Toward a Comprehensive Developmental Model of Prescription Opioid Use Disorder

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ABSTRACT

Objective: To develop a comprehensive etiologic model of *DSM-5* prescription opioid use disorder (POUD) based on Kendler and colleagues' development model for major depressive disorder.

Methods: Data were drawn from the National Epidemiologic Survey on Alcohol and Related Conditions-III (2012–2013). Risk factors were divided into 4 developmental tiers (childhood/early adolescence, late adolescence, adulthood, past year). Hierarchical logistic regression models were used to examine the independent contribution of each risk factor. Separate models were built to predict 12-month nonmedical use of prescription opioids and risk of POUD among those with 12-month nonmedical use.

Results: After adjustment for other risk factors, the odds of past 12-month nonmedical use of prescription opioids were increased by history of trauma, social deviance, and use of drugs other than opioids in adulthood and by past-year pain, alcohol use disorder (AUD), tobacco use disorder, any Axis I disorder other than SUD, and number of stressful events. History of POUD in adulthood and pain, AUD, tobacco use disorder, and any Axis I disorder other than substance use disorders (SUD) in the past year increased the odds of 12-month POUD. History of SUD other than POUD in adulthood was associated with lower odds of POUD. For both outcomes, the effect of earlier development tiers was mediated by more proximal ones.

Conclusions: A modification of Kendler and colleagues' model for major depressive disorder provides a useful foundation for a comprehensive developmental model of nonmedical opioid use and opioid use disorder.

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Despite the efforts devoted to addressing the US opioid epidemic, the prevalence of prescription opioid use disorder (POUD) and opioid-related overdose deaths continues to increase.[1,2] At present, only a minority of individuals seek treatment for POUD, and there are no evidence-based preventive interventions for it.[1] A better understanding of the etiology of POUD may contribute to development of more effective prevention and treatment programs and help guide research and service priorities.[3]

Prior research[1,2,4] has identified several risk factors for POUD, including but not limited to family history of substance use disorders (SUD), antisocial behavior, and other SUD and psychiatric disorders. However, risk factors seldom act in isolation. A natural next step is to develop a conceptual model that integrates risk factors[5,6] and evaluates their joint and independent effects in the risk of POUD.

The goal of this study was to build on prior work to adapt and test a developmental model of POUD based on Kendler and colleagues' prior work. Although initially conceptualized to explain the etiology of major depressive disorder,[7] the model has been previously adapted to integrate a broad range of risk factors for addictive disorders.[8,9] On the basis of these prior adaptations of Kendler and colleagues' model, we hypothesized that (1) the etiology of POUD would be multifactorial and (2) the effect of earlier risk factors, such as childhood sexual abuse, would be partially mediated through later risk factors, such as childhood or adolescent onset of psychiatric comorbidities.

METHODS

Sample

The National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III) is a nationally representative in-person interview study of 36,309 adults aged 18 years and older residing in households and selected group quarters. Data collection occurred in 2012–2013. As detailed elsewhere,[10] probability sampling was used to select respondents. Hispanic, black, and Asian individuals were oversampled. The screener- and person-level response rates were 72.0% and 84.0%, respectively, yielding a total response rate of 60.1% (N = 36,309), comparable to most current US national surveys.[11,12] Data were adjusted for oversampling and nonresponse and then weighted to represent the US civilian population based on the 2012 American Community Survey.[13,14] The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Protocols were approved by National Institutes of Health and Westat Institutional Review Boards.

Measures

The NESARC used the Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5).[14] Psychiatric disorders were assessed as defined by *DSM-5*. Participants were assessed for alcohol use disorder, any drug use disorder, and tobacco use disorder; major depressive disorder, persistent depressive disorder, and bipolar disorder; panic disorder,

Clinical Points

- The etiology of prescription opioid use disorder (POUD) is complex, but there are no published models that integrate several risk factors for opioid use disorder.
- Developmental models of POUD provide a useful framework to integrate risk factors for opioid use disorder.
- A developmental approach to POUD suggests that addressing risk factors that occur earlier in life, such as childhood maltreatment, can help prevent opioid use disorder, whereas addressing risk factors that occur later in life, such as co-occurring psychiatric disorders, might improve treatment outcomes.

agoraphobia, social anxiety disorder, specific phobia, and generalized anxiety disorder; posttraumatic stress disorder; and schizotypal, borderline, and antisocial personality disorders. Test-retest reliability of these binary AUDADIS-5 diagnoses ranged from fair to good,[14] as did validity when compared to semistructured clinical assessments.[15,16]

Developmental Tiers

To be consistent with Kendler and colleagues' original model and its adaptations for other addictive disorders while minimizing overlap between tiers, we partitioned potential risk factors for past-year POUD into 4 developmental tiers: childhood/early adolescence (prior to 18 years of age), late adolescence (18 up to [but not including] 21 years of age), adulthood (21 years of age to prior to past year), and past year (12 months preceding the interview). All non-dichotomous predictors were standardized to facilitate interpretation.

The childhood/early adolescence tier included family history of SUD (lifetime history of alcohol use disorders [AUD] or drug use disorder of the biological parents or siblings), any sexual abuse before age 18, vulnerable family environment before age 18 (assessed using the childhood emotional neglect scale of the Childhood Trauma Questionnaire[17]), parental loss (parent's divorce or death of at least 1 parent before the participant was 18 years old), impulsivity (dichotomous, scored 1 if the respondents considered that they had often done things impulsively), low self-esteem (dichotomous, scored 1 if respondents stated they had often been very critical of themselves), early onset of anxiety disorders (with childhood onset before age 18),[6,18] and social deviance (assessed as the number of conduct disorder or antisocial personality disorder [ASPD] behaviors before age 15; range, 0–33).

The late adolescence tier included educational attainment (in years), number of Axis I disorders with onset before age 21, and number of personality disorders.

The adulthood tier included lifetime history of traumatic events, lifetime history of divorce, history of AUD prior to past year (ie, prior to the year preceding the interview), tobacco use disorder, POUD prior to past year, other drug use disorders prior to past year, and social deviance (measured as the number of ASPD behaviors in which the respondent engaged after age 15).

The past-year tier included lack of social support (assessed with the Interpersonal Social Support Evaluation List [ISEL-12],[19] a 12-item Likert scale); past-year AUD, tobacco use disorder, comorbidity with psychiatric disorders other than SUD, religious service attendance, and marital problems (whether the respondent got separated, divorced or broke off a steady relationship in the last 12 months); and number of stressful life events in the past year (range, 0–14). Pain was assessed using the pain item of the 12-item Medical Outcomes Study Short Form version 2,[20,21,22] which queries on a 5-point Likert scale about how much pain interfered with the participant's normal work. As in previous research,[23,24] the pain measure was collapsed into 2 levels depending on whether pain was associated with no or little interference ("no pain") or with moderate to extreme interference ("pain").

Statistical Analyses

We conducted our analysis in 2 stages because although not all individuals with nonmedical opioid use develop POUD, they may still benefit from targeted preventive and treatment interventions. In the first stage, we identified correlates of past-12-month nonmedical use of prescription opioids. To identify predictors of nonmedical use of prescription opioids, we compared data from respondents with nonmedical use versus those without nonmedical use. We used odds ratios (ORs) to examine bivariate relationships between each predictor and past-12-month nonmedical use of prescription opioids (Table 1; Model 1). We then examined the effect of each group of variables by constructing one logistic regression model for each tier and included age and ethnicity as covariates in each model (Table 2; Model 2). In the last step, we constructed one logistic regression model with all of the variables included in the bivariate analyses (Table 2; Model 3).

The second stage involved identification of predictors of past-12-month POUD among the subsample with past-year use of prescription opioids. We followed procedures similar to those used to construct our model for nonmedical use of prescription opioids and built successive models starting from bivariate associations, followed by within-tier logistic regressions (Table 3; Model 4), and finally logistic regressions with all of the predictors (Table 4; Models 5 and 6). Predictive accuracy of 12-month nonmedical use of prescription opioids and 12-month POUD across the different models was assessed with the C-index.[25] The C-index is a measure of concordance between the predicted and the observed outcome equal to the area under the receiver operating characteristic curve such that values of 0.50 represent prediction no better than chance and values of 1.0 represent perfect prediction.

To be conservative due to the number of candidate variables in the model, we set our significance level at $P \leq .01$ and considered ORs significant if their 99% CIs did not cross 1. Furthermore, because less than 4% of the sample had any missing data, we used listwise deletion of the cases with missing data. All analyses, including ORs and CIs, were estimated using SUDAAN[26] to adjust for the design effects of NESARC-III.

Table 1. Bivariate Associations of Risk Factors and Prevalence of Past-Year Nonmedical Opioid Use in NESARC-III (N = 36,309)[a]

	No Past-Year Nonmedical Use of Opioids (n = 34,730)		Past-Year Nonmedical Use of Opioids (n = 1,579)		Model 1	
Variable	Value	99% CI	Value	99% CI	OR	99% CI
Age, %, y						
18–29	21.32	20.38–22.29	29.97	26.05–34.21	1.00	
30–39	16.65	15.92–17.40	18.42	15.27–22.05	0.79	0.59–1.05
40–49	18.06	17.29–18.86	18.48	15.64–21.70	**0.73**	**0.57–0.93**
≥ 50	43.97	42.73–45.22	33.13	29.62–36.85	**0.54**	**0.43–0.66**
Sex, %						
Female	52.05	51.25–52.85	48.68	45.02–52.37	0.87	0.75–1.02
Male	47.95	47.15–48.75	51.32	47.63–54.98	1.00	
Race/ethnicity, %						
White, non-Hispanic	66.08	64.00–68.09	68.82	64.39–72.92	1.00	
Black, non-Hispanic	11.66	10.04–13.49	14.87	11.66–18.78	1.22	0.94–1.60
Native American	1.53	1.25–1.87	2.23	1.21–4.08	1.40	0.77–2.57
Asian	5.88	4.74–7.28	2.16	1.21–3.83	**0.35**	**0.21–0.60**
Hispanic	14.86	13.14–16.75	11.92	9.56–14.78	**0.77**	**0.60–0.99**
Childhood/early adolescence, %						
Family history of SUD	46.98	45.87–48.09	65.63	61.54–69.50	**2.15**	**1.80–2.58**
Sexual abuse	10.87	10.23–11.55	20.11	17.39–23.14	**2.06**	**1.74–2.45**
Vulnerable family environment[b]	0.62	0.61–0.63	0.80	0.74–0.86	**1.19**	**1.11–1.28**
Parental loss	25.92	25.05–26.81	37.67	33.94–41.56	**1.73**	**1.46–2.04**
Impulsivity	9.87	9.20–10.59	28.28	24.26–32.67	**3.60**	**2.90–4.47**
Low self-esteem	29.48	28.02–30.98	43.31	38.75–47.99	**1.83**	**1.51–2.21**
Childhood-onset anxiety	8.16	7.65–8.70	15.29	12.87–18.07	**2.03**	**1.65–2.50**
Social deviance[b]	0.02	0.019–0.021	0.06	0.05–0.07	**1.41**	**1.35–1.46**
Late adolescence						
Education, mean, y[b]	14.14	14.09–14.19	13.63	13.44–13.82	**0.86**	**0.79–0.94**
No. of Axis I disorders excluding SUD, mean[b]	0.05	0.054–0.046	0.11	0.08–0.14	**1.13**	**1.08–1.19**
No. of personality disorders, mean[b]	0.16	0.15–0.17	0.52	0.46–0.58	**1.49**	**1.42–1.57**
Adulthood, %						
History of trauma	48.86	47.25–50.48	68.31	63.89–72.43	**2.26**	**1.87–2.72**
Ever divorced	26.16	25.04–27.31	30.96	27.28–34.91	**1.27**	**1.05–1.52**
History of SUD						
Alcohol	22.15	21.01–23.34	45.73	40.58–50.98	**2.96**	**2.43–3.60**
Drug other than opioids	6.80	6.20–7.45	25.09	21.40–29.18	**4.59**	**3.72–5.67**
Tobacco	19.59	18.26–21.00	41.44	37.37–45.63	**2.90**	**2.45–3.44**
Social deviance[b]	0.06	0.059–0.061	0.16	0.15–0.17	**1.70**	**1.61–1.78**
Past year, %						
Pain	10.07	9.30–10.89	26.14	20.83–32.25	**3.16**	**2.42–4.13**
Lack of social support[b]	17.82	17.74–17.90	19.02	18.62–19.42	**1.21**	**1.13–1.29**
Alcohol use disorders	12.96	12.20–13.76	35.09	30.42–40.06	**3.63**	**2.97–4.43**
Tobacco use disorder	18.90	17.90–19.94	46.34	41.71–51.04	**3.71**	**3.11–4.41**
Any Axis I disorder (excluding SUD)	22.06	21.12–23.02	43.64	39.67–47.70	**2.74**	**2.32–3.23**
Religious service attendance	50.06	48.62–51.51	36.82	32.70–41.14	**0.58**	**0.49–0.69**
Marital problems	6.28	5.83–6.77	13.48	11.10–16.28	**2.32**	**1.83–2.95**
Stressful life events[b]	0.10	0.098–0.102	0.18	0.17–0.19	**1.62**	**1.53–1.71**

[a]Significant variables ($P < .05$) are shown in boldface.
[b]Standardized predictor in logistic regression.
Abbreviations: NESARC-III = National Epidemiologic Survey on Alcohol and Related Conditions-III, OR = odds ratio, SUD = substance use disorders.

RESULTS

12-Month Non-Medical Use of Prescription Opioids

Among NESARC-III participants, 3.5% met criteria for past-year nonmedical opioid use and 0.9% met criteria for POUD. Table 1 presents bivariate analyses of variables included in our theoretical model in the sample with and without lifetime history of nonmedical use of prescription opioids (Model 1). There was a strong gradient of decreasing odds of nonmedical use of prescription opioids as age increased. Most variables were significantly associated with increased odds of nonmedical use of prescription opioids. However, sex and being black or Native American were not significantly associated with increased odds of nonmedical use of prescription opioids. Furthermore, being Asian or Hispanic, having higher educational attainment, and religious service attendance in the last year significantly decreased the odds of past-year nonmedical use.

In Model 2 (Table 2)—which examined the effect of each variable adjusted for age, race/ethnicity, sex, and all other variables within the same tier—family history of SUD, sexual abuse, parental loss, impulsivity, and social deviance remained significant in the childhood/early adolescent tier; number of personality disorders remained significant in the late adolescence tier; all variables except having ever been divorced remained significant in the adulthood tier; and all

Table 2. Multivariable Associations of Risk Factors and Past-Year Nonmedical Use in NESARC-III (N = 36,309)[a]

	Model 2[b]		Model 3[c]	
Variable	AOR	99% CI	AOR	99% CI
Childhood/early adolescence[d]				
Family history of SUD	**1.56**	**1.29–1.88**	1.18	0.97–1.44
Sexual abuse	**1.39**	**1.13–1.70**	1.05	0.84–1.31
Vulnerable family environment	1.02	0.94–1.12	1.00	0.91–1.10
Parental loss	**1.32**	**1.10–1.58**	1.17	0.96–1.41
Impulsivity	**1.96**	**1.52–2.52**	1.11	0.84–1.46
Low self-esteem	1.07	0.87–1.32	0.81	0.65–1.00
Childhood-onset anxiety	1.16	0.90–1.49	0.85	0.64–1.12
Social deviance[e]	**1.23**	**1.18–1.28**	1.01	0.94–1.08
Late adolescence[f]				
Education years[e]	0.89	0.80–1.00	1.05	0.94–1.19
No. of Axis I disorders excluding SUD (mean)[e]	1.04	0.99–1.10	0.99	0.93–1.05
No. of personality disorders (mean)	**1.44**	**1.36–1.52**	0.99	0.91–1.19
Adulthood[g]				
History of trauma	**1.44**	**1.18–1.76**	**1.26**	**1.02–1.56**
Ever divorced	1.23	0.98–1.54	1.10	0.87–1.39
History of SUD				
Alcohol	**1.39**	**1.09–1.76**	1.13	0.88–1.44
Drugs other than opioids	**1.55**	**1.19–2.02**	**1.48**	**1.14–1.93**
Tobacco	**1.43**	**1.16–1.77**	1.01	0.79–1.29
Social deviance[e]	**1.42**	**1.33–1.51**	**1.24**	**1.12–1.37**
Past year[h]				
Pain	**2.69**	**1.97–3.67**	**2.58**	**1.88–3.55**
Lack of social support[e]	1.03	0.95–1.10	1.01	0.94–1.09
Alcohol use disorders	**2.16**	**1.73–2.70**	**1.85**	**1.47–2.34**
Tobacco use disorder	**1.98**	**1.65–2.38**	**1.58**	**1.24–2.01**
Any Axis I disorder (other than SUD)	**1.52**	**1.25–1.84**	**1.31**	**1.05–1.62**
Religious service attendance	**0.81**	**0.68–0.96**	0.87	0.72–1.04
Marital problems	0.89	0.67–1.20	0.91	0.67–1.23
Stressful life events[e]	**1.31**	**1.21–1.40**	**1.18**	**1.09–1.29**

[a]Significant variables ($P < .05$) are shown in boldface.
[b]Model 2 adjusted for age, race/ethnicity, sex, and other variables within the same tier.
[c]Model 3 adjusted for all variables in the bivariate analysis.
[d]Childhood/early adolescence C-index = 0.688.
[e]Standardized.
[f]Late adolescence C-index = 0.623.
[g]Adulthood C-index = 0.728.
[h]Past-year C-index: Model 2 = 0.744, Model 3 = 0.769.
Abbreviations: AOR = adjusted odds ratio, NESARC-III = National Epidemiologic Survey on Alcohol and Related Conditions-III, SUD = substance use disorders.

variables except lack of social support and marital problems were significant in the past-year tier.

In Model 3 (Table 2), which included all of the predictors in the bivariate analyses, the odds of past-12-month nonmedical use of prescription opioids were increased by lifetime history of trauma, history of SUD other than POUD prior to past year, and social deviance in adulthood and past-year pain, AUD, tobacco use disorder, any Axis I disorder other than SUD, and number of stressful events. The C-index of the model was 0.769, indicating good predictive power.

12-Month Prescription Opioid Use Disorder

As in the bivariate models of nonmedical use of prescription opioids, 12-month POUD among individuals with lifetime nonmedical use of prescription opioids was significantly associated with most predictors in the model (Model 4; Table 3). Prior history of POUD (OR = 6.52; 99% CI, 4.44–9.58) had by far the strongest association with last-year POUD. The ORs of the other significant variables ranged from 1.20 (vulnerable family environment) to 4.83 (pain). Higher educational attainment decreased odds of last-year POUD.

In Model 5, the within-tier analysis that adjusted for age and race/ethnicity and examined variables within their tier, the odds of POUD were increased by social deviance in the childhood/early adolescence tier; number of personality disorders in the late adolescence tier; history of POUD prior to last year and social deviance in adulthood; and past-year pain, AUD, tobacco use disorder, and any Axis I disorder other than SUD. Greater educational attainment in late adolescence and history of SUD other than POUD in adulthood were associated with lower odds of POUD.

In Model 6, which included all predictors in the bivariate analyses, history of POUD in adulthood and pain, AUD, tobacco use disorder, and any Axis I disorder other than SUD in the past year were associated with increased odds of POUD. History of SUD other than POUD was the only variable associated with lower odds of POUD after adjustment for the other covariates in the model. The C-index of the model was 0.808, indicating a high ability to predict POUD among individuals with past-year nonmedical use of prescription opioids.

DISCUSSION

In a nationally representative sample of US adults, an array of variables in several developmental tiers individually correlated with 12-month nonmedical use of prescription opioids and 12-month POUD. However, after mutual adjustment for the effect of other covariates, the number of significant predictors was reduced for both outcomes. The predictive power of the models for 12-month nonmedical use and POUD was high, suggesting potential targets for interventions at different developmental stages. The predictors of the models only partially overlapped, indicating that different targets should be considered for interventions directed at nonmedical use of prescription opioids and POUD.

Consistent with prior research,[1,2,4,5] a broad range of variables increased the likelihood of nonmedical use of prescription opioids. However, after adjustment for the effects of covariates, a more restricted set of variables remained significant. As hypothesized by Kendler and colleagues' model, variables in the later developmental tiers were more likely to remain significant than those in earlier tiers, suggesting that the effects of earlier risk factors are mediated by later tiers.

In accord with the findings on nonmedical use of prescription opioids, although several variables predicted POUD in the bivariate and within-tier analyses, most distal predictors were no longer significant after adjustment for more proximal ones. Our results for opioids are consistent with the findings of Kendler and colleagues on the etiology of major depressive disorder[7] and several addictive disorders,[8,9] showing that most of the effects of earlier-tier

Table 3. Bivariate Associations of Risk Factors and Prevalence of 12-Month Prescription Opioid Use Disorder (POUD) Among Individuals With Lifetime Nonmedical Opioid Use in NESARC-III (n = 4,090)[a]

	No POUD (n = 3,760)		POUD (n = 330)		Model 4	
Variable	Value	99% CI	Value	99% CI	OR	99% CI
Age, mean, y						
18–29	28.37	25.95–30.93	28.24	20.62–37.35	1.00	
30–39	19.63	17.42–22.05	19.12	12.92–27.34	0.98	0.57–1.69
40–49	18.11	16.04–20.38	18.52	12.73–26.16	1.03	0.56–1.89
≥ 50	33.89	31.43–36.43	34.13	25.79–43.58	1.01	0.61–1.69
Race/ethnicity, %						
White, non-Hispanic	75.26	71.98–78.28	71.15	64.14–77.28	1.00	
Black, non-Hispanic	9.98	8.03–12.34	13.76	9.29–19.91	1.46	0.89–2.38
Native American	1.89	1.20–2.98	2.49	0.85–7.11	1.39	0.42–4.62
Asian	2.40	1.53–3.75	1.02	0.19–5.25	0.45	0.09–2.17
Hispanic	10.47	8.64–12.63	11.58	7.93–16.60	1.17	0.71–1.92
Sex, %						
Female	44.33	41.70–46.99	50.46	41.82–59.08	1.28	0.89–1.85
Male	55.67	53.01–58.30	49.54	40.92–58.18	1.00	
Childhood/early adolescence, %						
Family history of SUD	64.53	61.04–67.86	74.54	65.32–81.99	**1.61**	**1.02–2.55**
Sexual abuse	16.06	14.09–18.26	29.38	23.11–36.53	**2.17**	**1.51–3.13**
Vulnerable family environment[b]	0.79	0.74–0.84	0.80	0.74–0.86	**1.20**	**1.02–1.41**
Parental loss	35.46	32.86–38.15	39.28	31.02–48.21	1.18	0.80–1.73
Impulsivity	26.07	22.95–29.46	41.04	33.27–49.30	**1.97**	**1.36–2.33**
Low self-esteem	44.35	40.75–48.00	55.05	45.11–64.59	**1.54**	**1.02–2.33**
Childhood-onset anxiety	13.41	11.61–15.4	26.05	19.19–34.32	**2.27**	**1.47–3.52**
Social deviance[b]	0.050	0.046–0.054	0.06	0.05–0.07	**1.34**	**1.17–1.52**
Late adolescence						
Education, mean, y[b]	14.08	13.93–14.23	13.63	13.44–13.82	**0.65**	**0.52–0.81**
No. of Axis I disorders excluding SUD, mean[b]	0.10	0.08–0.12	0.11	0.08–0.14	1.12	0.98–1.29
No. of personality disorders, mean[b]	0.42	0.38–0.46	0.52	0.46–0.58	**1.47**	**1.29–1.68**
Adulthood, %						
History of trauma	66.22	63.03–69.27	79.33	71.93–85.18	**1.96**	**1.31–2.94**
Ever divorced	30.76	28.35–33.27	36.14	27.29–46.03	1.27	0.84–1.94
History of SUD						
Opioid	11.18	9.40–13.23	45.08	36.77–53.66	**6.52**	**4.44–9.58**
Alcohol	48.63	44.51–52.77	58.52	49.74–66.80	**1.49**	**1.04–2.14**
Drugs other than opioids	29.07	26.00–32.35	31.38	22.67–41.63	1.12	0.71–1.76
Tobacco	41.49	37.50–45.60	55.41	46.39–64.10	**1.75**	**1.18–2.60**
Social deviance[b]	0.15	0.14–0.16	0.16	0.15–0.17	**1.45**	**1.25–1.68**
Past year, %						
Pain	14.46	12.22–17.04	44.97	35.13–55.21	**4.83**	**3.21–7.27**
Lack of social support[b]	18.23	17.93–18.53	19.02	18.62–19.42	**1.27**	**1.12–1.45**
Alcohol use disorders	28.75	25.33–32.42	42.35	33.61–51.59	**1.82**	**1.19–2.79**
Tobacco use disorder	41.55	38.06–45.13	63.38	54.93–71.08	**2.43**	**1.66–3.58**
Any Axis I disorder (except SUD)	36.10	33.06–39.26	65.16	57.36–72.23	**3.31**	**2.33–4.70**
Religious service attendance	36.33	33.19–39.60	33.78	26.60–41.80	0.89	0.62–1.30
Marital problems	11.22	9.62–13.06	14.87	10.10–21.35	1.38	0.83–2.29
Stressful life events[b]	0.15	0.14–0.16	0.18	0.17–0.19	**1.45**	**1.25–1.69**

[a]Bivariate model. Significant variables ($P < .05$) are shown in boldface.
[b]Standardized.
Abbreviations: NESARC-III = National Epidemiologic Survey on Alcohol and Related Conditions-III, OR = odds ratio, SUD = substance use disorders.

variables are indirect, ie, explained by the effect of later-tier variables.

As expected, a history of POUD was the single strongest predictor for 12-month POUD. For many individuals, SUD are persistent disorders with an episodic course.[27,28] The genetic predisposition,[29] developmental factors,[30,31] and environmental cues[32] that made individuals vulnerable to POUD in the past are also likely to increase their risk of current POUD. By contrast, all other ORs were of moderate magnitude, indicating that no other variable alone, except pain, substantially increased the risk of POUD. This pattern converges with findings from other addictive disorders[8,9] and contrasts with theories of the opioid crisis focused on a single narrative such as economic adversity.[33] Our findings emphasize the multifactorial etiology of POUD and suggest that approaches that address several risk factors simultaneously are likely to yield greater effects than those focused on a single cause. The multifactorial etiology of POUD further suggests that the population with POUD is heterogeneous and may require flexible evidence-based approaches to help the full range of individuals at high risk for nonmedical opioid use and POUD. A variety of preventive strategies will be necessary to accommodate the diverse needs of these different populations. For example, individuals with pain may not respond to the same interventions as those without pain but with non-SUD Axis I disorders.

History of trauma and social deviance in adulthood predicted 12-month nonmedical use of prescription opioids in the general population but did not predict POUD among those with 12-month nonmedical use of prescription opioids. These findings illustrate the complexity of pathways from nonmedical use initiation to POUD and are in line with prior studies documenting that risk factors for drug initiation do not fully overlap with those predicting transition to dependence on other drugs.[9,34] They highlight that some risk factors may be shared while others impact only 1 stage of the trajectory from initiation of nonmedical use to POUD. These findings may have implications for targeting interventions directed at preventing nonmedical use and interventions directed at preventing POUD among those with nonmedical use of prescription opioids.

At present, there are no evidence-based preventive interventions for nonmedical use of prescription opioids or POUD among adults, an important gap in current approaches to the opioid epidemic because only a minority of individuals with POUD seek treatment.[35] Because the effect of variables in the earlier developmental tiers is mediated through those in later tiers, interventions targeted at early tiers, by stopping the cascade of risk factors before it reaches later tiers, could decrease the risk of POUD as well as the risk of other addictive disorders, which share many of those early-tier predictors.[8,9] Potential targets in later stages of the model could guide the development of interventions for individuals who may not have responded to interventions during earlier developmental stages.

Our models suggest some potential targets for interventions. Because individuals in pain are at increased risk of POUD,[23] improved pain management and prescription practices and development of effective non-addictive analgesics could reach a large proportion of individuals at risk for nonmedical use of opioids and POUD.[36] There is a need to target for screening and intervention of individuals with other SUD and other psychiatric disorders. Although randomized controlled trials are needed to confirm causality, the available evidence suggests that remission of SUD[37] or another psychiatric disorder increases the likelihood of remission of other disorders.[38] The availability of effective treatments makes psychiatric disorders excellent targets for POUD prevention. Preventing childhood maltreatment and other traumatic events, expanding educational opportunities, and developing and implementing interventions that improve coping skills and decrease impulsivity could also be effective.

While the findings of this study contribute to our understanding of nonmedical use of prescription opioids and POUD, certain limitations should be noted. First, information on several variables was collected retrospectively and is thus subject to recall bias. Second, although for clarity we organized the predictors into 4 discrete developmental periods, there is overlap and considerable between-subject variability across those periods. Nevertheless, developmental periods provide some structure, however imperfect, to organize this diverse set of variables. Furthermore, because the final models included all bivariate predictors, inclusion in one or another tier did not influence their significance in those models. Third, although our model is extensive, it is not exhaustive. To be parsimonious, we limited the number of variables. Even with a limited number of variables, the models were highly accurate.

Table 4. Multivariable Associations of Risk Factors and 12-Month Prescription Opioid Use Disorder (POUD) Among Individuals With Lifetime Nonmedical Opioid Use in NESARC-III (n = 4,090)[a]

	Model 5[b]		Model 6[c]	
Variable	AOR	(CI 99%)	AOR	(CI 99%)
Childhood/early adolescence[d]				
Family history of SUD	1.22	0.75–1.98	0.99	0.57–1.73
Sexual abuse	1.49	1.00–2.22	1.35	0.87–2.07
Vulnerable family environment	1.00	0.83–1.21	0.92	0.75–1.14
Parental loss	1.01	0.68–1.52	1.00	0.67–1.51
Impulsivity	1.53	0.94–2.49	1.11	0.67–1.83
Low self-esteem	1.01	0.62–1.63	0.92	0.51–1.66
Childhood-onset anxiety	1.64	1.00–2.70	0.99	0.56–1.74
Social deviance[e]	**1.20**	**1.01–1.44**	1.14	0.87–1.48
Late adolescence[f]				
Education years[e]	**0.69**	**0.55–0.8**	0.82	0.62–1.07
Number of Axis I disorders excluding SUD[e]	1.06	0.90–1.24	1.01	0.84–1.22
Number of personality disorders[c]	**1.41**	**1.22–1.63**	0.97	0.74–1.28
Adulthood[g]				
History of trauma	1.54	0.95–2.49	1.12	0.68–1.85
Ever divorced	1.15	0.71–1.87	1.05	0.61–1.80
History of SUD				
Opioid	**7.24**	**4.66–11.24**	**6.24**	**3.81–10.20**
Alcohol	1.00	0.64–1.57	0.92	0.57–1.51
Drugs other than opioids	**0.40**	**0.23–0.69**	**0.39**	**0.23–0.65**
Tobacco	1.35	0.82–2.22	0.82	0.48–1.39
Social deviance[e]	**1.30**	**1.03–1.64**	0.95	0.69–1.30
Past year[h]				
Pain	**4.08**	**2.57–6.46**	**3.37**	**2.11–5.37**
Lack of social support[e]	1.03	0.80–1.18	1.02	0.87–1.18
Alcohol use disorders	**1.68**	**1.10–2.59**	**2.03**	**1.23–3.36**
Tobacco use disorder	**1.65**	**1.09–2.50**	**1.62**	**1.03–2.55**
Any Axis I disorder (no SUD)	**2.21**	**1.55–3.15**	**2.14**	**1.29–3.56**
Religious service attendance	1.11	0.74–1.67	1.06	0.70–1.62
Marital problems	0.82	0.46–1.46	0.84	0.44–1.61
Stressful life events[e]	1.20	1.00–1.45	1.16	0.94–1.43

[a]Significant variables ($P < .05$) are shown in boldface.
[b]Model 5 adjusted for age, race/ethnicity, and other variables within the same tier.
[c]Model 6 adjusted for all variables in the bivariate analysis.
[d]Childhood/early adolescence C-index = 0.638.
[e]Standardized.
[f]Late adolescence C-index = 0.662.
[g]Adulthood C-index = 0.728.
[h]Past-year C-index: Model 5 = 0.747, Model 6 = 0.808.
Abbreviations: AOR = adjusted odds ratio, NESARC-III = National Epidemiologic Survey on Alcohol and Related Conditions-III, SUD = substance use disorders.

CONCLUSIONS

A modification of Kendler and colleagues' model for major depressive disorder provided a foundation for a developmental model of POUD. The model included 4 developmental tiers in which the effects of more distal tiers were mediated by more proximal ones. We hope these findings are helpful in developing more effective preventive and treatment interventions to decrease the burden of the opioid crisis.

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REFERENCES

1. Han B, Compton WM, Jones CM, et al. Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003–2013. *JAMA*. 2015;314(14):1468–1478.
2. Saha TD, Kerridge BT, Goldstein RB, et al. Nonmedical prescription opioid use and *DSM-5* nonmedical prescription opioid use disorder in the United States. *J Clin Psychiatry*. 2016;77(6):772–780.
3. Blanco C, Volkow ND. Management of opioid use disorder in the USA: present status and future directions. *Lancet*. 2019;393(10182):1760–1772.
4. Blanco C, Alderson D, Ogburn E, et al. Changes in the prevalence of non-medical prescription drug use and drug use disorders in the United States: 1991–1992 and 2001–2002. *Drug Alcohol Depend*. 2007;90(2–3):252–260.
5. Blanco C, Rafful C, Wall MM, et al. The latent structure and predictors of non-medical prescription drug use and prescription drug use disorders: a national study. *Drug Alcohol Depend*. 2013;133(2):473–479.
6. Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2011;115(1–2):120–130.
7. Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for major depression in women. *Am J Psychiatry*. 2002;159(7):1133–1145.
8. Blanco C, Hanania J, Petry NM, et al. Towards a comprehensive developmental model of pathological gambling. *Addiction*. 2015;110(8):1340–1351.
9. García-Rodríguez O, Blanco C, Wall MM, et al. Toward a comprehensive developmental model of smoking initiation and nicotine dependence. *Drug Alcohol Depend*. 2014;144:160–169.
10. Grant BF, Chu A, Sigman R, et al. *Source and Accuracy Statement: National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III)*. Bethesda, Maryland: National Institute on Alcohol Abuse and Alcoholism; 2014.
11. Adams PF, Kirzinger WK, Martinez M. Summary health statistics for the US population: National Health Interview Survey, 2012. *Vital Health Stat 10*. 2013;(259):1–95.
12. Substance Abuse and Mental Health Services Administration. *Results From The 2012 National Survey On Drug Use And Health: Summary Of National Findings*. NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
13. Bureau of the Census. *American Community Survey, 2012*. Suitland, Maryland: Bureau of the Census; 2013.
14. Grant BF, Goldstein RB, Smith SM, et al. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5): reliability of substance use and psychiatric disorder modules in a general population sample. *Drug Alcohol Depend*. 2015;148:27–33.
15. Hasin DS, Greenstein E, Aivadyan C, et al. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5): procedural validity of substance use disorders modules through clinical re-appraisal in a general population sample. *Drug Alcohol Depend*. 2015;148:40–46.
16. Hasin DS, Shmulewitz D, Stohl M, et al. Procedural validity of the AUDADIS-5 depression, anxiety and post-traumatic stress disorder modules: substance abusers and others in the general population. *Drug Alcohol Depend*. 2015;152:246–256.
17. Bernstein DP, Fink L, Handelsman L, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry*. 1994;151(8):1132–1136.
18. Dawson DA, Goldstein RB, Chou SP, et al. Age at first drink and the first incidence of adult-onset *DSM-IV* alcohol use disorders. *Alcohol Clin Exp Res*. 2008;32(12):2149–2160.
19. Cohen S, Mermelstein R, Kamarck T, et al. Measuring the functional components of social support. In: Sarason IG, Sarason BR, eds. *Social Support: Theory, Research, and Applications. NATO ASI Series (D: Behavioral and Social Sciences), vol 24*. Dordrecht, the Netherlands: Springer; 1985.
29. Ware J Jr, Kosinski M, Keller SDA. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220–233.
21. Rubio JM, Olfson M, Pérez-Fuentes G, et al. Effect of first episode axis I disorders on quality of life. *J Nerv Ment Dis*. 2014;202(4):271–274.
22. Rubio JM, Olfson M, Villegas L, et al. Quality of life following remission of mental disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2013;74(5):e445–e450.
23. Blanco C, Wall MM, Okuda M, et al. Pain as a predictor of opioid use disorder in a nationally representative sample. *Am J Psychiatry*. 2016;173(12):1189–1195.
24. Olfson M, Wall MM, Liu SM, et al. Cannabis use and risk of prescription opioid use disorder in the United States. *Am J Psychiatry*. 2018;175(1):47–53.
25. Harrell FE Jr, Lee KL, Califf RM, et al. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984;3(2):143–152.
26. Software for Survey Data Analysis (SUDAAN) version 9.0.3. Research Triangle Park, NC: Research Triangle Institute; 2007.
27. Blanco C, Krueger RF, Hasin DS, et al. Mapping common psychiatric disorders: structure and predictive validity in the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*. 2013;70(2):199–208.
28. McLellan AT, Lewis DC, O'Brien CP, et al. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000;284(13):1689–1695.
29. Kendler KS, Jacobson KC, Prescott CA, et al. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am J Psychiatry*. 2003;160(4):687–695.
30. Carpentier PJ, Knapen LJ, van Gogh MT, et al. Addiction in developmental perspective: influence of conduct disorder severity, subtype, and attention-deficit hyperactivity disorder on problem severity and comorbidity in adults with opioid dependence. *J Addict Dis*. 2012;31(1):45–59.
31. Kristjansson S, McCutcheon VV, Agrawal A, et al. The variance shared across forms of childhood trauma is strongly associated with liability for psychiatric and substance use disorders. *Brain Behav*. 2016;6(2):e00432.
32. Johnson H, Paulozzi L, Porucznik C, et al; Hal Johnson Consulting and Division of Disease Control and Health Promotion, Florida Department of Health. Decline in drug overdose deaths after state policy changes—Florida, 2010–2012. *MMWR Morb Mortal Wkly Rep*. 2014;63(26):569–574.
33. Pincus HA, Blanco C. The opioid crisis in America: an overview. In: Weil AR, Dolan R, eds. *Confronting Our Nation's Opioid Crisis. A report of the Aspen Health Strategy Group*. Washington, DC: The Aspen Institute; 2017:21–48.
34. Kendler KS, Gardner CO, Prescott CA. Toward a comprehensive developmental model for alcohol use disorders in men. *Twin Res Hum Genet*. 2011;14(1):1–15.
35. Han B, Compton WM, Blanco C, et al. Prescription opioid use, misuse, and use disorders in US adults: 2015 National survey on drug use and health. *Ann Intern Med*. 2017;167(5):293–301.
36. Collins FS, Koroshetz WJ, Volkow ND. Helping to end addiction over the long-term: the research plan for the NIH HEAL Initiative. *JAMA*. 2018;320(2):129–130.
37. Blanco C, Okuda M, Wang S, et al. Testing the drug substitution switching-addictions hypothesis: a prospective study in a nationally representative sample. *JAMA Psychiatry*. 2014;71(11):1246–1253.
38. Blanco C, Wall MM, Wang S, et al. Examining heterotypic continuity of psychopathology: a prospective national study. *Psychol Med*. 2017;47(12):2097–2106.