ORIGINAL ARTICLE

Exploratory study examining associations between prescription opioid dose and delay discounting in patients with chronic pain

Benjamin J. Morasco, PhD; Steven K. Dobscha, MD; Stephanie Hyde, MA; Suzanne H. Mitchell, PhD

ARTICLE INFO

Keywords:
chronic pain
prescription opioids
delay discounting
opioid dose

DOI:10.5055/jom.2019.0482
© 2019 Journal of Opioid Management, All Rights Reserved.

ABSTRACT

Objective: *Although some research has identified correlates of high-dose opioid prescriptions, relatively little is known about factors that lead to higher doses. Delay discounting (DD), defined as the subjective value of a reward declining as a function of the delay to that reward, is an objective measure of impulsivity. DD is commonly studied in the context of addictive behaviors, and findings consistently demonstrate greater DD among individuals with opioid use disorders. The authors conducted a preliminary investigation to examine the extent to which DD is associated with prescription opioid dose among patients with musculoskeletal pain.*

Design: *Cross-sectional study.*

Setting: *A single veterans affairs medical center located in the Pacific Northwest.*

Subjects: *Participants with chronic musculoskeletal pain. The authors identified patients prescribed with high doses of opioids (100 mg morphine equivalent per day [MED] or more; n = 17), traditional doses of opioids (5-99 mg MED; n = 34), and patients with pain who were not prescribed opioids (n = 24).*

Methods: *All participants completed a battery of self-report measures assessing demographic characteristics, pain-related variables, and psychiatric symptoms. Participants also completed a computerized DD task.*

Results: *DD was negatively correlated with average daily opioid dose (p = 0.003) and positively correlated with anxiety (p = 0.013). In a multivariable regression analysis, after controlling for the effects of demographic and clinical factors, DD was significantly associated with prescription opioid dose.*

Conclusions: *Contrary to study expectations, higher opioid dose was associated with less DD. These findings call for prospective research to further elucidate the relationships between DD and other measures of impulsivity and prescription opioid doses.*

INTRODUCTION

Prescription opioid medications are commonly prescribed for the treatment of chronic pain,[1,2] and data indicate that higher doses of opioids are prescribed more frequently than in past decades.[3,4] While high doses of opioid medications may be prescribed to optimally help manage increased pain intensity, they also increase risk for adverse events.[5]

Little is known about the factors that lead to higher prescription opioid doses. The patient's subjective experience of discomfort and willingness to endure it may play a critical role. An influence on patient coping/anxiety reduction may be the presence of specific comorbidities, and prior research does suggest that patients prescribed high doses of opioids are more likely to have comorbid psychiatric and substance use disorders than those prescribed lower doses.[6-9] Using more longitudinally focused data, opioid dose escalation may be more common among patients with substance use disorders and those with more frequent visits to primary

care.[10] However, although these data suggest that patients with complex mental health conditions are most likely to have prescriptions for high doses of opioids, they provide little information about the mechanisms that may lead to high-dose opioid use.

One factor that might contribute to high-dose opioid use is delay discounting (DD). This refers to the process by which the subjective value of a reward declines as a function of delay to the reward.[11-13] This preference for small but immediate rewards over larger but delayed rewards may be conceptualized as impulsivity. Impulsivity is a stable personality trait and is distinct from, but also frequently associated with, substance craving[14] and distress tolerance.[15] In the case of prescription opioids, a patient might request opioid dose escalation because the perceived positive effects of immediate pain relief outweigh potential future adverse effects of high-dose opioid use. Here, the level of distress may interact with impulsivity level to determine patient behavior around opioid prescription preferences.

DD is widely studied in the context of alcohol and substance use disorders. Research demonstrates that those with substance use disorders consistently exhibit higher DD than control participants,[16,17] suggesting a preference for immediate over delayed rewards. Individuals with opioid dependence often discount delayed rewards significantly more than other non-substance-using participants.[18] This finding has been replicated with patients who misuse other illicit substances; findings consistently indicate that patients with opioid and other substance use disorders are more likely to discount delayed rewards than patients with no history of a substance use disorder.[19,20] DD has not previously been the focus of research among patients with chronic pain; however, recent findings suggest that DD can help identify individuals at increased risk for prescription opioid misuse[21] and that common brain mechanisms have been hypothesized between chronic pain and addiction.[22]

In this study, we examined three groups of patients, all of whom were receiving treatment for musculoskeletal pain. We included participants who were prescribed high doses of opioids, traditional doses of opioids, and patients who were not prescribed opioids. Our study goal was to examine factors associated with high-dose prescription opioid use. We hypothesized that DD would be significantly positively associated with prescription opioid dose, even after controlling for the effects of other clinical and demographic variables, and that patients who were prescribed higher opioid doses would evidence more DD.

METHODS

Participants

Participants were recruited from a single veterans affairs (VA) medical center in the Pacific Northwest by posted advertisements throughout the medical center. As an exploratory study, our goal was to recruit about 25 participants for each of three groups based on opioid dose (High Dose, Traditional Dose, and No Opioid Groups).

Inclusion criteria for this study were a history of musculoskeletal pain diagnosis, current pain of at least moderate severity (ie, rated as a 4 or higher on a pain numeric rating scale of 0-10, where 0 = no pain and 10 = worst pain possible), duration of pain condition greater than 12 weeks according to patient report, and the ability to read and write in English. Patients were excluded if they reported any pending litigation or disability claim related to a pain condition, age greater than 70 years, history of cancer diagnosis in the past 5 years, surgery in the past 6 months, have been enrolled in an opiate treatment program in the last 3 months, current suicidal ideation, or current untreated schizophrenia or bipolar disorder. Participants in the "No Opioid" Group had to self-report no use of opioid medications in the last 6 months, which was corroborated by review of the electronic medical record.

A total of 200 patients were screened for study inclusion. Individuals were excluded for pending disability claim related to pain (n = 21), mild pain or no current musculoskeletal pain-related diagnosis (n = 12), recent surgery (n = 11), current cancer diagnosis (n = 8), age > 70 (n = 6), current enrollment in methadone maintenance (n = 3), or other reason (n = 10). Forty potentially eligible participants were excluded after we had met recruitment targets for two of the dose groups. Of those who were eligible, 14 participants ultimately chose not to enroll in the study or did not follow through. A total of 75 participants enrolled and completed study-related measures. This included 24 participants in the No Opioid Group, 34 participants in the Traditional Dose Group (defined as 5-99 mg morphine equivalents per day [MED]), and 17 participants in the High Dose Group (defined as 100 mg MED or more).

Measures

Demographic characteristics were collected by self-report. These included age, gender, race, marital status, years of education, and yearly income.

Current prescription opioid dose data were extracted from the electronic medical record and confirmed with self-report. Current opioid dose was converted to an average daily MED. The average daily dose for each drug was the total MED dispensed during the 90 days prior to recruitment divided by the total number of days dispensed for those prescriptions.

Pain severity and pain interference were assessed with the Multidimensional Pain Inventory (MPI).[23] The MPI is a frequently used and well-validated self-report measure. Scale scores on the MPI range from 0 to 6, with higher scores reflecting more severe pain or interference.

The Beck Depression Inventory-2 (BDI-II) was used to assess for severity of depressive symptoms.[24] The BDI-II is a 21-item self-report measure. Scores are summed, and higher scores reflect more severe symptoms of depression.

The Generalized Anxiety Disorder-7 (GAD-7) is a brief self-report measure used to assess the severity of anxiety symptoms.[25] It has been validated as a robust predictor of the different anxiety disorders.[26] Scores on the GAD-7 are summed and higher scores indicate more severe symptoms of anxiety.

The Pain Medication Questionnaire (PMQ) is a self-report measure designed to assess beliefs and behaviors related to risk of misuse of pain medications.[27] Scores on the PMQ are summed, and higher scores reflect greater risk for misuse of prescription opioids. The PMQ was included as prior literature suggests DD may help predict risk for prescription opioid misuse.[19]

The Timeline Followback (TLFB) was used to assess self-reported use of prescription opioids, alcohol, and illicit substances in the 30 days prior to the study assessment. The TLFB is a reliable and valid method that uses calendar prompts to track the frequency of alcohol or substance use.[28]

All participants completed a computerized DD task to assess relative preference for immediate rewards despite their smaller size.[29] DD is measured using a series of questions presented one at a time. For each question, participants indicate which of two hypothetical items they prefer: a larger amount of money delivered following a delay or smaller, immediate money. The delayed money is $100 available after one of six delays (0, 7, 30, 90, 180, or 365 d). The immediate money is an amount of money (ranging from $1 to $100) available after 0 days. During the task, a delayed and immediate option are selected at random, without replacement, to form a question (eg, "Would you rather have $10 now or $100 in 90 days?"). Participants select whether they prefer the larger later or smaller immediate money.

The amount of immediate money at which preference switched from the delayed to immediate money was obtained for each delay (indifference points).[29] A hyperbolic function was fitted to these indifference points and the slope of this function (k) was used to summarize the degree of discounting.[30] Larger k values indicated steeper slopes, and more devaluation/discounting of delayed rewards. As is typically found, k-values in this study were skewed (8.21) and so were transformed to their natural logarithm values (skew = 0.23) for all statistical analyses.

Data analysis

Participants were recruited such that they could be assigned to one of three groups based on average daily opioid dose. Analyses examining differences among groups were conducted using χ^2 tests for categorical data and analysis of variance, with Scheffe post hoc tests, for continuous data. A linear regression model was constructed to examine variables significantly associated with prescription opioid dose in average daily MED. Variables included in the analysis were age, gender, years of education, pain severity, depression severity, and DD. A significance level of $p < 0.05$ was used for all analyses.

RESULTS

A comparison of demographic differences among the three groups indicates that patients in the High Dose Group had more years of education (mean = 15.2) than those in the Traditional Dose Group (mean = 13.5) or No Opioid Group (mean = 13.8). There were no other significant differences among groups on other demographic variables. Participants averaged 53.5 (SD = 9.9) years, and 72 percent reported Caucasian race/ethnicity. Thirty-two percent were married, 44 percent divorced or separated, and 21.3 percent were single. Most participants were receiving disability (53.3 percent) or were unemployed (29.3 percent). See Table 1 for a comparison of demographic characteristics among

Table 1. Comparison of demographic characteristics based on prescription opioid dose groups				
	High Dose Group (n = 17)	**Traditional Dose Group (n = 34)**	**No Opioid Group (n = 24)**	**p value**
Age	54.2 (9.7)	53.0 (10.0)	53.7 (10.4)	0.918
Male gender	82.4 percent (14)	73.5 percent (25)	75.0 percent (18)	0.778
Caucasian	88.2 percent (15)	70.6 percent (24)	62.5 percent (15)	0.538
Years of education	15.2 (2.6)	13.5 (2.0)	13.8 (2.2)	0.028
Marital status				0.160
Married	41.2 percent (7)	32.4 percent (11)	25.0 percent (6)	
Separated/divorced	47.1 percent (8)	47.1 percent (16)	37.5 percent (9)	
Single	11.8 percent (2)	14.7 percent (5)	37.5 percent (9)	
Widowed	0	5.9 percent (2)	0	
Employment status				0.211
Employed	5.9 percent (1)	8.9 percent (3)	12.5 percent (3)	
Unemployed	17.6 percent (3)	20.6 percent (7)	50.0 percent (12)	
Receiving disability	70.6 percent (12)	58.8 percent (20)	33.3 percent (8)	
Other	5.9 percent (1)	11.8 percent (4)	4.2 percent (1)	

the three groups. A total of 30.7 percent of the sample endorsed smoking cigarettes, which did not differ among the groups ($\chi^2 = 1.51$, p = 0.469).

Table 2 provides a summary of comparisons of clinical data among the three groups. Participants in the High Dose Group were prescribed an average daily opioid dose of 220.2 (SD = 96.3) mg MED. Those in the Traditional Dose Group had an average daily opioid dose of 38.3 (SD = 27.2) mg MED. There were no differences among the three groups on measures of pain intensity, pain-related function, symptoms of depression or anxiety, risk for prescription opioid misuse, or past-month frequency of alcohol use (all p values > 0.05). However, DD slope (k) was significantly different. Post hoc tests revealed that participants in the High Dose Group had significantly lower scores (ie, shallowed discounting functions) than participants in the No Opioid Group (Figure 1). There were no significant differences between the slopes for the High Dose and Traditional Dose Groups, or between the Traditional Dose and the No Opioid Groups.

Correlations between DD slope and clinical variables are presented in Table 2. DD was negatively correlated with average daily opioid dose ($r = -0.36$, p = 0.003) and positively correlated with anxiety ($r = 0.30$, p = 0.013).

A linear regression analysis was conducted to examine variables significantly associated with prescription opioid dose (Table 3). Variables included in the model were age, gender, years of education, pain severity, depression severity, and DD. The overall model was significant and accounted for 25.1 percent of the variance in prescription opioid dose (f = 3.065, p = 0.012). In the final model, the only variables that were significantly associated with average daily opioid dose were male gender and DD.

DISCUSSION

The primary finding from this study is that DD is significantly associated with prescription opioid dose. Participants not prescribed opioids demonstrated the steepest DD curves. Given prior literature indicating that greater exposure to opioids is positively associated with DD,[18] and the consistently identified relationship between SUDs and DD,[31] the study findings are contrary to our initial hypotheses. However, results from this study are consistent with some other research indicating that individuals who are stable in their opioid use (such as in an opioid treatment program) may have lower DD overall.[32] That is, when opioid substitution medications are taken as prescribed, DD curves are less steep.[33]

Table 2. A comparison of clinical variables based on prescription opioid status and correlation with DD*					
	Correlation with DD	High Dose Group (n = 17)	Traditional Dose Group (n = 34)	No Opioid Group (n = 24)	p value
DD slope		–5.8[a] (2.3)	–4.8[a,b] (2.0)	–3.9[b] (2.0)	0.027
Average daily opioid dose	–0.36***	220.2 (96.3)	38.3 (27.2)	–	–
Pain severity	0.22	4.5 (1.0)	4.1 (0.9)	3.9 (1.3)	0.317
Pain interference	0.02	4.7 (1.0)	4.6 (1.0)	4.2 (1.3)	0.287
Depression	0.14	21.5 (12.1)	20.0 (13.7)	18.3 (14.6)	0.784
Anxiety	0.30**	9.9 (5.6)	9.9 (6.0)	9.4 (6.6)	0.947
Risk for prescription opioid misuse	0.23	26.6 (6.4)	25.3 (9.2)	27.8 (14.7)	0.716
Days of alcohol use in past 30 d	–0.02	0.6 (1.3)	2.1 (5.1)	1.2 (3.1)	0.395

*Scores with different superscripts differed significantly in post hoc testing.
**$p < 0.05$.
***$p < 0.01$.

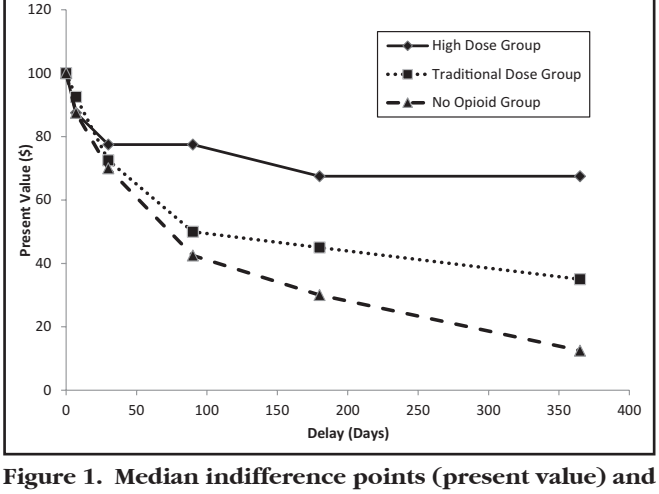

Figure 1. Median indifference points (present value) and associated DD functions based on prescription opioid group.

Note. Because of skewness, DD data reported here reflect median indifference points at each delay. A hyperbolic function was fit to the indifference points for each individual, and the slope of this function used to identify group differences. There were statistically significant differences among the three groups on delay discounting ($p < 0.05$). In post hoc testing, the High Dose Group was significantly different from the No Opioid Group. There was not a significant difference between the High Dose and Traditional Dose Groups or between the Traditional Dose Group and No Opioid Group.

Table 3. Regression analysis examining variables associated with prescription opioid dose				
	B	Standard error	t	p value
Age	0.3	1.1	0.3	0.784
Male gender	55.3	25.6	2.2	0.034
Years of education	9.7	5.1	1.9	0.063
Pain intensity	15.7	10.7	1.5	0.149
Depression	0.7	0.9	0.8	0.422
DD	–16.8	5.5	–3.1	0.003

Little is known about the multidimensional factors that lead to high-dose prescription opioid use for chronic pain. Some prior research suggests that patients who are prescribed the highest doses of opioids have more severe pain and the highest rates of comorbid psychiatric and substance use disorders.[6-9] However, these studies did not examine potential causes that may lead to the development of high-dose opioid use. Further research is needed on this topic, particularly prospective research that could examine the impact of baseline factors on the development of high-dose opioid therapy.

Clinician-related variables might also be evaluated in future research examining factors associated with prescription opioid dose escalation. Clinician factors have demonstrated importance in the development of prescription opioid use,[34] risky opioid prescribing,[35] opioid dose escalation,[10] and prescription opioid overdose.[36,37] Some opioid prescribers may increase prescription opioid doses because the immediate rewards of reduced stress and conflict during clinical interactions are perceived as larger than the delayed benefits of reducing patient reliance on prescription opioids.[38] Future research might examine patient and clinician clusters to assess potential interactive effects.

There may be several reasons why people prescribed higher opioid doses might display less steep

DD curves (suggesting less impulsivity) than those not prescribed opioids. At higher doses of opioids, the opioid reward pathway may be impaired.[39] It is possible that opioid dose contributes to more lethargy or amotivation, or otherwise quiets the limbic system in a way that allows people to delay rewards.[40,41] Some patients may self-select to not take opioids or restrict themselves to lower doses because of concern about potential adverse effects.[42,43] There may be factors that emerge from the clinician-patient relationship. For example, patients whose clinicians write for higher doses may present their pain symptoms or requests in a certain, perhaps more compelling manner, suggesting some type of selection bias may be present. Finally, there may be a selection bias, as individuals in this study who were prescribed higher opioid doses may have been on opioids the longest period of time, and this potential subsample of patients may have enhanced ability to delay rewards (eg, adhering to opioid treatment agreements, not raising concerns to the prescribing clinician).

There are several limitations to consider when reviewing results from this study. First, this study included only one measure of impulsivity. Future research examining the relationship between opioid dose and impulsivity may include other measures of DD, neuropsychological testing, and self-report measures. Second, due to the cross-sectional design of our study, we are unable to determine causation. Prospective research would be needed to better understand the relationships between opioid dose and DD. Third, the sample size for the regression analysis was low and these results should be interpreted with caution. Finally, study participants were predominately male and recruited from a single VA medical center. Results may not be generalizable to women, other patient populations, or patients recruited from specialty care clinics.

In summary, in this study, we examined factors associated with higher prescription opioid doses. Contrary to initial hypotheses, we identified an inverse relationship between DD and prescription opioid dose. DD is the process of placing less value on a reward as it becomes delayed[11-13] and our findings suggest that higher DD is associated with lower prescription opioid doses. These results remained consistent after controlling for the effects of other demographic and clinical factors. Future research is needed elucidate the potential impact of DD on prescription opioid dose. Understanding more about the influence of patient impulsivity surrounding treatment for chronic pain may open new avenues for clinical intervention in this difficult to treat population.

ACKNOWLEDGMENTS

Research reported in this article was supported by grant 034083 from the National Institute on Drug Abuse of the National Institutes of Health. The work was also supported by resources from the VA Health Services Research and Development-funded Center to Improve Veteran Involvement in Care at the VA Portland Health Care System (CIN 13-404). No author reports having any potential conflict of interest with this study. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs or the National Institute on Drug Abuse.

Benjamin J. Morasco, PhD, Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Portland, Oregon; Department of Psychiatry, Oregon Health & Science University, Portland, Oregon.

Steven K. Dobscha, MD, Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Portland, Oregon; Department of Psychiatry, Oregon Health & Science University, Portland, Oregon.

Stephanie Hyde, MA, Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Portland, Oregon; Department of Psychiatry, Oregon Health & Science University, Portland, Oregon.

Suzanne H. Mitchell, PhD, Department of Psychiatry, Oregon Health & Science University, Portland, Oregon; Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon; Oregon Institute for Occupational Health Sciences, Portland, Oregon.

REFERENCES

1. Boudreau D, Von Korff M, Rutter CM, et al.: Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol Drug Saf.* 2009; 18: 1166-1175.

2. Caudill-Slosberg MA, Schwartz LM, Woloshin S: Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain.* 2004; 109: 514-519.

3. Becker WC, Gordon K, Edelman J, et al.: Trends in any and high-dose opioid analgesic receipt among aging patients with and without HIV. *AIDS Behav.* 2016; 20: 679-686.

4. Weisner CM, Campbell CI, Ray GT, et al.: Trends in prescribed opioid therapy for non-cancer pain for individuals with prior substance use disorders. *Pain.* 2009; 145: 287-293.

5. Chou R, Turner JA, Devine EB, et al.: The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 2015; 162: 276-286.

6. Kobus AM, Smith DH, Morasco BJ, et al.: Correlates of high-dose opioid medication use for low back pain in primary care. *J Pain.* 2012; 13: 1131-1138.

7. Merrill JO, Von Korff M, Banta-Green CJ, et al.: Prescribed opioid difficulties, depression and opioid dose among chronic opioid therapy patients. *Gen Hosp Psychiatry.* 2012; 34: 581-587.

8. Morasco BJ, Duckart JP, Carr TP, et al.: Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain. *Pain.* 2010; 151: 625-632.

9. Morasco BJ, Yarborough BJ, Smith NX, et al.: Higher prescription opioid dose is associated with worse patient-reported pain outcomes and more health care utilization. *J Pain.* 2017; 18: 437-445.

10. Dasgupta N, Jonsson M, Proescholdbell S, et al.: Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med.* 2016; 17: 85-98.

11. Madden GJ, Johnson PS: A delay-discounting primer. In Madden GJ, Bickel WK (eds.): *Impulsivity: The Behavioral and Neurological Science of Discounting.* Washington, DC: American Psychological Association, 2010: 213-242.

12. Rachlin H: Diminishing marginal value as delay discounting. *J Experimental Analysis Behav.* 1992; 57: 407-415.

13. Robles E, Huang BE, Simpson PM, et al.: Delay discounting, impulsiveness, and addiction severity in opioid-dependent patients. *J Sub Abuse Treat.* 2011; 41: 354-362.

14. Dennhardt AA, Murphy JG: Associations between depression, distress tolerance, delay discounting, and alcohol-related problems in European American and African American college students. *Psychol Addict Behav.* 2011; 25: 595-604.

15. Joos L, Goudriaan AE, Schmaal L, et al.: The relationship between impulsivity and craving in alcohol dependent patients. *Psychopharmacology.* 2013; 226: 273-283.

16. Kirby KN, Petry NM: Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addict.* 2004; 99: 461-471.

17. Yi R, Mitchell SH, Bickell WK: Delay discounting and substance abuse. In Maden GJ, Bickel WK (eds.): *Impulsivity: The Behavioral and Neurological Science of Discounting.* Washington, DC: American Psychological Association, 2010: 191-211.

18. Madden GJ, Petry NM, Badger GJ, et al.: Impulsive and self-control choices in opioid-dependent patients and non-drug-using control patients: Drug and monetary rewards. *Exp Clin Psychopharmacol.* 1997; 5: 256-262.

19. Bickel WK, Koffarnus MN, Moody L, et al.: The behavioral- and neuro-economic process of temporal discounting: A candidate behavioral marker of addiction. *Neuropharmacology.* 2014; 76(Pt B): 518-527.

20. Mackillop J, Amlung MT, Few LR, et al.: Delayed reward discounting and addictive behavior: A meta-analysis. *Psychopharmacology.* 2011; 216: 305-321.

21. Tomkins DA, Johnson PS, Smith MT, et al.: Temporal preference in individuals reporting chronic pain: Discounting of delayed pain-related and monetary outcomes. *Pain.* 2016; 157: 1724-1732.

22. Elman I, Borsook D: Common brain mechanisms of chronic pain and addiction. *Neuron.* 2016; 89: 11-36.

23. Kerns RD, Turk DC, Rudy TE: The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). *Pain.* 1985; 23: 345-356.

24. Beck AT, Steer RA, Brown GK: *The Beck Depression Inventory.* 2nd ed. San Antonio, TX: The Psychological Corporation, 1996.

25. Spitzer RL, Kroenke K, Williams JBW, et al.: A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Int Med.* 2006; 166: 1092-1097.

26. Kroenke K, Spitzer RL, Williams JB, et al.: Anxiety disorders in primary care: Prevalence, #impairment, |comorbidity, and detection. *Ann Intern Med.* 2007; 146: 317-327.

27. Adams LL, Gatchel RJ, Robinson RC, et al.: Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. *J Pain Symptom Manage.* 2004; 27: 440-459.

28. Sobell LC, Sobell MB: Timeline follow-back: A technique for assessing self-reported alcohol consumption. In Litton RZ, Allen JP (eds.): *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods.* Clifton, NJ: Human Press, 1992: 41-72.

29. Mitchell SH: Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology.* 1999; 146: 455-464.

30. Mazur JE: An adjusting procedure for studying delayed reinforcement. In Commons ML, Mazur JE, Nevin JA, Rachlin H (eds.): *The Effect of Delay and of Intervening Event on Reinforcement Value. Quantitative Analyses of Behavior.* Vol. 5. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc, 1987: 55-73.

31. Amlung M, Vedelago L, Acker J, et al.: Steep delay discounting and addictive behavior: A meta-analysis of continuous associations. *Addict.* 2017; 112: 51-62.

32. Ersche K, Roiser J, Clark L, et al.: Punishment induces risky decision-making in methadone-maintained opiate users but not in heroin users or healthy volunteers. *Neuropsychopharmacology.* 2005; 30: 2115-2124.

33. Giordano LA, Bickel WK, Loewenstein G, et al.: Mild opioid deprivation increases the degree that opioid-dependent outpatients discount delayed heroin and money. *Psychopharmacology.* 2002; 163: 174-182.

34. Dobscha SK, Corson K, Flores JA, et al.: Veterans Affairs primary care clinicians' attitudes toward chronic pain and correlates of opioid prescribing rates. *Pain Med.* 2008; 9: 564-571.

35. Fredheim OMS, Borchgrevink PC, Mahic M, et al.: A pharmacoepidemiological cohort study of subjects starting strong opioids for nonmalignant pain: A study from the Norwegian Prescription Database. *Pain.* 2013; 154: 2487-2493.

36. Henry SG, Wilsey BL, Melnikow J, et al.: Dose escalation during the first year of long-term opioid therapy for chronic pain. *Pain Med.* 2015; 16: 733-744.

37. Hirsch A, Proescholdbell SK, Bronson W, et al.: Prescription histories and dose strengths associated with overdose deaths. *Pain Med.* 2014; 15: 1187-1195.

38. Siegler JE, Kable JW, Chatterjee A: Resident decision making: Opioids in the outpatient setting. *J Grad Med Educ.* 2016; 8: 138-141.

39. Le Merrer J, Becker JAJ, Befort K, et al.: Reward processing by the opioid system in the brain. *Physiol Rev.* 2009; 89: 1379-1412.

40. Dhingra L, Ahmed E, Shin J, et al.: Cognitive effects and sedation. *Pain Med.* 2015; 16(suppl 1): S37-S43.

41. Zlott DA, Byrne M: Mechanisms by which pharmacologic agents may contribute to fatigue. *Phys Med Rehabil.* 2010; 2: 451-455.

42. Paterson C, Ledgerwood K, Arnold C, et al.: Resisting prescribed opioids: A qualitative study of decision making in patients taking opioids for chronic noncancer pain. *Pain Med.* 2016; 17: 717-727.

43. Schumacher KL, West C, Dodd M, et al.: Pain management autobiographies and reluctance to use opioids for cancer pain management. *Cancer Nurs.* 2002; 25: 125-133.