Prescription Opioids in Adolescence and Future Opioid Misuse

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abstract

BACKGROUND AND OBJECTIVE: Legitimate opioid use is associated with an increased risk of long-term opioid use and possibly misuse in adults. The objective of this study was to estimate the risk of future opioid misuse among adolescents who have not yet graduated from high school.

METHODS: Prospective, panel data come from the Monitoring the Future study. The analysis uses a nationally representative sample of 6220 individuals surveyed in school in 12th grade and then followed up through age 23. Analyses are stratified by predicted future opioid misuse as measured in 12th grade on the basis of known risk factors. The main outcome is nonmedical use of a prescription opioid at ages 19 to 23. Predictors include use of a legitimate prescription by 12th grade, as well as baseline history of drug use and baseline attitudes toward illegal drug use.

RESULTS: Legitimate opioid use before high school graduation is independently associated with a 33% increase in the risk of future opioid misuse after high school. This association is concentrated among individuals who have little to no history of drug use and, as well, strong disapproval of illegal drug use at baseline.

CONCLUSIONS: Use of prescribed opioids before the 12th grade is independently associated with future opioid misuse among patients with little drug experience and who disapprove of illegal drug use. Clinic-based education and prevention efforts have substantial potential to reduce future opioid misuse among these individuals, who begin opioid use with strong attitudes against illegal drug use.

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Dr Miech conceptualized and designed the study and drafted the initial manuscript; Drs Johnston and O'Malley contributed to the conceptualization of the project and critically reviewed the manuscript; Dr Keyes contributed to the conceptualization of the project, critically reviewed the manuscript, and provided assistance with the methodology; Dr Heard contributed to the conceptualization of the project and critically reviewed the manuscript with an eye toward the significance of the study for clinical practice; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Legitimate opioid is a risk factor for subsequent misuse of opioids among adults. This study provides the first population-based estimate of the risk of future opioid misuse associated with legitimate opioid use among adolescents.

WHAT THIS STUDY ADDS: Use of prescribed opioids before the 12th grade is independently associated with future opioid misuse among patients with little drug experience and who disapprove of illegal drug use.

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An increased risk for opioid misuse among adults who receive legitimate prescriptions has long been acknowledged as a possible consequence of opioid prescribing.[1] Weighing and addressing this risk of iatrogenic opioid misuse is a key concern for medical professionals, and the risk figures prominently in opioid position articles published by professional medical organizations.[2–5] One such position article recently revealed that the risk of future opioid misuse is so substantial that it outweighs the benefits of opioids for certain conditions, such as chronic back pain.[4] Yet despite the importance of the risk associated with iatrogenic opioid misuse, estimates of the size of this risk for adolescents in the general population are not currently available.

This study estimates the risk of future opioid misuse associated with legitimate use of prescription opioids among adolescents who have not yet graduated high school. An association between legitimate opioid use before high school completion and an increased risk of subsequent misuse after high school could change the risk/benefit considerations for clinicians who treat pediatric patients with painful conditions. Using prospective, nationally representative cohorts, the analyses examine the future risk of opioid misuse among respondents with and without a history of legitimate use of prescription opioids by 12th grade. We stratify the analyses by adolescents' levels of preexisting, baseline risk levels for future opioid misuse on the basis of drug use behaviors, attitudes, and other characteristics at the initial baseline survey. This analytic strategy builds on and contributes to the literature revealing that these individual-level factors strongly predict future opioid misuse by taking into account their potential confounding and moderating effects.[6]

METHODS

Subjects

Data come from the annual Monitoring the Future study, which since 1975 has used questionnaires administered in classrooms to survey nationally representative samples of US 12th graders in the 48 contiguous states.[7] The project has been approved by the University of Michigan Institutional Review Board. Each year, the survey selects ~130 public and private schools containing 12th graders. Students are randomly assigned to 1 of 5 (1975–1988) or 6 (since 1989) questionnaire forms, which contain both core and form-specific questions. The survey and sampling procedures are described in detail elsewhere.[7,8] Every year, ~2450 high school seniors are randomly selected from the baseline sample to participate in follow-up mail surveys that include questions on opioid misuse. Individuals with higher levels of illicit drug use at baseline are oversampled in the follow-up surveys, and weighting is used in all analyses to take into account this oversampling.[7]

This analysis uses information from the (a) first 3 follow-up waves of baseline 12th graders who (b) received form 1 of the survey, and (c) completed a baseline questionnaire between 1990 and 2012 inclusive. The first 3 waves of the follow-up (ages 19–23) are strategic because misuse of analgesics peaks in this age range.[9] The analysis focuses on form 1 because it is the only 1 with baseline information on legitimate use of prescription opioids. We limit the study period to the baseline years 1990 and later because only in these years did form 1 include attitudinal questions that are included in the analyses to stratify by baseline risk for future opioid misuse. The analysis centers on 6220 individuals who answered questions about opioid misuse in at least 1 of the first 3 follow-up surveys, for a weighted response rate of 71% (the response rate is 69% for the unweighted sample) among respondents who completed a baseline survey.[10]

Measures

Opioid misuse at follow-up is coded 1 for respondents who reported that in the last 12 months they had on 1 or more occasions taken "narcotics other than heroin on your own—that is, without a doctor telling you to take them." This question provided a list of example drugs that qualified as "narcotics other than heroin"; the list has been updated over time and currently includes methadone, opium, morphine, Vicodin, MS Contin, codeine, Demerol, Roxycodone, hydrocodone (Lortab, Lorcet, Norco), Suboxone, OxyContin, Percocet, Tylox, Percodan, Ultram, and tramadol. Frequency of opioid misuse is measured at follow-up and is the number of occasions respondents report misusing opioids in the last 12 months. Opioid misuse at follow-up to get high or relax is coded 1 for respondents who indicated from a list of 17 potential reasons to misuse opioids[11] that they misused them "to relax or relieve tension" or "to feel good or get high," and 0 otherwise.

All other variables were measured at the baseline 12th-grade assessment. Table 1 lists these predictor variables, their definition, response categories, and their proportions/means.

Analysis

The analysis presents results from generalized estimating equations.[12] Each individual contributes up to 3 follow-up observations to the analysis pool. The generalized estimating equation methodology adjusts for nonindependence of observations from the same individual. Respondents contributed a mode of 2 follow-up observations (out of 3 possible), for an analysis pool of 13 542 observations. The dependent variable of the analysis is the dichotomous variable of any opioid misuse in the past 12 months at a follow-up, and the analysis uses

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TABLE 1 Means and Proportions of Sample Characteristics in 12th Grade (SEs in Parentheses)

Variable	Mean/Proportion
Legitimate use of opioids by 12th grade	
Question: "Have you ever taken any narcotics other than heroin because a doctor told you to use them?" Note: This variable is coded 1 for the response category "Yes, and it was the first time I took any." Accompanying this question is a list of example drugs that has been updated over time and currently includes methadone, opium, morphine, Vicodin, MS Contin, codeine, Demerol, Roxycodone, hydrocodone (Lortab, Lorcet, Norco), Suboxone, OxyContin, Percocet, Tylox, Percodan, Ultram, and tramadol.	0.15 (0.0048)
Lifetime marijuana use by 12th grade	
Question: "On how many occasions (if any) have you used marijuana?"	
None	0.62 (0.0064)
1–2	0.092 (0.0040)
3–5	0.059 (0.0032)
6–9	0.043 (0.0028)
10–19	0.049 (0.0029)
20–39	0.040 (0.0026)
40+	0.098 (0.0034)
Cigarette smoking history by 12th grade	
Question: "Have you ever smoked cigarettes?"	
Never	0.48 (0.0067)
Once or twice	0.22 (0.0056)
Occasionally but not regularly	0.14 (0.0046)
Regularly in the past	0.05 (0.0030)
Regularly now	0.11 (0.0039)
Lifetime opioid use by 12th grade	
Question: "On how many occasions (if any) have you taken narcotics other than heroin on your own; that is, without a doctor telling you to take them?" Note: question includes an extensive list of example prescription opioids that is updated from year to year.	
None	0.91 (0.0035)
1–2	0.041 (0.0025)
3–5	0.018 (0.0016)
6–9	0.010 (0.0012)
10–19	0.010 (0.0011)
20–39	0.005 (0.0008)
40+	0.006 (0.0008)
Lifetime use of barbiturates and sedatives by 12th grade	
Question: "On how many occasions (if any) have you taken sedatives on your own; that is, without a doctor telling you to take them?" Note: question includes an extensive list of example prescription barbiturates and sedatives that is updated from year to year.	
None	0.96 (0.0023)
1–2	0.018 (0.0016)
3–5	0.008 (0.0010)
6–9	0.006 (0.0008)
10–19	0.0037 (0.0006)
20–39	0.0025 (0.0004)
40+	0.0035 (0.0005)
Binge drinking in past 2 wk at baseline, 12th grade survey	
Question: "During the last 2 weeks, how many times (if any) have you had 5 or more drinks in a row?"	
None	0.79 (0.0054)
Once	0.085 (0.0037)
Twice	0.056 (0.0030)
3–5	0.055 (0.0029)
6–9	0.012 (0.0013)
10+	0.007 (0.0010)
Disapproval of regular marijuana use in 12th grade	
Question: "Do you disapprove of people (who are 18 or older) smoking marijuana regularly?"	
Don't disapprove	0.18 (0.0053)
Disapprove	0.26 (0.0064)

a binomial regression with a log link[13] to estimate relative risk of this outcome for respondents with and without a history of prescription opioid use by 12th grade.

The analysis uses multiple imputation to handle missing data[14] and uses the chained equations algorithm[15] with 20 imputed data sets. The final analytic steps exclude cases with imputed values for the dependent variable of opioid misuse. All variables in the analysis have missing values of less than 4%, with the exception of personal disapproval of marijuana use, which has a missing prevalence of 15%. The disapproval question appears near the very end of the form 1 questionnaire, when some respondents may run out of time or energy to answer. In total, 75% of the sample had complete data on all variables, and 25% of the sample had at least 1 imputed data value.

Because random assignment of prescription opioids is not a feasible design to answer this research question for ethical and logistical reasons, we used a risk stratification approach (commonly used in randomized trials and meta-analyses[16]) to optimally control for potential confounding by known covariates, and to allow for assessment of effect measure modification through stratified analyses on the basis of the risk score. Specifically, we estimated a probability of future opioid use by using baseline covariates measured in 12th grade to predict opioid use after high school, and stratified individuals on the basis of this probability. The cut points for risk group strata are set so that each group is "balanced"; that is, none of the independent variables significantly differ across respondents who did and did not go on to misuse opioids after high school. The result is that the independent variables modeled in the risk stratification score cannot play a confounding role in the within-strata analyses. These risk strata allow for

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TABLE 1 Continued

Variable	Mean/Proportion
Strongly disapprove	0.55 (0.0070)
Women	0.57 (0.0066)
Average course marks in 12th grade	2.42 (0.025)
Question: "Which of the following best describes your average grade so far in high school?" Values range from 9 for a "D" (69 or below) to 1 for an "A" (93–100).	
Parent with college degree	0.52 (0.0067)
Coded 1 for respondents with either a mother or father with a college degree and 0 otherwise	
Racial/ethnic minority	0.27 (0.0060)
Coded 0 for respondents who are non-Hispanic white and 1 otherwise	

efficient assessment of both main effects, unconfounded by observed covariates, and effect measure modification, on the basis of the strata of risk score for future misuse. This risk stratification approach is a variant of general propensity score approaches, which have been shown to be more valid than traditional approaches, such as statistical control for factors in a regression analysis.[17,18]

The analysis consists of 3 models. First, we build a predictive model that uses information from the 12th grade baseline survey to prospectively predict future misuse after high school (model 1). This model includes a wide range of factors known to predict opioid misuse that are presented in Table 1. Second, for model 2 we add prescription opioid use by 12th grade to model 1 to examine its independent, predictive contribution. This model predicts an average risk across all respondents. Third, the analysis examines whether this average association differs by baseline risk for opioid misuse in 12th grade by calculating the association in different, baseline risk strata groups that are demarcated by using the predicted probabilities calculated in model 1.[19] The stratified analyses use risk ratios, which have the advantage of "collapsibility" so that estimates are independent of the outcome's prevalence level.[20]

The validity of this approach relies on the assumption of ignorability[21,22]; that is, conditional on these covariates as modeled, differences in those who receive opioid medications and those who do not should be ignorable, thus replicating to the extent possible the conditions of a randomized controlled trial. Although such assumptions are difficult to make in observational data of this nature, causal inference approaches such as those taken here have been shown to be more valid than traditional approaches such as statistical control for factors in a regression analysis.[17,18]

RESULTS

Table 2 presents the results from regressions of opioid misuse at ages 19 to 23 as a function of predictors measured in 12th grade. We calculate an individualized, predicted risk of future opioid misuse on the basis of model 1. This predicted probability is the sum of all individual-level characteristics in the model, weighted by the associated regression coefficients. It varies from 0.06% to 76%, indicating that 12th grade information provides substantial range in the prediction of opioid misuse after high school.

Model 2 of Table 2 adds to model 1 the predictor of legitimate opioid use by 12th grade. The relative risk of 1.33 ($P < .05$) indicates that a legitimate prescription for opioids in 12th grade is independently associated with a 33% increase in the risk of future opioid misuse net of the other factors in the model. This 33% increase is an average score across all respondents and may vary by predicted risk of future opioid misuse as measured in 12th grade.

Table 3 presents the analysis pool stratified by the risk score calculated from model 1 of Table 1. Across the strata, levels of 12th grade drug use across all drugs increase steadily and monotonically with increases in predicted risk of future opioid misuse. The risk strata are balanced so that within each stratum none of the variables significantly differ across respondents who do and do not misuse opioids by ages 19 to 23.

Table 4 presents analyses stratified by risk strata and displays the risk ratio of future opioid misuse for those with versus without a legitimate prescription for opioids by 12th grade. The results vary substantially by risk stratum. The risk ratio is highest among youth in the lower (but not lowest) risk strata. Stratum 2 is the largest stratum and 1 with a low predicted probability of future opioid misuse. In this stratum, youth with a legitimate prescription for opioids by 12th grade are 3 times more likely to subsequently misuse opioids than youth without a prescription. In stratum 3, the risk is ~2 times higher. Among the higher risk strata, a legitimate prescription for opioids is not associated with an increased risk for future opioid misuse.

Among those who misused opioids in the lower risk strata, the frequency of misuse is low. In stratum 2, which has the highest association between legitimate prescription opioid use and later opioid misuse, >80% of young adults who misuse opioids limit their misuse to a maximum of 5 times or fewer in the past year. Frequent use, as measured by 40 or more occurrences of opioid misuse over the past year, is <3%. In contrast, frequent opioid misuse (40+ occurrences in the past year) in the eighth and highest risk stratum is 7

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TABLE 2 Misuse of Prescription Opioids in Past 12 Months at Follow-Ups 1 to 3 as a Function of 12th Grade Characteristics: Relative Risk Ratios and 95% CIs

Variable	Model 1		Model 2	
	Relative Risk	95% CI	Relative Risk	95% CI
Legitimate use of prescription opioids by 12th grade			1.33*	1.04–1.7
Lifetime marijuana use occasions by 12th grade				
None (reference)				
1–2	1.44	0.98–2.12	1.43	0.97–2.11
3–5	1.31	0.83–2.08	1.31	0.83–2.08
6–9	2.18**	1.40–3.37	2.21**	1.43–3.43
10–19	2.73**	1.87-3.99	2.74**	1.88-3.99
20–39	2.52**	1.66–3.82	2.56**	1.69–3.89
40+	2.83**	2.02–3.96	2.92**	2.09–4.08
Cigarette smoking history by 12th grade				
Never (reference)				
Once or twice	1.56**	1.14–2.13	1.56**	1.15–2.13
Occasionally but not regularly	1.75**	1.26–2.42	1.73**	1.25–2.4
Regularly in the past	2.09**	1.41–3.11	2.08**	1.4–3.09
Regularly now	1.78**	1.25–2.52	1.78**	1.26–2.52
Lifetime prescription opioids misuse occasions by 12th grade				
None (reference)				
1–2	2.21**	1.59–3.07	1.97**	1.4–2.77
3–5	3.00**	1.94–4.61	2.8**	1.83–4.29
6–9	3.36**	2.17–5.20	3.2**	2.06–4.96
10–19	3.71**	2.35–5.85	3.58**	2.26–5.65
20–39	6.07**	3.3–11.17	5.88**	3.19–10.8
40+	4.94**	2.97–8.22	4.63**	2.79–7.67
Lifetime misuse prescription barbiturates/ sedatives occasions by 12th grade				
None (reference)				
1–2	1.63*	1.00–2.64	1.63*	1.01–2.65
3–5	1.96**	1.18–3.27	1.97**	1.19–3.26
6–9	1.5	0.82–2.76	1.57	0.85–2.89
10–19	2.52*	1.17–5.42	2.56*	1.2–5.45
20–39	2.86**	1.57–5.21	2.93**	1.61–5.33
40+	1.03	0.53–2	1.04	0.53–2.01
Binge drinking in last 2 wk				
None (reference)				
Once	1.16	0.87–1.56	1.16	0.86–1.55
Twice	1.05	0.76–1.44	1.05	0.77–1.44
3–5	1.44*	1.05–1.96	1.44*	1.06–1.97
6–9	0.80	0.46–1.37	0.83	0.48–1.42
10+	0.87	0.43–1.74	0.86	0.42–1.74
Disapproval of regular marijuana use				
Don't disapprove (reference)				
Disapprove	0.72*	0.56–0.93	0.72*	0.56–0.93
Strongly disapprove	0.52**	0.39–0.69	0.52**	0.39–0.69
Women	1.2	0.99–1.46	1.2	0.99–1.46
Average course marks in 12th grade	0.94*	0.89–0.99	0.95*	0.9–1
Racial/ethnic minority	0.61**	0.47–0.79	0.62**	0.48–0.8
Parent with college degree	1.24*	1.03–1.49	1.23*	1.02–1.48
Constant	0.03**	0.02–0.04	0.03**	0.02–0.04

Variables that did not significantly contribute to this model include school truancy, no. evenings out per week, 2-parent household, age at survey, perceived risk of regular marijuana use, no. occasions misuse of prescription amphetamines and prescription tranquilizers, and no. occasions lifetime cocaine use. Model 2 adds to model 1 the 1 variable "legitimate use of prescription opioids by 12th grade." CI, confidence interval. *$P < .01$; **$P < .05$.

times higher at 21%, and only 35% limit their misuse to 5 or more occasions in the past year. Legitimate prescription opioid use by 12th grade does not predict *frequent* opioid misuse in any of the risk strata.

We examine the stated reasons for misuse of opioids. Reasons other than to relieve physical pain are common: 69% of respondents who report misuse of opioids in the follow-ups say they do so to feel good or get high or to relax or relieve tension. Regressions parallel to those in Table 3 predict opioid misuse specifically to get high or relax. In stratum 2, a legitimate opioid prescription by 12th grade increases the risk of future misuse of opioids to get high or relax by a factor of 2.7 ($P < .05$). This association in the second risk stratum is significantly higher than in the other strata combined (using same testing procedures described in the footnote to Table 3). In no risk stratum other than the second does a legitimate opioid prescription by 12th grade significantly increase risk for future misuse of opioids to get high or relax.

DISCUSSION

Legitimate opioid use by 12th grade significantly predicts future opioid misuse after high school. However, this association is concentrated among adolescents who are least expected to misuse opioids: 12th grade students who have little to no history of drug use and strong disapproval of marijuana use.

In the overall sample, individuals who have an opioid prescription by 12th grade are, on average, 33% more likely to misuse prescription opioids after high school by age 23 than those with no history of an opioid prescription. This association varies by risk of future opioid misuse at baseline. Specifically, among respondents with low predicted risk of future opioid misuse in 12th grade (a 1.75% to 3% probability), an opioid prescription by 12th grade increases risk for opioid misuse after high school threefold. In the next highest risk stratum (with a predicted baseline risk of 3% to 5%), an opioid prescription doubles the risk for opioid misuse after high school. In no

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TABLE 3 Means and Proportions of Selected 12th Grade Characteristics by Risk Strata for Future Misuse of Prescription Opioids (SE in Parentheses)

Strata No.	1		2		3		4		5		6		7		8	
Range of Predicted Probability for Future Opioid Misuse Post High School	0%–<1.75%		1.75%–<3%		3%–<5%		5%–<10%		10%–<20%		20%–<30%		30%–<45%		≥45%	
	No Opioid Misuse Age 19–23	Opioid Misuse Age 19–23	No Opioid Misuse Age 19–23	Opioid Misuse Age 19–23	No Opioid Misuse Age 19–23	Opioid Misuse Age 19–23	No Opioid Misuse Age 19–23	Opioid Misuse Age 19–23	No Opioid Misuse Age 19–23	Opioid Misuse Age 19–23	No Opioid Misuse Age 19–23	Opioid Misuse Age 19–23	No Opioid Misuse Age 19–23	Opioid Misuse Age 19–23	No Opioid Misuse Age 19–23	Opioid Misuse Age 19–23
Number of individuals[a]	*n* = 1470	*n* = 12	*n* = 1570	*n* = 23	*n* = 924	*n* = 43	*n* = 842	*n* = 79	*n* = 561	*n* = 138	*n* = 163	*n* = 59	*n* = 134	*n* = 82	*n* = 54	*n* = 66
No. occasions used marijuana in lifetime by 12th grade	0.094 (0.011)	0.075 (0.054)	0.39 (0.031)	0.27 (0.092)	3.54 (0.20)	3.27 (0.97)	17 (0.50)	20 (1.83)	35 (0.74)	34 (1.77)	38 (1.53)	37 (2.51)	49 (1.33)	48 (2.13)	57 (0.98)	57 (1.03)
Proportion who regularly used cigarettes in 12th grade	0.005 (0.0012)	0 (0)	0.020 (0.0024)	0.027 (0.019)	0.10 (0.0069)	0.14 (0.039)	0.22 (0.010)	0.19 (0.033)	0.38 (0.015)	0.37 (0.035)	0.44 (0.032)	0.43 (0.054)	0.47 (0.033)	0.49 (0.045)	0.59 (0.048)	0.63 (0.052)
No. occasions misused opioids in lifetime by 12th grade	0.0020 (0.00082)	0 (0)	0.014 (0.0029)	0.021 (0.021)	0.21 (0.058)	0.32 (0.11)	0.58 (0.081)	0.63 (0.18)	1.50 (0.19)	1.61 (0.30)	5.75 (0.57)	5.88 (0.87)	13 (0.93)	17 (1.78)	26 (1.67)	27 (1.92)
No. occasions misused sedatives/ barbiturates in lifetime by 12th grade	0.02 (0.011)	0 (0)	0.020 (0.0050)	0.12 (0.10)	0.15 (0.029)	0.33 (0.26)	0.51 (0.079)	0.92 (0.35)	0.71 (0.11)	1.17 (0.33)	3.43 (0.78)	2.72 (0.57)	4.91 (0.80)	5.71 (1.10)	11 (1.32)	10 (1.26)
Proportion any binge drinking in past 2 wk at 12th grade survey	0.04 (0.0034)	0.03 (0.028)	0.11 (0.0053)	0.09 (0.032)	0.26 (0.010)	0.26 (0.049)	0.37 (0.012)	0.38 (0.042)	0.55 (0.016)	0.54 (0.037)	0.53 (0.033)	0.56 (0.055)	0.66 (0.033)	0.60 (0.045)	0.64 (0.050)	0.71 (0.048)
Proportion who strongly disapproved of marijuana use when in 12th grade	0.86 (0.0070)	0.82 (0.69)	0.67 (0.0083)	0.69 (0.058)	0.49 (0.012)	0.52 (0.057)	0.28(0.012)	0.23 (0.040)	0.11 (0.012)	0.14 (0.028)	0.15 (0.027)	0.098 (0.036)	0.068 (0.021)	0.05 (0.022)	0.055 (0.031)	0.053 (0.030)
Women	0.54 (0.0088)	0.61 (0.083)	0.63 (0.0081)	0.68 (0.053)	0.59 (0.011)	0.59 (0.054)	0.61 (0.012)	0.60 (0.042)	0.58 (0.016)	0.57 (0.036)	0.55 (0.032)	0.54 (0.055)	0.66 (0.030)	0.59 (0.044)	0.64 (0.047)	0.60 (0.050)
Average course marks in 12th grade	2.45 (0.032)	2.55 (0.30)	1.89 (0.031)	1.55 (0.19)	2.39 (0.043)	0.219 (0.21)	2.73 (0.048)	2.50 (0.16)	2.56 (0.059)	2.86 (0.14)	2.77 (0.12)	2.98 (0.23)	2.70 (0.11)	2.85 (0.20)	2.69 (0.20)	2.75 (0.20)
Parent with college degree	0.35 (0.0086)	0.50 (0.084)	0.63 (0.0082)	0.68 (0.054)	0.55 (0.011)	0.61 (0.053)	0.58 (0.013)	0.57 (0.043)	0.60 (0.016)	0.57 (0.037)	0.64 (0.030)	0.52 (0.057)	0.60 (0.032)	0.49 (0.046)	0.65 (0.048)	0.69 (0.045)
Minority	0.51 (0.0089)	0.42 (0.084)	0.17 (0.0064)	0.15 (0.042)	0.15 (0.0082)	0.15 (0.038)	0.17 (0.0092)	0.20 (0.033)	0.07 (0.0077)	0.09 (0.019)	0.10 (0.019)	0.14 (0.042)	0.07 (0.019)	0.03 (0.012)	0.06 (0.020)	0.04 (0.027)

Variables and their coding are described in Table 1. For calculation of average, the number of drug use occasions response categories are coded to their mean value (eg, the response of "1–2" occasions is coded to 1.5, "3–5" occasions is coded to 4, etc), and top value of "40+" is coded to 60.

[a] *n* = Number of individuals (on average, each individual contributed 2.2 follow-up observations to analysis pool).

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TABLE 4 Relative Risk Ratio for Misuse of Prescription Opioids in Follow-ups 1 to 3 for Respondents With Versus Without Legitimate Prescription Opioid Use by 12th Grade, by Risk Strata (95% Confidence Intervals in Parentheses)

Strata No.	1	2	3	4	5	6	7	8
Predicted probability of opioid misuse after high school	0%–<1.75%	1.75%–<3%	3%–<5%	5%–<10%	10%–<20%	20%–<30%	30%–<45%	≥45%
Legitimate prescription opioid use by 12th grade	0.97 (0.22–4.29)	3.01** (1.79 –5.07)	1.95* (1.15–3.34)	1.24 (0.81–1.91)	0.98 (0.66–1.44)	1.06 (0.64–1.73)	0.56 (0.31–1.01)	0.86 (0.49–1.63)

The risk ratios in stratums 2 and 3 are significantly higher than those in the other stratums combined, as tested with multiplicative interaction terms. Test models included (a) all the predictors in model 2 of Table 2, (b) an indicator variable for risk stratum, and (c) a multiplicative interaction term of the risk stratum indicator and legitimate opioid prescription by 12th grade. In separate models, interactions were statistically significant ($P < .05$) when including an indicator for risk stratum 2, risk stratum 3, and an indicator for risk strata 2 and 3 combined. *$P < .05$; **$P < .01$.

other risk stratum does an opioid prescription strongly or significantly predict future opioid misuse.

Novelty of drug use effects may help explain why an opioid prescription predicts future opioid misuse most strongly among individuals with little to no experience with use of illegal drugs. For these drug-naïve individuals, an opioid prescription is likely to be their initial experience with an addictive substance. Most likely the initial experience of pain relief is pleasurable, and a safe initial experience with opioids may reduce perceived risk. A pleasurable and safe initial experience with a psychotropic drug is a central factor in theories of who goes on to misuse drugs.[23]

In contrast, among individuals with more extensive drug experience, the legitimate use of prescription opioids may be expected to make relatively less of an impression in comparison with the other controlled substances they have used. Although these experienced individuals may go on to misuse prescription opioids, such misuse does not appear to result from an introduction to opioids through a legitimate prescription.

Among inexperienced drug users, legitimate opioid prescription use predicts opioid misuse to get high or to relax, although this use does not occur on a frequent basis. Opioid misuse in the lower risk strata is most often limited to 5 or fewer occasions of misuse in the last 12 months. These results do not support legitimate opioid prescription use, by itself, as a major contributor to chronic opioid misuse, at least not by age 23.

For clinical practice, the results suggest an unrecognized risk of opioid prescribing. This risk should be incorporated into prescribing decisions and patient counseling. Until recently, the short-term use of opioids to treat pain was thought to carry a negligible risk for precipitating future misuse.[24] Our current study and others[25,26] have associated short-term prescriptions with misuse for some youth. When informed of these risks for children, parents may opt for nonopioid options as the initial treatment of minor painful conditions. Opioids could be prescribed if nonopioid treatments were insufficient. Recent work has highlighted the importance of knowledge about adverse events as parents evaluate the best way to manage pain in their children.[27]

Our study identifies adolescent patients without a history of illegal drug use as a group of concern when prescribing opioids. These results underscore the call of prominent scholars to devote for more research to this group,[28] which has received considerably less attention than patients who have or are suspected to have a history of drug misuse.[29] Presumably the patients without a history of illegal drug use would be attentive to doctor-provided advice about prescription opioids, given that at baseline these patients already have strong attitudes against illegal drug use. This group is readily identifiable, because the study results suggest that little to no lifetime marijuana use could potentially serve as an indicator to identify this (counterintuitively) high risk group.

In the very lowest risk stratum (1), legitimate use of prescription opioids before high school completion does not predict opioid misuse after high school. One distinguishing characteristic of this stratum is its composition of ~50% minority youth, which is more than twice the minority composition of any other risk stratum. This finding is consistent with previous work revealing low prevalence of drug misuse among minority adolescents,[30,31] and underscores the importance of research efforts underway to identify the protective factors that are at work.

It is important to note 3 limitations of this study. First, our data do not have information on the dose, length, reason for, effectiveness of, or age of treatment of opioid prescriptions. Consequently, the results of this study represent an average effect and may differ if stratified by any of these factors. Second, the data do not contain information on unmeasured confounding factors, such as family history or mental illness, although it is likely that by 12th grade drug use history and drug attitudes serve as

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proximate causes for these more distal influences on drug misuse. Third, the data do not include youth who have dropped out of high school by 12th grade. On average this group appears to have higher levels of drug use,[32] and therefore if included in the analysis this group would likely increase the size of the strata with higher predicted probability for future drug use.

CONCLUSIONS

Among 12th grade students who have little experience with illegal drug use and strongly disapprove of marijuana use, a legitimate opioid prescription predicts opioid misuse after high school. This increase in the future risk of opioid misuse should be considered when determining the risks and benefits of opioid prescriptions to youth.

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