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Pathways between nonmedical opioid use/dependence and psychiatric disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions

Silvia S. Martins[a,*], Katherine M. Keyes[b,c], Carla L. Storr[a,d], Hong Zhu[e], Howard D. Chilcoat[a,f]

[a] Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA
[b] New York State Psychiatric Institute, New York, NY 10032, USA
[c] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032, USA
[d] Department of Family and Community Health, University of Maryland School of Nursing, Baltimore, MD 21201, USA
[e] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA
[f] GlaxoSmithKline Worldwide Epidemiology, Research Triangle Park, NC 27709, USA

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ABSTRACT

Background: While nonmedical use of opioids and psychiatric disorders are prevalent in the population, little is known about the temporal ordering between nonmedical opioid use and dependence and psychiatric disorders.
Method: Data were gathered in a face-to-face survey of the United States conducted in the 2001–2002 (NESARC wave 1). Participants were household and group quarters residents aged 18 years and older (n = 43,093). Cox proportional hazards models with time-dependent covariates were used to investigate potential pathways between lifetime nonmedical opioid use/dependence and psychiatric disorders.
Results: Preexisting psychiatric disorders (mood disorders, major depressive disorder, bipolar I disorder, anxiety disorders, panic and generalized anxiety disorders) were associated with an increased risk of nonmedical opioid use, with hazard ratios ranging from 2.2[95% CI = 1.6–3.1] (any anxiety disorder) to 3.1[95% CI = 2.4–2.4] (bipolar I disorder). Preexisting nonmedical opioid use was associated with an increased risk of onset of psychiatric disorders, with hazard ratios ranging from 2.8[95% CI = 2.2–3.6] (generalized anxiety disorder) to 3.6[95% CI = 2.6–4.9] (bipolar I disorder), adjusted for demographics and other illegal drug use. Nonmedical use of opioids led to the development of dependence more often among individuals with preexisting psychiatric disorders, hazard ratios were particularly strong for generalized anxiety disorder (HR = 10.8, 95% CI = 4.9–23.7) and bipolar I disorder (HR = 9.7, 95% CI = 5.4–17.3). Preexisting opioid dependence resulting from nonmedical opioid use was associated with an increased risk of onset of psychiatric disorders, with hazard ratios ranging from 4.9[95% CI = 3.0–7.9] (mood disorders) to 8.5[95% CI = 4.5–16.0] (panic disorder), adjusted for demographics and alcohol and/or other illegal drug dependence.
Conclusions: Our findings support a general vulnerability to nonmedical opioid use and major psychopathologies, as well as evidence for a 'self-medication' model for dependence resulting from nonmedical opioid use with bipolar disorder and generalized anxiety disorder.

1. Introduction

Nationally representative surveys such as the 2006 National Survey on Drug Use and Health (NSDUH) estimate that 13.6% of the U.S. population aged 12 years of age or older have used an opioid for nonmedical purposes (defined as 'use to get high, using more than prescribed, using it for indications other than those intended by the prescriber, or for other experiences, sensations, or effects beyond the boundaries of approved prescribing procedures or indications as dispensed' – see Anthony et al., 1994) at least once in their lifetime. The prevalence of nonmedical opioid use has been on the rise over the past few years (from 5.8% in 1998 to 9.8% in 2001) (Substance Abuse and Mental Health Services Administration [SAMHSA], 2007). In addition, an estimated 2.2 million individuals used these substances nonmedically for the first time during 2006, the largest number of recent drug initiates among persons aged 12 and older, representing a substantial increase since 1990 (627,000 initiates) (SAMHSA, 2007). Clinical and epidemiological studies have shown that nonmedical opioid use is associated with several psychiatric disorders (Busto et al., 1998; Chilcoat and

* Corresponding author at: Johns Hopkins Bloomberg School of Public Health, Department of Mental Health, 624 N. Broadway, 8th floor, Suite 896, Baltimore, MD 21205-1900, USA. Tel.: +1 410 614 2852; fax: +1 410 955 9088.
E-mail address: smartins@jhsph.edu (S.S. Martins).

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Breslau, 1998b; Romach et al., 1999; Reid et al., 2002; Rosenblum et al., 2003; Sullivan et al., 2005; Dowling et al., 2006; Becker et al., 2008; Tetrault et al., 2008). As such, further investigation of pathways between psychiatric disorders and use and dependence on opioids is a public health priority.

Similar to use of many legal and illegal substances, nonmedical opioid use is robustly associated with a broad range of comorbid psychiatric conditions in nationally representative samples. For example, Sullivan et al. (2005) reported that individuals with a variety of psychiatric disorders in a nationally representative sample were more likely than those without psychiatric disorders to report concurrent nonmedical opioid use, with odds ratios ranging from 4.13 [generalized anxiety disorder] to 8.46 [panic disorder]. Several reports from various NSDUH surveys indicate associations between nonmedical opioid use and psychiatric disorder symptom scales and indicators. For instance, Becker et al. (2008) report small but significant associations between nonmedical nonmedical opioid use and panic, depressive, and social phobic/agoraphobic symptoms but not manic, generalized anxiety, or post-traumatic stress symptoms in the 2002–2004 NSDUH surveys. Additionally, Tetrault et al. (2008) and Dowling et al. (2006) documented a strong association between nonmedical opioid use and likely psychiatric disorder as measured with a non-diagnostic scale in the 2002 and 2003 NSDUH surveys. Clinical and community samples generally concur with these national data across a broad range of populations and settings (Busto et al., 1998; Romach et al., 1999; Reid et al., 2002; Rosenblum et al., 2003).

Few studies have explored associations of between DSM-IV dependence resulting from nonmedical opioid use with psychiatric disorder diagnoses. Strong evidence is provided by the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) data; Huang et al. (2006) reported significant associations with every Axis-I and Axis-II disorder measured, and particularly strong relationships with other externalizing disorders such as illegal drug dependence, nicotine dependence, and antisocial personality disorder. While studies on both nonmedical opioid use and dependence have added to our understanding of psychiatric disorders related to the use of opioids, none has attempted to investigate the temporal order of the relationship of psychiatric disorders with nonmedical opioid use and dependence resulting from nonmedical opioid use.

These studies fit into a more broad well-documented area of research indicating that psychiatric disorders occur more frequently in drug using and dependent individuals than among non-drug using individuals (Kessler et al., 2003; Kessler, 2004; Kandel et al., 1997; Regier et al., 1990; Rounsaville et al., 1991; Grant and Harford, 1995; Compton et al., 2007). This established association has motivated interest on the temporal ordering of drug use and psychiatric disorders, as the temporal direction of the association has important implications for prevention and intervention work. For instance, if drug use occurs before psychiatric disorders, then drug use prevention strategies may reduce the associated psychiatric morbidity in addition to the known physical and psychological sequelae. With regard to substance use disorders in general, research has shown that median age of onset for several psychiatric disorders usually occur before the median age of onset for substance use disorders (Kessler et al., 2005). However, preexisting psychiatric disorders also signal increased risk of subsequent substance dependence (Chilcoat and Breslau, 1998a,b; Breslau et al., 2003; Zimmermann et al., 2003), with particularly strong associations documented for PTSD as a risk factor for dependence on prescription drugs (e.g., stimulants, sedatives, tranquilizers, and analgesics).

Three main non-mutually exclusive models to sequentially explain these associations have been postulated. The first is the self-medication model (Conger, 1956; Lader, 1972; Markou et al., 1998), whereby psychiatric disorders cause increases in alcohol and drug use due to anxiolytic or other qualities of substances for the relief of symptoms. The self-medication model is defined by two assumptions: the first, that individuals start using a drug and become dependent on it to alleviate distress and psychiatric symptoms; the second, that there is correspondence between the neurobiological effects of the drug used and the specific symptomotology of the psychiatric disorder (Khantzian, 1997, 2003). The second model is the precipitational model, whereby heavy use of alcohol and drugs may trigger mood or anxiety disorders due to neuroadaptation in brain reward pathways that can lead to subsequent development of psychiatric disorders (McEwen, 2000; Brady and Sinha, 2005). Finally, behavioral genetic studies evidence some support for an underlying shared liability to both drug use/dependence and some psychiatric disorders which may have a heritable component (Kendler et al., 2003; Krueger et al., 2001; Young et al., 2000). Thus, underlying vulnerability or another third factor influencing risk for both drug use/dependence and psychiatric disorders may explain the observed association. While these three models are proposed to explain the general observed association between drug use and psychiatric disorders, specific classes of drugs may exhibit unique pathways toward specific psychiatric disorders (Bierut et al., 1998). These models are not necessarily mutually exclusive. For example, a subset of cases could be explained by self-medication, while another subset results from the precipitational model. In light of secular trends in opioid use and dependence resulting from nonmedical opioid use exhibited in the population, further understanding of the specificity of pathways across psychiatric disorder and drug class remains important to establish in the literature. As such, the goal of this study is to shed light on which model or models may shed light on the association between nonmedical opioid use and dependence and psychiatric disorders by exploring the temporal sequencing of events. The hypotheses will be tested first for nonmedical opioid use, then for dependence that has resulted from nonmedical opioid use. The study's aims are: (1) test whether preexisting mood and anxiety disorders precede the onset of nonmedical opioid use/dependence resulting from nonmedical opioid use (self-medication hypothesis); and (2) examine if preexisting nonmedical opioid use/dependence resulting from nonmedical opioid use precedes the onset of mood or anxiety disorders (precipitational model); keeping in mind that these are not mutually exclusive pathways and that temporality does not imply causality.

2. Methods

2.1. Sample and measures

Data were drawn from 2001 to 2002 wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions, a nationally representative United States survey of civilian non-institutionalized participants aged 18 and older, using a cross-sectional design and in-person interviews. Details of the sampling frame are described elsewhere (Grant et al., 2004, 2003a). The NESARC has a longitudinal component (wave 2, data collected in 2004–2005), which is not yet publicly available. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) sponsored the study and supervised the fieldwork, conducted by the U.S. Bureau of the Census. Details of interviewing, training, and field quality control can be found elsewhere (Grant et al., 2003). Young adults, Hispanics, and African–Americans were oversampled, and observations were weighted to the 2000 decennial census in terms of age, race, sex, and ethnicity and were further weighted to adjust for sampling probabilities. The study achieved an overall response rate of 81%.

The Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS-IV; Grant et al., 2001), a structured diagnostic interview, was administered to the NESARC participants using computer-assisted software with built-in skip, logic, and consistency checks. This instrument was specifically designed for experienced lay interviewers and was developed to advance measurement of substance use and mental disorders in large-scale surveys.

Nonmedical use of opioids was defined to respondents as using an opioid: "without a prescription, in greater amounts, more often, or longer than prescribed, or for a reason other than a doctor said you should use them". After the initial probe item, the respondent was given an extensive list of examples of opioids and asked if s/he used any of the opioids on the list or similar drugs 'nonmedically'. If the response

was positive the respondent was asked to specify which opioid s/he has used and the interviewer recorded the response. Follow-up questions inquired about lifetime and current quantity, frequency, age of onset and recency of use of opioid drugs as a class. Over 30 symptom items are used by the AUDADIS to operationalize DSM-IV criteria to assess lifetime dependence according to DSM-IV criteria (APA, 1994). The interview also captures age of onset of nonmedical opioid use ("How old were you when you FIRST used painkillers?") and age of onset of dependence (when the respondent endorsed at least three dependence symptoms related to their nonmedical opioid use they were asked these follow-up questions: "You just mentioned some other experiences you had with *painkillers* in the past, that is, before 12 months ago. Before last (*Month one year ago*) was there ever a period when SOME of these experiences with *painkillers* were happening around the same time most days for at least a month, on and off for a few months or longer or within the same 1-year period?" and "About how old were you the FIRST time SOME of these experiences with *painkillers* BEGAN to happen around the same time?"). Test–retest reliability for AUDADIS-IV diagnosis of lifetime nonmedical opioid use and dependence resulting from nonmedical opioid use in general population and clinical settings is good to fair with kappas ranging from 0.59 for lifetime dependence and 0.66 for lifetime use (Grant et al., 1995; Hasin et al., 1997).

Separately the AUDADIS-IV assessed lifetime use of other illegal drugs (e.g., marijuana, cocaine, heroin, hallucinogens, inhalants, and nonmedical use of stimulants, sedatives, and tranquilizers) with similar sets of questions as those described in the above paragraph. For the purpose of this study we used data on other illegal drug use that occurred prior to any nonmedical opioid use as a control variable in the models that estimated the relative hazards of psychiatric disorders in relation to preexisting nonmedical opioid use. Data from the other illegal drugs cited above were collapsed in one variable and age of onset information was based on youngest age of onset of any of these other illegal drugs if the respondent had used more than one other illegal drug.

The AUDADIS-IV separately assessed *DSM*-IV criteria for alcohol and drug-specific dependence for the following classes of drugs: hallucinogens, cannabis, cocaine (including crack cocaine), inhalants/solvents, heroin, and nonmedical use of sedatives, tranquilizers, or stimulants (Compton et al., 2007). The AUDADIS-IV used an extensive list of over 40 questions to assess alcohol dependence. Diagnoses were indicated according to the DSMIV (American Psychiatric Association, 1994); at least three of seven criteria for alcohol dependence. The reliability and validity of alcohol dependence diagnosis has been extensively documented in the U.S. and abroad. The reliability of the alcohol dependence diagnosis has achieved a minimum kappa of 0.74 (Canino et al., 1999; Grant et al., 1995, 2003, 2003a; Chatterji et al., 1997). For the purpose of this study we used data on alcohol dependence that preceded dependence resulting from nonmedical opioid use as a control variable in the models that estimated the relative hazards of psychiatric disorders in relation to preexisting dependence resulting from nonmedical opioid use.

Mood disorders included DSM-IV primary major depressive disorder (MDD), bipolar I, bipolar II, and dysthymia. Anxiety disorders included DSM-IV primary panic disorder with and without agoraphobia, social and specific phobias and generalized anxiety disorder (GAD). Diagnostic methods used in the AUDADIS-IV are described in detail elsewhere (Grant et al., 2004, 2005; Hasin et al., 2005). In DSM-IV, "primary" excludes substance-induced disorders or those due to medical conditions; specific AUDADIS questions about the chronological relationship between intoxication or withdrawal and the full psychiatric syndrome implement DSM-IV criteria differentiating primary from substance-induced disorders. MDD diagnoses also ruled out bereavement. The AUDADIS assessed age of onset for all the psychiatric disorders. For example, to assess age of onset of MDD the AUDADIS questionnaire includes the following question: "About how old were you the FIRST time you BEGAN (to feel sad, blue, depressed or down/not to care about things or enjoy things) for at least 2 weeks and when you also had some of the other experiences you just mentioned?" Age of onset questions for other psychiatric disorders was similarly worded. Test–retest reliability for AUDADIS-IV mood and anxiety diagnoses in general population and clinical settings was good to fair with kappa agreement statistics ranging from 0.42 for specific phobia to 0.64 for MDD (Grant et al., 1995, 2003; Hasin et al., 1997; Canino et al., 1999).

We examined the following potential correlates of nonmedical opioid use/dependence resulting from nonmedical opioid use for inclusion as control variables: sex, age, race/ethnicity, family income, education, and employment status (see Table 1).

2.2. Statistical analysis

Cross-tabulations and chi-square tests were used to describe the demographic characteristics of the selected sample. Cox proportional hazards models with time-dependent covariates were used to investigate potential pathways between lifetime opioid use/dependence resulting from nonmedical opioid use and psychiatric disorders (Cox, 1974, 1975). Hazards ratios from Cox proportional hazards models provide estimates of the relative risk of an outcome over time for those with a specified risk factor versus those without the factor. By using time-dependent covariates it is possible to take into account the change in the respondent's independent variable status (e.g., using MDD as a time-dependent covariate, a respondent will be non-depressed until the year their MDD disorder began and then be counted as depressed from there on afterwards). These survival analysis regression models also provide for statistical adjustments (e.g., for suspected confounding variables such as sex and race), and allow testing of hypotheses about possible interactions (e.g., see Kalbfleisch and Prentice, 1980). Chronological age was used as the indicator of time, and data from respondents not experiencing the specified outcome by the time of the final interview were censored. In cases in which the outcome and time-dependent covariate occurred during the same year (e.g., ties), it was impossible to determine which came first. To avoid imposing a temporal sequence based on a priori assumptions, observations with tied onset times were censored just before the year in which the tie occurred. The proportional hazards assumption was met in all models (StataCorp, 2007). Stata 10.0 survey commands were used in all analysis to account for sample weighting and the complex survey design (StataCorp, 2007).

We began by testing the self-medication hypothesis (aim 1) by estimating the relative hazard of lifetime nonmedical opioid use in relation to six different preexisting psychiatric disorders first in unadjusted models and then in a model including other covariates (for sex, race, income, education, and employment status). For example, in this set of models, the time-dependent explanatory variable (mood disorders, MDD, bipolar I disorder, anxiety disorders, panic disorder [with/without agoraphobia] and GAD, respectively) preceded nonmedical opioid use. Then, to test the precipitational model (aim 2), we estimated the unadjusted and adjusted relative hazard of psychiatric disorders in relation to preexisting lifetime nonmedical opioid use. In these models, to adjust not only for demographics but also for prior other illegal drug use (e.g., marijuana, cocaine, heroin, hallucinogens, inhalants, and nonmedical use of stimulants, sedatives, and tranquilizers), a time-dependent covariate was created (based on youngest age of onset of any of these other illegal drugs). Notably, taking into account age of onset of nonmedical opioid use and use of other illegal drugs, 42% ($n = 773$) of lifetime nonmedical opioid users ($n = 1755$ with complete data on age of onset) were lifetime users of other illegal drugs, and 57% ($n = 443$) of them had initiated other drug use at a younger age than the age in which they initiated nonmedical opioid use, an extra 8% ($n = 62$) had initiated other illegal drug use at the same age in which they initiated nonmedical opioid use.

Finally, similar sets of Cox proportional hazards models as described above focused on the association between psychiatric disorders and dependence that had resulted from nonmedical opioid use. In the models that estimated the relative hazards of psychiatric disorders following the onset of dependence developed from nonmedical opioid use (aim 2), demographics were included as covariates; prior lifetime alcohol dependence and lifetime other illegal drug dependence were also included as a single time-dependent covariate (based on age of onset of alcohol dependence and of other illegal drug use – youngest age of onset of alcohol dependence or of dependence on any of these other illegal drugs was entered into the model). Among the respondents that met criteria for lifetime dependence resulting from opioid use ($n = 131$), 76% ($n = 100$) also met criteria for lifetime alcohol dependence and for 59% ($n = 59$) of them the age of onset of alcohol dependence preceded the age of onset for dependence from their nonmedical opioid use; for 10% ($n = 10$) the age of onset was tied; 64% ($n = 85$) of those with opioid dependence also met criteria for other illegal drug dependence, 3% ($n = 30$) of them had met criteria for other illegal drug dependence before meeting criteria for nonmedical opioid dependence, for 9% ($n = 12$) the age of onset was tied. In addition, there was a great overlap between respondents with nonmedical opioid dependence that met criteria for both other illegal drug dependence and alcohol dependence (88% of the 85 respondents with other drug dependence also had alcohol dependence, and in 95% of these cases alcohol dependence occurred at an earlier age than other illegal drug dependence).

If pathways were significant for both aims 1 and 2 one could possibly infer that an underlying generalized vulnerability exists, or more generally, for more than one of the comorbidity causation models.

3. Results

3.1. Demographics

There were 1815 lifetime nonmedical opioid users among 43,093 subjects in the 2001–2002 NESARC (representing 4.74% of the general population). Males were more likely to be lifetime nonmedical opioid users than females. Respondents aged 18–29 years old were more likely to be lifetime nonmedical opioid users as compared to those in older age groups (Table 1). African–American and Hispanics were less likely to be lifetime nonmedical opioid users as compared to Whites (Table 1). Respondents with an annual family income of more than $20,000 were less likely to be lifetime nonmedical opioid users as compared to those with an annual family income of less than $20,000 (Table 1). Those that completed high school and had some college education were more likely than those less educated to be lifetime nonmedical opioid users (Table 1). Respondents who were employed were more likely to be lifetime nonmedical opioid users than those who were unemployed (Table 1).

There were 131 subjects who met criteria for dependence resulting from nonmedical opioid use in the 2001–2002 NESARC

Table 1
Lifetime nonmedical opioid use and dependence resulting from nonmedical opioid use by selected demographic characteristics, NESARC 2001–2002.

	All persons	Lifetime nonmedical opioid use				Lifetime dependence resulting from nonmedical opioid use			
	n	*n*	Row wt.%	OR (95% CI)	*p*-Value	*n*	Row wt.%	OR (95% CI)	*p*-Value
Total	43,093	1815	4.7	–	–	131	0.3	–	–
Sex									
Male	18,518	1014	6.1	1.0	–	64	0.4	1.0	–
Female	24,575	801	3.5	0.6 (0.5, 0.6)	<0.001	67	0.3	0.7 (0.5, 1.0)	0.057
Age									
18–29	8,666	559	7.4	1.0	–	34	0.5	1.0	–
30–44	13,382	701	5.7	0.8 (0.7, 0.9)	<0.001	47	0.4	0.8 (0.5, 1.4)	0.454
45–64	12,840	474	3.9	0.5 (0.4, 0.6)	<0.001	47	0.4	0.8 (0.5, 1.5)	0.514
65+	8,205	81	1.1	0.1 (0.1, 0.2	<0.001	3	0.02	0.05 (0.01, 0.2)	<0.001
Race/ethnicity									
White	24,507	1254	5.3	1.0	–	86	0.4	1.0	–
African–American	8,245	204	2.6	0.5 (0.4, 0.6)	<0.001	17	0.2	0.6 (0.3, 1.3)	0.195
Hispanic	8,308	260	3.1	0.6 (0.5, 0.7)	<0.001	12	0.2	0.6 (0.2, 1.7)	0.318
Other[a]	2,033	97	4.8	0.9 (0.7, 1.2)	0.386	16	0.7	2.0 (1.1, 3.7)	0.033
Annual family income									
0–$19,999	12,648	551	5.7	1.0	–	57	0.6	1.0	–
$20,000–$34,999	9,361	407	4.7	0.8 (0.7, 10)	0.016	31	0.4	0.6 (0.3, 1.1)	0.090
$35,000–$69,999	12,938	564	4.8	0.8 (0.7, 1.0)	0.011	32	0.2	0.4 (0.2, 0.6)	<0.001
$70,000+	8,146	293	3.8	0.7 (0.6, 0.8)	<0.001	11	0.2	0.3 (0.1, 0.6)	0.001
Education									
<12 yrs	7,849	271	4.6	1.0	–	33	14.1	1.0	–
High school	12,547	504	4.7	1.2 (1.0, 1.4)	0.040	32	6.6	0.6 (0.4, 0.9)	0.044
Some college	12,663	688	5.9	1.6 (1.4, 1.9)	<0.001	54	6.9	1.0 (0.7, 1.6)	0.949
College or more	10,034	352	3.6	1.0 (0.9, 1.2)	0.841	12	3.1	0.3 (0.1, 0.5)	<0.001
Employment status									
Employed	26,979	1287	5.3	1.5 (1.3, 1.7)	<0.001	75	0.3	0.7 (0.4, 1.1)	0.129
Unemployed	16,114	528	3.8	1.0	–	56	0.4	1.0	–
Mood disorders									
Present	8,746	851	10.6	3.5 (3.1, 3.9)	<0.001	100	1.3	13.6 (7.9, 23.4)	<0.001
Absent	34,347	964	3.3	1.0	–	31	0.1	1.0	
Major depression									
Present	7,742	745	10.5	3.2 (2.9, 3.6)	<0.001	83	1.2	8.6 (5.3, 13.9)	<0.001
Absent	35,351	1070	3.5	1.0	–	48	0.2	1.0	
Bipolar I disorder									
Present	1,055	183	17.73	4.7 (3.8, 5.7)	<0.001	38	4.1	17.1 (9.1, 29.5)	<0.001
Absent	42,000	1632	4.41	1.0	–	93	0.3	1.0	
Anxiety disorders									
Present	7,437	605	8.9	2.4 (2.2, 2.8)	<0.001	78	1.2	8.5 (5.6, 13.0)	<0.001
Absent	35,656	1210	3.9	1.0	–	53	0.2	1.0	
Panic disorder (with/without agoraphobia)									
Present	2,251	266	12.3	3.1 (2.6, 3.7)	<0.001	45	2.4	11.1 (7.2, 17.1)	<0.001
Absent	40,842	1549	4.3	1.0	–	86	0.2	1.0	
Generalized anxiety disorder									
Present	1,927	194	10.4	2.5 (2.0, 3.0)	<0.001	35	1.9	7.1 (4.5, 11.2)	<0.001
Absent	41,166	1621	4.5	1.0	–	96	0.3	1.0	

[a] Includes Native-Americans and Asians.

(representing 0.3% of the general population). We did not see any differences by sex. Native-Americans and Asians were more likely to be dependent on opioids as a result of their nonmedical use as compared to Whites (Table 1). Those who completed high school and those that had a college degree were less likely to meet criteria for dependence resulting from nonmedical opioid use as compared to those with less than 12 years of education, as were respondents with an annual family income higher than $35,000 as compared to those with an annual family income of less than $20,000 (Table 1).

3.2. Hazard of nonmedical opioid use by preexisting psychiatric disorders

Preexisting mood disorders, bipolar I disorder, MDD, anxiety disorders, panic disorder [with/without agoraphobia] and GAD were significantly associated with an increased likelihood of subsequent nonmedical opioid use in unadjusted and adjusted models (adjusted HR = 2.2[95% CI = 1.9–2.6]–3.1[95% CI = 2.4–4.0], Table 2).

3.3. Hazard of dependence resulting from nonmedical opioid use by preexisting psychiatric disorders

Preexisting mood disorders, MDD, bipolar I disorder, anxiety disorders, panic disorder [with/without agoraphobia] and GAD were significantly associated with an increased likelihood of subsequent onset of dependence resulting from nonmedical opioid use in unadjusted and adjusted models (adjusted HR = 4.6[95% CI = 2.8–7.6]–10.8[95% CI = 4.9–23.7], Table 2). In some cases (bipolar I disorder, anxiety disorders, and GAD) the hazard ratios were appreciably greater for dependence resulting from nonmedical opioid useresulting from nonmedical opioid useresulting from nonmedical opioid use than for nonmedical opioid use alone (Table 2).

Table 2
The unadjusted and adjusted relative hazard ratios of nonmedical opioid use and opioid dependence resulting from nonmedical opioid use among users by presence of preexisting psychiatric disorders. Results from Cox proportional hazard models with time-dependent covariates, NESARC, 2001–2002.

	Nonmedical opioid use		Opioid dependence resulting from nonmedical opioid use	
	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[a]95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
Mood disorders				
Present	4.3 (3.7, 5.0)*	2.9 (2.5, 3.4)*	9.2 (5.6, 15.0)*	5.7 (3.4, 9.5)*
Major depression				
Present	4.2 (3.6, 4.9)*	2.8 (2.4, 3.4)*	7.4 (4.6, 12.1)*	4.6 (2.8, 7.6)*
Bipolar I disorder				
Present	5.2 (4.1, 6.7)*	3.1 (2.4, 4.0)*	19.0 (11.0, 32.8)*	9.7 (5.4, 17.3)*
Anxiety disorders				
Present	2.6 (2.2, 2.9)*	2.2 (1.9, 2.6)*	7.4 (4.6, 11.9)*	6.0 (3.7, 9.7) *
Panic disorder (with/without agoraphobia)				
Present	3.6 (2.7, 4.8)*	2.6 (1.9, 3.4)*	12.1 (6.1, 23.7)*	6.9(3.3, 14.2)*
Generalized anxiety disorder				
Present	3.4 (2.4, 4.6)*	2.2 (1.6, 3.1)*	17.8 (8.2, 38.3)*	10.8 (4.9, 23.7)*

[a] Adjusted for sex, age, race, income, education and employment status.
* $p < 0.001$.

We also conducted analyses to test whether preexisting psychiatric disorders were associated with an increased likelihood of subsequent dependence among the subset of individuals who used opioids nonmedically. Results were similar, but of somewhat weaker magnitude (data available upon request).

3.4. Hazard of specific psychiatric disorders by preexisting nonmedical opioid use

Preexisting nonmedical opioid use was significantly associated with an increased likelihood of subsequent mood disorders, bipolar I disorder, MDD, anxiety disorders, panic disorder [with/without agoraphobia], and GAD in unadjusted and adjusted models, even when adjusted for other illegal drug use (adjusted HR = 2.8[95% CI = 2.2–3.6]–3.6[95% CI = 2.6–4.9], Table 3). In addition, preexisting other illegal drug use was significantly associated with an increased likelihood of subsequent psychiatric disorders, even when adjusted by preexisting nonmedical opioid use (adjusted HR = 1.7[95% CI = 1.6–1.9]–2.2[95% CI = 1.7–2.7], Table 4). In all adjusted models, the magnitude of the hazard ratios for preexisting nonmedical opioid use was higher than for preexisting other drug use (Tables 3 and 4).

3.5. Hazard of psychiatric disorders by preexisting dependence resulting from nonmedical opioid use

Preexisting dependence resulting from nonmedical opioid use was significantly associated with an increased likelihood of mood disorders, MDD, bipolar I disorder, anxiety disorders, panic disorder [with/without agoraphobia], and GAD in the unadjusted and adjusted models, even when adjusted for alcohol and/or other illegal drug dependence (adjusted HR = 4.1[95% CI = 1.9–9.0]–8.5[95% CI = 4.5–16.0], Table 3). With the exception of associations with panic disorder, the relative magnitude of the associations were similar to those found with preexisting nonmedical opioid use (Table 3).

Preexisting alcohol and/or other illegal drug dependence was significantly associated with an increased likelihood of psychiatric disorders, even when adjusted for preexisting dependence resulting from nonmedical opioid use (adjusted HR = 2.5[95% CI = 2.2–2.7]–3.4[95% CI = 2.9–3.9], Table 4). In some models (mood

Table 3
The unadjusted and adjusted relative hazard ratios of psychiatric disorders by presence of preexisting nonmedical opioid use and opioid dependence resulting from nonmedical opioid use. Results from Cox proportional hazard models with time-dependent covariates, NESARC, 2001–2002.

	Nonmedical opioid use		Opioid dependence resulting from nonmedical opioid use	
	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[b] (95% CI)
Opioid use/dependence preceding mood disorders				
Present	3.8 (3.4, 4.3)**	3.2 (2.9, 3.7)**	5.5 (3.3, 9.2)**	4.9 (3.0, 7.9)**
Opioid use/dependence preceding major depression				
Present	3.6 (3.2, 4.1)**	3.1 (2.7, 3.5)**	5.9 (3.5, 9.7)**	5.2 (3.2, 8.2)**
Opioid use/dependence preceding bipolar I disorder				
Present	4.7 (3.5, 6.3)**	3.6 (2.6, 4.9)**	6.8 (2.1, 22.6)**	5.0 (1.5, 16.4)*
Opioid use/dependence preceding anxiety disorders				
Present	2.9 (2.4, 3.4)**	2.8 (2.4, 3.4)**	6.4 (3.3, 12.4)**	6.1 (3.1, 12.2)**
Opioid use/dependence preceding panic disorder (with/without agoraphobia)				
Present	4.1 (3.4, 5.0)**	3.6 (2.9, 4.4)**	11.0 (6.4, 19.0)**	8.5 (4.5, 16.0)**
Opioid use/dependence preceding generalized anxiety disorder				
Present	3.3 (2.6, 4.2)**	2.8 (2.2, 3.6)**	4.7 (2.1, 10.5)**	4.1 (1.9, 9.0)**

[a] Adjusted for sex, age, race, income, education, employment status and other drug use (time-varying covariate).
[b] Adjusted for sex, age, race, income, education, employment status and alcohol and/or other illegal drug dependence (time-varying covariate).
* $p < 0.005$.
** $p < 0.001$.

Table 4
The unadjusted and adjusted relative hazard ratios of psychiatric disorders by presence of preexisting other illegal drug use and alcohol and/or other illegal drug dependence. Results from Cox proportional hazard models with time-dependent covariates, NESARC, 2001–2002.

	Other illegal drug use		Alcohol + other illegal drug dependence	
	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio[b] (95% CI)
Other illegal drug use/alcohol and/or other illegal drug dependence preceding mood disorders				
Present	2.2 (2.1, 2.4)*	1.8 (1.7, 2.0)*	3.1 (2.8, 3.3)*	2.6 (2.4, 2.8)*
Other illegal drug use/alcohol and/or other illegal drug dependence preceding major depression				
Present	2.1 (2.0, 2.3)*	1.7 (1.6, 1.9)*	2.9 (2.6, 3.1)*	2.5 (2.2, 2.7)*
Other illegal drug use/alcohol and/or other illegal drug dependence preceding bipolar I disorder				
Present	2.5 (2.0, 3.1)*	2.2 (1.7, 2.7)*	4.1 (3.2, 5.2)*	3.2 (2.5, 4.1)*
Other illegal drug use/alcohol and/or other illegal drug dependence preceding anxiety disorders				
Present	2.1 (1.9, 2.3)*	1.9 (1.7, 2.1)*	3.2 (2.8, 3.6)*	3.1 (2.7, 3.5)*
Other illegal drug use/alcohol and/or other illegal drug dependence preceding panic disorder (with/without agoraphobia)				
Present	2.2 (2.0, 2.6)*	2.0 (1.7, 2.2)*	3.9 (3.4, 4.5)*	3.4 (2.9, 3.9)*
Other illegal drug use/alcohol and/or other illegal drug dependence preceding generalized anxiety disorder				
Present	2.3 (2.0, 2.7)*	1.9 (1.6, 2.2)*	3.4 (2.8, 4.0)*	2.8 (2.4, 3.3)*

[a] Adjusted for sex, age, race, income, education, employment status and nonmedical opioid use (time-varying covariate).
[b] Adjusted for sex, age, race, income, education, employment status and dependence resulting from nonmedical opioid use (time-varying covariate).
* $p < 0.001$.

disorders, MDD, and panic disorder) the magnitude of the association was stronger for dependence resulting from nonmedical opioid use as compared to alcohol and/or other illegal drug dependence (Tables 3 and 4).

Restricting the sample to the subset of individuals who used opioid nonmedically, we also found similar, but weaker magnitude, in models estimating the association between preexisting dependence resulting from their nonmedical opioid use and subsequent psychiatric disorders (data available upon request).

4. Discussion

We found support for pathways in both directions between nonmedical opioid use and onset of psychiatric disorders. All of the psychiatric disorders tested were estimated to be three times as likely to precede nonmedical opioid use (HR ranging from 2.8 to 3.1). Nonmedical use of opioids was linked to subsequent increased risk of mood disorders (MDD and bipolar I disorders) and anxiety disorders (panic and GAD), with hazard ratios ranging from 2.8 to 3.6, even in the presence of preexisting other illegal drug use. In sum, these data provide support for the presence of a general vulnerability to both psychiatric disorders and nonmedical opioid use (hazard ratios in opposite directions were of similar magnitude), for a self-medication pathway and for a precipitational model pathway.

The conclusions for the associations between psychiatric disorders and dependence resulting from nonmedical opioid use are more complex. Individuals with preexisting psychiatric disorders were estimated to be at increased risk for the onset of dependence resulting from the nonmedical opioid use, with particularly strong hazard ratios documented for GAD and bipolar I disorder (HR∼10). The estimated associations between preexisting dependence resulting from nonmedical opioid use and the onset of psychiatric disorders were also increased at a strong but generally lower magnitude than the reverse ordering (HR ranging from 4.1 to 8.5) This again indicates support for pathways in both directions (self-medication and precipitational model) and a general vulnerability model for dependence resulting from nonmedical opioid use and psychiatric disorders, but more strongly for a self-medication model for the onset of dependence from nonmedical use of opioids after preexisting bipolar I disorder and GAD.

An underlying general vulnerability to both opioid use and mood/anxiety disorders may be the explanatory factor in the observed associations between opioid use and psychiatric disorders. While a robust literature has suggested a shared etiology for illegal drug use and externalizing psychopathology with a large heritable component (Hicks et al., 2004; Krueger, 1999; Krueger et al., 1998, 2003; Vollebergh et al., 2001; Sullivan and Kendler, 1998), the underlying pathways linking drug use to mood and anxiety disorders remains debated in the literature. Certainly, the etiologic pathways between drug use and psychopathology are complex and multifactorial; as such, the aggregation of illegal drug use and dependence into one class may obscure rather than illuminate relevant mediational models. Due to the large sample size of the NESARC, we can examine drug-specific pathways to motivate research questions and refine hypothesis testing. While broad phenotype definition of "internalizing" and "externalizing" psychopathology are common in genetic studies (Young et al., 2000, 2002; Jorm et al., 2000, 2001; Rowe et al., 1998), these results suggest that productive genetic linkage and association studies could test relevant shared vulnerability hypotheses by aggregating nonmedical opioid use and dependence with mood and anxiety disorders for phenotype definition. Additionally, subgroups of individuals with distinct pathways might exist; for instance, some individuals who self-medicate, some who develop psychopathology in response to use, and some with shared vulnerability. Further research in this area and other large datasets using growth modeling and latent class analysis to disaggregate pathways of users might be productive.

As previously described, the self-medication pathway is predicated on two necessary assumptions: the psychiatric disorder preceded the onset of the drug use and/or disorder, and the use of the drug alleviates symptoms of the specific psychiatric disorder (Khantzian, 1997, 2003). We found that bipolar I disorder and GAD were strongly associated to the subsequent onset of dependence resulting from nonmedical opioid use with weaker evidence for the converse. Additionally, evidence from clinical and psychopharmacologic studies indicates that the acute effect of opioids include antidepressant, anti-panic, and anti-anxiety symptom reduction (Gold et al., 1979, 1982; Emrich et al., 1982). As such, the use of opioids amounts leading to opioid dependence to relieve these symptoms in individuals with bipolar disorder and GAD could be a reasonable hypothesis. Additionally, while we found evidence for a shared vulnerability between opioid use/dependence and other psychiatric disorders, shared vulnerability does not rule out the possibility that some individuals use opioids for symptom reduc-

tion during acute phases of psychiatric illness. We also conducted analyses for the temporal sequencing of dependence resulting from nonmedical opioid use and psychiatric disorders among the subset of individuals who used opioids nonmedically (available upon request) to shed light on whether unique genetic components may be implicated in use versus dependence (Heiman et al., 2008). Results were similar in direction as those obtained in the overall population, but of somewhat weaker magnitude, indicating further support for a generalized non-specific vulnerability model for the association between dependence resulting from nonmedical opioid use and psychiatric disorders.

Case reports and small clinical studies have suggested that opioid use can induce manic episodes in subjects with pre-existing affective disorders (Shaffer et al., 2007; Watts and Grady, 1997; Gonzalez-Pinto et al., 2001; Orr et al., 1998). While we do not have information on reasons for opioid use among individuals with bipolar disorder (e.g., to self-medicate back pain symptoms – analgesia or simply to "get high" – euphoria), we did find strong and significant associations for an increased risk of opioid use and dependence in the presence of bipolar disorder. This provides some epidemiologic support for a link between opioids and mania in the general population.

Several study limitations merit mention. First, all information is based on self-report, as in all large-scale epidemiologic surveys. As such, the validity of these results is predicated on the accuracy of the age of onset information provided by respondents. Further, as the wave 1 NESARC survey is a cross-sectional design relying on retrospective reports, older respondents may be reporting age of onset information that occurred several decades previously, which might lead to recall bias. However, we do not think recall bias would be differential across any relevant subpopulations, thus having limited effect on our hazard ratios and other effect estimates. We are currently planning follow-up analyses on temporal ordering of substance use and psychiatric disorders as the 3-year follow-up of NESARC participants becomes available, however, these analyses will be limited to the time-frame of the NESARC study. Moreover, due to the nature of the NESARC data we relied on information on age of onset of psychiatric disorders and not on age of onset of sub-threshold psychiatric symptoms, respondents might have been experiencing sub-threshold symptoms before the onset of the psychiatric disorder. Further, we do not have information on whether nonmedical opioid users initiate opioid seeking euphoria (via medical prescription or not) or analgesia (via medical prescription or not) and where the first significant exposure occurred. Subtypes of opioid users may be unique in many aspects of comorbidity and demographics. Because the NESARC does not focus on opioid use specifically, this level of detail in a large-scale survey is untenable. Future research specifically focusing on opioid use and dependence may be able to provide more information on subtypes of opioid users in the general population. In addition, the use of time-varying covariates assumes that once the disorder appears, it remains indefinitely, however, substance use disorders and other psychiatric disorders often remit, or remit and relapse. With NESARC data it is not possible to take into account age of remission and relapse in these models.

Despite these limitations, the present study adds substantial information to the literature on opioid use and dependence and psychopathology. The large sample size of the NESARC allows for statistical power to test temporal ordering of not only opioid use but also the less common condition of dependence that had resulted from nonmedical opioid use with psychiatric disorders. Further, the AUDADIS-IV has documented reliability and validity in assessing drug use disorders as well as psychiatric disorders. Thus, the NESARC study is well suited to provide much-needed information about the temporal ordering of use and dependence on drugs such as the relationship between nonmedical opioid use with psychiatric disorders. As both the incidence and prevalence of opioid use and dependence in the population continue to show increases over the past decade, information of causal pathways is an important public health goal to better understand the specific comorbidities of opioid users as they may be distinct from other drug users. Our findings support a general vulnerability to opioid use and major psychopathologies, as well as evidence for a 'self-medication' model for dependence resulting from nonmedical opioid use with bipolar disorder and GAD. Future research with the longitudinal aspects of the NESARC study may be able to refine and extend these findings but using age of onset information less distal from some individuals in the study.

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Contributors

Drs. Martins and Chilcoat wrote the research questions. Dr. Martins and Ms. Zhu undertook the statistical analyses, Dr. Martins wrote the first draft of the manuscript. Drs. Martins and Storr and Ms. Keyes managed the literature searches and summaries of previous related work. All authors revised the manuscript drafts. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Chilcoat is currently employed by GlaxoSmithKline. All other authors declare that they have no conflicts of interest.

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