Behavioral Health Risk Factors for Nonmedical Prescription Opioid Use in Adolescence

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abstract

BACKGROUND: Adolescent nonmedical prescription opioid use is associated with overdose and other adverse outcomes, but its risk factors are poorly understood.

METHODS: Data were drawn from a prospective cohort study of Los Angeles, California, high school students. At baseline (mean age = 14.6 years), students completed self-report screening measures of problem alcohol, cannabis, and drug use and 6 mental health problems (major depression, generalized anxiety, panic disorder, social phobia, obsessive-compulsive disorder, and hypomania or mania). Past 6-month nonmedical prescription opioid use (yes or no) was assessed across 7 semiannual follow-ups.

RESULTS: Among baseline never users of nonmedical prescription opioids ($N = 3204$), average past 6-month prevalence of new nonmedical prescription opioid use across the 42-month follow-up was 4.4% (range 3.5%–6.1%). In a multivariable model co-adjusting for 9 baseline behavioral problems and other factors, major depression, hypomania or mania, cannabis, alcohol, and other drug use problems were associated with increased odds of nonmedical prescription opioid use over follow-ups. Cumulative indices of behavioral health comorbidity showed successively greater odds of subsequent nonmedical prescription opioid use for students with 1 (odds ratio [OR]: 3.74; 95% confidence interval [CI]: 2.79–5.01), 2 (OR: 8.79; 95% CI: 5.95–12.99), or 3 (OR: 9.69; 95% CI: 5.63–16.68) vs 0 baseline substance use problems, and similar increases were associated with increasing number of mental health problems (1 [OR: 1.60; 95% CI: 1.03–2.88] to all 6 [OR: 3.98; 95% CI: 1.09–14.82] vs 0).

CONCLUSIONS: Behavioral health problems may be associated with increased risk of subsequent nonmedical prescription opioid use during mid to late adolescence, with successively greater risk for those with greater behavioral health comorbidity. In pediatric clinical practice or school-based prevention, behavioral health screeners may be useful for identifying youth at high risk for nonmedical prescription opioid use.

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Dr Cho conceptualized and designed the study, conducted the analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Kelly-Quon conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Barrington-Trimis, Axeen, and Kechter made contributions to the conception and design of the study and critically reviewed the manuscript for important intellectual content; Dr Leventhal conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

WHAT'S KNOWN ON THIS SUBJECT: Nonmedical use of prescription opioids is a public health crisis and often originates in adolescence. Whether other substance use or mental health problems are prospectively associated with subsequent nonmedical prescription opioid use in adolescence is unknown.

WHAT THIS STUDY ADDS: This study provides the first evidence indicating prospective associations of problematic substance use and mental health problems with subsequent nonmedical prescription opioid use in adolescence and evidence that a higher number of comorbid behavioral health problems successively increase nonmedical prescription opioid use.

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The incidence of hospitalizations for opioid overdoses among adolescents has significantly increased in North America and elsewhere over the past decade.[1] Opioid-related overdose is a leading cause of accidental death among adolescents in the United States.[2] Nonmedical prescription opioid use (use of opioid medication without following a prescriber's orders[1,3,4]) can increase a youth's risk of addiction, injury, and death, and was reported by 6.8% of high school seniors in the United States in 2017.[5] To prevent opioid-related morbidity and mortality in youth, it is essential to identify vulnerability factors that precede the onset of nonmedical prescription opioid use and that could be targeted in risk screening and intervention.

Behavioral health problems (ie, substance use or mental health problems) are often associated with nonmedical prescription opioid use in adults[6,7] and with risk-taking behaviors in adolescents.[8] Previous longitudinal studies of administrative claims data also highlight an association between preexisting mental health disorders and new onset of long-term prescription opioid use among adolescents.[9,10] The only existing data on the association of behavioral health problems and nonmedical prescription opioid use in youth are cross-sectional[8,11–14] and leave key evidence gaps. First, because the mechanisms of this association could be bidirectional (ie, opioid misuse may result from or lead to other behavioral health problems),[11,14] it is imperative that researchers on this topic apply prospective longitudinal designs that preclude reverse causality explanations. Second, whether self-reported behavioral health screening tools can identify risk of later nonmedical prescription opioid use is unknown. The ability to use self-report screeners to prognosticate risk would be useful for implementing opioid-related risk prevention in both clinical service settings and school or other population-based community settings. Finally, although a number of substance use and mental health problems are plausible risk factors for nonmedical prescription opioid use,[11–14] whether each of these problems independently increase risk or whether experiencing multiple comorbid behavioral health problems compounds risk is unknown.

In this prospective cohort study of youth never users of nonmedical prescription opioids at baseline in Los Angeles, California, we examined whether behavioral problems predicted subsequent nonmedical prescription opioid use over a 42-month follow-up spanning mid to late adolescence. In addition to examining the independent associations of each behavioral health problem with subsequent nonmedical prescription opioid use, we also tested the cumulative number of substance use or mental health problems as predictors to determine if comorbid behavioral health problems compounded risk of future nonmedical prescription opioid use.

METHODS

Participants and Procedures

Data were drawn from a longitudinal cohort study of behavioral health that enrolled students from 10 high schools in the Los Angeles, California, metropolitan area, described previously.[15] In brief, all ninth-grade students not enrolled in special education at the 10 participating schools in 2013 with active student assent and parental consent to participate were enrolled in the cohort (N = 3396 [82.8%]; see Fig 1). Eight semiannual assessments from baseline (fall of ninth grade, 2013) to the final 42-month (spring of 12th grade, 2017) follow-up were conducted through paper-and-pencil surveys administered on-site in classrooms. Students not in class during data collection completed surveys by telephone, Internet, or mail. The University of Southern California Health Sciences Campus Institutional Review Board approved the study.

Measures

Nonmedical Prescription Opioid Use

Informed by the well-validated items derived from the Youth Risk Behavior Surveillance[4] and Monitoring the Future[16,17] surveys, nonmedical prescription opioid was assessed. At each wave, the following question was administered: "Have you ever used prescription painkillers (eg, Vicodin, Oxycontin, Percocet, Codeine, Percodan, Lortab), including pills or medications without a doctor's order used to get 'high' for fun, in your life?" Response options included the following: "no," "yes, but not in the last 6 months," and "yes, in the last 6 months." At baseline, participants reporting ever (lifetime) use were removed from the sample. At each of the 7 semiannual follow-ups, nonmedical prescription opioid use in the preceding 6 months (versus no use or used before the last 6 months) was coded as a primary outcome variable of this study. Of note, although infrequently prescribed, Percodan was included in the list of prescription painkillers because it was US Food and Drug Administration approved at the time of this study and has been previously identified as an oxycodone product used nonmedically among adolescents in the United States.[18]

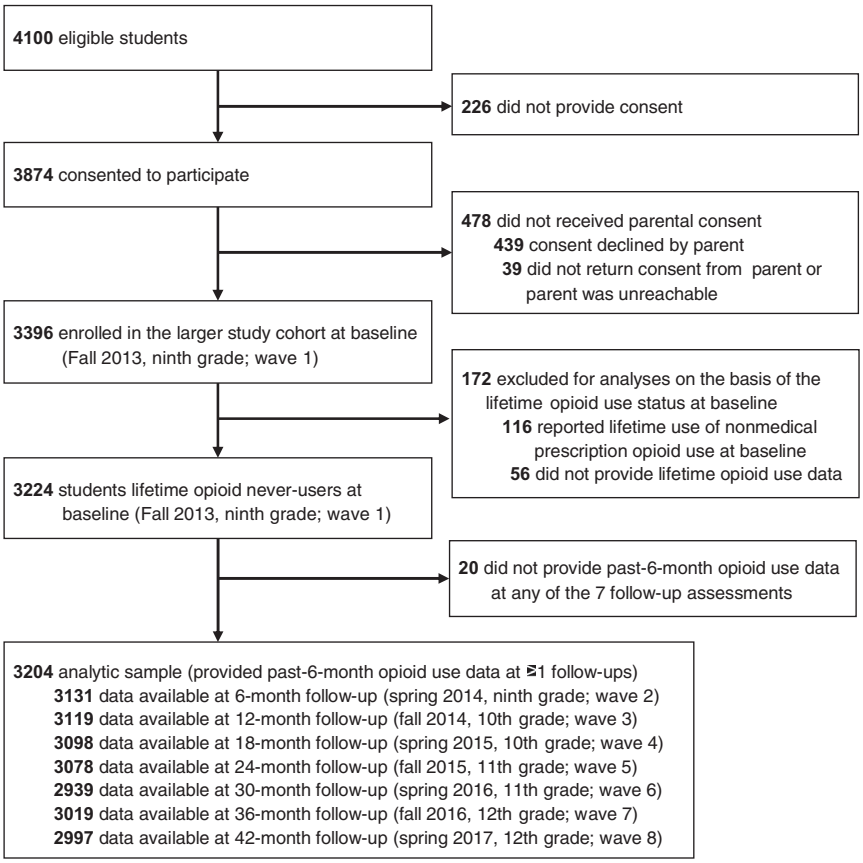

FIGURE 1

Study accrual flowchart. Note: among the analytic sample ($N = 3204$), 10.8% of students ($n = 347$) who did not complete the survey in earlier follow-up waves completed the survey in later follow-up waves.

Substance Use Problems

The 6-item Cannabis Abuse Screening Test (CAST), which rates the frequency of problems due to cannabis use in the past 12 months using 5-point scales (0 [nonuse or never] to 4 [very often]), was assessed, and a cutoff score (Cannabis Abuse Screening Test sum score ≥4) indicating a positive screen for problematic use was used.[19] The 23-item Rutgers Alcohol Problems Index (RAPI) instructs participants to report the frequency of alcohol-related problems (eg, got into fights, missed school and/or work) on a scale from 0 (never) to 4 (≥10 times) in the past 12 months ($\alpha = .91$). Rutgers Alcohol Problems Index scores ≥15 were classified to indicate a positive screen for high-problem drinking.[20] The Drug Abuse Screening Test (DAST)[21] is a 10-item survey querying the degree of problems to related to use or abuse of any licit and illicit substance other than alcohol (eg, blackouts, withdrawal symptoms). Responses (0 [nonuse or no problematic use] versus 1 [problematic use]) were summed ($\alpha = .82$) and dichotomized to none or low (score = 0–2) versus medium or high (score = 3–10) problem drug use.

Mental Health Problems

The Revised Children's Anxiety and Depression Scales (RCADS)[22] instructs respondents to rate the frequency to which they experienced symptoms of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) depressive and anxiety disorders on a 4-point scale (0 [never] to 3 [always]). Separate subscales are used for major depression (10 items; $\alpha = .94$), generalized anxiety disorder (6 items; $\alpha = .91$), social phobia (9 items; $\alpha = .93$), panic disorder (9 items; $\alpha = .93$), and obsessive-compulsive disorder (6 items; $\alpha = .86$) symptoms. The composite symptom frequency sum scores within each subscale are converted to age- and sex-normed T scores, with ≥70 indicating a positive screen result for scoring above the clinical threshold. The 15-item Mood Disorder Questionnaire[23] instructs respondents to indicate whether they experienced 13 different DSM-IV symptoms indicative of hypomania or mania in the past 12 months (yes or no) and whether any of the symptoms caused moderate or serious problems in their lives. Respondents

reporting ≥7 symptoms, ≥2 of which causing moderate or serious problems, were considered as screening positive for possible hypomania or mania.

Baseline Covariates

We measured several a priori baseline covariates shown to be associated with use of nonmedical prescription opioids or other substances in previous research.[8,15] These included the sociodemographic characteristics age, sex, race and/or ethnicity, and parental education level, which were assessed with investigator-defined forced-choice self-reported items (see response categories in Table 1). To address family liability to substance use, we measured youth-reported history of smoking, alcohol problems, or drug problems in siblings or parents (yes or no). Youth also reported whether their close friends used nonmedical prescription opioids in the past 30 days (yes or no). Delinquent behaviors were measured as the sum of frequency ratings for engaging in 11 behaviors in the past 6 months (eg, stealing; score range: 1 [never] to 6 [≥10 times]; α = .79).[24] Finally, as another externalizing problem covariate, attention-deficit/hyperactivity disorder (ADHD)[25] was considered. Although an ADHD symptom measure was lacking at baseline, a supplemental analysis was conducted to examine potential influences of ADHD symptoms on the primary results (Supplemental Table 9).

Statistical Analysis

Descriptive statistics of study variables are presented in Table 1. Given the potential for reciprocal pathways or selection effects in which youth who used nonmedical prescription opioids might be more liable to seek out use of other substances and have psychiatric symptoms,[11,26,27] primary analyses included baseline never users of nonmedical prescription opioids (N = 3204; Fig 1). Cohort characteristics among students included in (versus excluded from) the primary analytic sample are reported for comparison purposes (see Supplemental Table 4).

Logistic random-effect repeated-measures regression modeling was

TABLE 1 Descriptive Statistics of Study Sample

Variables	No. (%) Students or Mean (SD)[a]
Baseline covariates	
Female sex, *n* (%)	1707 (53.3)
Age, mean (SD), y	14.6 (0.4)
13 y, *n* (%)	115 (3.6)
14 y, *n* (%)	2713 (84.7)
15 y, *n* (%)	368 (11.5)
16 y, *n* (%)	8 (0.2)
Race and/or ethnicity, *n* (%)	
Hispanic	1510 (47.8)
Asian American	545 (17.3)
African American	153 (4.8)
Non-Hispanic white	519 (16.4)
Multiracial	214 (6.8)
Other[b]	216 (6.8)
Parent(s) without high school diploma, *n* (%)[c]	357 (12.8)
Family history of substance use, *n* (%)	2124 (69.4)
Friends' opioid use, *n* (%)	175 (5.6)
Delinquent behavior, mean (SD)[d]	15.5 (4.8)
Baseline behavioral health problems, positive screen results, *n* (%)	
Substance use problems	
Cannabis Abuse Screening Test[e]	238 (7.7)
Rutgers Alcohol Problems Index[f]	335 (10.8)
Drug Abuse Screening Test[g]	136 (4.4)
Mental health problems	
Major depression[h]	443 (14.5)
Generalized anxiety disorder[h]	434 (14.2)
Panic disorder[h]	334 (11.0)
Social phobia[h]	311 (10.2)
Obsessive-compulsive disorder[h]	280 (9.3)
Hypomania or mania[i]	223 (7.2)
Past-6-mo nonmedical prescription opioid use at follow-up, *n* (%)	
6-mo follow-up	190 (6.1)
12-mo follow-up	135 (4.4)
18-mo follow-up	137 (4.5)
24-mo follow-up	127 (4.2)
30-mo follow-up	126 (4.3)
36-mo follow-up	104 (3.5)
42-mo follow-up	112 (3.8)

N = 3204 baseline never users of prescription opioids for nonmedical purposes.

[a] The number of students with (nonmissing) data available for each variable and denominators for percentages are reported for categorical variables (range of available data n = 2781–3204).

[b] American Indian or Alaskan native, native Hawaiian or Pacific Islander, or "other" responses constituted an "other" category.

[c] In addition to 17 students who did not respond to the survey question, 406 who marked "don't know" are not included in the denominator.

[d] Score ranges from 11 to 66, with higher scores indicating greater frequency of engaging in 11 different delinquent behaviors. Each behavior is rated from 1 (never) to 6 (≥10 times) for 11 behaviors.

[e] Positive screen results are indicative of possible DSM-IV cannabis use disorder in the past 12 mo (scores ≥4).

[f] High-problem drinkers in the past 12 mo (scores ≥15).

[g] Medium or high levels of drug use problems in the past 12 mo (scores ≥3).

[h] Surpassed age- and sex-normed clinical cutoff on the RCADS.

[i] Positive screen results for hypomania or mania (scores ≥7 symptoms, ≥2 of which causing moderate or serious problems).

used to test the association of baseline behavioral health problems with likelihood of past 6-month opioid use outcomes across 7 follow-up assessments. We tested (1) univariable models that included a single behavioral health problem as the sole regressor, (2) multivariable models that included all 9 behavioral health problems as simultaneous regressors to adjust for their co-occurrence, and (3) final regression models that included each cumulative comorbidity index (ie, number of substance use problems [range = 0–3] and number of mental health problems [range = 0–6]) as a regressor. The corresponding regressor estimates indicated the averaged association of each exposure variable with the probability of past 6-month opioid use collapsed across the 7 follow-ups. Each model included time effects (range = 0 [6 months] to 6 [42 months]). Baseline predictor × time interaction terms were added in subsequent models to test whether the behavioral health risk factors were associated with different slopes indicative of the timing and persistence of use. Analyses were tested in Mplus 7 by using 2-level random effects. Time was nested within students, and school random effects were included to account for clustering by school.[28] Odds ratios (ORs) and 95% confidence intervals (CIs) were reported with statistical significance set at $P < .05$ (two tailed). Benjamini–Hochberg multiple testing corrections were applied to control the false discovery rate at .05.[29] Missing data were managed with full information maximum likelihood estimation.

RESULTS

Descriptive Results

Descriptive statistics of baseline covariates and behavioral health variables in the analytic sample of baseline never users of nonmedical prescription opioids ($N = 3204$) are reported in Table 1. The sample was balanced on sex and was socio-demographically diverse. The prevalence of positive behavioral health problem screen results in the overall analytic sample varied across the specific problems and ranged from 4.4% for nonalcohol drug problems to 14.5% for major depression. Among baseline never users of nonmedical prescription opioids, the cumulative incidence of any use of nonmedical prescription opioids across the 42-month follow-up was 17.9% (past-6-month use by wave = 3.5%−6.1%).

Associations of Baseline Behavioral Health Problems With Nonmedical Prescription Opioid Use at Follow-ups

Risk Associated With Each Behavioral Health Problem

Table 2 displays the estimated mean prevalence of past 6-month nonmedical prescription opioid use averaged over the 7 follow-ups, stratified by baseline behavioral health problem status, as well as results of repeated-measures random-effect logistic regression models. Univariable regression models testing a single behavioral health problem as the sole regressor with adjustment covariates showed that 8 of the 9 baseline behavioral health problems were positively associated with subsequent occurrence of nonmedical prescription opioid use, averaged across follow-ups; the sole exception was social phobia ($P = .15$). In the multivariable regression model, which included covariates and all 9 behavioral health problem variables as simultaneous regressors to adjust for their co-occurrence, 5 of 9 behavioral health problems were associated with greater odds of subsequent nonmedical prescription opioid use. In this model, adolescents were at greater odds of nonmedical prescription opioid use, averaged across follow-ups, if they screened positive for baseline (mean prevalence of opioid use over follow-ups, by positive versus negative baseline status) cannabis problems (16.3% vs 3.5%; adjusted OR: 2.93 [95% CI: 1.93–4.44]; $P < .001$), alcohol problems (10.3% vs 3.7%; OR: 1.59 [95% CI: 1.15–2.21]; $P = .005$), drug problems (19.3% vs 3.7%; OR: 1.96 [95% CI: 1.19–3.22]; $P = .008$), major depression (8.0% vs 3.8%; OR: 1.52 [95% CI: 1.08–2.13]; $P = .012$), and hypomania or mania (9.7% vs 3.9%; OR: 1.42 [95% CI: 1.05–2.26]; $P = .02$).

Risk Associated With Behavioral Health Comorbidity Indices

In Fig 2, we report the estimated mean prevalence of past 6-month nonmedical prescription opioid use over the 42-month follow-up, stratified by each baseline behavioral health problem comorbidity index score. As presented in Table 3, after we adjusted for covariates, each additional positive screen result for the cumulative number of substance use problems at baseline was associated with incrementally greater odds of nonmedical prescription opioid use over follow-ups. For example, adolescents who screened positive for 1 vs 0 substance use problems were at 3.74 greater odds of follow-up nonmedical prescription opioid use (mean opioid use prevalence 8.2% vs 3.1%; OR: 3.74 [95% CI: 2.79–5.01]; $P < .001$), whereas those who screened positive for 3 vs 0 substance use problems were at 9.69 greater odds (23.3% vs 3.1%; OR: 9.69 [95% CI: 5.63–16.68]; $P < .001$). This model also found successive increases in odds of nonmedical opioid use over follow-ups associated with a greater baseline cumulative number of mental health problems (eg, 1 vs 0

TABLE 2 Associations of Baseline Behavioral Health Problems With Past 6-Month Nonmedical Prescription Opioid Use at Follow-ups

Regressors: Behavioral Health Problem Positive Screen Results	Mean Estimated Prevalence of Past 6-Month Opioid Use Across Follow-ups, by Baseline Regressor Status		Association With Past 6-Month Nonmedical Prescription Opioid Use Across Follow-ups			
			Univariable Model[a]		Multivariable Model[b,f,g]	
	Negative % (95% CI)	Positive % (95% CI)	Adjusted OR (95% CI)[c]	*P*	Adjusted OR (95% CI)[c]	*P*
Substance use problems[d]						
Cannabis Abuse Screening Test	3.5 (3.2–3.8)	16.3 (14.4–18.2)	4.13 (2.87–5.93)	<.001[e]	2.93 (1.93–4.44)	<.001[e]
Rutgers Alcohol Problems Index	3.7 (3.4–4.0)	10.3 (9.0–11.6)	2.40 (1.76–3.29)	<.001[e]	1.59 (1.15–2.21)	.005[e]
Drug Abuse Screening Test	3.7 (3.5–4.0)	19.3 (16.6–21.9)	4.42 (2.90–6.73)	<.001[e]	1.96 (1.19–3.22)	.008[e]
Mental health problems[d]						
Major depression	3.8 (3.5–4.1)	8.0 (7.0–9.0)	1.96 (1.47–2.63)	<.001[e]	1.52 (1.08–2.13)	.01[e]
Generalized anxiety disorder	4.0 (3.8–4.3)	6.6 (5.7–7.5)	1.39 (1.01–1.91)	.04[e]	1.07 (0.75–1.53)	.62
Panic disorder	4.0 (3.7–4.3)	7.9 (6.8–9.0)	1.84 (1.32–2.57)	<.001[e]	1.25 (0.86–1.86)	.22
Social phobia	4.2 (4.0–4.5)	5.4 (4.4–6.4)	1.32 (0.91–1.92)	.15	1.00 (0.66–1.52)	.99
Obsessive-compulsive disorder	4.0 (3.7–4.3)	7.3 (6.1–8.5)	1.71 (1.19–2.45)	.003[e]	1.24 (0.82–1.88)	.24
Hypomania or mania	3.9 (3.6–4.2)	9.7 (8.1–11.2)	1.95 (1.34–2.84)	.001[e]	1.42 (1.05–2.26)	.02[e]

$N = 3204$ baseline never users of prescription opioids for nonmedical purposes.

[a] Univariable models included a single baseline behavioral health problem, time, and baseline covariates (ie, sex, age, race and/or ethnicity, parental education level, family substance use history, friends' opioid use, and delinquent behaviors) as simultaneous regressors.

[b] The multivariable model included all baseline behavioral health problems, time, and baseline covariates (ie, sex, age, race and/or ethnicity, parental education level, family substance use history, friends' opioid use, and delinquent behaviors) as simultaneous regressors.

[c] Estimate of the association of each regressor with past 6-mo nonmedical prescription opioid use (versus no use), averaged across follow-ups, in repeated-measures binary logistic regression models that included school random effects.

[d] See Table 1 and Methods section for operational definition of positive screen results for each variable.

[e] Statistically significant after Benjamini–Hochberg corrections for multiple testing to control false discovery rate at .05 (based on a 2-tailed corrected *P* value).

[f] Time-continuous variable (scored as follows: 6 mo, 0; 12 mo, 1; 18 mo, 2; 24 mo, 3; 30 mo, 4; 36 mo, 5; and 42 mo, 6): adjusted OR 0.92 (95% CI: 0.88–0.96; $P < .001$).

[g] Interaction terms of baseline predictors × time were tested in subsequent models and were not significant in all models ($P \geq .08$).

substance use problems [5.1% vs 3.1%; OR: 1.59 (95% CI: 1.03–2.74); $P = .04$] and 5 or 6 vs 0 mental health problems [10.1% vs 3.1%; OR: 4.07 (95% CI: 2.24–7.44); $P < .001$]).

Supplemental Analyses

Sensitivity analyses showed that the results remained consistent when considering multicollinearity among anxiety disorder variables, excluding youth with a positive screen for ADHD, and using different approaches to handling missing data and clustering effects (see Supplemental Tables 6 through 12 and the Results section in the Supplemental Information).

DISCUSSION

With this study, we provide new evidence that substance use and mental health problems that commonly occur in adolescence are prospectively associated with subsequent occurrence of nonmedical prescription opioid use over a 42-month follow-up period. Positive screens for mood problems (ie, depression, hypomania or mania) and hazardous alcohol, cannabis, and other nonopioid drug use were each incrementally predictive of risk of nonmedical prescription opioid use, and the presence of multiple comorbid behavioral health problems successively increased this risk. The application of a rigorous 8 time-point repeated-measures longitudinal design permitted regressor-by-time interaction tests, which provided no evidence that the elevated risk of nonmedical prescription opioid use associated with baseline behavioral health problems degraded throughout adolescence. This advances what was previously a cross-sectional evidence base demonstrating association between nonmedical prescription opioid use in several ways.[8,11–14]

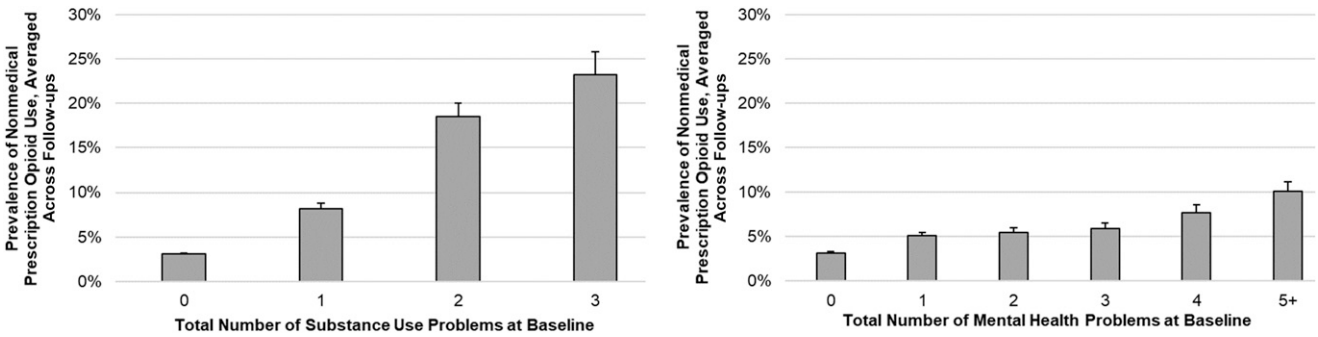

FIGURE 2
Mean prevalence (percentage + SE) of past 6-month nonmedical prescription opioid use across follow-ups, by baseline cumulative substance use and mental health problem indices.

By eliminating baseline nonmedical prescription opioid ever users and using a prospective design, the results suggest that the previously documented cross-sectional association[8,11–14] is not solely explained by a pathway leading from nonmedical prescription opioid use to other behavioral health problems. Because this study established such temporal precedence and used self-report tools to assess behavioral health, the results indicate that behavioral health screening measures could be used to prospectively identify youth at risk for later initiation of nonmedical prescription opioid use, pending replication and tests of generalization of findings. Although the current study did not assess the source of opioid pills from students, medical use of prescription opioids often precedes nonmedical use.[26] Thus, implementing behavioral health problem screens in a variety of pediatric health services settings could be useful for informing cases in which considerable caution is required when considering opioid prescriptions for adolescent patients. Behavioral health screening could also be useful in school-based prevention, including identifying students at risk who may benefit from opioid misuse education programs.

Because this is the first study on this topic and uses an observational design, strong causal inferences about the association cannot yet be

TABLE 3 Associations of Baseline Cumulative Number of Substance Use or Mental Health Problem Indices With Past 6-Month Nonmedical Prescription Opioid Use at Follow-ups

	Outcome: Nonmedical Prescription Opioid Use in the Past 6 Months Across Follow-ups[a,f,g]	
Baseline Regressors	Adjust OR (95% CI)[b]	*P*
Cumulative No. substance use problems[c]		
0 (n = 2645, 83.8%)	Reference	—
1 (n = 360, 11.4%)	3.74 (2.79–5.01)	<.001[d]
2 (n = 104, 3.3%)	8.79 (5.95–12.99)	<.001[d]
3 (n = 47, 1.5%)	9.69 (5.63–16.68)	<.001[d]
Cumulative No. mental health problems[e]		
0 (n = 1782, 56.8%)	Reference	—
1 (n = 583, 18.6%)	1.59 (1.03–2.74)	.04[d]
2 (n = 322, 10.3%)	2.05 (1.51–2.80)	.003[d]
3 (n = 196, 6.2%)	3.26 (1.86–5.13)	.001[d]
4 (n = 139, 4.4%)	3.63 (1.78–7.38)	<.001[d]
5 or 6 (n = 115, 3.7%)	4.07 (2.24–7.44)	<.001[d]

Includes 3204 participating students who did not ever use nonmedical prescription opioids at baseline and who provided past 6-mo opioid use data at ≥1 follow-up. —, not applicable.
[a] The model included each cumulative index, time, and baseline covariates (ie, sex, age, race and/or ethnicity, parental education level, family substance use history, friends' opioid use, and delinquent behaviors) as simultaneous regressors.
[b] The estimate of the association of each regressor with past 6-mo nonmedical prescription opioid use (versus no use), averaged across follow-ups, in repeated-measures binary logistic regression models that included school random effects.
[c] Sum of positive screen results at the clinical level for the Cannabis Abuse Screening Test, Rutgers Alcohol Problems Index, and Drug Abuse Screening Test (range 0–3).
[d] *P* values were statistically significant after Benjamini-Hochberg corrections for multiple testing to control false discovery rate at .05 (based on a 2-tailed corrected *P* value).
[e] Sum of positive screen results at the clinical level for major depression, generalized anxiety disorder, panic disorder, social phobia, obsessive-compulsive disorder, and hypomania or mania (range 0–6). Because of the small sample size of students with all 6 mental health problems (n = 26, 0.8%), the categories for 5 and 6 problems were merged.
[f] Time-continuous variable (scored as follows: 6 mo, 0; 12 mo, 1; 18 mo, 2; 24 mo, 3; 30 mo, 4; 36 mo, 5; and 42 mo, 6): adjusted OR 0.92 (95% CI: 0.88–0.96; $P < .001$).
[g] Interaction terms of baseline predictors × time were tested in subsequent models and were not significant in all models ($P \geq .24$).

made. If future research were to establish a causal path from behavioral health problems to nonmedical prescription opioid use, the applications of this research would go beyond risk identification and point toward potential targets for such interventions (ie, mood problems and nonmedical substance use). Of note, early problematic substance use, including cannabis and alcohol, exhibited even larger odds of later opioid misuse in the multivariable model. To prevent nonmedical prescription opioid use in youth, it is critical that prevention efforts also focus on identifying problematic substance use that extends beyond experimentation in adolescents. By addressing mood and problematic substance use early in adolescence, the adverse sequelae associated with opioid misuse early in life, including addiction, transition to heroin use,[30,31] and other health and social consequences,[6] could perhaps be prevented.

This study provides a new comprehensive picture that the positive screen for various mood and substance use problems may confer risk for nonmedical prescription opioid use. Although 4 of 5 anxiety-related conditions were associated with later nonmedical prescription opioid use without adjustment for co-occurrence with other behavioral health problems, none of the anxiety disorders were associated with opioid use in a multivariable model, adjusting for multiple behavioral health comorbidities. By contrast, positive screen results for scoring above the clinical threshold of baseline major depression and hypomania or mania were associated with later nonmedical prescription opioid use over and above other behavioral health problems, which concords with and extends a cross-sectional study finding associations between depressive symptoms and opioid use among college students.[7] To our knowledge, this is the first longitudinal report linking positive screens for hypomania or mania with later nonmedical prescription opioid use in any population.

There are several reasons why mood, but not anxiety-related disorders, may confer increased risk of nonmedical opioid use. Harm avoidance and other similar personality traits (which are protective against youth substance use[32,33]) are more pronounced in anxiety than in mood disorders. Additionally, certain symptoms present in mood but not anxiety disorders have been implicated in risk of adolescent substance use onset.[33] Some evidence suggests that anhedonia (ie, a cardinal symptom of depression reflecting inability to experience pleasure) is key to youth substance use uptake because youth with anhedonia are inclined to seek out drugs to experience pleasure that they otherwise cannot obtain from healthier leisure activities enjoyable to most youth.[34] Impulsive pleasure-seeking behavior is common in hypomania and mania,[35] and using prescription opioids to get high could be an expression of this tendency.

The finding in this study that hazardous use of nonopioid substances was a consistent risk factor for nonmedical prescription opioid use aligns with well-established knowledge about cross-drug use transition risk in youth[36] and extends these results to opioid misuse. It is possible that these results reflect that some youth have a tendency toward externalizing behaviors or socializing with deviant peers,[36] and this study also found significant associations of peer opioid use and delinquent behavior with subsequent nonmedical prescription opioid use (Supplemental Table 5). However, our primary analysis adjusting for these externalizing behaviors and a sensitivity analysis excluding youth with possible ADHD also revealed a relation of nonopioid substance use problems and later nonmedical prescription opioid use (Supplemental Table 9). It is possible that youth engaging in hazardous use of nonopioid substances may enjoy the experience of substance-induced intoxication and may be more inclined to seek out other drugs also capable of providing a euphorigenic high, including opioids.

Frequently, clinicians caring for youth with multiple behavioral health problems desire the ability to better understand additive risks associated with comorbidity. These data reveal that incremental increases in the number of behavioral health comorbidities were associated with an increasing likelihood of later nonmedical prescription opioid use, particularly for youth with multiple substance use problems. The graded relationship remained significant for both cumulative substance use and mental health problems. The added risk of each problem underscores the potential utility for comprehensive assessment of a variety of behavioral health problems to identify youth at greatest risk for later opioid misuse.

This study is limited by the self-reported nature of survey data in the adolescent population. Because these scales were screening tools, whether the results would generalize to mental disorders diagnosed by a clinician is unclear and warrants future research. Although these scales have been used in similar populations, the use in other studies does not mean the scales have been validated for use in

our study population.[37,38] Future validation studies of these scales would be useful in a general population setting among adolescents with characteristics that more closely match the composition of this study's sample. Also, the current study made changes to the Monitoring the Future and Youth Risk Behavior Surveillance survey questions that could affect whether respondents reported nonmedical prescription opioid use. Although the examples of medications in the question are all prescription opioids, respondents were asked about painkiller use, which was not pretested to confirm that it is synonymous with prescription opioids. Adolescents in the current study were also asked specifically about nonmedical opioid use with the intent to get high, making our study's results possibly more sensitive and specific to teenagers with pleasure-seeking behavior tied to opioid use rather than nonmedical prescription opioid use that is not pleasure seeking (ie, taking a higher dose of prescription opioids than was prescribed to treat pain or using another person's prescription opioids to treat pain). Therefore, the potential generalizability of the findings may be limited to youth with pleasure-seeking motivations. In addition, we did not assess pain conditions or medical prescription opioid use. The extent to which pain and prescriptions are implicated in the pathway from behavioral health problems to nonmedical opioid use should be addressed in future work because previous studies have revealed that youth with mental health problems are more likely to receive chronic opioid prescriptions from their clinician,[9,36] and chronic prescriptions are associated with greater odds of nonmedical opioid use, opioid use disorder, and overdose.[39] Notably, behavioral health conditions, including sleep disorders, and receipt of psychotherapy are also associated with long-term opioid prescriptions in youth[9] and may prove to be useful targets for future interventions geared toward minimizing risk of future prescription opioid misuse in adolescents. Although potential confounding effects of some externalizing problems were considered in this study, further longitudinal studies examining the presence of externalizing disorders and subsequent occurrence of nonmedical prescription opioid use are needed. This is especially relevant because nonmedical opioid use as a pleasure-seeking behavior may be further exacerbated in youth with externalizing problems. Like any observational longitudinal study, there is a potential risk of bias when considering participant dropout, making our estimates more conservative because dropouts likely have a higher risk of nonmedical prescription opioid use. A series of supplemental analyses were conducted to determine if the missing data procedure to handle nonresponse or attrition influenced the findings (see the Results section in the Supplemental Information). Finally, this study was conducted in a large city. The results may vary in rural or other locations where nonmedical prescription opioid use, overdose, and heroin use are common.

CONCLUSIONS

On the basis of the results of this prospective cohort study of youth, behavioral health problems may be associated with increased risk of subsequent nonmedical prescription opioid use during mid to late adolescence, with successively greater risk for those with greater behavioral health comorbidity. In pediatric clinical practice or school-based prevention, behavioral health screeners may be useful for identifying youth at high risk for nonmedical prescription opioid use. In future research, investigators should examine whether these associations are causal.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
CI: confidence interval
DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
OR: odds ratio
RCADS: Revised Children's Anxiety and Depression Scales

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