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Comparison of the Risks of Shopping Behavior and Opioid Abuse Between Tapentadol and Oxycodone and Association of Shopping Behavior and Opioid Abuse

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Objectives: This study compared the risks of opioid shopping behavior and opioid abuse between tapentadol immediate release and oxycodone immediate release and, to validate the definition of shopping, examined the association between opioid shopping and opioid abuse further.

Materials and Methods: This retrospective cohort study using linked dispensing and diagnosis databases followed opioid-naive patients for development of shopping behavior and/or opioid abuse during 1 year after initial exposure to tapentadol or oxycodone. Shopping was defined by having overlapping opioid prescriptions from >1 prescriber filled at ≥ 3 pharmacies; abuse by having International Classification of Diseases, 9th revision diagnoses reflecting opioid abuse, addiction, or dependence. To determine their association, we cross-tabulated shopping and opioid abuse and calculated odds ratios. Risks of developing each outcome were estimated using logistic regression.

Results: Among 277,401 participants initiating opioid use with tapentadol (39,524) or oxycodone (237,877), 0.6% developed shopping behavior, 0.75% developed abuse. Higher proportions of patients in the oxycodone group developed shopping behavior and abuse than in the tapentadol group (shopping: adjusted odds ratio [95% confidence interval], 0.45 [0.36-0.55]; abuse: 0.44 [0.37-0.54]). Shopping behavior and abuse were associated; of those with shopping behavior, 6.5% had abuse. Age (18 to 64 y), sex (male), prior benzodiazepine use, paying cash, and history (mood disorders, abuse of nonopioid medications, and back pain) were risk factors for developing either outcome.

Discussion: Shopping behavior and abuse measure complementary, but associated, constructs, which further validates the current definition of shopping. The risk of developing either is lower among patients who initiate opioid use with tapentadol than those who initiate opioid use with oxycodone.

Key Words: opioids, tapentadol, oxycodone, opioid abuse, opioid dependence, cohort studies

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Opioids are important components of pain management, but opioid diversion and abuse are serious and growing public health problems.[1,2] Previous research suggests that the risk of shopping behavior[3] and opioid abuse[4] are lower with tapentadol than with oxycodone, findings that are consistent with the lower affinity of tapentadol for the mu-opioid receptor relative to other opioids.[5] It is the activation of the opioid receptor that is responsible for the mood alterations and the euphoria associated with opioids.

Prior work separately assessed the relative risk of shopping behavior[3] and of opioid abuse.[4] In those studies,[3,4] shopping behavior was assessed using a longitudinal prescription database (LRx), and opioid abuse was assessed using claims databases. LRx includes cash transactions (important because approximately 45% of participants exhibiting shopping behavior pay in cash[6]) and has data on the pharmacies used to fill the prescriptions, but it does not include diagnoses and thus is suitable for examining shopping behavior,[7] but not opioid abuse. The claims databases lack information on the pharmacies used to fill the opioid prescriptions, but have diagnosis information and thus are unsuitable for examining shopping behavior, but are suitable for examining opioid abuse. The LRx database can now be linked to a diagnosis database (IMS DX), which allows assessing shopping behavior and opioid abuse concurrently.

The aims of this study were to compare the risks of shopping behavior and opioid abuse between patients who initiate opioid use with tapentadol immediate release (IR) versus oxycodone IR, and, to further validate the current definition of shopping, examine the association between opioid shopping and opioid abuse.

MATERIALS AND METHODS

This is a population-based retrospective cohort study. We linked 2 databases: the IMS LRx database and the IMS DX database. The IMS LRx database is a prescription database that covers 65% of all retail dispensing in the United States and includes all types of pharmacies (chains, food stores, mass merchandisers, and independent stores). From each of the pharmacies in the panel, the database captures *all* prescriptions that were dispensed, regardless of payment type.

The IMS DX database is a physician claims database. It captures claims from approximately 505,000 American

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Medical Association (AMA) office-based practitioners in the United States (87% of all AMA office-based practitioners), independently of their specialty, and collects approximately 1.2 billion claims per year. On a monthly basis, all claims are captured for approximately 17% of these practices and at least one claim for the remaining practices. To identify each patient uniquely so the databases could be linked, a probabilistic match was performed using a proprietary algorithm based on encrypted, nonidentifiable data elements, including sex, date of birth, last name, first name, address, city, state, zip code, and payer identification.

Inclusion Criteria

We included opioid-naive patients, defined as patients without any opioid prescription in the 90 days before the first exposure to tapentadol IR or oxycodone IR, which occurred between January 2010 and July 2011. The date of this first exposure is each patient's index date and each patient was followed for 1 year from the index date. The list of medications is displayed in Appendix 1 (see supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A143).

Exclusion Criteria

We excluded patients with a history of opioid abuse/dependence 12 months before or at the index date (date of the first exposure to tapentadol or oxycodone), and patients who filled a prescription for an opioid other than the index opioid within 3 days after the index date. In addition, we excluded patients with no claims related to diagnoses from 12 months before the index date to 12 months after the index date.

OUTCOMES

Shopping Behavior

A patient exhibited shopping behavior if he or she had any opioid dispensings with ≥ 1 day of overlap, written by ≥ 2 different prescribers, and filled in ≥ 3 pharmacies. This definition of shopping behavior differentiates opioids (widely known to be subject of abuse) from diuretics (believed to be abused only rarely) and has been used in previous research.[3,6–8]

Abuse or Dependence

A patient was considered to have developed opioid abuse, opioid addiction, or opioid dependence if International Classification of Diseases, 9th revision (ICD-9) codes that reflected diagnoses of opioid abuse, opioid addiction, or opioid dependence were present after the index date. As noted above, patients who had such diagnoses before their index date were excluded. The list of the ICD-9, Healthcare Common Procedure Coding System, and Current Procedural Terminology codes used is found in Table 1. This definition of opioid abuse/dependence has been used in previous research.[4,9]

Analyses

To compare the risks of shopping behavior and opioid abuse between tapentadol and oxycodone, we built logistic regression models that included the following potential confounders. At the index date: age, sex,[10] and types of payments (cash, Medicaid, Medicare, and commercial insurance); in the 3 months before the index date: benzodiazepine use[11]; in the 12 months before the index date: major depression, mood and anxiety disorders, abuse of nonopioid drugs (such as alcohol or tobacco), and pain-related diagnoses. We looked back 12 months for diagnoses, but 3 months for medication dispensings because the former persist longer than the latter. The grouping of the pain diagnoses was obtained from published ICD-9 groupings[12] of potentially painful conditions and types of pain. These included arthritis, back pain, fractures, headache, malignancies, musculoskeletal pain, neuropathic pain, reproductive system pain, visceral pain, wound/injury, and others. Daily dose of opioid at baseline was calculated and to allow comparison converted into tapentadol equivalent doses using a 5 to 1 conversion ratio.[13]

To determine the association between shopping behavior and opioid abuse, we cross-tabulated development of shopping behavior and opioid abuse and calculated odds ratios (ORs) and 95% confidence intervals (CIs). We also calculated an adjusted OR controlling for age, sex, and type of opioid (tapentadol vs. oxycodone).

To assess the commonality of the risk factors associated with shopping behavior and opioid abuse, 2 logistic regression models were created, one for each of the outcomes. The models included age, sex, types of payments, benzodiazepine use, presence of major depression, mood and anxiety disorders, or abuse of nonopioid medications, and pain-related diagnoses. We also calculated time to first diagnosis of shopping behavior or opioid abuse.

TABLE 1. Codes Used to Identify Opioid Abuse, Dependence, and Addiction

ICD-9 code	Description
305.50	Opioid abuse, unspecified use
305.51	Opioid abuse, continuous use
305.52	Opioid abuse, episodic use
304.00	Opioid type dependence, unspecified use
304.01	Opioid type dependence, continuous use
304.02	Opioid type dependence, episodic use
304.70	Combinations of opioid type drug with any other drug dependence, unspecified use
304.71	Combinations of opioid type drug with any other drug dependence, continuous use
304.72	Combinations of opioid type drug with any other drug dependence, episodic use
4306F	Patient counseled regarding psychosocial and pharmacologic treatment options for opioid addiction

ICD-9 indicates International Classification of Diseases, 9th revision.

RESULTS

A total of 277,401 participants met the inclusion criteria and were included in the analysis: 39,524 who initiated opioid exposure with tapentadol and 237,877 who did so with oxycodone. Figure 1 shows the flow of participants.

Patients in the tapentadol group were more likely to be women, have back pain and have commercial insurance than patients in the oxycodone group (Table 2). The daily dose of opioid at baseline was slightly higher in the tapentadol group than in the oxycodone group in both databases. The median tapentadol equivalent daily dose in the tapentadol group was 300.0 mg and 200.0 mg in the oxycodone group. In oxycodone-equivalent doses, this translates to 60 and 40 mg, respectively.

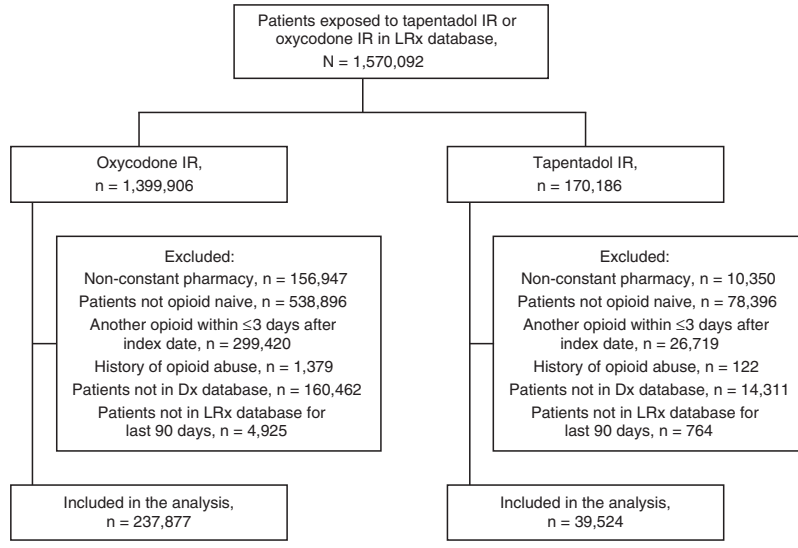

FIGURE 1. Flow diagram of participants in the study. IR indicates immediate release.

Higher proportions of patients in the oxycodone group developed shopping behavior and opioid abuse than in the tapentadol group (Table 3). After controlling for potential confounders, the risks for developing shopping behavior and abuse diagnosis remained statistically significantly lower for those in the tapentadol group than those in the oxycodone group, as seen from the ORs in Table 3.

Of the 277,401 participants included, 0.6% developed shopping behavior and 0.75% developed opioid abuse. Shoppers and abusers were more likely to be younger, male, pay in cash, have mood disorders, have a history of abuse of nonopioid drugs, have a history of benzodiazepine use, have back pain than the overall cohort, and were less likely to have malignancies than the overall cohort (Table 2).

Ignoring which condition came first, 6.5% of the patients who developed shopping behavior developed opioid abuse and 5.2% of the patients who developed abuse also developed shopping behavior (Table 4). The risk of developing shopping behavior was 9.6 times higher with opioid abuse (OR = 9.6; 95% CI, 7.9-11.8). The association remains strong after adjustment for age, sex, and index opioid (OR = 6.8; 95% CI, 5.6-8.3).

The risk factors for shopping behavior and opioid abuse were similar (Table 5). Age was one of the most important risk factors, with ORs for patients 18 to 64 years of age that ranged from 5 to 14 relative to patients 65 years or older. Other risk factors included benzodiazepine use, paying in cash, having mood disorders, and a history of

TABLE 2. Characteristics of Study Patients Who Developed Shopping Behavior or Opioid Abuse

Characteristics	Tapentadol (n = 39,524)	Oxycodone (n = 237,877)	Shoppers (n = 1656)	Abusers (n = 2086)	All (n = 277,401)
Age (mean ± SD) (y)	53.7 ± 14.7	53.1 ± 17.5	43.1 ± 13.4	42.0 ± 13.5	53.1 ± 17.1
Female (%)	69.6	58.7	51.3	54.8	60.3
Type of payment (%)					
Cash	5.2	5.3	20.0	12.6	5.3
Medicaid	2.2	9.9	13.5	27.3	8.8
Medicare	5.3	20.8	14.3	15.1	18.6
Commercial insurance	87.3	64.0	52.2	45.0	67.3
Benzodiazepine use (%)	1.7	1.6	2.3	2.0	1.6
Abuse of nonopioid drugs (%)	0.5	0.7	1.6	2.0	0.7
Mood disorders (%)	3.1	2.5	4.5	6.1	2.6
Painful condition (%)					
Arthritis	10.4	8.1	6	7.3	8.4
Back pain	10.2	6.2	11.1	10.9	6.7
Fractures	1.1	1.6	1.6	1.7	1.5
Headache	2.7	1.8	2	3.1	1.9
Malignancy	7.9	7.9	4	2.5	7.9
Musculoskeletal pain	9.1	6.3	5.8	7.3	6.7
Neuropathic pain	1.9	1.1	1.3	1.3	1.2
Other pain	0.9	0.7	0.5	0.8	0.7
Reproductive pain	0.6	0.3	0.3	0.4	0.4
Visceral pain	5.5	5.3	5.6	6.4	5.3
Wound injury	0.4	0.5	0.6	0.5	0.5

TABLE 3. Adjusted and Unadjusted Risk of Shopping Behavior and Opioid Abuse Diagnoses

	n (%)		OR (95% CI)	
Outcomes	**Tapentadol (n = 39,524)**	**Oxycodone (n = 237,877)**	**Unadjusted**	**Adjusted**
Shopping	97 (0.25)	1559 (0.66)	0.37 (0.30-0.46)	0.45 (0.36-0.55)
Abuse	109 (0.28)	1977 (0.83)	0.33 (0.27-0.40)	0.44 (0.37-0.54)

CI indicates confidence interval; OR, odds ratio.

abuse of nonopioid drugs. Back pain increased the risk of developing shopping or abuse, while malignancy-related pain was protective.

The median number of days (25th to 75th percentile) from the index date to developing shopping behavior was 163 (78 to 261) days; the median number of days to developing abuse was 142 (45 to 249) days.

DISCUSSION

This study confirms the lower risk of abuse among patients who are initially treated with tapentadol compared with oxycodone. Pharmacovigilance studies have also found a lower risk of abuse with tapentadol compared with other opioids.[14,15]

This study assessed shopping behavior in the same database used in a previous study[3] with a slightly different observation period (a 6-mo difference). Therefore, it included almost the same group of patients and though it provides new data on opioid abuse, it does not provide independent confirmation of a lower risk of shopping behavior associated with tapentadol.

Shopping behavior is an increasingly understood outcome. It is known that, relative to patients without shopping behavior, patients with shopping behavior more often fill prescriptions for schedule II opioids, less often fill prescriptions for opioid combination products, and more often pay in cash.[6] Opioid shoppers obtain prescriptions from a relatively small number of prescribers, typically ≤ 4 prescribers,[6] and the top 25% of opioid prescribers, those with >65 patients receiving opioids, prescribe to 82% of all shoppers.[8] Opioid shoppers also cross state lines to fill their prescriptions more often, and their dispensings account for a disproportionate number of opioid dispensing compared with nonshoppers.[16]

The relation between opioid shopping behavior and opioid abuse is, however, less understood. The definition of shopping behavior used in the current study discriminates opioids from diuretics, so it has construct validity, but it has not previously been linked to opioid abuse. The current study makes that link and thus further validates the current definition of shopping behavior.

Previous work that assessed separately some of the components of the shopping definition used in the present study (ie, filling prescriptions in different pharmacies and having a large number of prescriptions per month) found that these components were independent risk factors for opioid abuse.[9] In the current study, we also found that shopping behavior and opioid abuse were strongly associated and shared risk factors. In contrast, only a small percentage of patients with shopping behavior had a diagnosis of substance abuse. These findings suggest that shopping behavior and opioid abuse measure different constructs, but that these constructs are nonetheless associated with one another.

Results of the present study indicate that age is a very important risk factor for both constructs. Patients aged 18 to 64 years are at higher risk of developing shopping behavior or opioid abuse than the older patients. Although age has been recognized as a risk factor for shopping behavior and opioid abuse,[9] the magnitude of association was much stronger in our study. Male sex, having a history of benzodiazepine use, mood disorders, back pain, and abuse of other drugs are risk factors for both shopping behavior and opioid abuse. All these factors have been previously found to be associated with an increased risk of abuse.[17–23]

TABLE 4. Association Between Shopping Behavior and Opioid Abuse

	Shopper (n [%])	Nonshopper (n [%])	Total
Abuse	108 (6.5)	1978 (0.7)	2086
No abuse	1,548 (93.5)	273,767 (99.3)	275,315
Total	1656	275,745	277,401

TABLE 5. Risk Factors (OR [95% CI]) for Shopping Behavior and Opioid Abuse

Risk Factors	Shopping Behavior	Opioid Abuse
Age (y)		
< 18	0.9 (0.5-1.8)	0.7 (0.3-1.4)
18-39	9.8 (7.9-12.0)	13.9 (11.2-17.2)
40-64	4.6 (3.8-5.6)	6.7 (5.5-8.3)
> 64	Reference	Reference
Male	1.6 (1.4-1.7)	1.5 (1.3-1.6)
History of benzodiazepine use	1.6 (1.1-2.2)	1.4 (1.0-1.9)
Type of payment		
Cash	Reference	Reference
Medicaid	0.3 (0.3-0.4)	1.1 (0.9-1.2)
Medicare	0.4 (0.3-0.4)	0.7 (0.6-0.8)
Commercial insurance	0.2 (0.2-0.2)	0.3 (0.3-0.4)
History of mood disorders	1.4 (1.1-1.8)	1.9 (1.5-2.3)
History of abuse of nonopioid drugs	1.5 (1.0-2.2)	1.5 (1.1-2.1)
Painful condition		
Arthritis	0.8 (0.7-1.0)	1.0 (0.8-1.1)
Back pain	2.0 (1.7-2.3)	1.7 (1.5-2.0)
Fractures	1.1 (0.751.7)	1.2 (0.8-1.6)
Headache	0.8 (0.6-1.2)	1.2 (0.9-1.5)
Malignancy	0.7 (0.5-0.9)	0.4 (0.3-0.5)
Musculoskeletal pain	0.9 (0.7-1.1)	1.1 (0.9-1.3)
Neuropathic pain	1.2 (0.8-1.8)	1.1 (0.7-1.6)
Other pains	1.2 (0.6-2.3)	1.7 (1.0-2.8)
Reproductive pain	0.7 (0.3-1.8)	0.8 (0.4-1.7)
Visceral pain	1.0 (0.8-1.2)	1.1 (0.9-1.3)
Wound injury	1.0 (0.5-1.8)	0.7 (0.4-1.4)

Each pain type was independently assessed as present/absent.
CI indicates confidence interval; OR, odds ratio.

The linkage of the databases was based on a proprietary algorithm from which neither further details nor validation data are available. Any matching errors would seem likely to be random and thus expected to bias the results of this study toward the null (no association).

This large population-based study assessed simultaneously shopping behavior and opioid abuse using real world data; however, it lacks randomization. Physicians prescribed tapentadol or oxycodone to the patients for clinical reasons, and it was not a random decision. In fact, the 2 groups had differences at baseline. We controlled for these imbalances in the analysis, but unmeasured confounders could remain and could affect or even explain the study results on the relative risk of opioid shopping and opioid abuse among patients who began opioid use with tapentadol versus oxycodone.

In the present study, opioid abuse included the diagnoses of opioid abuse and opioid dependence. Opioid dependence does not necessarily imply opioid abuse. Opioid abuse is the use of an opioid for psychic effects or any harmful use of the opioid,[24] while opioid dependence is a state of adaptation that is manifested by withdrawal syndrome, diminution of the analgesic effect over time (tolerance) or dose escalation.[24–27] However, health care providers use these terms interchangeably, and studies that have assessed opioid abuse combined the codes as well.[4,17,18]

The absolute risk of opioid abuse in the present study was $<1\%$. Although similar to other claims database studies,[9] it is substantially lower than the range of 5% to 31% reported in prospective or cross-sectional studies.[20,21,28] Opioid abuse is likely to be under ascertained in claims databases. Potential reasons for under recording include: lack of recognition, reluctance to put a potentially damaging diagnosis in the patient's record, reimbursement considerations, and failure of the DX database to capture referrals to opioid treatment programs, that are made without recording of the abuse diagnosis, or opioid abuse diagnosis claims because of lack of 100% coverage of health care providers. The absolute risks for shopping behavior could be underestimated in our study as well. The definition of shopping behavior is a very specific one with a low rate of false positives. The LRx database does not have 100% coverage of the pharmacies. To the extent that these limitations are not related to being exposed to one or the other opioid, the observed relative risk provides a valid estimate of the true relative risk for abuse or shopping behavior. Nonetheless, continued monitoring of the pattern of abuse of tapentadol is warranted because the risk of abuse with opioids could change over time.[29]

In summary, starting opioid treatment with tapentadol was associated with a lower risk of abuse and a lower risk of shopping than starting opioid treatment with oxycodone. Shopping behavior and opioid abuse measure different, but complementary, constructs.

REFERENCES

1. CDC. Policy impact: prescription painkiller overdoses 2013. Available at: http://www.cdc.gov/homeandrecreationalsafety/rxbrief/. Accessed January 23, 2013.
2. Alexander G. Rethinking opioid prescribing to protect patient safety and public health. *JAMA*. 2012;308:1865–1866.
3. Cepeda MS, Fife D, Vo L, et al. Comparison of opioid doctor shopping for tapentadol and oxycodone: a cohort study. *J Pain*. 2013;14:158–164.
4. Cepeda MS, Fife D, Ma Q, et al. Comparison of the risks of opioid abuse or dependence between tapentadol and oxycodone: results from a cohort study. *J Pain*. 2013;14:1227–1241.
5. Tzschentke TM, Christoph T, Kogel B, et al. (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. *J Pharmacol Exp Ther*. 2007;323:265–276.
6. Cepeda MS, Fife D, Chow W, et al. Opioid shopping behavior: how often, how soon, which drugs, and what payment method. *J Clin Pharmacol*. 2013;53:112–127.
7. Cepeda MS, Fife D, Chow W, et al. Assessing opioid shopping behaviour: a large cohort study from a medication dispensing database in the US. *Drug Saf*. 2012;35:325–334.
8. Cepeda MS, Fife D, Berlin JA, et al. Characteristics of prescribers whose patients shop for opioids: results from a cohort study. *J Opioid Manag*. 2012;8:285–291.
9. White AG, Birnbaum HG, Schiller M, et al. Analytic models to identify patients at risk for prescription opioid abuse. *Am J Manag Care*. 2009;15:897–906.
10. Back SE, Payne RL, Simpson AN, et al. Gender and prescription opioids: findings from the National Survey on Drug Use and Health. *Addict Behav*. 2010;35:1001–1007.
11. Hermos JA, Young MM, Gagnon DR, et al. Characterizations of long-term oxycodone/acetaminophen prescriptions in veteran patients. *Arch Intern Med*. 2004;164:2361–2366.
12. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA*. 2012;307:940–947.
13. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother*. 2010;11:1787–1804.
14. Surrat HL, Kurtz SP, Cicero TJ, et al. Street prices of prescription opioids diverted to the illicit market. 74th *Annual Meeting College of Problems of Drug Dependence (CPDD)*. Palm Springs, CA; June 9–14, 2012.
15. Dart RC, Cicero TJ, Surratt HL, et al. Assessment of the abuse of tapentadol immediate release: the first 24 months. *J Opioid Manag*. 2012;8:395–402.
16. Cepeda MS, Fife D, Yuan Y, et al. Distance traveled and frequency of interstate opioid dispensing in opioid shoppers and nonshoppers. *J Pain*. 2013;14:1158–1161.
17. Edlund MJ, Steffick D, Hudson T, et al. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain*. 2007;129:355–362.
18. Edlund MJ, Martin BC, Fan MY, et al. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. *Drug Alcohol Depend*. 2010;112:90–98.
19. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res*. 2006;6:46.
20. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain*. 2008;24:497–508.
21. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146:116–127.
22. Sullivan MD, Edlund MJ, Fan MY, et al. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: the TROUP Study. *Pain*. 2010;150:332–339.
23. Fischer B, Lusted A, Roerecke M, et al. The prevalence of mental health and pain symptoms in general population samples reporting nonmedical use of prescription opioids: a systematic review and meta-analysis. *J Pain*. 2012;13:1029–1044.

24. Zacny J, Bigelow G, Compton P, et al. College on problems of drug dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug Alcohol Depend*. 2003;69:215–232.
25. American Academy of Pain Medicine, American Pain Society, American Society of Addiction Medicine. Definitions related to the use of opioids for the treatment of pain: consensus statement. 2001. Available at: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=4&ved=0CD4QFjAD&url=http%3A%2F%2Fwww.fda.gov%2Fohrms%2Fdockets%2FDOCKETS%2F01n0256%2F01N-0256_emc-000019-02.doc&ei=IADHUoW0ConLsATC_oKgDQ&usg=AFQjCNFS700r3CJZb-o0EWUPgrykYYsS4A&sig2=yEfdZkhU7dlcDE1yBg_M_w&bvm=bv.58187178,d.cWc. Accessed January 3, 2014.
26. Rinaldi RC, Steindler EM, Wilford BB, et al. Clarification and standardization of substance abuse terminology. *JAMA*. 1988;259:555–557.
27. Cepeda MS, Etropolski M, Weinstein R, et al. Dose patterns in commercially insured subjects chronically exposed to opioids: a large cohort study in the United States. *BMC Palliative Care*. 2010;9:14.
28. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction*. 2010;105:1776–1782.
29. Dasgupta N, Bailey EJ, Cicero T, et al. Post-marketing surveillance of methadone and buprenorphine in the United States. *Pain Med*. 2010;11:1078–1091.

