores (mean [SD] 41 [25.2] versus 72.6 [22.6]), a higher number of nonpain medical conditions (11 [5.2] versus 8.9 [4.6]), a higher Charlson score (1.3 [1.4] versus .8 [1.1]), lower physical functioning (56.8 [26.7] versus 80.6 [19.7]), slightly higher BMI (29.5 [6.9] versus 27.3 [5.8]), were more likely to be disabled (13.5% versus 1.9%) and were more likely to screen positive for depression (20.5% versus 11.1%) ($P < .001$ for all differences noted). Women with baseline opioid use also were more likely to report having each of the 4 pain symptoms examined in our study than those without baseline opioid use. The most common pain type reported by those with baseline opioid use was low back pain (80.6%, N = 1,272).

Logistic Regression Models

Tables 2 and 3 present results from multinomial logistic regression models examining variables associated with change in pain and physical functioning between baseline and year 3 among women with recurrent pain conditions. The effect size of many of the covariates tended to be small, particularly for the psychosocial variables other than depression.

Table 2: Change in Pain

Baseline opioid use (OR [95% CI] .42 [.36, .49], $P < .001$), and being disabled at baseline (.37 [.31, .44]), were strongly associated with a lack of improvement (ie, decreased odds of improvement versus no change) in pain. BMI ≥30 versus <25 (1.54 [1.45, 1.63]) was strongly associated with a worsening in pain.

A positive screen for depression, baseline hormone therapy use, higher Charlson index score, and higher number of nonpain symptoms were all associated with lack of improvement and worsening of pain between

Table 2. Multinomial Logistic Regression Models:* Change in Pain† Among Post-Menopausal Women With Recurrent Pain Conditions

	Change Between Baseline and Year 3: Improved vs. No Change		Worsened vs. No Change	
Independent Variables‡	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Depressed: ≥.06 vs. <.06 on shortened CES-D	.91 (.84, .99)	.031	1.13 (1.05, 1.22)	.001
Physical activity: +1 hour/day sitting or lying down	1.00 (.99, 1.01)	.880	1.00 (1.00, 1.01)	.603
Ambivalence over emotional expressiveness construct (+1 unit)	1.00 (.97, 1.04)	.807	1.01 (.98, 1.04)	.716
Cynicism construct (+1 unit)	1.01 (1.00, 1.02)	.108	1.01 (1.00, 1.02)	.146
Social support construct (+1 unit)	1.00 (1.00, 1.01)	.214	.99 (.99, .99)	<.001
Disabled	.37 (.31, .44)	<.001	1.03 (.87, 1.23)	.705
Charlson index (+1 unit)	.97 (.94, .99)	.004	1.06 (1.04, 1.08)	<.001
Baseline hormone replacement therapy use	.92 (.87, .96)	<.001	1.15 (1.10, 1.20)	<.001
BMI: 25–<30 vs. <25	.99 (.94, 1.05)	.786	1.20 (1.14, 1.26)	<.001
BMI: ≥30 vs. <25	.80 (.75, .85)	<.001	1.54 (1.45, 1.63)	<.001
Number of nonpain symptoms (+1 unit)	.97 (.96, .97)	<.001	1.04 (1.03, 1.04)	<.001
Baseline opioid use vs. no baseline opioid use	.42 (.36, .49)	<.001	1.13 (.97, 1.32)	.127
Baseline pain severity (+1 unit)	.95 (.95, .95)	<.001	1.01 (1.01, 1.02)	<.001

Abbreviation: BMI, body mass index.
*Adjusted for age at screening, highest education level, family income, employment status-disabled, race/ethnicity.
†Based on scores from SF-36 pain subscale.
‡All variables from baseline interview.

Table 3. Multinomial Logistic Regression Models:* Change in Physical Functioning† Among Post-Menopausal Women With Recurrent Pain Conditions

	Change Between Baseline and Year 3			
	Improved vs. No Change		Worsened vs. No Change	
Independent Variables‡	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Depressed: ≥.06 vs. <.06 on shortened CES-D	.99 (.90, 1.08)	.781	1.10 (1.01, 1.19)	.028
Physical activity: +1 hour/day sitting or lying down	.99 (.99, 1.00)	.082	1.01 (1.00, 1.02)	.002
Ambivalence over emotional expressiveness construct (+1 unit)	1.06 (1.02, 1.10)	.004	1.05 (1.02, 1.08)	.004
Cynicism construct (+ 1 unit)	1.00 (.99, 1.01)	.961	1.00 (.99, 1.01)	.961
Social support construct (+1 unit)	1.00 (1.00, 1.00)	.513	.99 (.99, .99)	<.001
Disabled	.39 (.31, .49)	<.001	.71 (.57, .87)	.001
Charlson index (+1 unit)	.94 (.92, .97)	<.001	1.05 (1.03, 1.08)	<.001
Baseline hormone replacement therapy use	1.02 (.97, 1.08)	.393	1.10 (1.05, 1.15)	<.001
BMI: 25–<30 vs. <25	1.07 (1.01, 1.14)	.018	1.32 (1.25, 1.39)	<.001
BMI: ≥30 vs. <25	.99 (.92, 1.06)	.747	1.83 (1.71, 1.95)	<.001
Number of nonpain symptoms (+1)	1.00 (1.00, 1.01)	.351	1.03 (1.03, 1.04)	<.001
Baseline opioid use only vs. no baseline opioid use	.88 (.72, 1.08)	.236	1.25 (1.04, 1.51)	.020
Baseline physical functioning (+1 unit)	.99 (.98, .99)	<.001	.95 (.95, .95)	<.001

Abbreviation: BMI, body mass index.
*Adjusted for age at screening, highest education level, family income, employment status-disabled, race/ethnicity.
†Based on scores from SF-36 physical functioning subscale.
‡All variables from baseline interview.

baseline and year 3. More social support was associated with decreased likelihood of worsening of pain. We also ran the regression model including the different pain types (ie, joint pain or stiffness, low back pain, neck pain, migraine or headaches) as additional covariates. We did this as a sensitivity analysis to rule out potential confounding of the results for baseline opioid use by responsiveness of pain type to prescription opioid treatment. Results for the model were not significantly changed by this addition. All of the pain types were associated with worse pain and lack of improvement between baseline and year 3, with the exception that migraines or headaches were not significantly associated with worsening of pain.

Table 3: Change in Physical Functioning

BMI ≥30 versus <25 (OR [95% CI] 1.83 [1.71-1.95]) was strongly associated with worsened physical functioning between baseline and year 3. Being disabled at baseline was strongly associated with lack of improvement in physical functioning (.39 [.31, .49]). A positive screen for depression, increased hours of sedentary activity per day, higher ambivalence over emotional expressiveness score, baseline hormone therapy use, higher Charlson index score, higher number of nonpain symptoms, and baseline opioid use were associated with a worsening of physical functioning between baseline and year 3. More social support was associated with decreased likelihood of worsened physical functioning.

Discussion

In this longitudinal study of 67,963 postmenopausal women with recurrent pain, we examined demographic, medical, and psychosocial variables associated with change in pain and physical functioning over 3 years of follow up. To the best of our knowledge this is the largest prospective observational study to look at factors associated with change in pain. Previous prospective studies have focused primarily on recovery after acute trauma or injury.[17,44,46] In our study, recurrent pain was very common among study participants, endorsed by nearly 75%. This is consistent with prior studies reporting the prevalence of pain complaints among postmenopausal women,[9,20,24] and extends these findings by demonstrating the recurrence of pain over a several-year period in this population. Almost 40% of the women in our study reported worse pain at year 3 compared to baseline. BMI in the overweight or obese range (≥25) was associated with worsened pain and physical functioning at year 3 and the associations were greatest in those with BMI ≥30. Prior cross-sectional studies have demonstrated an association between chronic pain and obesity,[32,37,50,56] and prospective studies suggest that overweight/obesity early in life is a risk factor for development of pain.[33] In the Longitudinal Aging Amsterdam Study, adults age 55 to 85 years in the highest quartile of BMI had 2-fold increased odds for incident pain after 3 years of follow-up.[31] Our study results are consistent with these findings and add to them by suggesting that elevated BMI also is associated with worsening of pre-existing pain conditions over time.

Even after controlling for baseline pain, pain type, and depression, women reporting prescription opioid use at baseline were more likely to report lack of improvement in pain and worsened physical functioning 3 years later. It is possible that the women reporting prescription opioid use had pain that was both more severe and more difficult to treat. Nearly all the women in our study with baseline opioid use reported use for 90 days or longer, suggesting they were receiving chronic opioid therapy for a chronic pain condition. Meta-analyses have

shown opioids to be more effective than placebo for treatment of chronic pain over 12 weeks of therapy,[26] but there are no controlled trials that examine efficacy over years of therapy. A large cross-sectional observational study in Denmark showed higher pain intensity, pain interference, and worse quality of life for patients treated with opioids than those not treated with opioids, but it was not possible to rule out selection bias in this study.[23] There also is some evidence that longer term use of opioids could be associated with the development of hyperalgesia, ie, increased sensitivity to pain.[16,51] Individuals receiving prescription opioids had higher baseline pain which could result in decreased physical activity levels and subsequent weight gain, further worsening of pain and overall physical functioning. Consistent with this assessment, more hours per day of sedentary activity at baseline was associated with a worsening of physical functioning at year 3. Being disabled at baseline was also associated with lack of improvement in pain over the 3-year period, and may similarly reflect a subpopulation more refractory to treatment. Results from our study highlight the need for clinical effectiveness studies to evaluate the long-term use and tolerability of prescription opioids, and to evaluate functional outcomes, in the treatment of recurrent pain among postmenopausal women.

The nonpain symptom count captured information on symptoms of distress that might be obtained in a review of symptoms—eg, nausea, hot flashes, dizziness, and fatigue—and was associated with worse pain outcomes over the 3-year period. This variable reflects overall symptom burden and is associated with both medical and psychiatric comorbidity.[34] Results from our study are consistent with prior studies, which have found a positive association between elevated levels of nonspecific physical symptoms and pain severity, negative affect, and disability among individuals with chronic pain.[38,41,54] The association between baseline hormone therapy use and worse pain outcomes may reflect use of HT to treat postmenopausal symptoms, which include pain (eg, joint and back pain) as well as nonpain symptoms (eg, fatigue, mood lability, sleep disturbance, memory changes, night sweats).

One of the primary objectives of our study was to examine psychosocial predictors of a change in pain interference, pain severity, and physical functioning. Prior cross-sectional studies have shown an association between depression and higher pain interference and severity,[2,4,8] and prospective studies have found that depression and persistent pain equally predict the subsequent onset of the other.[27] Consistent with this, a positive screen for depression at baseline was associated with worsening of pain at year 3 among women in our study. The association was modest, possibly reflecting the healthier baseline mental health status of the study population in comparison with clinical populations. In addition, the shortened CES-D screening instrument used in this study is less specific than the full CES-D or a diagnostic interview, and thus women screening positive likely included some with more minor depressive symptoms that would not necessarily prompt help-seeking or clinical intervention. Ambivalence over emotional expression and cynicism were not consistent or strong predictors of pain outcomes. This may be because the women in this study had relatively low baseline scores on these construct measures.

Strengths of our study include the large population-based sample with longitudinal follow-up and availability of data on a variety of psychosocial, medication use, and medical variables. There are several limitations to our study that should be mentioned. The data available on prescription opioid use from this study was limited to self-report of duration of use at the baseline and year 3 interviews. Hence, we are unable to determine whether use continued between the 2 interviews, and we lack data on prescribed dose. In addition, because this is an observational study and opioid use was obtained by self-report, we cannot verify what pain condition the opioids were prescribed to treat. We also are unable to rule out the possibility that patients selected for opioid therapy had more progressive pain problems. Information on pain conditions and depressive symptoms were based on self-report, not diagnoses from a health care provider or via a structured diagnostic interview. In addition, we lacked information on anxiety, which has previously been shown to be associated with persistent pain,[47,53] and illicit drug or alcohol use, as well as information on the presence and severity of pain complaints at time points between the baseline and year 3 interviews. Pain complaints included in the definition of recurrent pain were limited to 4 of the more common conditions seen in primary care,[28] but did not include others of clinical importance, such as fibromyalgia. The study population consisted of primarily white, middle-class postmenopausal women and results therefore may not be generalizable to all individuals with recurrent pain conditions.

In summary, elevated BMI in the overweight/obese range, a positive screen for depression, higher medical comorbidity, and number of nonpain symptoms were all associated with worsening pain and physical functioning over a 3-year period in this cohort of postmenopausal women with recurrent pain conditions. Baseline prescription opioid use was not associated with worsening pain but was associated with lack of improvement in pain and with worsened physical functioning at year 3. This is consistent with concerns of some experts that long-term opioid use may decrease physical function by promoting rest or inactivity.[29]

While it is impossible to rule out selection bias in opioid prescription in this observational study, results suggest further inquiry into the efficacy and tolerability of opioid treatment in this population is warranted. Results support prior recommendations to screen for and treat depression among those with recurrent pain conditions[51] and highlight the role of obesity and weight management in long-term pain outcomes. In addition, results suggest that individuals reporting multiple physical symptoms in addition to pain are at risk for worsening pain over time. Additional prospective and comparative effectiveness studies are needed to further examine the effects of obesity, depression, and opioid therapy on the course of recurrent pain conditions.

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