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ORIGINAL RESEARCH

Prescription pain reliever misuse and levels of pain impairment: 3-year course in a nationally representative outpatient sample of US adults

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Background: The primary aim of this work was to present the prevalence data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a representative 3-year longitudinal survey (ages 18+ years) that captured information on patterns of self-reported pain interference and prescription pain reliever misuse. A second aim was to assess the degree to which the risk of various types of opioid misuse (onset, desistance, and incidence of dependence) was related to the longitudinal course of self-reported pain interference over the 3-year period.

Methods: We used a two-wave, nationally representative sample of adults (aged 18+ years) in which the baseline data were collected during 2001–2002 and a single follow-up was obtained ~3 years later (2004–2005 with 34,332 respondents with complete data on study variables for both waves).

Results: Our findings indicated that ~10% reported high pain interference in the past month at each wave. There was tremendous stability in levels of pain, with ~5% reporting consistent levels of high impairment over the 3-year study, a proxy for chronic pain. Levels of pain were more strongly associated with prescription pain reliever misuse concurrently rather than prospectively, and the association was largely linear, with the likelihood of misuse increasing with levels of pain. Finally, health service factors were also prominent predictors of onset, but not the outcomes, of desistance or transitions to problem use.

Conclusion: This study is the first to use a nationally representative sample with measures of pain and drug use history collected over an extended period. These results may help provide clinicians with an understanding that the risk of misuse is greatest when pain is active and may help guide the selection of appropriate intervention materials and monitor strategies for those at greatest risk.

Keywords: prescription drug abuse, opioids, pain

Introduction

The recent release of the Institute of Medicine's (IOM) report on chronic pain in America has called for greater recognition and more efficient treatment of pain, specifically chronic pain lasting several months or longer.[1] Planning for these efforts requires clinical and outpatient data that can accurately depict the scope of pain in diverse subgroups. In fact, the IOM report goes on to state that there is a lack of nationally representative data that can be used to monitor the incidence and prevalence of various types of pain. This lack of information is not surprising, as there is widespread recognition that pain is a uniquely personal experience, making it difficult to measure in the context of large epidemiological surveys using self-report items that are free from measurement error.[2–4]

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There are only a few nationally representative epidemiological studies that include measures that collect information on pain. The National Health Interview Survey is an annual cross-sectional survey of adults aged 18 years or older.[5] This self-reported, computer-assisted questionnaire asks the respondent to identify the presence and location of any pain lasting several weeks or longer, and asks about interference with activities as a result of pain. As reported in 2011, lower back pain was the most frequently reported (28%) pain, followed by migraines (16%). The National Health and Nutrition Examination Survey is a unique nationally representative epidemiological surveillance system because it uses a mobile examination laboratory to conduct physical examinations, biological assays, and screening examinations across the entire age spectrum.[6] There are also supplemental in-person interviews (typically with participants aged 12 years or older), which capture rich details on physical disease and disability; however, no measures of self-reported physical pain are available, but only the actual level of impairment related to specific disease/illness states. There are other surveys, such as the National Survey on Drug Use and Health or the Behavioral Risk Factor Surveillance System, which collect information on physical health but not specific aspects of pain.[7] Available evidences from these surveillance systems indicate that pain is highly prevalent and largely concentrated in the elderly, women, and those of lower socioeconomic status.

Many of the data sources described earlier are serial, cross-sectional designs, making it difficult to distinguish between chronic and acute pain. The available evidence from clinical populations indicates that pain interference appears remarkably stable over time, showing gradual declines in interference with advanced age.[8] The IOM report has drawn significant attention because it projects that nearly 100 million US adults suffer from chronic pain, which translates to ~43% (2008). Yet it is important to acknowledge that pain can vary by the test or measure used to assess its presence and severity. A study in Norway found that pain interference, using the SF-8, was relatively stable across several measurements (intra class correlation [ICC] =0.66) taken over a 12-month period.[10] While the pain may meet the criteria for "chronic" due to high level of persistence, the actual levels of interference did vary over the 12-month study period. Mild and moderate pain interference was reported in 31% and 17% of respondents, respectively, and severe pain interference was reported by 2% of respondents during all four quarterly observations taken over the 12-month period. When based on two of the four observations, the prevalence was 13% for mild pain, 11% for moderate pain, and 4% for severe pain. Therefore, the definition of chronic pain rests on the time frame of observation, as well as the type of pain (eg, actual levels, interference).

In terms of planning for long-term pain management needs, there are several guidelines for the use of opioids.[11–13] The guidelines typically outline recommendations for initiating and monitoring different types of opioid therapies (eg, chronic opioid therapy, breakthrough pain, titration, and tapering). A common recommendation of these guidelines is that the treatment of pain should be initiated with non-opioids, consistent with the World Health Organization's Pain Relief Ladder, where pain should be treated initially with non-opioids (aspirin, paracetamol) and progressing to mild opioids (codeine), and then strong opioids (morphine) when the pain persists or increases.[14] The primary goal undergirding these recommendations is a desire to strike an effective balance in maximizing pain relief while minimizing potential side effects due to exposure to pain reliever medications. A common thread linking the recommendations put forth by the various agencies and organizations is the theme of abuse, including the notion that drugs vary in their inherent biological abuse liability. There is also an emerging recognition that, in addition to the limited number of available opioid-based pain medications available to prescribers, patients also vary in their risk of abusing prescription pain relievers. For instance, the state of Utah has implemented a novel risk stratification system that outlines clinical strategies for patients who are at low, moderate, and high risk for abusing opioids/prescription pain relievers. Other state and local hospital managed care organizations have also developed similar risk stratification procedures. However, the report from the IOM, as well as other published federal strategies, have sounded a call to action for more research into the characteristics of those who abuse/misuse prescription drugs, particularly in high-risk categories such as those with long-term chronic pain or high levels of impairment.

There is strong evidence linking prescription opioid misuse and levels of pain, with studies showing a positive relation between the two phenomena in both patient and community samples.[15–19] Most of these studies are cross-sectional, so a significant gap exists in our understanding of how the relations between pain and opioid misuse are related over time. That is, does early onset of pain signal a subsequent increase/change in the risk of opioid misuse? Conversely, does the remission of pain increase the likelihood of abstinence among those with a history of opioid abuse? These very important questions are grounded in a need to better understand the causal nature of opioid mis-

use and pain. A comparable set of cross-sectional studies have shown significant psychiatric comorbidity among those misusing opioids,[15,20] though a longitudinal analysis among those with psychiatric disorders observed that the risk of onset of an opioid disorder was strongest when the psychiatric disorder was active.[21] As an aside, our previous published work showed that self-reported physical pain exerted an independent effect on prescription opioid misuse, controlling for psychiatric and substance abuse history.[15] Taken together, these studies indicate that pain and opioid misuse are independently related and likely not caused by a common underlying psychosocial pathway. However, more research is needed on the longitudinal history of the interaction between physical pain interference and opioid misuse to better characterize the degree to which this strong association may be attributed to a general vulnerability to physical pain and opioid misuse or a competing explanation in that the risk of opioid misuse is strongest when pain is active and at sufficient level of impairment.

The literature reviewed in the previous sections highlights several important research gaps, which are addressed in this current study. The first gap this report aims to fill is to present more comprehensive data on the national trends of physical pain impairment using a nationally representative survey of adults (aged 18 years or older), namely The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Unlike previous case studies or patient-based convenience samples, which focus on a narrow set of patient characteristics, this dataset provides the first nationally representative study that contains information on the longitudinal course of pain over an extended period of time, notably 3 years (~36 months). A second gap that is addressed in this study is to estimate the prevalence of opioid misuse in various types of pain trajectories. This strategy enables greater understanding of whether there are differences in the risk of misuse between those with active and remitted levels of pain interference.

Methods

Participants

The NESARC is a face-to-face household survey of respondents aged 18 years or older. A detailed discussion of the sampling scheme has been presented elsewhere.[22–24] The data presented in this report are from those with complete Waves 1 and 2 data, with the baseline occurring in August 2001 to May 2002 and the follow-up Wave 2 occurring ~3 years later, between August 2004 and September 2005. NESARC is a representative sample of non-institutionalized civilians aged 18 years and older, residing in the United States and the District of Columbia (including Alaska and Hawaii). This includes persons living in households and the following non-institutional group quarters (GQ): boarding houses, rooming houses, non-transient hotels and motels, shelters, facilities for housing workers, college quarters, and group homes. The sampling frame of the NESARC sample for housing units is the Census 2000/2001 Supplementary Survey (C2SS), a national survey of approximately 78,300 households per month conducted in 2000 and 2001 by the Bureau of the Census. The NESARC also included a GQ frame. The sampling frame for GQ derives from the Census 2000 Group Quarters Inventory.

The initial sample for Wave 1 was 43,093 (89% response rate) and sampling weights were derived to permit national estimates. The individual weight is a product of the base weight, capturing the respondent's probability of selection and adjustments for non-interviews, within-household selection weight, and undercoverage weight. All interviews were conducted using trained in-person interviewers. For the second wave, the original Wave 1 sample was re-contacted, among which 39,959 were eligible for Wave 2. There were 3,134 respondents who were no longer eligible for Wave 2, due to death or emigration from the United States. The Wave 2 completion rate was 86.7%, resulting in a final complete analytic Wave 1/Wave 2 sample of 34,653 respondents. The final sample weights were also adjusted to account for attrition among demographic factors known to introduce nonrandom attrition between Wave 1 and Wave 2. This study uses the complete Wave 1/Wave 2 data file for all analyses, except initial descriptive statistics that present the prevalence estimates for those completing the baseline (n=43,093) and 3-year follow-up interviews (n=43,559). The inferential and longitudinal analyses use the sample of those with complete Wave 1 and Wave 2 data (n=34,332).

All potential NESARC respondents were informed in writing about the nature of the survey, the statistical uses of the survey data, the voluntary aspect of their participation, and the Federal laws that rigorously provide for the strict confidentiality of identifiable survey information. Those respondents consenting to participate after receiving this information were interviewed. Respondents were paid $80 for completing the survey. The research protocol, including informed consent procedures, received full ethical review and approval from the US Census Bureau and US Office of Management and Budget. A data use agreement between International (RTI) and the National Institutes of Health (NIH) was established, with the analytic methods

and confidentiality requirements reviewed by Institutional Review Board of RTI.

Diagnostic assessment

The assessment was the Alcohol Use Disorder and Associated Disability Interview Schedule (DSM-IV, AUDADIS-IV).[25,26] Self-reported pain interference was captured with a single question from the SF-12, which asked the respondent to identify how much physical pain interferes with normal work average over the past month, including activities inside and outside the home.[27,28] The five-point responses ranged from: 1) not at all; 2) a little bit; 3) moderate; 4) quite a bit; to 5) extreme. Given the need to reduce the number of categories for theoretical and analytic considerations post hoc, preliminary item response analyses (ie, using item response theory) revealed that the data could be best represented by three primary categories: 1) no pain interference (1= not at all); 2) mild/moderate pain interference (2= a little bit and 3= moderate); and 3) high pain interference (4= quite a bit, and 5= extreme).

The primary outcome was based on the binary classification of any prescription pain reliever misuse in the past month. The question asked the respondent to endorse misuse if they had consumed prescription opioids "on their own, either without a doctor's prescription, in greater amounts more often or longer than prescribed, or for a reason other than a doctor said you should use them." The question also asked "sometimes people use these medicines on their own to feel more alert; to relax or quieten their nerves or to feel better to enjoy themselves; or to get high or just to see how they would work." The upper-case words were emphasized in the reading of the item to the respondent, and the item captured two distinct patterns of consumption: 1) abuse to get high; and 2) use to self-medicate an undiagnosed or undertreated condition. Therefore, "misuse" was used because it captured both types of consumption practices. The item captured use of prescription "painkillers, for example, codeine, Darvon, Percodan, Dilaudid, or Demerol." The question is asked in reference to past month. Debriefs with this item indicated that non-opioid products, such as tramadol, were also typically included in the respondent's response set.[7] Additional items captured problematic levels of consumption involving diagnostic criteria for abuse (eg, use with harmful consequences) and dependence (eg, physical tolerance and withdrawal).

An additional focus of this work was to understand how health care utilization may also influence prescription opioid misuse. In NESARC, all respondents were also asked if they had sought treatment from an emergency department, and those with five or more visits were coded as high utilizers. Multiple visits with a clinician is consistent with doctor shopping, a phenomenon that may be attributed to prescription drug abuse.[29] In addition, NESARC also captured whether a person stayed overnight in a hospital in the past year. Unfortunately, NESARC does not inquire as to whether a person actually received opioids as part of their health care visits, so these two measures are to be taken as proxy measures in which there may be a high likelihood of dispensing prescription narcotic pain relievers. Insurance status was also asked, including public (Medicare/Medicaid/Veterans Affairs), private (eg, health maintenance organization), or no current health insurance coverage. Only those with consistent levels of coverage, or non-coverage for those with no insurance, were included in this sub-analysis. The rationale is to better isolate the effect of constant exposure or nonexposure to health care environments where opioids may be accessed by patients. Lack of a medical home is a potential risk factor for misuse,[13] and we coded those who typically seek care at one of the five locations in our analyses. Other key measures included prescription drug misuse for substances other than opioids, such as tranquilizers/benzodiazepines and stimulants. Illicit drug use (marijuana, cocaine/crack, heroin, hallucinogens, inhalants, and other drugs) was also captured.

Analytic strategy

Cross-tabulations were used to identify the prevalence of each of the three levels of pain interference among youth (aged 18–20 years) and adults (21 years or older) and past-month prescription pain reliever misuse. Next, logistic regression analyses were used to examine three specific outcomes. Model 1 examined the onset of first misuse using prescription pain relievers over the 3-year interval, and these were compared with those who did not initiate during this period (Onset). Model 2 examined those who misused at baseline, but reported no misuse at follow-up (Desistance). Finally, Model 3 examined the factors that predicted the onset of any disordered level of consumption (ie, abuse/dependence as indicated by DSM-IV criteria), with the reference levels being those who used prescription pain relievers, but did not exhibit any clinical signs of abuse/dependence. The primary units of comparison were the categories of pain interference across Waves 1 and 2. These Markov-type regression models simultaneously adjusted for demographics, health care utilization, and mental health characteristics. All results presented in this study were adjusted for multistage design effects using the Taylor series

method in SUDAAN version 10 (RTI International, NC, USA) unless otherwise noted. Statistical significance was based on two-sided design-based tests evaluated at a 0.05 level of significance.[30] Based on missing data at the item level, 361 respondents who completed the 3-year follow-up interview were removed from the analyses because they did not have complete data on self-reported pain interference or substance use.

Results

Among the 43,093 respondents completing Wave 1, ~65.5% reported no pain interference, 22.5% reported mild/moderate interference, and 12% endorsed high interference (Table 1). The follow-up estimates were similar, and although slight differences were observed, there were no statistically significant changes in aggregate pain interference status between baseline and 3-year follow-up ($P>0.05$). Translating these estimates to population figures yields an estimate of ~19–25 million adults (aged 18+ years) who reported some level of pain interference and had either mild/moderate or high levels of interference at any given time at either baseline or the 3-year follow-up. In terms of opioid misuse, the past-month estimates are similar to those from other national surveys of drug use (eg, National Survey on Drug Use and Health), which found that ~1% (1.8 million adults) reported misusing prescription opioids for either self-treatment of a medical condition using medication/dosage that had not been authorized by a licensed prescriber or reported using these drugs for euphoria. Among those reporting past-month use, about 42% (population estimate 730,000) met diagnostic criteria for either abuse and/or dependence and 15% met the diagnostic criteria for dependence at baseline. In considering the baseline and follow-up estimates, the prevalence of opioid dependence, an indicator of those in need of specialty substance abuse treatment, ranged between 267,000 and 323,000 adults.

Table 2 presents the transitions in pain interference that occurred between the baseline and 3-year follow-up. Table 1 presents the descriptive statistics at baseline and 3-year follow-up, and Table 2 presents the conditional percentage of follow-up among the three separate levels of pain interference at baseline. In other words, the results show pain status at follow-up (three levels) stratified by the three baseline levels, hence the three follow-up levels sum to the stratification baseline level. The total population distribution is detailed along with the likelihood of transitioning between stages conditional on the baseline stage of pain. Among the entire sample, slightly less than two-thirds (64.3%) had no change in pain interference status compared to about one-third (35.7%) who had some change. As expected, the largest movement occurred between those with no pain at baseline and those who had reported mild pain at follow-up (13.6%). This estimate is similar to those who reported the opposite sequence, moving from mild pain at baseline to no pain at follow-up (9.9%). Approximately 4% of the entire sample reported high levels of pain interference at both waves, indicative of those meeting a possible classification for long-term chronic pain (population estimate of 1.36 million), which is defined as having high pain at both waves. Of those with high pain interference at baseline, approximately one-third stayed at high pain, one-third moved to mild/moderate pain, and one-third had complete remittance altogether. Only a small percentage (3.5%) of those with no reported pain at baseline moved to high pain interference at follow-up.

Figure 1 is a companion to the data presented in Table 2, which presents the distribution of prescription opioid misuse

Table 1 Prevalence of past-month pain interference and prescription opioid misuse in NESARC at baseline (2001–2002) and at 3-year follow-up (2004–2005)

	Baseline (2001–2002)				3-year follow-up (2004–2005)			
	Sample (n)	Population estimate[a]	Percent[a]	Standard error[a]	Sample (n)	Population estimate[a]	Percent[a]	Standard error[a]
No pain interference[b]	27,746	136,180,000	65.5	0.43	21,394	131,790,000	63.45	0.46
Mild/moderate pain interference[b]	9,734	46,664,000	22.5	0.36	9,605	56,700,000	27.3	0.37
High pain interference[b]	5,613	25,037,000	12.0	0.23	3,553	19,391,000	9.2	0.24
Total	43,093	207,881,000	100.0		34,552	207,881,000	100.0	
Past-month opioid misuse	346	1,749,000	0.9	0.06	294	1,891,000	0.9	0.06
Past-month opioid misuse, any disorder[c]	211	730,000	41.8[d]	3.42	134	800,000	50.7	3.64
Past-month opioid misuse, dependence[c]	48	267,000	15.3[d]	2.57	52	323,000	20.5	3.00

Notes: [a]All estimates are adjusted using SUDAAN (Release 10.0) to account for multistage sample of National Epidemiologic Survey on Alcohol and Related Conditions. Population estimates are rounded to the nearest 1,000. [b]Pain interference levels measured by SF-12 standard instrument (ages 18 years or older). [c]Disorders are defined by any Diagnostic and Statistical Manual fourth edition criteria for prescription opioid abuse and/or dependence. [d]Among those with past-month opioid use.

Table 2 Transitions in pain interference status between baseline and 3-year follow-up

Baseline				3-year follow-up									Total percent 3-year follow-up		
				None[b]			Mild/moderate[b]			High[b]			None[c]	Mild/moderate[c]	High[c]
Base	n[a]	%[a]	SE[a]	n[a]	%[a]	SE[a]	n[a]	%[a]	SE[a]	n[a]	%[a]	SE[a]	%	%	%
None[b]	22,330	65.7	0.42	→ 16,728	75.8	0.39	4,720	20.7	0.37	882	3.5	0.16	49.8	13.6	2.3
Mild/moderate[b]	7,953	23.0	0.35	→ 3,357	42.9	0.75	3,555	45.1	0.73	1,041	12.0	0.45	9.9	10.3	2.7
High[b]	4,269	11.3	0.24	→ 1,309	32.5	1.16	1,330	30.8	0.94	1,630	36.7	1.02	3.7	3.5	4.2

Notes: [a]All estimates are adjusted using SUDAAN (Release 10.0) to account for multistage sample of National Epidemiologic Survey on Alcohol and Related Conditions. Population estimates are rounded to the nearest 1,000. [b]Pain interference levels measured by SF-12 standardized instrument (ages 18 years or older). [c]Cells sum to 100%.

levels within each of the nine unique stages of pain interference between waves. The height of the bars represents the percent who endorsed any opioid misuse at either wave. The levels of misuse include onset between baseline and follow-up, persistent use at both waves, and desistence. The largest group of opioid misusers comprised those who reported stable levels of high pain interference over the 3-year study. The group was nearly evenly divided among those in the onset group and those who desisted. The pattern was largely similar for the other types of transition stages. The largest group experiencing onset of misuse between waves comprised those who reported no pain interference at baseline and high pain at follow-up. The next largest group experiencing onset comprised those who transitioned into high pain from mild/moderate pain. Those reporting stable levels of no pain had the lowest levels of opioid misuse (<1%) at either wave, followed by those who transitioned from high to no impairment 1.2%).

Tables 3 and 4 examine the transitions in prescription pain reliever misuse between waves, with a focus on the levels of pain interference (Table 3) and health care utilization (Table 4). In terms of initiation of use (Model 1), the odds ratios (ORs) are in reference to the other categories, so there is no specific reference category. Therefore, there were nine separate models estimated for each outcome, and the models also contained covariates for age, race, and sex. Levels of pain interference were significantly associated with onset of first use at the 3-year follow-up (ie, no prior misuse and past-month misuse at follow-up). The three most powerful predictors all involved high levels of pain at follow-up,

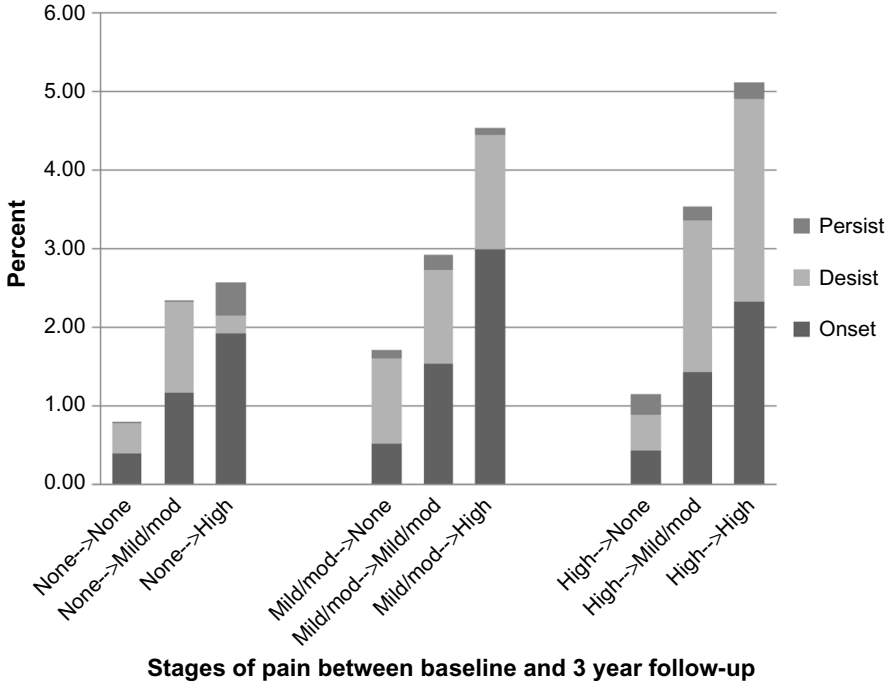

Figure 1 Prescription opioid misuse among the stages of pain interference between baseline and 3-year follow-up.
Notes: "Onset" refers to cases that did not use lifetime at baseline and initiated lifetime use by the follow-up, ~3 years post baseline. "Desist" refers to cases that used in past month at baseline but did not report past month use at follow-up, ~3 years post baseline. "Persist" refers to cases that used in past month at baseline and also used in the past month use at follow-up, ~3 years post baseline.
Abbreviation: Mod, moderate.

Table 3 Predictors of prescription opioid drug misuse patterns by levels of pain inference between baseline and 3-year follow-up

	Model 1			Model 2			Model 3		
	Onset from baseline to FU			Desistance from baseline to FU			Onset of disordered use at FU		
	OR[a]	CI[a]	*P*-value[a]	OR[a]	CI[a]	*P*-value[a]	OR[a]	CI[a]	*P*-value[a]
Pain group (baseline to FU)[b]									
None→none	0.3	0.2–0.4	<0.001	2.5	0.7–9.2	0.147	0.4	0.2–0.7	0.006
None→mild/moderate	1.4	0.9–2.2	0.185	1.3	0.3–5.5	0.725	1.9	1.01–3.6	0.046
None→high	3.2	1.5–6.5	0.002	0.1	0.01–0.6	0.020	3.3	0.8–13.1	0.091
Mild/moderate→none	0.5	0.3–0.9	0.030	1.1	0.2–5.5	0.888	0.5	0.2–1.4	0.159
Mild/moderate→mild/moderate	2.3	1.6–3.5	<0.001	0.7	0.2–3.3	0.644	1.0	0.5–1.9	0.871
Mild/moderate→high	3.7	1.9–7.2	<0.001	1.9	0.2–17.2	0.558	4.4	1.5–12.4	<0.001
High→none	0.4	0.2–0.9	0.030	0.02	0.04–0.7	0.019	0.4	0.3–0.5	<0.001
High→mild/moderate	1.7	0.8–3.3	0.150	1.3	0.2–11.6	0.800	0.7	0.3–1.9	0.451
High→high	2.5	1.3–4.7	0.006	1.4	0.4–5.2	0.590	1.5	0.4–3.1	0.777

Notes: [a]Models estimated via SUDAAN (Release 10.0) to account for multistage sampling design of NESARC. Controls for age, sex, and race. [b]Reference category for each pain interference group is the combined effect of the other eight categories. *P*-value <0.05 denotes statistical significance for two-tailed test.
Abbreviations: FU, follow-up; OR, odds ratio, CI, 95% confidence interval; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions.

Table 4 Predictors of prescription opioid drug misuse patterns by health status and type of health care utilization between baseline and 3-year follow-up

	Model 1			Model 2			Model 3		
	Onset from baseline to FU			Desistance from baseline to FU			Onset of disordered use at FU		
	OR[a]	CI[a]	*P*-value[a]	OR[a]	CI[a]	*P*-value[a]	OR[a]	CI[a]	*P*-value[a]
Overnight in hospital, PY									
No→no	0.5	0.4–0.7	<0.001	1.2	0.6–2.7	0.614	0.7	0.4–1.4	0.322
No→yes	1.8	1.1–2.8	0.020	0.3	0.1–0.8	0.016	1.8	1.1–2.8	0.020
Yes→no	1.4	0.8–2.4	0.260	2.9	0.6–14.6	0.198	1.4	0.8–2.4	0.260
Yes→yes	2.9	1.7–5.0	<0.001	8.4	4.5–15.6	<0.001	1.2	0.5–3.2	0.694
More than five ER visits, PY									
No→no	0.6	0.3–1.1	0.079	1.3	0.5–11.1	0.376	0.8	0.3–1.9	0.593
No→yes	1.4	0.6–3.3	0.407	0.6	0.2–2.8	0.262	0.6	0.1–2.9	0.460
Yes→no	1.3	0.6–2.9	0.569	0.6	0.1–3.3	0.384	1.7	0.6–4.3	0.294
Yes→yes	6.7	1.6–27.6	<0.001	8.8	4.8–16.6	<0.001	0.4	0.3–0.5	<0.001
Health insurance (stable)									
Private/veterans	0.5	0.4–0.7	<0.001	1.5	0.7–3.3	0.269	1.2	0.7–2.0	0.567
Medicare/Medicaid	1.1	0.6–1.8	0.821	0.3	0.1–0.7	0.008	0.8	0.3–2.3	0.731
None	1.8	1.1–2.9	0.028	2.1	0.5–9.5	0.317	1.2	0.6–2.5	0.653
Medical home (FU)									
None	0.8	0.4–1.5	0.457	2.0	0.4–10.5	0.393	0.4	0.2–1.2	0.097
Doctor/HMO	0.5	0.4–0.8	<0.001	0.7	0.4–.2	0.542	1.1	0.9–3.3	0.123
Community Clinic	2.1	1.2–3.4	0.010	1.1	0.2–5.1	0.964	0.3	0.1–0.9	0.049
ER	3.9	1.7–8.7	0.001	1.1	0.2–5.2	0.917	1.8	0.6–5.4	0.287
Other	3.4	1.7–6.8	0.001	1.0	0.2–5.4	0.957	1.4	0.8–6.7	0.105
Illicit drug use, PY									
No→no	0.05	0.04–0.07	<0.001	4.9	1.1–21.6	0.033	0.7	0.4–1.2	0.229
No→yes	12.7	8.6–19.9	<0.001	1.1	0.3–4.9	0.888	1.9	0.9–3.9	0.097
Yes→no	1.4	0.5–4.1	0.532	0.7	0.3–1.9	0.504	0.5	0.2–1.5	0.186
Yes→yes	11.1	6.5–19.9	<0.001	0.2	0.1–0.6	0.001	1.3	0.6–2.5	0.522
Prescription drug misuse, PY									
No→no	0.04	0.03–0.06	<0.001	4.3	2.1–8.8	<0.001	0.6	0.4–1.1	0.098
No→yes	42.8[b]	27.7–66.3	<0.001	0.09	0.03–0.28	<0.001	3.4	1.9–6.1	<0.001
Yes→no	8.2	4.2–15.6	<0.001	0.3	0.1–1.4	0.121	0.5	0.2–1.0	0.049
Yes→yes	60.2[b]	23.9–151.8	<0.001	0.11	0.04–0.28	<0.001	0.9	0.3–2.5	0.783

Notes: Models were estimated via SUDAAN (Release 10.0) to account for multistage sampling design of NESARC. Controls for age, sex, and race. Estimates are based on skewed distribution, with cell sizes greater than 25 cases.
Abbreviations: FU, follow-up; OR, odds ratio, CI, 95% confidence interval; PY, per year; ER, emergency room; HMO, health maintenance organization; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions.

namely transitions from no pain interference at baseline (OR =3.2), mild pain interference at baseline (OR =3.7), and high pain interference at baseline that was also stable over both observations (OR =2.5). Interestingly, transitions to no pain at follow-up from either of the three pain categories at baseline were negatively associated with initiation. Taken together, the concurrent pain status at follow-up is strongly correlated with initiation, and the baseline values of pain appeared to predict initiation insofar as they predicted the likelihood of the follow-up pain state. The relation between pain interference and desistance was less clear (Model 2). Those who transitioned from no pain interference at baseline to high pain at Wave 2, as well as those who moved from high interference at baseline down to no interference at Wave 2, were more likely to desist compared to the other pain groups. In terms of onset of a substance use disorder involving prescription pain relievers, stable levels of no pain interference were protective in reducing the likelihood of onsetting problem use after exposure. Those with high pain interference at baseline who transitioned to no pain interference at Wave 2 follow-up were also less likely to begin problem use (onset) relative to the other groups. Conversely, those with mild pain who transitioned to high pain (OR =4.4) had a significant likelihood of initiating disordered use (OR =4.4).

Table 4 examines how health care utilization was associated with prescription pain reliever misuse. Similar to the models in Table 3, each factor was estimated separately, and covariates for race, age, and sex were included as controls. As a way to better ensure the causal ordering between exposure and outcome, each of the risk factors did not change between baseline and 3-year follow-up. This strategy eliminates the possibility of reverse causation, in which the hypothesized predictor may have actually changed after prescription pain reliever outcome, rather than changing prior to the outcome. Holding the effect of the predictor constant across waves eliminates this type of confounding.

In terms of overnight stays in the hospital at baseline, findings from the logistic regression models indicate that poor health requiring overnight hospitalization was significantly related to onset of prescription pain reliever misuse between baseline and 3-year follow-up. Emergency room (ER) visits indicative of poor health or doctor shopping were also highly associated with onset (OR =6.7). Those without insurance were 1.8 times more likely to onset compared to those with any private or public insurance. Having a medical home reduced the risk of onset, as did the presence of a regular (family) doctor. Those seeking care through the ER or community clinic as their regular point of care had a greater risk of initiation of prescription pain reliever misuse relative to the other groupings included in the model. Not surprisingly, illicit drug use and prescription drug use were highly predictive of initiation, and the risk was only slightly higher for those using at both waves compared to those who used at either wave, but not both.

In terms of desistance, having poor health involving a history of overnight hospital stays at baseline and follow-up and high-volume ER visits (>5) was positively related to desistance. Being abstinent from illicit drugs and misusing prescription drugs was also positively associated with desistence. In terms of health care, patients in Medicare/Medicaid/Veterans Affairs plans were less likely to desist than those having either no insurance or private insurance. There was no correlation between medical home and desistance, as measured at follow-up.

Finally, there were very few significant associations between onset of disordered use at follow-up and health care/drug use history. Those effects that were significant were of weak-to-moderate effect sizes. The lone exception was observed for prescription drug misuse. Those who reported onset of first use between baseline and 3-year follow-up were more than three times more likely to onset prescription opioid abuse/dependence compared to the other patterns of prescription drug misuse.

Discussion

In the last decade, there has been a dramatic rise in the rate of unintentional overdoses, death, and addiction in the United States involving prescription opioid pain relievers. These figures have raised questions about the most appropriate use of opioid pharmacotherapy in the management of various types of pain, including acute and long-term chronic pain, in patient populations. To help clinicians better identify patients at risk for misuse and addiction involving pain reliever products, better data are needed to identify the magnitude of risk in various levels of pain interference. This study is among the first to describe the course of pain and associated risk of prescription pain reliever misuse over a 3-year interval using a nationally representative, community-based epidemiological design. Within the context of this design, there were five key findings that emerged with the two broad specific aims articulated in the "Introduction" section.

The first aim of this study was to examine the prevalence of pain interference using two measurements taken 3 years apart. There are differences in the estimates of chronic pain, which are likely due to differences in the definitional criteria for classifying chronic pain across studies. We could not

reconstruct other competing definitions of chronic pain and are therefore unable to comment how our sample estimates directly compare with clinical studies. However, a key finding from this study was that nearly one in ten will report high levels of pain interference. This translates to a population burden of about 25 million people, using a conservative estimate of 207 million non-institutionalized adults. This figure is likely to be higher if one also accounts for the number of individuals who reside in institutional settings, such as hospice care, in-patient hospital settings, or incarcerated settings. These settings are likely to have individuals with a greater burden than the general population, and also the military population, which tends to be younger and healthier than other types of institutionalized populations.

A second key finding from this study is that, a rather low percentage (~5%) reported high levels of pain interference at both observations. Most of the sampled population (50%) reported no pain interference over the 3-year period, though the converse is that about one-half was reporting some degree of physical impairment related to pain. The level of reliability was actually quite high across all levels of pain interference (ICC =0.66). While the time interval was ~3 years, the reliability was actually similar in magnitude to studies that used designs with measurements taken much closer together, such as several months apart.[10]

A third key finding was related to the rather low prevalence of prescription pain reliever misuse within each of the categories of pain interference. Studies will often use any level of use within the past year as an indicator of misuse. To strengthen the causal pathway between the predictor and outcomes, this study narrowed the window of the outcome to past-month misuse. As an aside, this method permits a better characterization of current use and likely regular use because occasional users have a low probability of answering this item (~1 in 12) within a shorter time frame. In other words, this measure likely has good sensitivity and specificity for capturing regular misusers rather than those who experiment with pain reliever misuse on an infrequent basis. National data sources often quote the past-year prevalence as being ~4% for nonmedical use. Restricting the measure to past-month misusers, the prevalence was slightly <1%, or ~1.7 million adults (aged 18+). Among misusers, a very small percentage (15%) met clinical criteria for dependence, which is a strong proxy for need of treatment. The 2012 strategic framework policy report issued by the Office of National Drug Control Policy, the drug policy arm of the White House, described prescription drug abuse as a public health epidemic.[33] The report goes on to say that MarketScan data have observed an increase in the number of prescriptions written for opioid pain relievers and that a corresponding increase in adverse events involving overdoses and deaths have also occurred. However, our findings show no radical change in the prevalence over time, which is consistent with other studies that find that the rate of nonmedical use has remained largely unchanged over the past decade.[31,32]

Fourth, high severity of pain interference was most strongly related to prescription opioid misuse concurrently but less so prospectively. In substance abuse research, early onset of several neuropsychiatric characteristics has been shown to portend subsequent changes in drug abuse, but the strongest risk of substance use occurs during periods of active symptomatology. For instance, Breslau et al[34] found in a nationally representative epidemiological study in the United States that major depressive disorder and several types of anxiety disorders that were in remission were significantly related to the initiation of smoking. However, the strength of the effect was much stronger during the period in which the disorders were "active". The most intuitive conclusion is that individuals may be self-medicating for symptoms of pain. However, there are no direct measures of motivation, so future laboratory studies using neurological imaging and biomarkers would help identify the internal pathways that heighten use during periods of high-pain interference.

Other important findings from this study may also be noted. While the pain indicators were strongly related to use (onset or desistance), the predictors were less influential in understanding the initiation of dependence on these medications. In drug abuse research, environmental (eg, social) factors have been more strongly related to initiation than biological factors (eg, genetics, neurologic) but less important in the transition periods to dependence once exposure has occurred.[11,13] The measurement of pain interference may capture more environmental proxies related to pain (eg, not being able to complete daily activities, quality of life) relative to the biological underpinnings of pain. The ideal study would be one that combines laboratory measures (eg, cold-press task, pain reactivity) in the context of a longitudinal study that is long enough to observe individuals as they transition through the periods of initiation to dependence.

A final finding to briefly highlight involves the health services characteristics in relation to opioid misuse patterns. Insurance and medical home statuses were differentially related to misuse. Again, lack of motivational data and thorough medical claims data prevented us from more clearly understanding the mechanisms through which medical

environments affected prescription pain reliever misuse. However, the increased level of risk has implications for the management of patients in these settings, perhaps suggesting the need for risk stratification and patient pain contracts to reduce the risk of prescription pain reliever misuse.

There are several limitations that must be considered when interpreting findings from this study. Most importantly, the measure of pain was limited to one specific dimension, namely interference. Pain is a multifactorial construct with core dimensions that include intensity, duration, location, as well as measures that are wholly self-reported and biometrically generated. Given the vast number of measures that are available to capture pain, we are unable to comment on how the study findings would differ if another dimension of pain had been measured. However, impairment is a scientifically acknowledged dimension that is useful both in a clinical and research setting, so additional studies that use a broader set of pain measures would complement the findings presented in this study. A second limitation to note is that measures within each wave were captured contemporaneously. This type of design limits the ability to definitively assign causality because the three conditions to support causal inference are insufficiently met (temporality, non-spuriousness, confounding). In this study, we were limited in our ability to correct for non-spuriousness and confounding in our statistical models. The issue of assigning temporal priority is problematic, even with longitudinal data. With two discrete time points, we are able to understand how changes in the predictor (eg, pain) were related to the onset and course of prescription opioid misuse over time at a second time point. This analytic strategy is stronger than examining the likelihood of opioid misuse at follow-up using a lagged effect of pain interference measured at baseline. This is because we are able to understand how observed changes in one predictor variable are associated with potential changes in the outcome variable, which is akin to an experimental manipulation in a randomized controlled design. However, nationally representative observational designs are less robust in establishing causality compared to randomized controlled trials because they typically collect only a single measurement. A randomized controlled trial, or a smaller community study, can more effectively use finite resources toward collecting multiple measurements on a smaller sample size. Additional longitudinal studies will add to the weight of the evidence, thus helping to establish a causal pathway in a refined way to isolate changes in pain in relation to different levels of drug use risk. Nonetheless, the measurement of pain interference and prescription pain reliever misuse was limited to the past month as measured at baseline and the 3-year follow-up, so we are unable to fully understand the course of these measures over the intervening 3 years to fully eliminate the possibility of reverse causality. There are also many possible moderators and confounders that may affect the nature of these estimates, such as race, sex, age, and drug use history. The goal of this study was to provide an initial survey of the larger landscape over time, setting up the field for future investigations to more intensively probe the nature of these relationships in key subgroups. Another issue to consider is the number of emergency department visits, which we argue is a proxy for doctor shopping. It is also possible that persons with high levels of pain may also be seeking treatment in the emergency department, though the observed finding controls for the effects of pain and prior health conditions that may have been present at the time of the interview. Finally, there is a possibility that, in real-world clinical settings, the patients may misrepresent their pain as a way to secure prescriptions for power pain relievers. However, this study draws on data obtained from measurements taken during a research study, which may exhibit less reporting error than those taken in clinical settings where patients may be motivated to lie on self-report screeners. The findings help explain how the risk of pain reliever misuse is longitudinally related to physical pain impairments.

The current clinical climate seems to be moving toward a high level of vigilance in evaluating and monitoring patients for prescription opioid misuse. The Food and Drug Administration recently released the Risk Evaluation and Mitigation Strategy educational guidelines for prescribers of extended release/long-acting opioids. These medications are typically channeled to patients with high levels of pain intensity, often lasting several months to even many years. This study might inform the pain management field of the risk of misuse among patients with varying degrees of pain interference, while other safety mechanisms, such as new abuse deterrent formulations, may also hold promise in reducing prescription drug misuse. However, these strategies work only for those who abuse via tampering. Therefore, patient and provider education programs may benefit from this study as they continue to develop clinical and public health interventions to better identify and manage patients to prevent and treat prescription drug misuse.

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Authors contributions

SPN conceptualized the hypothesis and oversaw the preparation and writing of the paper. CG conducted the longitudinal analyses in close collaboration with SPN and CLR. SPN wrote the manuscript, and CG reviewed and wrote portions of the measures methods, and results section. CLR wrote sections of the introduction section and discussion section. All authors reviewed drafts of the manuscript and critically revised it.

Disclosure

The first author (SPN) and the second author (CG) are employees of RTI International, who were paid contractors to Pfizer in the development of this paper. CLR is a current employee of Pfizer. The results and interpretations of the findings from this study are solely those of the authors. The authors report no other conflicts of interest in this work.

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