Research Paper

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Self-reports of medication side effects and pain-related activity interference in patients with chronic pain: a longitudinal cohort study

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Abstract

The primary purpose of this study was to examine the association between self-reports of medication side effects and pain-related activity interference in patients with chronic pain. The potential moderators of the association between reports of side effects and pain-related activity interference were also examined. A total of 111 patients with chronic musculoskeletal pain were asked to provide, once a month for a period of 6 months, self-reports of medication use and the presence of any perceived side effects (eg, nausea, dizziness, headaches) associated with their medications. At each of these time points, patients were also asked to provide self-reports of pain intensity, negative affect, and pain-related activity interference. Multilevel modeling analyses revealed that month-to-month increases in perceived medication side effects were associated with heightened pain-related activity interference ($P < 0.05$). Importantly, multilevel models revealed that perceived medication side effects were associated with heightened pain-related activity interference even after controlling for the influence of patient demographics, pain intensity, and negative affect. This study provides preliminary evidence that reports of medication side effects are associated with heightened pain-related activity interference in patients with chronic pain beyond the influence of other pain-relevant variables. The implications of our findings for clinical practice and the management of patients with chronic pain conditions are discussed.

Keywords: Chronic pain, Medication side effects, Negative affect, Pain-related activity interference

1. Introduction

Over the past decade, there has been a substantial rise in the use of prescription medications for the management of patients with chronic pain. In addition to opioids, patients are often concurrently prescribed several other analgesic and nonanalgesic medications, including antidepressants, anxiolytics/sedatives, anticonvulsants, muscle relaxants, and nonsteroidal anti-inflammatory drugs (NSAIDs).[8,12,17,43] Despite the potential benefits of each of these medications for the management of patients with pain, it is well known that the combination of a wide range of medications may lead to a number of adverse side effects, including nausea, dizziness, headaches, constipation, and weakness. These medication side effects are frequently observed in clinical settings and represent a complex pain management issue.[8,11,17,20,34,65]

To date, the bulk of research that has been conducted on medication side effects has focused on the determinants of various side effect profiles. Surprisingly, little research has addressed the association between medication side effects and pain-related activity interference (eg, reductions in daily life activities due to pain). Among patients with chronic pain, medication side effects have been found to be associated with decreased quality of life[2,3] and reduced treatment satisfaction,[16,20,33] but the association between patients' reports of side effects and pain-related activity interference remains largely unexplored. Until now, only one cross-sectional study has found that patients' reports of side effects were associated with decreased daily functioning,[65] while another one found that side effects were associated with decreased work productivity.[2]

Another shortcoming of previous studies in this area is the lack of information on the relative (ie, unique) association between reports of medication side effects and pain-related activity interference. In previous studies, this association has not been examined while controlling for other important variables known to be associated with activity interference, such as patient demographics,[14,39,57] pain intensity,[29,67,74,76] or negative affect.[35,56,66,69,76] Moreover, previous studies have not examined the variables that might moderate the association between reports of medication side effects and pain-related activity interference. For example, it is possible that medication side effects are associated with pain-related activity interference, but only among certain subgroups of patients, such as men or women, or only among patients experiencing high levels of pain intensity or negative affect. Further research investigating the association between reports of medication side effects and

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pain-related activity interference is of high clinical relevance, as it has implications for the pharmacological management of patients with pain conditions.

In this study, 111 patients with chronic musculoskeletal pain were asked to provide, once a month for a period of 6 months, self-reports of medication use and the presence of any side effects associated with their medications. The primary purpose of the study was to examine the unique (ie, independent) association between self-reports of medication side effects and pain-related activity interference. It was also of interest to examine whether the association between reports of medication side effects and pain-related activity interference was moderated by patient gender, pain intensity, or negative affect.

2. Methods

2.1. Participants

The Human Subjects Committee of Brigham and Women's Hospital (BWH) approved the study procedures, and written informed consent was obtained from every participant. This study was performed in a single, large, urban university-based pain management center. All patients received a thorough history and underwent a physical examination by a pain physician at BWH. Patients included in this study (n = 111) were part of a randomized clinical trial of a behavioral intervention designed to improve prescription opioid compliance (for methods of the trial, see Ref. 28). Among the patients included in this study, 32% (n = 35) were part of the experimental treatment arm and 68% (n = 76) were part of control arms. Given that the pattern of findings obtained in this study did not differ as a function of treatment groups, data were collapsed and analyses were conducted on the overall sample.

Patients included in this study met the following inclusion criteria: (1) chronic back or neck pain for more than 6 months, (2) able to speak and understand English, (3) prescribed opioid medication for more than 6 months, and (4) at risk of prescription opioid misuse based on their responses on the Screener and Opioid Assessment for Patients with Pain (SOAPP-R)[5] or based on past records of abnormal urine screens. Patients were excluded from participation if they met any of the following criteria: (1) current diagnosis of cancer, (2) acute osteomyelitis or acute bone disease, (3) diagnosis of any psychotic disorder, or (4) current substance abuse or dependence of any kind within the past year (ie, positive on the M.I.N.I. International Neuropsychiatric Interview [M.I.N.I. v.5.0[61]]). Patients with an active substance use disorder (SUD) were excluded given the current clinical practice guidelines and principles at the BWH Pain Center regarding the management of patients with an active SUD. Patients with an active SUD are generally referred to a local addiction treatment facility before undergoing pain treatment at the Pain Center and before being eligible for study participation.

2.2. Measures and procedures

2.2.1. Demographic questionnaire

During their first visit, patients were asked to complete a demographic questionnaire, which included information about age, gender, ethnicity, marital status, education level, and employment status.

2.2.2. Screening for substance use disorder

The M.I.N.I. v.5.0[61] was used to screen for active opioid addiction and any other active addiction disorder. The M.I.N.I. is a brief structured interview for the major Axis I psychiatric disorders included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). We used section K to assess the presence of a current nonalcohol psychoactive SUD. Section K is designed to identify the use of (1) stimulants, (2) cocaine, (3) nonprescription opioids, (4) hallucinogens, (5) heroin, (6) inhalants, (7) marijuana, (8) nonprescription tranquilizers, and (9) other substances of abuse. The M.I.N.I. was administered and scored by a trained research assistant. The M.I.N.I. has been shown to be a reliable and valid screening tool for SUDs in patients with and without chronic pain conditions.[21,28,53,61]

2.2.3. Self-reports of medication use, medication side effects, pain intensity, negative affect, and pain-related activity interference

Using a personal digital assistant (PDA) (iPAQ; Hewlett-Packard, Palo Alto, CA) running the Pain Electronic Calendar software (New England Research Institutes, Watertown, MA), patients were asked to provide, once a month for a period of 6 months, self-reports of medication use, medication side effects, pain intensity, negative affect, and pain-related activity interference. As will be seen below, all ratings were made on 0 to 10 visual analog scales (VASs). These ratings were then automatically converted and stored on a 0 to 100 scale.

2.2.3.1. Self-reports of medication use

Using the PDA, patients were asked to report which medications they were currently taking (**Fig. 1**). Patients' reports of medication were verified by a research assistant using the electronic medical record system, and published tables were used to convert opioid doses into morphine equivalents.

2.2.3.2. Self-reports of medication side effects

Using the PDA, patients were asked to report whether they were currently experiencing any of the following medication side effects: (1) nausea, (2) constipation, (3) headaches, (4) dry mouth, (5) itching, (6) sneezing, (7) sweating, (8) weakness, (9) dizziness, (10) confusion, (11) memory problems, and (12) visual problems. Patients were then asked to rate the intensity of each perceived medication side effect on a VAS that ranged from 0 (minimum) to 10 (maximum). Patients were not asked to provide ratings of medication side effects based on a specific medication, but rather based on all the medications they were taking. Given that chronic

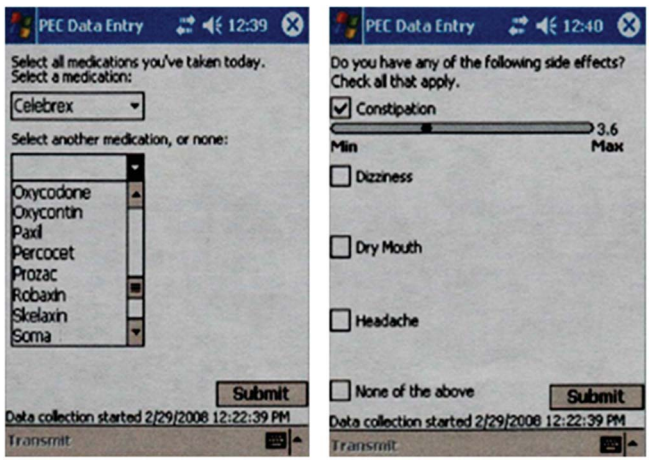

Figure 1. Sample of a personal digital assistant screen used to assess medication use and perceived medication side effects.

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pain patients are known to use a wide range of medications concurrently,[17,18,32,59] this global medication side effect assessment was assumed to be the most adequate. Self-reports are currently the most commonly used method for assessing side effects among ambulatory patients, whether in the context of observational studies[1,3,77] or randomized controlled trials.[20,34,64] Items used to assess medication side effects in our study are similar to those that have been used in previous work, and the proposed medication side effects rated on the PDA have been found to be among the most frequent side effects associated with opioid and nonopioid analgesic medications.[20,23,33,46]

2.2.3.3. Self-reports of pain intensity

Patients were asked to rate their current level of pain on a VAS that ranged from 0 (no pain) to 10 (worst pain possible). This measure is an adaptation of the standard VAS commonly used in the Brief Pain Inventory[68] to assess pain intensity levels among patients with chronic pain.

2.2.3.4. Self-reports of negative affect

Patients were asked to rate their current level of anxiety ("How tense and anxious have you been today?") and depression ("How depressed and discouraged have you been today?") on a VAS that ranged from 0 (not much) to 10 (very much). These 2 measures have been used in our previous studies to assess negative affect among patients with chronic pain.[26,27,48,50,81]

2.2.3.5. Self-reports of pain-related activity interference

Patients were asked to rate the degree to which pain interfered with their daily routine activities, outdoor activities, and social activities. Ratings were made separately for these 3 items on a VAS that ranged from 0 (not much) to 10 (very much). Higher scores on these items represent greater pain-related activity interference. These items have been used in our previous studies conducted among patients with chronic pain.[27,48,49]

2.3. Data reduction and analysis

Given the high intercorrelations (ranging from 0.73 to 0.80; Cronbach's $\alpha = 0.91$) among the 3 items of activity interference, ratings on these items were averaged to create a single index of pain-related activity interference. Consistent with previous research,[26,50,79,80] an index of negative affect was also computed by averaging the patients' ratings of anxiety and depression.

The total number of medications used by patients was calculated by summing, for each patient, the different types of medications being used at each of the assessment time points. A medication side effect index (MSE-I) was computed by summing the intensity of each medication side effect being reported. This index was derived to simultaneously take into account the "number" and the "intensity" of medication side effects being reported by patients. Previous studies have highlighted the importance of assessing both the incidence and the intensity of medication side effects.[23,34,47,54] This represents a more clinically meaningful medication side effect assessment than assessing the incidence or the intensity of medication side effects independently.

Descriptive data were computed using IBM-SPSS v.21 (Chicago, IL). Descriptive data for continuous variables were presented as mean and SDs and were analyzed using independent samples *t* tests. Descriptive data for categorical variables were presented as percentages and were analyzed using χ^2 tests.

Multilevel modeling analyses were conducted using the MIXED command in IBM-SPSS. Multilevel modeling was well suited to handle the hierarchical nested data structure of this study, in which repeated monthly assessments (level 1 units) were nested within participants (level 2 units). Multilevel modeling was also well suited to handle the unequal number of data points across participants due to missing data. Given that multilevel modeling can account for unbalanced data set and/or missing data,[52,63] all 111 participants could be included in multilevel analyses without using any data imputation procedure.

Across all assessment time points, compliance in our study was high, with an overall completion rate of 87%. For example, when combining the 4 main level 1 variables that were assessed on a monthly basis in this study (ie, medication side effects, pain-related activity interference, pain intensity, negative affect), there was a total of 2664 possible data points (111 participants $\times$ 6 waves per time points $\times$ 4 variables). A total of 2338 data points were observed (87%), with varying response rates as a function of waves. Response rates were as follows: wave 1 (100%); wave 2 (99.3%); wave 3 (95.5%); wave 4 (89.1%); wave 5 (75.6%); wave 6 (62.8%). For any given wave, there was a total of 444 possible data points (111 $\times$ 4 variables); the lowest/minimum response rate was observed at wave 6 (279/444; 62.8%), whereas the highest/maximum response rate was observed at wave 1 (444/444; 100%). Analyses indicated that patients with and without missing data did not differ significantly in terms of age, $t(109) = -0.34$, nonsignificant (ns), gender, $\chi^2(1) = 0.01$, ns, or in any other demographic variable (all $P > 0.05$). Also, patients with and without missing data did not differ significantly on any of the main study variables, such as pain $t(109) = 1.6$, ns, negative affect, $t(109) = 0.54$, ns, medication side effects, $t(109) = 0.19$, ns, or pain-related activity interference, $t(109) = 0.83$, ns.

For each independent variable of interest (ie, perceived medication side effects, pain intensity, negative affect), level 1 observations (ie, scores) were centered within participants, a procedure that has been referred to as group-mean centering.[15,51] This was performed by computing, for each participant, the mean of level 1 scores across assessment time points. Mean scores were then subtracted from monthly scores, resulting in a set of "deviation scores" for each independent variable. These scores represent the extent to which a participant, on a given month, deviated from his/her own mean on a specific independent variable.[15,38] Deviation scores allowed us to examine whether elevations on independent variables of interest (eg, perceived medication side effects) were associated with the study outcome even when controlling for month-to-month changes in relevant covariates. Deviation scores based on this centering procedure also permitted an interpretation of the intercept on the basis of participants' means on each independent variable.[7,15]

Model building was initially guided by examination of variance components for the unconditional (null) models of the main study outcome (ie, pain-related activity interference). Examination of variance components indicated that the within-person variability in pain-related activity interference was 316.40 ($z = 13.41$, $P < 0.001$), whereas the between-person variability was 253.94 ($z = 5.47$, $P < 0.001$). The intraclass correlation coefficient was 0.45, indicating that approximately 45% and 55% of the total variance in ratings of pain-related activity interference can be explained by between-person variability (level 2) and within-person variability (level 1), respectively. Given the significant variance components and results from the intraclass correlation coefficient, it was thus appropriate to model both between- and within-person variance in pain-related activity interference.

To examine the unique (ie, independent) association between perceived medication side effects and pain-related activity

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interference, a multilevel model was built using the pain-related activity interference index as the dependent variable. In this model, patient gender (level 2), pain intensity (level 1), and negative affect (level 1) were first added simultaneously to the model as independent variables. The MSE-I was then added to the model as a level 1 independent variable, which permitted examination of the independent association between reports of medication side effects and pain-related activity interference.

To examine the potential moderators of the association between medication side effects and pain-related activity interference, 3 distinct multilevel models were built using the activity interference index as the dependent variable. We were particularly interested in examining whether the association between reports of medication side effects and pain-related activity interference was moderated by patient gender (level 2), pain intensity (level 1), or negative affect (level 1). In these models, 2-way interaction terms between the MSE-I and each of the other independent variables (ie, patient gender, pain intensity, negative affect) were specified. These interaction terms were included in 3 separate models, after the inclusion of appropriate main effects. Any significant 2-way interaction effect would suggest that the association between self-reports of medication side effects and pain-related activity interference is moderated by patient gender, pain intensity, or negative affect.

All the multilevel models that were built in this study followed a sequential procedure,[37,58,78] which first involved specifying a random intercept and fixed effects for independent variables. When significant fixed effects emerged, slopes were then treated as random effects and model fit was reevaluated using the likelihood ratio test. Random parameters were dropped if they resulted in a significantly worse model fit.[60,62,63] All models were carried out using maximum likelihood estimation and included a first-order autoregressive variance–covariance matrix (AR1) to account for autocorrelations between repeated assessments. As recommended,[24,52] effect sizes were estimated by calculating the percentage reduction in unexplained variance at both the between- and within-person level, relative to the unexplained variance of the null model. This measure of explained variance is analogous to the R^2 value traditionally reported when conducting linear regression.[24,25,52]

3. Results

3.1. Descriptive statistics

Descriptive statistics for study measures are presented in **Table 1**. On average, across assessment time points, men and women did not differ significantly in pain intensity, negative affect, or pain-related activity interference (all $P > 0.05$). However, men and women differed significantly on the MSE-I, with self-reports of medication side effects being greater among women than men, $t(109) = 2.1$, $P < 0.05$.

Table 2 shows the different types of medications that were used by patients included in our study. In addition to prescription opioids (100%; average daily opioid dose: mean = 141.2; SD = 209.6), the most common medications used by patients over the course of the study were antidepressants (41%), anticonvulsants (35%), anxiolytics/sedatives (29%), muscle relaxants (26%), and NSAIDs (24%). These different types of medications are representative of medications that are prescribed to patients treated in tertiary pain centers.[9,17,42,73] Analyses indicated that reports of medication side effects were not significantly higher among those who used, in addition to prescription opioids, either antidepressants, $t(109) = -0.94$, ns, anticonvulsants, $t(109) = -0.32$, ns, anxiolytics/sedatives, $t(109) = -0.28$, ns, muscle relaxants, $t(109) = -0.54$, ns, or NSAIDs, $t(109) = -0.88$.

Before specifying the effects of independent variables on the study outcome in multilevel models, the influence of demographic (ie, age, ethnicity, education, marital status, employment status) and medication regimen (ie, total number of medications) variables on pain-related activity interference was examined. Results indicated that employment status was significantly associated with pain-related activity interference, with unemployed patients reporting greater pain-related activity interference scores than employed patients, $F(1,106) = 12.07$, $P < 0.001$. None of the other variables were significantly associated with pain-related activity interference (all $P > 0.05$). Employment status was thus the only covariate retained in the multilevel model reported here.

Additional multilevel analyses were conducted to explore any potential systematic time effect on the main study outcome. In these analyses, the variable "time" was treated as a continuous level 1 independent variable, and the activity interference index was used as the dependent variable. Results indicated that the main effect of time was not significant, $\beta = 0.65$, SE = 0.50, ns. A follow-up multilevel analysis was then conducted to examine whether time interacted with medication side effects in predicting pain-related activity interference, but this interaction effect was not significant, $\beta = 0.02$, SE = 0.01, ns. The variable time was thus not included in any further models.

3.2. Association between self-reports of medication side effects and pain-related activity interference

As can been seen in **Table 3**, a multilevel model was built using the activity interference index as the dependent variable. Patient gender, pain intensity (level 1), and negative affect (level 1) were

Table 1

Sample characteristics and descriptive data for main study variables.

Variables	Overall sample	Men (n = 61)	Women (n = 50)	*P*
Age (years)	48.17 (8.60)	48.08 (8.43)	48.28 (8.90)	NS
Ethnicity (% white)	78	77	80	NS
Marital status (% married/relation)	50	52	49	NS
Employment status (% unemployed)	71	71	71	NS
Education (years)	12.46 (3.63)	12.27 (3.77)	12.68 (3.48)	NS
Pain intensity	59.49 (16.01)	58.25 (16.72)	61.01 (15.14)	NS
Negative affect	44.25 (22.68)	44.03 (20.90)	44.52 (24.90)	NS
Medication side effects (MSE-I)	124.11 (113.85)	103.90 (93.78)	148.76 (131.15)	<0.05
Pain-related activity interference	66.31 (18.51)	65.80 (18.97)	66.95 (18.11)	NS

Values in parentheses are SDs.
MSE-I, medication side-effect index; NS, nonsignificant.

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Table 2

Number of patients using the different types of medications.

Opioids	111 (100%)
Antidepressants	46 (41%)
Anticonvulsants	39 (35%)
Muscle relaxants	29 (26%)
Anxiolytics/sedatives	32 (29%)
NSAIDs	27 (24%)

NSAID, nonsteroidal anti-inflammatory drug.

first added simultaneously to the model as independent variables. Results indicated that the main effect of patient gender on pain-related activity interference was not significant, $\beta = 2.03$, SE = 3.38, ns. However, the main effect of pain intensity was significant ($\beta = 0.47$, SE = 0.05, $P < 0.001$), indicating that month-to-month increases in pain were associated with higher ratings of pain-related activity interference. The main effect of negative affect was also significant ($\beta = 0.13$, SE = 0.04, $P < 0.001$), indicating that month-to-month increases in negative affect were associated with higher ratings of pain-related activity interference. Results from a likelihood ratio test indicated that inclusion of pain intensity and negative affect as random effects resulted in a significantly worse model fit, $\chi^2(2) = 45$, $P < 0.001$; random parameters were thus dropped from the final model.

To examine the unique (ie, independent) association between self-reports of medication side effects and pain-related activity interference, the MSE-I was subsequently added to the model as a level 1 independent variable. Results indicated that month-to-month increases in perceived medication side effects were associated with higher ratings of pain-related activity interference, $\beta = 0.02$, SE = 0.01, $P < 0.05$. A likelihood ratio test indicated that inclusion of the MSE-I as a random effect resulted in a significantly worse model fit, $\chi^2(1) = 62$, $P < 0.001$; this random parameter was thus dropped from the final model. The within-person pseudo R^2 after the inclusion of the MSE-I was 0.03. Taken together, results from this model indicate that the association between self-reports of medication side effects (MSE-I) and pain-related activity interference was significant even after controlling for the main effects of patient gender, pain intensity, and negative affect.

Given that inspection of variance components from the previous model revealed substantial between-person variability in mean pain-related activity interference scores (ie, intercept) ($\beta = 261.09$, $P < 0.001$), a follow-up model was built to examine whether the association between self-reports of medication side effects and pain-related activity interference remained significant even after controlling for all potential between-person variables (ie, "observed" or "unobserved") that could have been responsible for this association. While the previous analysis controlled for month-to-month changes in pain and negative affect when examining the association between perceived side effects and pain-related activity interference, a wide range of preexisting (ie, time-invariant) variables could have also been responsible for this association. We thus retained all the parameters from the previous model, but we controlled for the influence of between-person variables by adding each participant (ie, ID) as a fixed effect in the model. Modeling each participant (ID) as a fixed effect was done by creating 110 dummy coded variables, which were then entered simultaneously in the multilevel model (see Refs. 5, 41, 53). This resulted in a model with 110 new parameters. The random effect for the intercept was set to zero, indicating that the between-person variance in the intercept was entirely accounted for by the inclusion of all participants (IDs) as fixed effects to the model). This model-building strategy allowed us to control for the influence of any observed or unobserved between-person variables on the study outcome.[4,41,55] Results from this model indicated that the main effect of medication side effects (MSE-I) on pain-related activity interference remained significant even after controlling for the fixed effects of participants ($\beta = 0.02$, SE = 0.01, $P < 0.01$). Taken together, results from this model suggest that the association between perceived medication side effects and pain-related activity interference cannot be entirely accounted for by any potential observed or unobserved between-person variables.

3.3. Moderators of the association between patients' reports of medication side effects and pain-related activity interference

Three distinct multilevel models were built to examine whether patient gender, pain intensity (level 1), or negative affect (level 1) moderated the association between self-reports of medication side effects and pain-related activity interference. As can be seen in **Table 4**, models were built using the activity interference index as the dependent variable. In all these models, 2-way interaction terms between the MSE-I and each of the other independent variables (ie, patient gender, pain intensity, negative affect) were specified and were preceded by appropriate main effects. Results indicated that 2-way interaction effects between the MSE-I and patient gender ($\beta = 0.001$, SE = 0.020, ns), pain intensity ($\beta = 0.000$, SE = 0.001, ns), and negative affect ($\beta = 0.001$, SE = 0.001, ns) were not significant. Taken together,

Table 3

Multilevel model examining the unique association between perceived medication side effects and pain-related activity interference.

Fixed effects	β	SE	*df*	*t*	*P*
Intercept	56.32	3.54	107	15.9	<0.001
Gender	1.95	3.40	114	0.58	NS
Pain intensity	0.47	0.05	511	10.35	<0.001
Negative affect	0.12	0.04	509	3.40	<0.005
MSE-I	0.02	0.01	499	2.07	<0.05

Random effects: covariance parameters	Subject	β	SE	*z*	*P*
Intercept	ID	261.09	43.73	5.97	<0.001
AR1	ID	0.15	0.06	2.68	<0.01
Residuals	ID	225.49	16.24	13.88	<0.001

Values are from the final model. Independent variables are within-person centered. Employment status was included as a covariate.
β, unstandardized regression coefficient; MSE-I, medication side effect index; NS, nonsignificant; SE, standard error.

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Table 4

Multilevel model examining the potential moderators of the association between perceived medication side effects and pain-related activity interference.

Fixed effects	β	SE	*df*	*t*	*P*
Model 4a					
MSE-I × gender	0.001	0.020	523	0.05	NS
Model 4b					
MSE-I × pain intensity	0.000	0.001	551	0.38	NS
Model 4c					
MSE-I × negative affect	0.001	0.001	562	1.91	NS

Values are from the final multilevel model. Level 1 independent variables are within-person centered. In all these models, appropriate main effects preceded the modeling of each interaction effect.
β, unstandardized regression coefficient; MSE-I, medication side-effect index; NS, nonsignificant.

results from these models indicated that the association between reports of medication side effects and pain-related activity interference was not moderated by any of these variables.

4. Discussion

The primary purpose of this study was to examine the unique (ie, independent) association between reports of medication side effects and pain-related activity interference in a sample of patients with chronic pain. It was also of interest to examine the potential role of patients' gender, pain intensity, and negative affect as moderators of the association between self-reports of medication side effects and pain-related activity interference.

In our study, we examined the unique association between reports of medication side effects and pain-related activity interference by controlling for a number of pain-relevant variables that have previously been found to be associated with activity interference in patients with chronic pain. For example, in line with many previous studies, we found that month-to-month increases in pain intensity were associated with higher ratings of pain-related activity interference.[29,67,74,75] We also found that increases in negative affect were associated with higher ratings of pain-related activity interference, which is consistent with the findings of previous studies that have examined the psychological determinants of pain-related disability.[35,40,56,66,76]

The main finding that emerged from our study is that increases in perceived medication side effects were associated with higher ratings of pain-related activity interference even after controlling for month-to-month changes in patients' levels of pain and negative affect. This "unique" association between perceived medication side effects and pain-related activity interference suggests that medication side effects have the potential to interfere with activities independent of patients' pain and affective states. We found that pain intensity, negative affect, and perceived medication side effects all emerged as having significant unique influences on pain-related activity interference, suggesting that these variables might represent additive risk factors for poor functional outcomes in patients with chronic pain.

The results of a subsequent analysis indicated that the unique association between reports of medication side effects and pain-related activity interference could not be attributable to differences across patients in any baseline or preexisting characteristics. While it was important to control for month-to-month changes in pain and negative affect when examining the association between perceived side effects and pain-related activity interference, a wide range of preexisting (ie, time-invariant) variables could have also been responsible for this association. In our study, we ruled out this possibility by including each participant as a fixed effect in the multilevel model. Although stringent, this model-building strategy allowed us to control for the influence of any observed or unobserved between-person variables on the study outcome. Importantly, this strategy allowed for a pure estimate of the within-person (level 1) association between perceived medication side effects and pain-related activity interference, without the influence of between-person variables. In our study, the magnitude of the association between self-reports of side effects and pain-related activity interference might possibly have been influenced by some unobserved variables (eg, patients' tendency to overreport symptoms), but results indicated that these variables could not entirely account for the association that was found between side effects and pain-related activity interference.

In the present study, we were also interested in examining some of the variables that might moderate the association between reports of medication side effects and pain-related activity interference. Consistent with previous studies,[6,54,70] we found that women experienced significantly greater medication side effects than men; however, the magnitude of the association between reports of side effects and pain-related activity interference did not differ significantly as a function of patient gender. Moreover, neither pain intensity nor negative affect moderated the association between reports of side effects and pain-related activity interference. The latter results suggest that the association between medication side effects and pain-related activity interference was not particularly more pronounced when pain or negative affect increased from month to month.

The findings of this study have implications for clinicians who are involved in the pharmacological management of patients with chronic pain. To date, most pain management guidelines encourage clinicians to identify and monitor the occurrence of various medication side effects. Prescribing clinicians have also repeatedly been encouraged to find a "satisfactory balance" between pain relief and the adverse effects of medication.[10–12,31,45,46,65] To the extent that one of the primary goals of chronic pain management is to enhance activity engagement or function,[22,30,36,44,72] our findings suggest that greater efforts should be placed on the assessment and treatment of medication side effects. The assessment of patients' side effects and pain-related activity interference, both before and after the initiation of any new medication, would be consistent with guidelines for the pharmacological management of patients with pain[11,12,19] and could facilitate clinicians' prescribing decisions. Importantly, if side effects do emerge as a result of medication use, they should be targeted directly and treated using specific interventions to prevent their potentially deleterious impact on patients' activity engagement.

A number of limitations must be considered when interpreting the findings of this study. First, the effect size observed in our study for the association between reports of side effects and pain-related activity interference was relatively small. However, small effect sizes are typical of most longitudinal studies that involve modest within-person changes in variables of interest. Second, our study was based on self-report measures of pain-related activity interference. While self-report instruments are the most frequently used methods for assessing activity interference,[13,30,71,74] future studies should include more objective measures. Similarly, our medication side effect assessment was based on patients' subjective perceptions of side effects associated with their medications. As with any other self-reported measures, self-reports of medication side effects are subject to potential response bias, and limits in patients' ability to

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accurately report their side effects must be considered when interpreting our findings. Moreover, although patients were questioned about potential symptoms or "side effects" associated with their medications, it remains unclear whether these symptoms were specifically due to their medication. Given that chronic pain itself may lead to symptoms such as headaches or weakness, the possibility that patients have erroneously attributed some of their symptoms to their medication must be considered. Third, patients included in this study were at risk for prescription opioid misuse due to their inclusion in the broader parent study. While this has no direct implications for the nature of findings observed in this study, this sample characteristic places limits on the generalizability of our findings. Finally, given that most patients were taking more than 1 medication, our findings on medication side effects are not specific to analgesic medications, and nonanalgesic medications might also have contributed to patients' reports of side effects. It is well known, however, that medication regimens of most patients being treated in tertiary care pain management settings, like in this study, involve more than 1 medication. The inclusion of polymedication users in our study sample should thus be seen as strength rather than a methodological limitation.

In summary, the findings of our study provide preliminary evidence that reports of medication side effects are associated with heightened pain-related activity interference in patients with chronic pain. The key finding of our study is that perceived medication side effects were associated with heightened pain-related activity interference even after controlling for patient demographics, pain intensity, and negative affect. Additional studies will need to be conducted using a more frequent (eg, day-to-day) data collection schedule to better capture the dynamic interrelationships between side effects and pain-related activity interference. Further research should also further examine the variables that might moderate the impact of medication side effects on pain-related activity interference in patients with pain. Advances in this domain might pave the way for the development of more effective pharmacological interventions and might ultimately lead to improved pain management outcomes in patients with pain-related conditions.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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