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Exploring the latent trait of opioid use disorder criteria among frequent nonmedical prescription opioid users



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ABSTRACT

Background: There is a need to explore the dimensional and categorical phenotypes of criteria of opioid use disorder among frequent nonmedical users of prescription opioids (NMUPO) users.

Methods: We used pooled data of 2011–2012 National Survey on Drug Use and Health to examine reliability and phenotypic variability in the diagnosis of OUD secondary to NMUPO in a nationally-representative sample of 18+ years-old frequent past-year NMUPO users (120+ days, n = 806). Through exploratory factor analysis (EFA) and latent class analysis (LCA), we examined 10 past-year OUD criteria. We examined associations between the latent classes and sociodemographic/psychiatric/NMUPO correlates.

Results: OUD criteria were unidimensional, and a three-class model was the overall best fitting solution for characterizing individuals into phenotypes along this unidimensional continuum: a “non-symptomatic class” (40.7%), “Tolerance-Time spent class” (29.0%) with high probability of endorsing Tolerance/Time Spent criteria, and a “High-moderate symptomatic class” (30.1%). The last class was significantly associated with being male, having insurance and obtaining prescription opioids (PO) nonmedically via “doctor shopping” as compared to the non-symptomatic class. “Tolerance-Time spent class” was significantly associated with being younger (18–25 years) and obtaining PO nonmedically from family/friends as compared to the non-symptomatic class.

Conclusion: This study revealed the different characteristics and routes of access to PO of different classes of frequent NMUPO users. It is possible that these groups may respond to different interventions, however such conclusions would require a clinical study.

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1. Introduction

In 2014, there was a higher number of opioid overdoses deaths than in any year on record (CDC, 2015). Overdoses from prescription opioid pain relievers play the main role in this increase in opioid overdose deaths – at least half of these deaths involve a

prescription opioid (CDC, 2015). Since 1999, U.S. prescription opioids sold nearly quadrupled (CDC, 2011). Despite the evident importance of opioid misuse in public health, few studies have examined the unidimensional diagnostic structure of Opioid Use Disorders (OUD) through factor analysis (FA) and item response theory (IRT) (Boscarino et al., 2011; Saha et al., 2012). Even fewer studies have focused on the diagnostic structure as it applies specifically to non-medical use of prescription opioids (NMUPO) (Wu et al., 2009, 2011). FA is a technique that allows reduction of a large number of interrelated variables, such as the DSM criteria (APA, 2013) for OUD, to a smaller number of hidden dimensions (or

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dormant), such as the unidimensional model proposed for OUD according to DSM-5 (APA, 2013). In addition, IRT provides mathematical models for the dimensional structure, proposing forms of representing how individuals fulfill each DSM-5 OUD criteria.

Considering that OUD can be a clinically heterogeneous syndrome (Kendler et al., 2013), studies have also used latent class analysis (LCA) to better understand phenotypic differences of DSM-IV OUD criteria among NMUPO (Ghandour et al., 2008; Wu et al., 2011). LCA generates categorical phenotypes (individuals subgroups, subtypes or clusters) based on the response pattern likelihood and is in line with the identification of categorical diagnosis within the unidimensional OUD structure. In the case of DSM-IV criteria for Opioid Dependence for NMUPO, there is a certain degree of uncertainty on which should be the best LCA model (2 or 4 classes) (Wu et al., 2011; Ghandour et al., 2008). A reliable model should be repeated in different samples of the general population of the same country. Therefore, it is important to continue investigating this matter in more recent samples. This is even more important nowadays, considering the new edition of DSM (DSM-5), which created a new categorization of symptoms that one needs to report to be classified as having an OUD (APA, 2013).

To date, no study has yet examined phenotypic variation in OUD criteria among frequent NMUPO users. Frequent NMUPO users are of interest because they reflect more accurately the experiences of individuals at high risk of becoming dependent and those already dependent. These frequent users also have a more active role in obtaining pharmaceutical opioids compared to infrequent users (Daniulaityte et al., 2014). In addition, between 2002 and 2010, the rate of NMUPO increased significantly in U.S., paralleling with increases in treatment admissions, overdose deaths, and other negative effects associated with NMUPO in the same period (Paulozzi et al., 2011; Jones, 2012). Examining the categorical phenotypes of OUD among frequent NMUPO users can provide insight into potential subtypes of the most problematic NMUPO users.

Knowing about the potential OUD subtypes (classes) among NMUPO, we gain the ability to identify groups of users that: have different socio-demographic correlates; seek for PO in different ways (i.e., doctor shopping); have different evolution over time and different clinical and psychiatric comorbidities; who respond and search differently to treatment available; among other characteristics of interest. For instance, knowing which are the subgroups that engage in doctor shopping is extremely useful information for practitioners and researchers. Doctor shopping is when someone consults different doctors obtaining overlapping prescriptions (Nordmann et al., 2013), and is considered one of the main means of diversion for prescription medications in the United States (Lineberry and Bostwick, 2004; Pradel et al., 2004).

Through confirmatory FA and IRT, we confirmed and explored the unidimensional model of OUD for a general population sample of frequent NMUPO users in the US. To do this, we generated a proxy of DSM-5 criteria. In addition, we use LCA to explore categorical phenotypes within the best dimensional model using 10 criteria from DSM-5 OUD. We further examine the sociodemographic, psychiatric and NMUPO sources (i.e., doctor-shopping, family/friends) correlates of membership in each latent class, comorbidity of each latent class with other types of substance use disorders, and treatment-seeking behavior.

2. Material and methods

2.1. Sample

In 2011–2012, the National Survey of Drug Use and Health (NSDUH) collected data from 138,418 respondents [n

(2011) = 70,109; n (2012) = 68,309] aged 12 or older and was designed to obtain representative samples from the 50 States and the District of Columbia (SAMHSA, 2012, 2013). Two consecutive NSDUH years were combined in order to increase the sample size of frequent NMUPO users (please see more details on Supplementary File 6).

2.2. Measures

The NSDUH questionnaire has reliability for substance use in the past-year and lifetime ranging from 0.72 to 0.93 and 0.71 to 0.95, respectively (Jordan et al., 2008; National Household Survey on Drug Abuse, 2010a,b, 2012, 2013). For past-year and lifetime NMUPO, kappa coefficient is respectively 0.73 and 0.78. As with all self-report surveys, the validity of responses to questions on substance use and diagnostic symptoms of SUD may be biased. Jordan et al. (2008) have conducted a study to investigate the clinical validity of SUD symptoms in the NSDUH using the Structured Clinical Interview for DSM-IV (SCID-IV) for adults and the Pittsburgh Adolescent Alcohol Research Center's Structured Clinical Interview (PAARC-SCID) for adolescents. Their study showed the level of agreement between the NSDUH and the SCID/PAARC-SCID interviews to be fair to moderate overall. There was somewhat better agreement for dependence than for abuse and for adults than for adolescents (CBHSQ, 2014).

2.2.1. Past-year frequent NMUPO users

NMUPO was defined as any self-reported use of prescription pain relievers that were not prescribed for the respondent or that the respondent took only for the experience or feeling they caused (National Household Survey on Drug Abuse, 2010a,b, 2012, 2013). In order to reduce false-positive responses, all respondents were given the following instructions: "These questions are about prescription pain reliever use. We are not interested in your use of over-the-counter pain relievers that can be bought in stores without a doctor's prescription." The survey used discrete questions and a card with pictures of many types of prescription opioids. The respondents were asked which ones he/she had used, as well as frequency of use. Users were classified both by whether they had ever used opioids non-medically and whether they had used in the past year. We defined as past-year frequent NMUPO users those that had used prescription opioids non-medically on at least 120 days in the past-year (n = 806). Because there is no standard definition for frequent NMUPO use, our definition of frequent users is similar to the definition existing literature proposed by Jones (2012) to explore different DSM phenotypes among those with a high likelihood of developing OUD (i.e., using POs nonmedically at least twice a week).

The 806 subjects who reported NMUPO at least 120 days in the past year were asked a series of 17 structured questions derived from past-year DSM-IV opioid abuse/dependence criteria embedded in the 2011–2012 NSDUH questionnaire. These questions were combined to generate 10 dichotomous variables matching 10 of the 11 DSM-5 criteria. The only DSM-5 OUD criterion that was not included in the 2011–2012 NSDUH questionnaire was the craving criterion, which is derived from ICD-10 diagnosis of dependence. The abbreviation of the variable names was based on previously published studies (Hasin and Beseler, 2009; Shmulewitz et al., 2010; Castaldelli-Maia et al., 2014a,b): Tolerance, Withdrawal, Larger/Longer, Quit/Control, Time Spent, Given Up, Physical/Psychological, Major Role, Social/Interpersonal, and Hazardous Use.

2.2.2. Sociodemographic correlates

The following sociodemographic correlates were included in the regression models based on a previous LCA study (Ghandour et al.,

2008): sex (female and male), age (categorized as 12–17, 18–25, 26–34, and ≥ 35 years); education (low: = less than high school; low-average: = high school graduate; high-average: = some college; high: = college graduate); race/ethnicity (non-Hispanic (NH) White, NH Black, Hispanic, and other); marital status (married/cohabiting, previously married: = separated/divorced/widowed, never married); and income, defined in categories (poverty, low income = up to twice the Federal poverty threshold, high income: = more than twice the Federal poverty threshold, students: = persons aged 18 to 22 living in a College dorm). We also included three variables that were described as important correlates of NMUPO use in non-LCA studies (Nielsen et al., 2011; Fibbi et al., 2012; Wang et al., 2013): Metropolitan Statistical Area (large metropolitan area, small metropolitan area, and non-metropolitan area); health insurance (yes or no); and employment status (employed, unemployed, and missing).

2.2.3. Psychiatric comorbidity, NMUPO sources, and other substance dependence

Three potential psychiatric-related correlates were included in the regression model: (i) past-year anxiety disorder; (ii) past-year major depressive episode (MDE); and (iii) antisocial behaviors. Three variables that indicated sources of NMUPO (how respondents obtained POs in the past month in the last time they used these drugs) were included in the regression model: (i) Doctor shopping; (ii) Bought from a drug dealer, and (iii) Obtained PO from family/friends. More details on psychiatric comorbidity, NMUPO sources, and other substance dependence can be found in [Supplementary File 6](#).

2.2.4. Lifetime treatment for prescription opioid disorders and mental health/addiction treatment

A respondent was classified as receiving past-year mental health or addiction treatment if she/he received treatment in any location for mental health disorders, or alcohol or drug problems, in the past year. Finally, we created a past-year prescription opioid treatment variable based on the self-report data of receiving treatment in the last 12 months, including current treatment (or counseling) for PO use.

2.3. Statistical analysis

All analyses were performed with Mplus version 7, using sampling weights and the complex survey design measures. Descriptive statistics were used to describe the sample. Specifically, counts and percentages were used to describe categorical variables.

A confirmatory factor analysis (CFA) unidimensional model was carried out using considering the 10 criteria as categorical variables. IRT models were used to study the latent opioid use disorder construct. IRT models analyze the relationship between the probabilities of an individual to endorse a certain response to an item. IRT analysis implemented in Mplus was used to derive two main parameters, the threshold and the discrimination parameters. The first refers to the 'severity' of a criterion (threshold), with high severity items being those that the individual should have worse OUD (the latent trait) in order to endorse the criterion. The second parameter measures the ability of a criterion to discriminate respondents from low to high levels of the disorder continuum (slope).

LCA was conducted using maximum likelihood ratio estimation. The random option in Mplus was used to ensure convergence of the most successful LCA models. Specifically, 500 sets of random starting values were used in the initial phase, and 5 optimizations were used in the final stage of convergence. This process ensured that the best log-likelihood value for each model was replicated

several times. Several statistical indices were used to assess the fit of the models, including log-likelihood (LL), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and sample-size-adjusted BIC (SSABIC). A low value of log-likelihood together with smaller amounts in AIC BIC, and SSABIC may reflect a more parsimonious model (Muthén, 2006). However, the BIC value has been shown to be more reliable than other information (Nylund et al., 2007).

Once the number of classes was determined, we used 2 polytomous logistic regression models (pseudo-class draw method) to investigate the association between latent classes and: (i) NMUPO sources; (ii) sociodemographic characteristics; and (iv) psychiatric correlates with adjustment for sociodemographic characteristics. The Mplus auxiliary option was used to identify the prevalence of alcohol, tobacco, cannabis, cocaine, stimulant, tranquilizer and pain relievers dependence, mental health/addiction treatment and treatment for pain relievers disorders, for which the equality of means across latent classes were tested using pseudo-class-based multiple imputations (Asparouhov, 2007). Chi-squared tests were used to compare the prevalence of these variables among the latent classes.

3. Results

[Table 1A](#) presents the results of CFA and IRT models. The one-dimensional (one-factor model) obtained high loadings (>0.7) on all 10 criteria of OUD among past-year frequent NMUPO. In the IRT models, the criteria with the lowest value on severity were Tolerance and Time Spent. Moreover, the criteria with greater severity in these models were Quit/Control and Hazardous Use. Other criteria that had greater severity were Neglect Roles and Larger/Longer. Regarding discrimination, all the criteria had strong values.

[Table 1B](#) presents the LCA model fit indices. The best LCA model was the 4-class model. However, one of the latent classes ("Non-loss control class") was too small to investigate correlates of NMUPO ($<8\%$ of the sample), which is an aim of the present study. The LCA graph for this model is presented in [Supplementary File 2](#). Based on the LCA index, the second best model was the 3-class model, which had acceptable latent classes sizes. Latent class structure did not differ by age: the 3-class model was the best fit when including the adolescent subsample ([Supplementary File 3 and 4](#)).

[Table 2](#) presents the weighted probability of endorsement of OUD criteria in the best-fit model, and the probability of reporting OUD criteria and prevalence for each latent class. The "Non-symptomatic class" included individuals with probability close to zero for all OUD criteria. The "Tolerance-Time Spent class" included individuals with low probabilities ($<30\%$) of meeting all diagnostic criteria, with the exception of a high probability of endorsement of the Tolerance and Time Spent criteria (above 80%), Withdrawal (48%) and Physical/Psychological (35%). Individuals in the "high-moderate symptomatic class" had high ($>70\%$) or moderate ($>40\%$) probabilities of endorsement all the criteria. The largest class was the "Non-symptomatic class" (40.7%), followed by the "Tolerance-Time Spent class" (29.0%) and the "High-moderate symptomatic class" (30.1%). Approximately half of the individuals who reported Tolerance and Time Spent criteria were in the "Tolerance-Time Spent control class". However, most of the individuals who reported all other criteria were in the "high-moderate symptomatic class". Tolerance was the criteria with highest prevalence (59.7%) in the total sample of frequent NMUPO, followed by Time Spent (55.6%). [Supplementary File 1](#) presents the weighted probability of endorsement of OUD criteria in the best-fit model.

[Table 3A](#) presents the results of the logistic regression models examining sociodemographic correlates of the two most

Table 1A

Confirmatory factor analysis (CFA) and item response theory (IRT) findings with DSM-5 opioid use disorder among past-year frequent nonmedical prescription opioid users (those that used at least 120 days) in the United States, 2011–2012.

	n*	%	CFA	IRT	
			One factor	Discrimination (SE)	Severity (SE)
Tolerance	513	63.6	0.911	2.25 (0.29)	−0.38 (0.05)
Withdrawal	314	39.0	0.743	1.11 (0.09)	0.37 (0.06)
Larger/longer	231	28.7	0.827	1.48 (0.12)	0.67 (0.06)
Quit/control	190	23.6	0.710	1.01 (0.08)	1.01 (0.08)
Time spent	485	60.2	0.918	2.35 (0.30)	−0.28 (0.04)
Given up	250	31.0	0.948	3.05 (0.36)	0.52 (0.05)
Physical/psychological	293	36.4	0.882	1.89 (0.16)	0.39 (0.05)
Neglect roles	203	25.2	0.934	2.66 (0.31)	0.71 (0.05)
Social/interpersonal	253	31.4	0.887	1.94 (0.16)	0.54 (0.05)
Hazardous	189	23.4	0.808	1.38 (0.11)	0.89 (0.06)

* Estimated value of n since after de imputation of weights/clusters/strata it is not possible to calculate the exact value of n.

** DSM-5 Opioid Use Disorder criteria: Tolerance - as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve Intoxication or desired effect; (b) markedly diminished effect with continued use of the same amount of opioid; Withdrawal - as manifested by either of the following: (a) the characteristic withdrawal syndrome for opioid (refer to Criteria A and B of the criteria sets for withdrawal from alcohol); (b) opioids (or a closely related substance) is used to relieve or avoid withdrawal criteria; Larger/Longer - opioids is often used in larger amounts or over a longer period than was intended; Quit/Control - there is a persistent desire or unsuccessful efforts to cut down or control opioid use; Time Spent - a great deal of time is spent in activities necessary to obtain opioid, use opioid, or recover from its effects; Given Up - important social, occupational, or recreational activities are given up or reduced because of opioid use; Physical/Psychological - alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioid; Neglect Roles - recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home; Social/Interpersonal - continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the opioid; Hazardous Use - recurrent opioid use in situations in which it is physically hazardous. Craving criterion was not included in the present study.

Table 1B

LCA model fit statistics of 10 of the 11 DSM-5 opioid use disorder criteria among those that used prescription opioids at least 120 days in the past year.

Model	LL	AIC	BIC	SSABIC	p-Vuong	Entropy	df	Low class %
Two-class	−3420.307	6930.614	7141.758	6998.857	0.046	0.931	1001	43.5
Three-class	−3103.551	6367.102	6742.469	6488.423	0.715	0.921	990	29.0
Four-class	−2956.643	6143.286	6682.875	6317.684	0.799	0.943	975	7.4
Five-class	−2878.842	6057.684	6761.497	6285.161	0.760	0.953	965	7.3
Six-class	−2760.087	5890.174	6758.209	6170.728	0.761	0.966	954	8.4
Seven-class	−2734.234	5908.469	6940.727	6242.100	0.755	0.967	943	3.2
Eight-class	−2693.464	5896.928	7093.410	6283.638	0.760	0.976	935	1.8

LL = Log-likelihood; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria; SSABIC = Sample-size adjusted BIC; p-Vuong = p of Vuong-Lo-Mendel-Rubin; df = degrees of freedom; NC = The model did not reach convergence.

Table 2

Conditional prevalence per three latent classes of DSM-5 opioid use disorder among past-year frequent nonmedical prescription opioid users (those that used at least 120 days) in the United States, 2011–2012.

Criteria	"Non-symptomatic class"			"Tolerance-time spent class"			"High-moderate symptomatic class"			Total	
	n*	%	SE	n*	%	SE	n*	%	SE	n*	%
Tolerance	59	13.8	0.02	301	89.0	0.02	242	97.0	0.01	601	59.4
Withdrawal	22	5.3	0.01	147	43.6	0.03	187	74.9	0.03	356	35.2
Larger/longer	5	1.1	0.01	94	27.9	0.03	154	61.8	0.03	253	25.0
Quit/control	11	2.6	0.01	66	19.4	0.03	125	50.3	0.03	202	20.0
Time spent	33	7.9	0.02	298	88.1	0.02	238	95.5	0.02	569	56.3
Activities given up	4	0.9	0.01	51	15.1	0.03	238	95.4	0.02	292	28.9
Physical/psychological	4	0.9	0.01	108	32.1	0.03	220	88.3	0.02	332	32.9
Neglect roles	10	2.3	0.01	22	6.6	0.02	211	84.7	0.03	243	24.0
Social/interpersonal	3	0.8	0.01	72	21.2	0.03	216	86.7	0.02	291	28.8
Hazardous use	0	0.0	0.00	62	18.3	0.02	165	66.4	0.03	227	22.5
Total	424	41.93	0.00	338	33.43	0.00	249	24.62	0.00	1011	100.00

* Estimated value of n since after de imputation of weights/clusters/strata it is not possible to calculate the exact value of n.

symptomatic classes, with the "Non-symptomatic class" as reference. Those in the "Tolerance-Time Spent class" were more likely than those in class the "Non-symptomatic class" to be younger (18–25 years) and Non-Hispanic White (vs. 'Other' racial/ethnic groups) while those in the "High-Moderate symptomatic class" were more likely than those in the "Non-symptomatic class" to be male, Non-Hispanic White (vs. 'Other' racial/ethnic groups) and to have insurance.

Table 3B presents the results of the logistic regression models examining psychiatric and sources correlates, with adjustment for all sociodemographics included in **Table 3A**. The two symptomatic classes (as compared to class the "Non-symptomatic class") were significantly associated with antisocial behaviors and buying POs from drug dealers in the past month as compared to the non-symptomatic class. Those in the "Tolerance-Time Spent class" were more likely than those in the "Non-symptomatic class" to

Table 3A

Logistic regression models results of sociodemographic correlates within latent classes of opioid use disorder among those that used prescription opioids at least 120 days in the past year.

Variable	“Non-symptomatic”		“Non-symptomatic”					“High-moderate symptomatic class”				
	n*	%	n*	%	aOR	95%CI	p	n*	%	aOR	95%CI	p
Gender												
Female	185	43.6	112	33.0	1.00			72	28.8	1.00		
Male	239	56.4	226	67.0	1.64	0.89–3.00	0.107	177	71.2	1.51	1.25–3.98	0.006
Income												
Medium income	121	28.6	93	27.6	1.00			65	26.3	1.00		
Poverty	114	26.8	81	23.9	1.37	0.50–3.71	0.532	61	24.5	1.09	0.45–2.64	0.835
High income	189	44.6	164	48.5	1.18	0.43–3.24	0.739	123	49.2	1.63	0.74–3.57	0.221
Metropolitan area												
Large	224	52.8	150	44.3	1.00			127	50.7	1.00		
Small	127	30.0	115	34.1	1.08	0.55–2.13	0.810	82	33.1	0.93	0.43–1.96	0.849
Non-metropolitan area	73	17.2	73	21.6	1.45	0.63–3.35	0.375	40	16.2	0.99	0.38–2.59	0.992
Insurance												
No	146	34.4	139	41.2	1.00			92	37.1	1.00		
Yes	278	65.6	199	58.8	1.10	0.62–1.94	0.732	157	62.9	2.08	1.11–3.87	0.021
Employment status												
Employed	259	61.0	222	65.7	1.00			138	55.3	1.00		
Unemployment	165	39.0	116	34.3	0.70	0.39–1.26	0.242	111	44.7	1.51	0.79–2.89	0.210
Race												
Non-hispanic white	270	63.6	274	81.2	1.00			216	86.7	1.00		
Non-hispanic black	60	14.2	21	6.2	0.63	0.20–1.90	0.413	7	2.9	0.28	0.05–1.35	0.114
Hispanic	67	15.9	30	8.8	0.63	0.26–1.48	0.294	19	7.6	0.41	0.17–0.96	0.040
Other	27	6.3	13	3.8	0.29	0.15–0.58	<0.001	7	2.8	0.30	0.09–0.92	0.037
Education (in years)												
Low	107	25.3	74	21.7	1.00			67	26.8	1.00		
Low-average	156	36.8	130	38.6	1.45	0.57–3.68	0.424	82	32.8	0.67	0.28–1.60	0.367
High-average	124	29.2	94	27.8	1.26	0.53–3.02	0.596	81	32.7	0.92	0.38–2.20	0.861
High	37	8.7	40	11.9	2.65	0.79–8.90	0.114	19	7.7	0.87	0.16–4.62	0.872
Marital status												
Never married	212	50.1	185	54.6	1.00			156	62.9	1.00		
Widow/separated/divorced	70	16.4	70	20.8	2.50	0.84–7.41	0.096	51	20.3	2.15	0.85–5.38	0.102
Married/cohabiting	142	33.5	83	24.6	1.24	0.47–3.26	0.660	42	16.8	0.59	0.21–1.60	0.302
Age (in years)												
18–25	19	4.4	31	9.1	1.00			19	7.4	1.00		
26–34	275	64.8	210	62.2	0.66	0.45–0.99	0.046	157	63.2	0.95	0.58–1.55	0.851
35 or more	131	30.8	97	28.7	0.18	0.07–0.48	0.001	73	29.4	0.46	0.17–1.24	0.221
Survey year												
2011	216	50.9	176	52.1	1.00			133	53.4	1.00		
2012	208	49.1	162	47.9	1.08	0.55–2.10	0.809	116	46.6	1.09	0.60–1.98	0.763

Bold: significant associations ($p < 0.05$).

* Estimated value of n since after de imputation of weights/clusters/strata it is not possible to calculate the exact value of n.

** Non-symptomatic class was the reference category for other latent classes.

have obtained PO from family/friends while those in the “High-Moderate symptomatic class” were more likely than those in the “Non-symptomatic class” to have obtained POs via Doctor shopping.

Table 4 presents progressively higher values (“High-moderate symptomatic class” > “Tolerance-Time Spent class” > “Non-symptomatic class”) of conditional prevalence of past-year other substance dependence, and previous or current treatment for PO disorders and Mental Health/Addiction, in each of the 3 latent classes. Despite a high past-year prevalence of opioid dependence among those on the “Tolerance-Time Spent class” and the “High-moderate symptomatic class” (63.1% and 98.6%, respectively), a very low proportion of respondents in “Tolerance-Time Spent class” sought treatment for opioid disorders secondary to NMUPO (8.2%), in contrast with those in “high-moderate class”, in which 36.4% sought treatment for opioid disorders secondary to NMUPO. The highest prevalence of comorbidity was found for tobacco dependence, followed by alcohol dependence (70.4% and 29.4%, respectively, in the “high-moderate symptomatic class” and 60.6%, 15.9%, respectively, in the “Tolerance-Time Spent class”, respectively). Cocaine dependence (15.5%) reached a higher value than cannabis dependence (14.4%) in “High-moderate symptomatic class” which

was not the case of “Tolerance-Time Spent class” (5.9% and 10.6%, respectively). [Supplementary File 5](#) presents the weighted counts and proportions, and the standard errors for each variable included in the logistic regression models and for latent class conditional prevalence.

4. Discussion

The CFA and LCA of an epidemiological household sample of US frequent nonmedical prescription opioid users yielded support for an unidimensional model of OUD criteria and for a three-class model (LCA) as the overall best solution for dividing frequent users in phenotypes along this unidimensional continuum. The three-class model identified a “Non-symptomatic” class, an intermediate class with high probability of endorsing Tolerance and Time Spent symptoms, and a high-moderate symptom class. There was also an increasing prevalence of past-month tobacco dependence, and past-year alcohol dependence from the “Non-symptomatic class” to the “Tolerance-Time spent class” to the “High-moderate symptomatic class”. Interestingly, those in the “Tolerance-Time Spent class” were more likely to obtain PO from family/friends while those in the “High-moderate symptomatic class” (vs.

Table 3B

Logistic regression models results of psychiatric and sources correlates within latent classes DSM-5 opioid use disorder among those that used prescription opioids at least 120 days in the past year.

Variable	"Non-symptomatic"		"Tolerance-time spent class"					"High-moderate symptomatic class"				
	n*	%	n*	%	aOR	95%CI	p	n*	%	aOR	95%CI	p
Anxiety disorders	56	13.1	66	19.4	1.31	0.58–2.98	0.506	66	26.7	1.88	0.82–4.29	0.132
Major depressive disorder	56	13.1	62	18.4	1.44	0.68–3.03	0.330	65	26.0	1.61	0.65–3.98	0.302
Antisocial behaviors	51	12.0	118	34.8	3.33	1.75–6.35	<0.001	150	60.2	9.43	4.53–19.66	<0.001
Doctor shopping	81	19.0	80	23.7	1.74	0.80–3.79	0.162	74	29.6	2.60	1.29–5.24	0.008
Bought from a drug dealer	28	6.7	94	27.7	4.81	1.79–12.88	0.002	78	31.3	6.58	2.89–14.98	<0.001
Obtained PO from family/friends	137	32.4	199	58.8	2.97	1.54–5.72	0.001	121	48.4	1.52	0.82–2.78	0.176

Bold: significant associations ($p < 0.05$).

* Estimated value of n since after de imputation of weights/clusters/strata it is not possible to calculate the exact value of n.

** Non-symptomatic class was the reference category for other latent classes.

PO = prescription opioids.

those in the "Non-symptomatic class") were more likely to be doctor shoppers.

Only two studies evaluated the dimensionality of OUD (Wu et al., 2009, 2011) by EFA and both examined the dimensionality of criteria among those any past-year NMUPO. Our study shares some similarities with these studies but focuses on a sample that included only frequent users. Frequent users are a group that is most likely to generate data that could inform prevention and treatment because these individuals are at considerable risk for having OUD. Both studies gave support to a unidimensional model (Wu et al., 2009, 2011), which allowed us to run a CFA in our more restricted sample of frequent users. Our study did not include the Legal Problems criterion because of its exclusion in DSM-5 (American Psychiatric Association, 2013), gives support to a unidimensional model for OUD, despite not including the Craving criterion. An important future direction is to assess LCA in data sources with complete DSM-5 criteria as it was carried out for the entire class of opioids (Tarrahi et al., 2015).

Our IRT model findings are presented in a similar way to the findings of previous studies with U.S. adolescent (Wu et al., 2009) and adult (Wu et al., 2011) samples of any nonmedical users. Larger/Longer and Quit/Control were found to be the criteria that endorsed by those individuals who probably endorsed several other OUD criteria. In contrast, Tolerance and Time Spent seem to be the first OUD criteria endorsed from the 10 criteria tested (Wu et al., 2009, 2011). Interestingly, Hazardous Use was more severe among individuals in our study than in Wu et al.' study (2011). Wu et al. (2011) divided their sample into most affected and less affected groups by factor mixture model. We compared our IRT results with the most affected group since we focused our analyses on frequent

users.

To date, only a few studies have used LCA to understand phenotypic differences of opioid dependence symptoms among nonmedical prescription opioid users and none of them focused on frequent users (Ghandour et al., 2008; Wu et al., 2011). Similarly to these studies (Ghandour et al., 2008; Wu et al., 2011), we also find a large non-symptomatic class and a class with a high probability of satisfying the criteria "Tolerance" and "Time Spent" with a moderate probability of endorsement of the other criteria. In addition, we also found a "high-moderate symptomatic class" as Ghandour et al.'s study (2008). The only class found by Ghandour et al. (2008) and not found in the present study was one latent class related to adolescents. This could be explained by the fact that we did not include adolescents in our analyses. Despite similarities regarding the latent classes found in Ghandour et al.' study and the present study, the sociodemographic correlates were quite different, maybe because we focused on frequent NMUPO users while the Ghandour study focused on any past-year NMUPO. For example, they reported that being female was significantly associated with the symptomatic classes, which differs from our finding of association of males having a higher likelihood of being in the most symptomatic class compared to females. Differences could be explained by the differences between the selected samples (any NMUPO and frequent NMUPO, respectively). We analyzed data from a sample of adults only, with more frequent use, and with data collected about a decade later. Unfortunately, Wu et al. (2011) did not analyze sociodemographic correlates of the latent classes.

Both symptomatic classes did not differ regarding the psychiatric correlates - both were more strongly associated with antisocial behaviors as compared to the "Non-symptomatic class".

Table 4

Conditional prevalence per three latent classes of DSM-5 opioid use disorder among those that used prescription opioids at least 120 days in the past year.

Latent class	"Non-symptomatic class"	"Tolerance-time spent class"	"High-moderate symptomatic class"	Chi-squared test p
	% (SE)	% (SE)	% (SE)	
Treatment for DSM-IV pain relivers (opioid) disorders	1.1 (0.01)	8.2 (0.01)	36.4 (0.03)	<0.001
Treatment for mental health/addiction	25.2 (0.02)	36.7 (0.03)	58.0 (0.03)	<0.001
DSM-IV alcohol dependence	15.2 (0.02)	15.9 (0.02)	29.4 (0.03)	<0.001
Tobacco dependence (FTND or NDSS)	48.6 (0.02)	60.6 (0.03)	70.4 (0.03)	<0.001
DSM-IV cannabis dependence	4.3 (0.01)	10.6 (0.02)	14.4 (0.02)	<0.001
DSM-IV cocaine dependence	5.5 (0.01)	5.9 (0.01)	15.5 (0.02)	0.001
DSM-IV stimulant dependence	0.6 (0.01)	3.9 (0.01)	11.7 (0.02)	<0.001
DSM-IV tranquilizers dependence	0.0 (0.01)	3.5 (0.01)	12.5 (0.02)	<0.001
DSM-IV pain relivers (opioid) dependence	0.0 (0.01)	63.1 (0.03)	98.6 (0.01)	<0.001

SE = Linearized Standard Error.

However, regarding sources of NMUPO, there was an interesting difference. Despite both symptomatic classes (as compared to the “Non-symptomatic class”) being more strongly associated with buying from a drug dealer, the “Time Spent-Tolerance class” was significantly associated with obtaining PO from family/friends, while the “High-Moderate symptomatic class” was significantly associated with “doctor shopping”. Most importantly, these differences persisted after adjustment for sociodemographic characteristics, including gender, which has been associated with these types of sources - i.e., female gender is more strongly associated with doctor-shopping (Back et al., 2010). It is important to target respondents from both classes to seek treatment, since despite the prevalence of DSM-IV Opioid Dependence in those classes being high, treatment prevalence is very low in both.

More than 60% of the individuals in the “high-moderate symptomatic class” did not seek for treatment for OUD. Considering the high prevalence of comorbid conditions, including multiple substance use disorders and a higher lifetime prevalence of mental health/addiction treatment (58%), it is possible that would be easier to find these individuals, who were predominantly Non-Hispanic White males with health insurance, in psychiatric and substance abuse treatment settings if they seek treatment for comorbid conditions. However, there must be a contingent of individuals in this class who do not seek treatment both for OUD and comorbid conditions.

Due to the cross-sectional design of the NSDUH survey, the associations reported here, even if statistically significant, reflect correlations and should not be viewed as providing evidence supporting etiological pathways. Although the NSDUH is an annually administered national survey, it does not capture the same individuals every year. A second limitation is the use of self-report. However, the use of a computerized reporting system, ACASI, minimizes social desirability biases, and yields data likely to be internally consistent and complete (Turner et al., 1998). We have also not included the Craving criterion in the present analyses since the NSDUH data does not include it, despite some recent studies that state the importance of this symptom for different samples of prescription opioid users (Ashrafioun and Carels, 2014; Wasan et al., 2012). In addition, the definition of doctor shopping used was broad, and has the potential to be misleading for policy makers. Unfortunately, the NSDUH does not have a more restrictive/refined definition of doctor shopping. We also could not distinguish whether these NMUPO users first started using these drugs when legitimately prescribed (e.g., pain relief) or when obtained illegally (i.e., to get high); such data were unavailable in the NSDUH. Gathering such data in future studies will help us better understand the profiles of these users, which may be distinct. Finally, the analytic focus of this manuscript was specifically on frequent NMUPO users. Thus, it was not possible to generalize it to people that less frequently engage NMUPO.

In summary, this study showed that frequent NMUPO users exhibit three different types of OUD phenotypes. Both the Tolerance and Time Spent criteria (which are included in DSM-5 OUD) seem important to identify phenotypes of frequent prescription opioid users in this and in previous studies. There is an intermediate class of Non-Hispanic White young adults who get PO from family and friends, with high probability of endorsing tolerance and spend a lot of time searching for, using or recovering from PO. Finally, the most symptomatic class consisting of White Non-Hispanic males with health insurance, and that is significantly associated doctor shopping. Both classes call attention because of their low level of treatment seeking. It is possible that these groups may respond to different interventions, however such conclusions would require a clinical study. The present study did not find very different phenotypes of individuals among frequent nonmedical

prescription opioid users (i.e., physical versus psychological), but the phenotypes found in this study are within the OUD continuum, which could corroborate with the findings of the several studies evaluating the dimensionality of the DSM-5 Substance Use Disorder (Shmulewitz et al., 2015). However, it is undeniable that both symptomatic classes described in this study have very different socio-demographic correlates, and present an important differentiation in regards to prescription opioids sources (doctor shopping versus family). Therefore, our study presents important public health implications to distinguish subgroups of frequent nonmedical prescription opioid users. Furthermore, this study may be of particular interest for future phenotypic investigations in different populations in the U.S. and in other countries.

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Contributors

Authors JMC-M, LHA and SSM designed the study. Authors JMC-M, LHA, KMK, MC, DJP and SSM managed the literature searches and summaries of previous related work. JMC-M and SSM undertook the statistical analysis. Author JMC-M and SSM wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Martins worked in 2014 as a consultant to Purdue Pharma on secondary data analyses of nonmedical prescription opioid and alcohol use in a different dataset, unrelated to the data described in this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpsychires.2016.05.007>.

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