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Adolescent context of exposure to prescription opioids and substance use disorder symptoms at age 35: A national longitudinal study

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Abstract

The objective of this study was to examine the association of context of prescription opioid exposure (i.e., medical and/or nonmedical) in adolescence with the subsequent risk of nonmedical use of prescription opioids (NMUPO) and substance use disorder (SUD) symptoms at age 35. Multiple cohorts of nationally representative probability samples of U.S. high school seniors ($n = 4072$) were surveyed via self-administered questionnaires and followed longitudinally from adolescence (modal age 18, graduating classes 1976–1996) to age 35 (1993–2013). Main outcome measures were past-year NMUPO and SUD symptoms. The medical and nonmedical use of prescription opioids during adolescence was significantly associated with NMUPO at age 35. Relative to no prescription opioid exposure, medical use of prescription opioids without any history of NMUPO during adolescence was not associated with SUD symptoms at age 35. In contrast, compared with no prescription opioid exposure during adolescence, the adjusted odds ratios (AORs) associated with SUD symptoms at age 35 were greater among those with a history of both medical use of prescription opioids and NMUPO during adolescence, AOR = 1.49 (95% confidence interval [CI], 1.13–1.97); and among those who reported NMUPO only, AOR = 2.61 (95% CI, 1.88–3.61). The findings indicate medical use of prescription opioids without any history of NMUPO in adolescence is not associated with SUD symptoms at age 35 while any NMUPO in adolescence predicts SUD symptoms at age 35. Screening instruments and preventative intervention programs to reduce NMUPO and SUDs must account for the context associated with prescription opioid exposure during adolescence.

1. Introduction

Although the U.S. represents less than 5% of the world's population, Americans consume over 80% of the global prescription opioid supply [19]. Despite the efficacy of prescription opioids when used properly for the treatment of acute pain-related conditions, there are growing concerns based on the misuse of leftover prescription opioids, increases in adverse consequences associated with nonmedical use of prescription opioids (NMUPO) and high abuse potential of opioid analgesics [5,14,17,20,23,24,29,32,38,42]. The number of U.S. emergency department visits involving NMUPO increased by approximately 183% between 2004 and 2011 [38]. In 2012, over 600,000 adolescents aged 12 to 17 years initiated NMUPO within the past 12 months which was greater than those who initiated use of any other illicit drug with the exception of marijuana [39].

There is growing evidence suggesting an association between medical use of prescription opioids and subsequent NMUPO during adolescence and young adulthood [20,23,26,30]. Furthermore, prevalence rates of substance use behaviors and substance-related problems are significantly greater among adolescents who report medical use of prescription opioids and a history of NMUPO based on cross-sectional and regional studies [20,23,26,32]. Although there are a few studies indicating most adolescents use their prescription opioids appropriately without an increased risk for substance use disorders (SUDs), the majority of these studies have been cross-sectional and/or regional and none of these studies have followed the same individuals from adolescence into adulthood [9,23,25,41]. Because prescription opioids are the leading controlled medications used medically and nonmedically by adolescents and young adults in the U.S. [10,17,20,26,29,39], and because approximately one in every four young adults in the U.S. develop a SUD involving alcohol or other drugs [12,13,16], an important question is the relationship between medical and nonmedical use of opioids during adolescence and the occurrence of SUDs in young adulthood.

The majority of NMUPO involves polydrug use during adolescence [21,27], making it challenging to isolate a given SUD that might follow from earlier NMUPO. Thus, diagnostic screening efforts that cover a wide range of substances for assessing the risk of developing SUDs and controlling for polysubstance use as an important potential confounder in the relationship between NMUPO during adolescence and subsequent substance use behaviors are needed. The findings from previous studies indicate that NMUPO during the transition from adolescence to young adulthood warrants a closer examination because this appears to be a key developmental period for the origins of behavioral patterns leading to SUDs. Although past studies have indicated that NMUPO is associated with an increased risk of other substance use behaviors during adolescence, it remains unclear whether context of prescription opioid exposure (i.e., medical and/or nonmedical) during adolescence can predict increased risk of NMUPO and SUD symptoms in adulthood (age 35). To address these knowledge gaps, we examined the associations between contexts of prescription opioid exposure in adolescence with the subsequent risk of NMUPO and SUD symptoms at age 35 in a national sample.

2. Methods

This study used national panel data from the Monitoring the Future (MTF) study [2,3,17,29]. Based on a three-stage sampling procedure, MTF has surveyed nationally representative samples of approximately 17,000 U.S. high school seniors each year since 1975, using questionnaires administered in classrooms. Stage 1 is the selection of geographic areas; stage 2 is the selection of schools; and stage 3 is the selection of students within each school. Approximately 2,400 high school seniors are selected for biennial follow-ups each year and then followed every five years after the age of 30 using mailed questionnaires. Individuals who, at age 18, reported 30-day marijuana use on 20 or more occasions, and/or any 30-day use of other illicit drugs (LSD, other hallucinogens, cocaine, heroin), and/or any 30-day nonmedical use of prescription opioids, sedatives, stimulants, or tranquilizers, were over-sampled for the follow-up surveys to help account for the heavier drug users. Corrective weighting was used to adjust for the unequal probabilities of selection and to best approximate the given population at follow-up. Consistent with recent work, we will examine several alternative approaches for assessing potential nonresponse bias when analyzing longitudinal MTF survey data in the present study [40]. The project design and sampling methods are described in greater detail elsewhere [2,3,17,29].

This study uses data from high school seniors who were randomly assigned to complete form 1 at baseline (one of six questionnaires provided at baseline) and the single form provided to all panel respondents at age 35. Form 1 at baseline was selected because it was the only form that contained information regarding both medical use of prescription opioids and NMUPO. The student response rates at baseline over the study period ranged from 77% to 86%; most all non-response was due to the given respondent being absent. Moreover, the analysis focuses on the age 35 follow-up because the single form provided to this age group included measures assessing SUD symptoms. The study period for respondents at age 35 was between 1993 (12th grade cohort in 1976) and 2013 (12th grade cohort in 1996).

As illustrated in Table 1, the weighted longitudinal sample included 4072 individuals (56.9% female and 43.1% male). The racial/ethnic distribution of the sample was 84.0% White, 7.0% Black, 3.5% Hispanic, and 5.5% from other racial/ethnic categories. The overall weighted response rate for the longitudinal sample was 54%. Attrition analyses compared those in the longitudinal sample who participated at both waves with those who participated at baseline only. Results showed that retention rates were not significantly different for parental education, urbanicity, medical use of prescription opioids, and NMUPO. There were statistically significant associations between sex and attrition status as well as race/ethnicity and attrition status; retention was higher among females and Whites.

The MTF study assesses a wide range of behaviors, attitudes, and values. For the present study, we selected specific measures for analysis, including demographic characteristics sex (i.e., Male and Female), race/ethnicity (i.e., White, Black, Hispanic, and other race), U.S. Census geographic location (i.e., Northeast, Midwest, South and West), urbanicity based on metropolitan statistical area (i.e., large MSA, other MSA, and non-MSA), parental education (college degree vs. no college degree), alcohol use, marijuana use, and other drug use.

Medical and nonmedical use of prescription opioids at baseline (age 18) was based on two separate questions measuring lifetime medical use (i.e., “taken any narcotics other than heroin because a doctor told you to use them?”) and lifetime NMUPO (i.e., “taken any narcotics other than heroin on your own—that is, without a doctor telling you to take them?”). Respondents were prompted that narcotics other than heroin are prescribed by doctors and cannot be sold without a prescription and were also provided a list several examples of prescription opioids such as “Vicodin®, OxyContin®, Percocet®, Demerol®, Dilaudid®, morphine, opium, and codeine.” Based on these two questions, a variable with four mutually exclusive categories was constructed to include the following categories for lifetime use of prescription opioids at baseline: (1) no medical use or NMUPO, (2) medical use only, (3) medical use and NMUPO, and (4) NMUPO only.

Substance use disorder (SUD) symptoms at age 35 were measured with several questions based on the DSM criteria for alcohol use disorders, marijuana use disorders, and other drug use disorders. Although these measures of SUD symptoms do not yield a clinical diagnosis, the items are largely consistent with how SUD have been measured in other large scale surveys [15,33,34] and have been used in the past to reflect DSM-IV and DSM-5 alcohol and marijuana use disorders [28,36,37]. Respondents were asked to report SUD symptoms over the past five years related to alcohol use, marijuana use and other drug use disorders. Fifteen items were used to develop eight of the eleven DSM-5 criteria that were consistent with alcohol, marijuana, and other drug use disorders: substance use resulting in a failure to fulfill major role obligations (e.g., “caused you financial difficulties”), continued substance use when physically hazardous (e.g., “caused you to drive unsafely”), continued substance use despite persistent or recurrent interpersonal or social problems, tolerance (e.g., “you found that over time you need more of the drug to get the same effect”), withdrawal (e.g., “stopping or reducing your use of the drug made you physically ill or sick”), persistent desire or unsuccessful efforts to cut down substance use (e.g., “you wanted to try to stop or cut down, but you found that you could not”), health related issue due to substance use (e.g., “caused your physical health to be bad”), and craving (e.g., “you felt such a strong desire to use the drug that you could not resist or think of anything else”). For each item, the responses were recoded to none vs. a little/some/a lot. For each criteria, the respondent was coded as exhibiting the criteria if they responded other than “none”. For criteria with multiple items, the respondent was coded as endorsing the criteria if he/she indicated other than “none” for any of the items. The eight criteria were summed to obtain an overall number of criteria endorsed. We followed recommended practice that any use disorder (including mild, moderate, or severe) is indicated by meeting two or more of the criteria [1,11,12,13].

All analyses were conducted using STATA 13.1 (Stata Corp, College Station, Texas) and were weighted to adjust for the unequal probabilities of selection. The analyses included both descriptive statistics and logistic regression to examine SUD symptoms at age 35 as a function of medical use of prescription opioids and NMUPO at age 18. Descriptive analyses provided the prevalence of two or more SUD symptoms based on eight DSM-5 criteria for alcohol, marijuana, and other drug use disorders. Logistic regression analyses provided adjusted odds ratios (AOR) and 95% confidence intervals for two or more SUD symptoms at age 35 as a function of medical use and NMUPO at age 18. Logistic regression analyses

controlled for respondent's sex (i.e., Male and Female), race/ethnicity (i.e., White, Black, Hispanic, and other race), U.S. Census geographic location (i.e., Northeast, Midwest, South and West), urbanicity based on metropolitan statistical area (i.e., large MSA, other MSA, and non-MSA), parental education (college degree vs. no college degree), annual alcohol use, annual marijuana use, annual other drug use, and baseline cohort year at age 18. All of the respondents were included in the analyses when possible, sample sizes varied across analyses due to item missing responses.

3. Results

As illustrated in Table 1, an estimated 22.0% of individuals indicated lifetime medical use of prescription opioids or NMUPO at age 18: approximately 13.6% of individuals indicated medical use only, while 5.4% reported both medical use and NMUPO, and 3.0% reported NMUPO only. Among individuals who reported any past-year NMUPO at age 18, approximately 96% also used other substances during the past-year and 55.7% simultaneously co-ingested at least one other substance with prescription opioids during the past year.

Table 2 shows the unadjusted prevalence of NMUPO and two or more SUD symptoms at age 35 as a function of four contexts of prescription opioid exposure at age 18. At age 35, the past-year prevalence of NMUPO was 2.4% among individuals who reported no medical use or NMUPO at age 18, 4.4% for medical use only, 8.4% for both medical use and NMUPO, and 5.8% for NMUPO only. Overall, we found that over 90% of individuals who reported any history of NMUPO at age 18 did not engage in past-year NMUPO at age 35. We also found that the majority (52.8%) of individuals who reported NMUPO only at age 18 reported two or more SUD symptoms at age 35. Moreover, individuals who had any prescription opioid exposure at age 18 were more likely to report two or more alcohol use disorder symptoms than other SUD symptoms at age 35.

As illustrated in Table 3, individuals who at 18 indicated lifetime medical use only (AOR = 1.74; 95% CI = 1.10, 2.76, $P < 0.05$), both lifetime medical use and NMUPO (AOR = 3.22; 95% CI = 1.93, 5.36, $P < 0.001$), and lifetime NMUPO only (AOR = 2.09; 95% CI = 1.10, 3.96, $P < 0.05$) had higher odds of past-year NMUPO at age 35 when compared to respondents who reported no lifetime medical use or NMUPO at age 18. Individuals who indicated NMUPO only at age 18 had the highest odds of two or SUD symptoms at age 35 including alcohol use disorder symptoms (AOR = 2.04; 95% CI = 1.50, 2.79, $P < 0.001$), marijuana use disorder symptoms (AOR = 2.73; 95% CI = 1.75, 4.26, $P < 0.001$), other drug use disorder symptoms (AOR = 4.39; 95% CI = 2.73, 7.06, $P < 0.001$), and any SUD symptoms (AOR = 2.61; 95% CI = 1.88, 3.61, $P < 0.001$), when compared to respondents who had no history of medical use or NMUPO at age 18. Moreover, no differences in the odds of any SUD symptoms at age 35 were found between respondents who indicated medical use only at age 18 and respondents who had no medical and nonmedical use at age 18.

We conducted additional logistic regression analyses using a lower cut-point threshold of one or more SUD symptoms and a higher cut-point threshold of three or more SUD

symptoms and found similar results (see eTable 1 and eTable 2). Additional analyses using both ordinary least squares regression and negative binomial regression were used to model the number of SUD symptoms (negative binomial regressions were used due to non-normal distributions of symptoms counts). Similar results across the four contexts of prescription opioid exposure at age 18 and SUD symptom counts for alcohol, marijuana, and other drug use disorders at age 35 were found in these additional analyses.

4. Discussion

To our knowledge, this is the first longitudinal study that has used a national sample to examine the association of medical and nonmedical contexts of prescription opioid exposure in adolescence with the subsequent risk of NMUPO and SUD symptoms at age 35. Previous cross-sectional and regional U.S. studies have found that the risk of substance use behaviors during adolescence was substantially increased if adolescents reported any history of NMUPO while appropriate medical use of prescription opioids did not appear to be associated with substance use behaviors [20,23,26]. The present study extended these previous results into early mid-life and found that medical use of prescription opioids during adolescence without any history of NMUPO was associated with an increased risk of later NMUPO at age 35 but was not associated with an increased risk of alcohol, marijuana and other SUD symptoms at age 35.

Health professionals prescribing opioid analgesics should be encouraged that medical use of prescription opioids without any history of NMUPO is feasible for most young patients and that appropriate medical use of prescription opioids appears unrelated to the development of SUD symptoms in adolescence and early to middle adulthood [23]. Despite these positive findings for clinical practice, it is particularly troubling that over one-quarter of adolescents reported medical use of prescription opioids with a history of NMUPO at age 18 and that this behavioral pattern in adolescence is associated with increased odds of NMUPO and SUD symptoms at age 35. We also found an association between medical use of prescription opioids (with or without NMUPO) during adolescence and subsequent past-year NMUPO at age 35 and these findings extended prior work that found similar associations during adolescence [23] and young adulthood [30]. The association between medical use of prescription opioids and subsequent NMUPO could be driven partially by high rates of peer NMUPO diversion and the fact that more than one-third of adolescents who report NMUPO used leftover opioid medications from their own previous prescriptions [24,29,39]. Taken together, these findings indicate to health professionals that enhanced vigilance is needed when prescribing opioids and monitoring their use among adolescents to reduce subsequent prescription opioid misuse and SUDs.

The present study also extended prior research in several other important ways. We found that over 90% of individuals who reported any history of NMUPO at age 18 did not engage in past-year NMUPO at age 35. These findings extended prior work that examined the developmental course of NMUPO over shorter periods of time and found the majority of individuals who reported NMUPO did not engage in this behavior in subsequent waves of data collection one to six years later, suggesting a strong tendency toward experimental use only [6,22,23]. In the present study, we used a large, national longitudinal sample of U.S.

high school seniors and focused on SUD symptoms involving a wide range of substances including alcohol, marijuana and other drugs. This wide range of substances was used to assess SUD symptoms to account for the high rates of polydrug use associated with NMUPO shown in the present study and prior work [6,21,27]. Indeed, the present study found that over 95% of NMUPO involved reported using other drugs in the past year and the majority of this polydrug use involved simultaneous co-ingestion of prescription opioids and other substances (primarily co-ingestion with marijuana and/or alcohol) [27].

We found that individuals who reported any lifetime NMUPO by age 18 were more likely to report two or more alcohol use disorder symptoms than other SUD symptoms at age 35. Prior work has also found that nonmedical users of prescription opioids are less likely to meet criteria for opioid use disorders than other SUDs [4,6,7,42]. For example, approximately 8% of young adults aged 18 to 24 who reported past-year NMUPO at wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) reported past-year prescription opioid use disorder while over 50% met criteria for any past-year SUD three years later at wave 2 of the NESARC [6]. Taken together, these findings indicate that any NMUPO in adolescence is a behavior that serves as a strong signal for future SUD and reinforces the importance for health professionals to screen a wide range of substances rather than be opioid-specific when assessing the risk for SUDs among nonmedical users of prescription opioids.

The MTF study has all of the limitations of large-scale longitudinal survey research using self-administered surveys including different methods for psychiatric diagnosis than clinical settings, self-reporting bias, and attrition. While the MTF study could not establish formal DSM-based diagnoses given the study methods, the prevalence of SUD symptoms for non-users in the MTF study closely resembles other national estimates [8,12,13,16]. Nevertheless, the present study did not include three of 11 DSM-5 SUD criteria and future research is needed to examine the sensitivity and specificity of the SUD symptoms examined in the present study. Further, the MTF study does not assess some factors (e.g., anxiety disorder, attention-deficit/hyperactivity disorder, conduct disorder, family history of SUD, and mood disorder) related to SUD symptoms at baseline and follow-up. Second, we acknowledge the potential for self-reporting bias and that there are two important segments that tend to report higher rates of drug use missing from the data collected at baseline: students absent from class at the time of data collection and students who dropped out of school. Although self-report data in the MTF study have been found to be reliable and valid, studies on youth suggest that misclassification and under-reporting of drug use does occur [18,31,35]. Third, as is typically the case in longitudinal studies regarding substance use, attrition is differential with respect to drug use, indicating that drug users are less likely to remain in longitudinal samples, suggesting that our findings reflect conservative estimates of the connections between adolescent NMUPO and early mid-life SUD symptoms. However, we would like to note that we examined several alternative approaches for assessing nonresponse bias in our longitudinal survey estimates and found similar results [40]. In addition, the longitudinal sample used here is not as representative of the population baseline samples, reflecting the common finding that women, Whites, and individuals from older cohorts are more likely to be retained. Finally, most of the adolescent data in the present study was collected in a period prior to significant increases in NMUPO in the U.S. that

started in the mid-1990's [17,38,39]. There is a need for more prospective research to examine the associations found in the present study over the adult lifespan from middle into older adulthood.

To our knowledge, this is the first study to examine the relationships between the medical use of prescription opioids and NMUPO in adolescence and subsequent NMUPO and SUD symptoms in adulthood (age 35) using a large, national, prospective multi-cohort panel in the U.S. The findings indicate medical and nonmedical prescription opioid exposure during adolescence along with other risk factors should be carefully taken into consideration when developing screening instruments and preventive interventions to reduce subsequent prescription opioid misuse and SUDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive statistics for the longitudinal sample at baseline (age 18)

Baseline Characteristics at Age 18	Study Sample (n = 4072)
Sex	%
Male	43.1%
Female	56.9%
Race/Ethnicity	
White	84.0%
Black	7.0%
Hispanic	3.5%
Other race	5.5%
Parental Education	
At least one parent has a college degree or higher	42.2%
Neither parent has a college degree	57.8%
Region	
Northeast	22.1%
Midwest	32.5%
South	29.4%
West	15.9%
Urbanicity	
Large metropolitan statistical area	23.5%
Other metropolitan statistical area	45.6%
Non-metropolitan statistical area	30.9%
12th Grade Cohort Year	
1976–1980	29.3%
1981–1985	24.5%
1986–1990	23.0%
1991–1996	23.3%
Context of lifetime prescription opioid exposure	
No lifetime medical or nonmedical use	78.0%
Lifetime medical use only	13.6%
Lifetime medical and nonmedical use	5.4%
Lifetime nonmedical use only	3.0%

Note: Weighted samples and estimates are provided.

Table 2
Prevalence estimates of nonmedical use of prescription opioids and substance use disorder symptoms at age 35 as a function of medical and nonmedical use of prescription opioids at age 18

Baseline Context of Lifetime Prescription Opioid Exposure at Age 18	Past-Year Nonmedical Use of Prescription Opioids at Age 35	Alcohol Use Disorder Symptoms at Age 35	Marijuana Use Disorder Symptoms at Age 35	Other Drug Use Disorder Symptoms at Age 35	Any Substance Use Disorder Symptoms at Age 35
	%	2+ Symptoms %	2+ Symptoms %	2+ Symptoms %	2+ Symptoms %
No medical or nonmedical use (n = 3,014)	2.4%	24.6%	4.9%	2.7%	25.7%
Medical use only (n = 527)	4.4%	26.2%	5.1%	3.4%	28.7%
Medical and nonmedical use (n = 207)	8.4%	31.8%	6.9%	8.9%	35.3%
Nonmedical use only (n = 116)	5.8%	44.7%	14.8%	13.0%	52.8%
² Sample size	<i>t</i> _n = 3576	<i>t</i> _n = 3768	<i>t</i> _n = 3817	<i>t</i> _n = 3631	<i>t</i> _n = 3549

¹Sample sizes vary due to missing data on the dependent measures (i.e., substance use disorder symptoms at age 35)

Adjusted odds of substance use disorder symptoms (2+) at age 35 as a function of medical and nonmedical use of prescription opioids at age 18

Table 3

Baseline Context of Exposure to Prescription Opioids (Age 18)	Past-Year Nonmedical Use of Prescription Opioids at Age 35 <i>I</i> AOR (95% CI)	Alcohol Use Disorder Symptoms at Age 35 2+ Symptoms <i>I</i> AOR (95% CI)	Marijuana Use Disorder Symptoms at Age 35 2+ Symptoms <i>I</i> AOR (95% CI)	Other Drug Use Disorder Symptoms at Age 35 2+ Symptoms <i>I</i> AOR (95% CI)	Any Substance Use Disorder Symptoms at Age 35 2+ Symptoms <i>I</i> AOR (95% CI)
No medical or nonmedical use (n = 3,014)	Reference	Reference	Reference	Reference	Reference
Medical use only (n = 527)	1.74 (1.10, 2.76) *	1.05 (.855, 1.31)	1.04 (.694, 1.57)	1.17 (.717, 1.92)	1.13 (.914, 1.40)
Medical and nonmedical use (n = 207)	3.22 (1.93, 5.36) ***	1.35 (1.03, 1.77) *	1.42 (.944, 2.15)	3.07 (1.93, 4.88) ***	1.49 (1.13, 1.97) **
Nonmedical use only (n = 116)	2.09 (1.10, 3.96) *	2.04 (1.50, 2.79) ***	2.73 (1.75, 4.26) ***	4.39 (2.73, 7.06) ***	2.61 (1.88, 3.61) ***
² Sample size	² n = 3576	² n = 3768	² n = 3817	² n = 3631	² n = 3549

* p<.05,
** p<.01,
*** p<.001

¹ All analyses control for race (i.e., White, Black, Hispanic, Other race), sex (i.e., Male and Female), geographic region (i.e., Northeast, Midwest, South and West), metropolitan statistical area (i.e., large MSA, other MSA, and non-MSA), parental education (college degree vs. no college degree) and cohort year at age 18. In addition, all models control for any substance use at baseline (i.e., annual alcohol use at age 18, annual marijuana use at age 18, and annual other drug use at age 18).

² Sample sizes vary due to missing data on the dependent measures (i.e., substance use disorder symptoms at age 35).