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# Diverse Diagnostic Profiles Associated with Prescription Opioid Use Disorder in a Nationwide Sample: One Crisis, Multiple Needs

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## Abstract

**Objective—**The opioid crisis has had devastating effects on individuals and communities, and it has rapidly increased in severity. However, we still lack nationally representative information on the diversity of comorbidity patterns among DSM-5 prescription opioid use disorder (P-OUD), other substance use disorders (SUDs), and psychopathology. This impedes planning for multiple aspects of intervention, including society-wide allocation of treatment resources, program design at individual treatment centers, and personalized care to individual patients.

**Method—**To address this critical gap in information, we evaluated clinical profiles of American adults via latent class analysis in a large, recently collected epidemiological dataset that uses structured diagnostic assessment for DSM-5 psychopathology (National Epidemiologic Survey on Alcohol and Related Conditions-III; N=36,309). Variables considered for profiles included lifetime diagnosis for multiple SUDs, a number of externalizing and internalizing conditions, and demographic variables. We then associated clinical profiles with demographic variables and functional impairment.

**Results—**Comorbid psychopathology and other SUDs were common in latent classes with elevated and very high rates of P-OUD. To illustrate, alcohol use disorder rates were greater than 45% and PTSD rates were greater than 28% in classes with higher P-OUD rates. Higher P-OUD rates were associated with White/non-Hispanic and American Indian/Alaska Native populations. Relationships between P-OUD rates and functional impairment were inconsistent.

**Conclusions—**Many current treatment delivery systems are not designed to accommodate the heterogeneous profiles associated with high P-OUD rates. We provide specific suggestions for improvements to the mental health service system, individual clinical care programs, and future research approaches.

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**Keywords**

Opioid crisis; personalized medicine; comorbidity

As noted throughout this special issue, the United States (US) is in the midst of an opioid crisis (Kanouse & Compton, 2015; Nelson, Juurlink, & Perrone, 2015). Unfortunately, consequences from prescription and non-prescription opioid misuse have been continuing to climb. Overdoses increased 27.9% from 2015 to 2016, and an estimated 42,249 US residents died from an opioid overdose in 2016, accounting for nearly two-thirds of drug overdose deaths (Seth, Scholl, Rudd, & Bacon, 2018). While recent increases in opioid-related overdose have been driven primarily by heroin and illicitly manufactured fentanyl, over 17,000 overdose deaths in 2016 were prescription opioid-driven (Seth et al., 2018).

A key component of the US federal response to the opioid epidemic is to promote access to prescription opioid use disorder (P-OUD) treatment (Johnson et al., 2018). Such treatment often includes medication-assisted treatment (MAT) with methadone, buprenorphine, or naltrexone, and MAT has considerable evidence of effectiveness in promoting opioid abstinence and reducing associated negative outcomes, such as overdose (Connery, 2015). Psychosocial interventions for P-OUD are generally recommended and less well studied, with more limited evidence of effectiveness (Kampman & Jarvis, 2015). Preliminary evidence suggests that cognitive-behavioral therapy (Moore et al., 2016), 12-step-oriented residential treatment (Schuman-Olivier, Claire Greene, Bergman, & Kelly, 2014), and mindfulness-based treatment (Garland et al., 2014) may promote opioid abstinence.

While efforts have been increasing to offer these treatments, they have a number of problems in application. Early treatment termination is common in MAT, with many trials retaining a roughly 50% or less of those initiating treatment for the entire treatment course (Carroll & Weiss, 2017; Soyka, Zingg, Koller, & Kuefner, 2008). Retention in psychosocial treatment without medication is not well characterized, but given known retention issues for treatment approaches for substance use disorders (SUDs), early psychotherapy termination may also be common (Dutra et al., 2008). This can further impact psychotherapy efficacy for P-OUD.

Efforts to address the opioid crisis also do not occur in isolation, as cross-sectional and longitudinal evidence link prescription opioid misuse and P-OUD with higher levels of other substance use and psychopathology (Kerridge et al., 2015; McCabe, West, Jutkiewicz & Boyd, 2017; Saha et al., 2016; Schepis & Hakes, 2011). This comorbidity can further attenuate MAT efficacy, as poorer MAT outcomes are associated with other substance use as well as depressive, anxiety, and PTSD symptoms (Benningfield et al., 2012; Huhn et al., 2018; King, Brooner, Peirce, Kolodner, & Kidorf, 2014; Leece et al., 2015; Soyka, 2015; Schafer et al., 2010). Research on the effects of comorbid psychopathology (e.g., PTSD, major depression, anxiety disorders) on the MAT process tends to be inconsistent, with some findings that associate comorbidity with early treatment termination or relapse to opioid use/misuse (Benningfield et al., 2012; Dreifuss et al., 2013; Ferri, Finlayson, Wang, & Martin, 2014; Leece et al., 2015; Martin et al., 2017; Saha et al., 2016). However, these studies often-use regional data, are frequently underpowered, and usually do not use the updated DSM-5 criteria. They also often combine participants who are dependent on heroin with those dependent on prescription opioids, potentially clouding an important moderator of outcomes. All of these factors limit the conclusions that can be drawn.

In considering the role of comorbid psychopathology and P-OUD, remarkably little is known about common symptom profiles. Prior work on associations between P-OUD and either psychopathology or SUDs have tended to examine bivariate associations, as opposed to examining multivariate symptom relationships. This lack of information makes it difficult to design treatment programs that are tailored to specific comorbid symptom profiles, and it impedes decision-making regarding allocation of resources to promote access (e.g., additional investment in evidence-based anxiety treatment may be needed for a specific subset of patients with P-OUD). To date, no studies have examined multivariate symptom profiles of patients with P-OUD in large clinical samples.

To address this critical gap in knowledge, we applied latent class analysis (LCA) to data from the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III), a large nationally representative survey of the US adult noninstitutionalized population that used structured assessment for DSM-5 diagnostic criteria. The present study aims to provide a nationwide characterization of common symptom patterns and highlight how they relate to P-OUD rates, to inform planning for clinic design across a wide range of settings as well as public policy strategy. We hypothesized that a discrete number of classes would best explain comorbidity patterns observed with P-OUD. In particular, we expected that comorbidity patterns would vary depending on different rates of P-OUD, with at least one class containing a high prevalence of individuals with P-OUD. We also hypothesized that classes would be differentially associated with both demographic variables (age, sex, race/ethnicity) and functional impairment.

## Method

### Participants and Procedure

The study sample included all participants who enrolled in the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III; N=36,309). The NESARC-III is a nationally representative survey which was conducted via in-person interview format from 2012 to 2013. Respondents were selected through multistage probability sampling (for details regarding the sampling design, please see Grant et al., 2014). The NESARC-III epidemiological study was approved by the National Institutes of Health and Westat, Inc. Institutional Review Boards, and all participants provided informed consent (Goldstein et al., 2016). Participants were civilian, non-institutionalized U.S. residents (including those in group quarters, such as college or work dormitories, but not including homeless or incarcerated individuals) over the age of 18[1] (*M=45.63, SD=17.53;* 56.3% female). With regards to race and ethnicity, the majority of participants identified as White/non-Hispanic (52.9%) followed by Black/non-Hispanic (21.4%) and Hispanic, any race (19.4%) with the lowest reported race/ethnicities being Asian/Native Hawaiian/Other Pacific Islander, non-Hispanic (5.0%) and American Indian/Alaska Native, non-Hispanic (1.4%). Prevalence of P-

[1]Age was measured continuously for all participants except for those age 90 or older (*n*=187); these participants had their ages fixed to age 90 during the construction of the NESARC dataset

OUD for the sample was 2.1%. Regarding diagnostic recency, 43.3% of participants with lifetime P-OUD had also experienced a P-OUD episode in the past year, and 67.7% of participants with lifetime P-OUD reported a symptom episode within the past 10 years.

## Measures

The *NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-5* (AUDADIS-5; Grant et al., 2015) is a structured diagnostic interview designed to assess DSM-5 diagnostic criteria for alcohol use disorder, nicotine use disorder, and selected drug use disorders and mental disorders. Lifetime diagnosis status was established by responses to questions asking whether psychopathology was experienced in the past year and prior to the past year. For the current study, lifetime diagnosis variables were used for all substance and mental disorder variables. Also consistent with DSM-5 criteria, mood and anxiety diagnoses did not include substance or medically induced occurrences (Grant et al., 2016).

The *Short Form Health Survey Version 2* (SF-12; Ware et al., 2002) is a 12-item measure that is commonly used in population surveys to measure functional health or disability. The SF-12 assesses the extent of problems experienced in work or other daily activities over a timeline of the last four weeks. We used the two main summary measures from the SF-12, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), as well as the SF-12 Bodily Pain Scale (BPS). Scores on all SF-12 subscales are standardized with a mean of 50 and a standard deviation of 10, with lower scores reflecting increased functional impairment. Using criteria established by Cohen (1988) regarding interpretation of standardized differences, differences of 2, 5, and 8 units on the SF-12 reflect small, medium, and large differences, respectively.

## Analytic Plan

To identify comorbidity profiles relative to lifetime diagnoses of P-OUD, we used latent class analysis (LCA). Latent class analysis evaluates whether participants can be classified into a discrete number of latent classes/groups based on an observed set of variables. It is based on a mixture modeling approach, which uses a categorical latent variable to allow for the possibility of multiple underlying distributions to explain the observed pattern of responses, as opposed to assuming that a variable (or set of variables) is properly represented by a single distribution.

In this investigation, we evaluated whether there were discrete distributions/classes that underlie a set of observed dichotomous diagnosis variables, which included P-OUD, a number of substance use disorders, and a number of externalizing and internalizing disorders (please see Table 1 for a list of all disorders that were used as a part of latent class formation). Latent class models were estimated in Mplus version 8 (Muthén and Muthén, 2017) using full-information maximum likelihood estimation with robust standard errors, while also incorporating complex sample features from the NESARC as a part of model estimation.

To establish the proper number of classes that underlie the observed diagnostic variables (i.e., class enumeration), an iterative process was used. A 1-class model was first fit to the data, and then a 2-class model was fit to the data and its fit was compared the 1-class model.

Subsequently, a 3-class model was fit to the data to see if it fit better than the 2-class model, and this sequence continued by comparing each *k* class model to a respective *k-1* class model, up through a 12-class model. The principal criterion used to determine the best final model was the Bayesian Information Criterion (BIC); Kass and Raftery (1995) indicate that a BIC difference of 10 between models suggests "very strong" evidence in favor of the model with lower BIC value. We also decided on the best final model based on the qualitative interpretability of classes as suggested by Masyn (2013), especially in the case of models with highly redundant class structures. Quality of class separation was evaluated via entropy, and quality of contribution of each observed variable to class differentiation was evaluated by variable-specific entropy (i.e., how much did each specific diagnosis contribute to class differentiation; Asparouhov & Muthen, 2018). Values of entropy range from 0 to 1 and values of .40, .60, and .80 have been associated with low, medium, and high degrees of class separation, respectively (Clark & Muthén, 2009).

To use demographic variables to predict class membership, multinomial logistic regression using 3-step model estimation was used following the procedures of Vermunt (2010); each demographic variable was considered as a separate predictor in separate models. To use class membership to predict physical, mental, and pain-related functional impairment on the SF-12, regression-based models using the BCH method of distal outcome evaluation developed by Bakk and Vermunt (2016) were employed. To evaluate how classes related to treatment seeking behavior, manual 3-step estimation (Asparouhov & Muthén, 2014) was used to identify inter-class variation regarding the proportion of patients who had received past treatment specifically for P-OUD. To evaluate equality of means and proportions across classes, Wald tests were used.

Because classes were identified empirically, analyses using class membership as a predictor or outcome reflect a post-hoc approach, and *p*-values for these analysis were evaluated based on false discovery rate procedures (FDR; Benjamini & Hochberg, 1995). In this case, each single predictor/outcome was considered as a separate family of hypotheses for evaluation (e.g., using age as a predictor of class membership resulted in 7 hypothesis tests, while using race/ethnicity as a predictor of class membership results in 28 hypothesis tests; the FDR procedure corrected for false discoveries based on 7 hypothesis tests for age and 28 hypothesis tests for race/ethnicity).

## Results

Based on evaluation of BIC values and qualitative class interpretation, we chose an 8-class model as an optimal fit to the data (please see Supplementary Table S1 for detail on BIC and entropy for all models considered). Two other models showed lower BIC values than the 8-class model, including a 9-class model ($\Delta$BIC=2.83 compared to 8-class model) and 10-class model ($\Delta$BIC=13.87 compared to 9-class model). The difference in BIC for a 9-class model was small compared to the 8-class model, and did not produce an additional class that added meaningful new information. A 10-class model showed a larger difference in BIC (though for comparison, an 8-class model showed a minimum $\Delta$BIC>125 relative to all models with fewer classes). The classes that were added in a 10-class model reflected much overlap with those from the 8-class model, with divisions that appeared artificial (e.g., class 2 from the 8-

class model was largely replicated by both classes 3 and 4 in the 10-class model, with the only major difference being that classes 3 and 4 in the 10-class model were split into 2 classes that had 0.00% and 100.00% rates of major depressive disorder). Entropy values were also not substantially different for the 8-class model (entropy=0.75) versus a 9-class (entropy=0.77) or 10-class (entropy=0.77) model.

## Class Enumeration Results

Clinical profiles associated with each class can be found in Table 1 with lower class numbers associated with a higher proportion of the overall sample. Qualitative class descriptions are also provided in Table 1, and a graphical depiction of disorder rates by class can be found in Figure 1. We defined P-OUD rates for each class in terms of the overall NESARC sample, with “elevated” classes reflecting a P-OUD rate that was more than twice the overall sample rate, and “very high” classes reflecting more than 10 times the overall P-OUD rate in the NESARC sample. With regard to the classes that reflected low-average P-OUD rates, class 1 (mentally healthy class, 60.75% of sample, 0.10% P-OUD rate) showed relatively low rates of psychopathology and average overall functioning as measured by the SF-12. Class 2 (depressed class, 15.21% of sample, 1.10% P-OUD rate) had high levels of major depressive disorder (MDD) and generalized anxiety disorder (GAD), relatively average alcohol and tobacco use disorder rates, and relatively low rates of clinical-level illicit drug SUDs. Quality of life was observed to be fairly low in this class, especially with regard to mental well-being (SF-12 Mental Component Summary=38.5). This stands in contrast to class 3 (alcohol-tobacco class, 15.03% of sample, 2.70% P-OUD rate), which had very high alcohol and tobacco use disorder rates, but otherwise relatively average disorder dates for other drug use and psychopathology and relatively higher mental well-being (SF-12 Mental Component Summary=45.6). Overall, these three classes accounted for a majority of participants (90.98% of total sample)

With regard to classes that reflected elevated P-OUD rates, class 4 (alcohol-tobacco-cocaine class, 3.88% of sample, 7.30% P-OUD rate) reflected high rates of PTSD as well as depression, alcohol, tobacco, cannabis, and other illicit use disorders. It also reflected notable functional impairment via scores on the SF-12 Physical Component Summary (39.28), Mental Component Summary (32.41), and Bodily Pain Scale (34.99). Class 5 (internalizing class, 2.35% of sample, 4.20% P-OUD rate) was high on anxiety and PTSD rates as well as for alcohol and tobacco use disorder, but had low disorder prevalence rates for illicit drug use disorders. Class 6 (bipolar class, 1.29% of sample, 7.70% P-OUD rate) was notable for reflecting high rates of bipolar disorder and alcohol use disorder, as well as elevated rates of cocaine use disorder.

With regard to classes that reflected very high P-OUD rates, class 7 (polysubstance class with elevated psychopathology, 1.1% of sample, 74.00% P-OUD rate) had relatively high rates of psychopathology for nearly all drug classes, but relatively low rates of anxiety disorders. Class 8 (polysubstance class with very high psychopathology rates, 0.40% of sample, 28.30% P-OUD rate) differentiated from class 7 in several ways. These include its lower P-OUD rates, higher prevalence of anxiety disorders and sedative use disorder, and relatively normal SF-12 scores compared to what might be expected for such high rates of psychopathology. Classes 7 and 8 both showed high rates of bipolar disorder and antisocial personality disorder.

### Demographic Predictors of Class Membership

Multinomial logistic regression models were used to predict class membership. These models rely on a ratio, where the chance of participant assignment to a specific class is compared to the chance of being assigned to the mentally healthy class. Specifically, these models evaluate if this ratio differs across levels of the predictor, producing an odds ratio (OR) for differences in odds across predictor levels. Predictor reference classes were White/non-Hispanic (for race/ethnicity) and female (for sex), and the outcome reference group was class 1 (mentally healthy class).

Results from analyses using demographic predictors of class membership can be found in Table 2. Increasing age was associated a lower probability of being assigned to classes other than the mentally healthy class (class 1), with the exception of the depressed class (class 2, which showed no significant difference in relationship with age relative to class 1, $p$=.24). Relative to females, males were less likely to be members of the depressed lass (class 2, OR=0.27) and the internalizing class (class 5, OR=0.36) but more likely to be members of the alcohol-tobacco class (class 3, OR=3.44) and the polysubstance/elevated psychopathology class (class 7, OR=1.65).

With regard to race/ethnicity, most findings reflected that minority race/ethnicity groups were associated with a lower probability of being in class of elevated P-OUD rates. Exceptions to this pattern included the American Indian/Alaska Native group being more likely than the White/non-Hispanic group to be a member of the alcohol-tobacco-cocaine class (class 4 , OR=4.87), the bipolar class (class 6, OR=3.59), and the polysubstance/very high psychopathology class (class 8, OR=6.12). Nonsignificant race/ethnicity differences were also observed in several cases. In particular, members of the American Indian/Alaska Native group did not show significant differences in being a member of the depressed, alcohol-tobacco, internalizing, and polysubstance/elevated psychopathology classes (classes 2, 3, 5, and 7, respectively). Members of the Hispanic group did not show a significant difference with regard to membership in the bipolar class (class 6), and members of the Black/non-Hispanic group also did not show a significant difference with regard to membership in class 6.

### Class Membership as a Predictor of Functional Impairment and Treatment Seeking

Relative to the mentally healthy class (class 1), all other classes showed significantly lower SF-12 scores on all SF-12 scales (please see Supplemental Table S2 for detail). Differences at the medium and large levels of magnitude were more frequently observed for the SF-12 Mental Component Summary and Bodily Pain Scale, where the depressed and alcohol-tobacco-cocaine classes (classes 2 and 4, respectively) showed large differences on both scales when compared to the mentally healthy class (class 1). On the Mental Component Summary, large differences were also observed between class 1 and the bipolar and polysubstance/elevated psychopathology classes (classes 6 and 7, respectively), and medium-large differences were observed for the alcohol-tobacco and internalizing classes

(classes 3 and 5, respectively). On the SF-12 Bodily Pain Scale, medium-sized differences were also observed for the internalizing, bipolar, and polysubstance/elevated psychopathology classes (classes 5, 6, and 7, respectively). On the SF-12 Physical Component Summary, the alcohol-tobacco-cocaine class (class 4) again showed a large-sized difference, and medium sized differences were observed for the depressed and internalizing classes (classes 2 and 5, respectively). With regard to treatment seeking, a minority of participants with P-OUD had ever received clinical treatment for the problem. Relative to the mentally healthy reference class (class 1), only those in the polysubstance/elevated psychopathology class (class 7) showed a significant difference in likelihood of receiving past treatment (37.2% vs. 4.7%)

## Discussion

Multiple population subgroups showed elevated P-OUD prevalence. In particular, 5 of the participant classes had a P-OUD prevalence above 4%. These classes represent 9% of the weighted sample, corresponding to over 25 million Americans. Also, these five classes were clinically heterogeneous, with great differences among them in prevalence of alcohol use disorder (45.9–89.9%), cannabis use disorder (12.5–66.7%), antisocial personality disorder (4.4–54.0%), major depressive disorder (0–71.1%) and anxiety disorders (2.5–87.2%). Overall, these data suggest that the American population presents with a number of discrete clinical presentations that reflect elevated P-OUD rates. Furthermore, these classes of patients are also associated with significant polysubstance use and multiple forms of psychopathology.

In terms of the opioid crisis, the polysubstance classes (classes 7 and 8) are of notable interest. Each was comprised of individuals with a greater than one in four probability of having lifetime P-OUD, with a nearly three in four chance in the polysubstance/elevated psychopathology class (class 7). While these classes had very similar prevalence rates of alcohol and tobacco use disorders, class 7 had the highest heroin use disorder rate, along with higher rates of other drug use disorders. Conversely, the polysubstance/very high psychopathology class (class 8) had higher prevalence rates of every examined form of psychopathology, except for MDD. For the three classes with moderately elevated P-OUD prevalence (classes 4 through 6), similar divergence in the associated substance use disorders and psychopathology was found. Class 4 (alcohol-tobacco-cocaine class) had the highest rates of alcohol, tobacco and cannabis use disorders, and class 5 (internalizing class) had the highest rates of psychopathology with the exceptions of bipolar disorder and PTSD. These were more prevalent in class 6 (bipolar class). Class 7 (polysubstance/elevated psychopathology) was also the only class to have a significantly higher rate of prior substance-related treatment seeking behavior relative to the mentally healthy class. While a minority of patients who stand to benefit from P-OUD treatment actually receive it (Saha et al. 2016), patients with a number of problems may have increased interactions with substance use and mental health treatment, increasing the likelihood of receiving targeted care. It would be beneficial for patients who have less severe symptom presentations but still have elevated P-OUD rates to be identified more frequently as candidates for specialized P-OUD care, such as those in the alcohol-tobacco-cocaine class (class 4).

Taken together, these results suggest that a single treatment approach to reducing P-OUD is unlikely to be successful. Recent models of integrated P-OUD care have emphasized the importance of consulting with or including behavioral health specialists in treatment planning and delivery and note the likelihood of polysubstance use in those presenting for P-OUD treatment (Stoller, Stephens, & Schorr, 2016). The latent classes uncovered here suggest that behavioral health specialists need to play a potentially even larger role in treatment, and that clinicians treating P-OUD will need expertise with the complexities of psychosocial and medication treatment for both P-OUD and other substance use. This can occur in the context of specialty care, as well as through brief interventions provided by psychologists housed in the offices of primary care physicians (an integrative treatment model that has been deployed in a number of Veterans Affairs hospitals). Given past findings that indicate that other substance use and psychopathology can reduce the effectiveness of P-OUD treatment, failure to adequately treat the varying patterns of polysubstance use and psychopathology present in those P-OUD subgroups will only prolong the US opioid epidemic. Results from class differences on SF-12 scores also suggest that treatment will also need to include effective behavioral pain management. For example, class 4 (alcohol-tobacco-cocaine) reported significant bodily pain in addition to polysubstance use.

In designing improved systems for intervention, a long-term approach will be needed to make the changes necessary. A majority of those with P-OUD had symptom onset within the prior 10 years, and other research using NESARC-III data has indicated that P-OUD in both the past year as well as across the lifespan is associated with substantial comorbidity with other substance use disorders and psychopathology (Saha et al., 2016). Thus, a large number of patients will need to be monitored over an extended period, and not all of them will develop symptoms at once. The timeframe for symptom onset that we considered naturally fits into the common 10-year timeframe used by the Congressional Budget Office for resource allocation planning. In this way, current federal program development systems are already designed to allocate resources over the extended period necessary to make the desired impact.

Within classes, higher rates of anxiety disorders co-occurred with relatively lower rates of P-OUD, consistent with data from adolescents suggesting that anxiety symptomatology can protect against substance use (e.g., Scalco et al., 2014). In contrast, higher levels of PTSD covaried with elevated P-OUD prevalence, indicating an acute need for PTSD treatment in those with P-OUD. Briefer interventions may be preferable in treating the common comorbid presentations of individuals with P-OUD, such as a five-session writing-based exposure treatment for PTSD (Sloan, Marx, Lee, & Resick, 2018), but it is unclear whether briefer treatments will be effective in those with significant comorbidity.

With that said, clinicians will likely encounter the challenge of matching treatment options for individuals with P-OUD. Based on the current study, many individuals with P-OUD may have limited or no comorbidity (i.e., those in classes 1 through 3) but those with P-OUD from classes 4 through 8 are also likely to have significant comorbidity and need multidisciplinary, integrated behavioral treatment and MAT. Per American Society of Addiction Medicine (ASAM) Guidelines (2015), MAT is indicated in those with moderate or severe DSM-5 P-OUD, which roughly corresponds to DSM-IV opioid dependence

(Compton et al., 2013). Future research, however, is needed to establish optimum treatment for those with moderate or severe P-OUD, whether that is MAT only, MAT with brief interventions for comorbidity or more intensive behavioral treatment for their complex pattern of P-OUD, other SUDs and psychopathology.

Similarly, research is needed to establish the best treatment course for those with mild P-OUD, as pharmacotherapy may not be appropriate for such individuals (Kampman & Jarvis, 2015). Furthermore, clinicians are encouraged to refer to the ASAM practice guidelines for the use of medications for treating OUD and P-OUD including special populations such as adolescents, individuals with pain, pregnant women, criminal justice and homeless populations, and individuals with co-occurring psychiatric disorders (Kampman & Jarvis, 2015). For instance, clinicians should be aware of potential interactions between medications used to treat co-occurring psychiatric conditions and P-OUD. Notably, the ASAM and World Health Organization guidelines (2009) recommend psychosocial treatment in combination of MAT for all individuals with opioid dependence, suggesting that comprehensive treatment may be warranted for all individuals with moderate to severe P-OUD.

Class membership was also associated with a significantly different demographic profile. While American Indian/Alaska Native respondents were more likely to be in three of the five elevated P-OUD prevalence classes than White/non-Hispanic respondents, Asian/Native Hawaiian/Other Pacific Islander, Black/non-Hispanic, and Hispanic respondents were significantly less likely to be in an elevated P-OUD class than White/non-Hispanic individuals. These results are consistent with other research suggesting that White/non-Hispanic and American Indian/Alaska Native individuals have the highest rates of opioid overdose (Case & Deaton, 2015; Venner et al., 2018). Sex was not consistently associated with membership in an elevated P-OUD class, but increasing age was associated with a decreased likelihood of class membership in each of the five highest P-OUD prevalence classes. While older adults have evidenced an increase in prescription opioid misuse prevalence over the past 15 years (Schepis & McCabe, 2016), adults 50 and older remain the lowest prevalence group for prescription opioid misuse (Schepis, McCabe, & Teter, 2018). Finally, the emergence of fentanyl and other synthetic opioids after 2013 indicates the need to account for these products in subsequent OUD investigations (O’Donnell et al., 2017).

## Limitations

Several limitations should be noted. First, the data are cross-sectional, which prevents causal inference in terms of the developmental trajectories leading to class membership. Second, self-report measures were used in some instances. At all points the NESARC-III uses assessments that have strong validity data, and while self-report of substance use is a reliable and valid assessment methodology (Grant et al., 2015; Johnston & O’Malley, 1985; O’Malley, Bachman, & Johnston, 1983), it remains possible that individuals can show limited insight into their own functioning. Third, several variables were not collected which could provide further mechanistic insight, including disorder-specific severity, neurobiological correlates, and physical dependence (i.e., opioid tolerance or withdrawal symptoms) as it relates to pain conditions on P-OUD. This information could inform the complex interplay between these concepts and their correspondence to latent class membership. Finally, the exclusion of some institutionalized subpopulations with higher rates of SUDs and mortality, including homeless individuals and incarcerated populations, may have led to underestimation of P-OUD prevalence in the NESARC-III (Keyes, Rutherford, Popham, Martins, & Gray, 2018).

Of additional note is that we used the entire NESARC-III sample in our analysis. We considered limiting the analysis only to participants with P-OUD, which would reduce heterogeneity among participants and could possibly improve clarity in class interpretation. However, looking at classes created using data solely from respondents with P-OUD is less representative of both the general American population as well as the overall clinical population who presents for treatment. Given that a large proportion of Americans have been exposed to opioids at some point, and also that opioids are the most frequently prescribed medications in America (Han et al. 2017; Volkow & McLellan, 2016), limiting analysis to the minority of Americans with P-OUD would lose the connection between exposure and real-world clinical profiles. While there is notable heterogeneity among our classes, utilizing the entire NESARC sample means that results are representative of what clinicians are likely to see in presenting patients. This results in a substantial increase in external validity, has clinical impact in suggesting how non-specialty treatment centers should adapt their capabilities to the opioid crisis, and better informs the design of public policy.

### Conclusions

Substantial heterogeneity in comorbid psychopathology and polysubstance use patterns were found in the latent classes with elevated P-OUD prevalence. Thus, when addressing P-OUD, healthcare professionals will likely need to assess and treat multiple conditions simultaneously with multidisciplinary teams. Behavioral health professionals will be key members of these teams, as a combination of medication and psychotherapy will almost certainly be needed for comorbid disorders associated with moderate to severe P-OUD. Public health systems will also need to consider resource allocation for P-OUD treatment in light of these results. While MAT and harm reduction approaches (e.g., naloxone distribution) are essential to reducing P-OUD and its consequences, healthcare and public health systems should expect to allocate significant resources to treat the comorbidities present in those with P-OUD.

At present, empirically-supported interventions for the observed comorbid conditions are often unavailable at treatment sites, which may impede successful P-OUD intervention. While a significant increase in resources has been provided to address the opioid crisis, simply amplifying current treatment initiatives will likely result in inefficient investment, ineffective outcomes, and wasted effort. Based on the diverse profiles in the present study, the likelihood of success can be maximized by tailoring research, clinical intervention strategies, and federal investment to empirical clinical profiles.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Appendix A: Data Collection and Transparency Statement

The data reported in this manuscript were obtained from publicly available data from the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III). The project website from the NESARC-III can be found at https://www.niaaa.nih.gov/research/nesarc-iii, and a bibliography of work resulting from NESARC-III research can be found at https://www.niaaa.nih.gov/sites/default/files/NESARC/NESARC-III%20publications_Final_8_10_16.pdf Prior NESARC-III papers have focused largely on establishing epidemiological estimates and univariate analyses. In this manuscript, we extend NESARC-III work by employing multivariate inference. The multivariate relationships among variables examined in the present article have not been examined in any previous or current articles, or to the best of our knowledge in any papers that will be under review soon.

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**Public Health Significance Statement**

A number of distinct clinical profiles are associated with elevated rates of prescription opioid use disorder. We highlight specific profiles that can include other substance use disorders, depression, anxiety, PTSD, and externalizing conditions. These profiles can be used to guide public policy, resource allocation, and the design of personalized care strategies for patients in need.

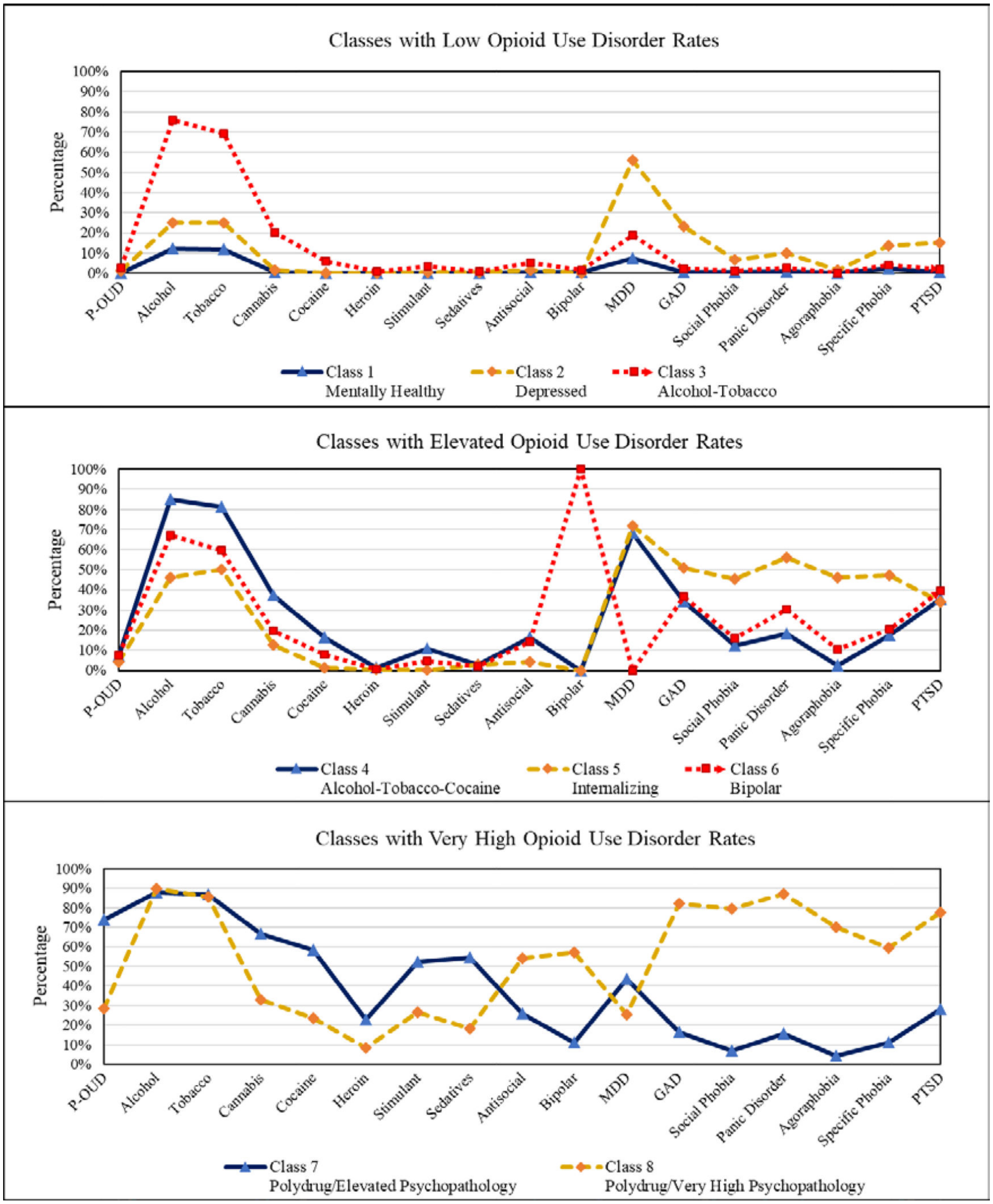


**Figure 1.**

Profile Plots of Disorder Prevalence Rates for Participants in Each Observed Class Note: P-OUD=Prescription opioid use disorder; alcohol, tobacco, cannabis, cocaine, heroin, stimulant and sedatives all refer to the substance use disorders corresponding to each respective substance; antisocial=antisocial personality disorder ; bipolar=bipolar 1 disorder; MDD=Major depressive disorder; GAD=Generalized anxiety disorder; PTSD=Posttraumatic stress disorder

## Table 1

Descriptive Characteristics of Observed Latent Classes

| | Low-Average P-OUD Rates | | | Elevated P-OUD Rates | | | Very High P-OUD Rates | | |
|---|---|---|---|---|---|---|---|---|---|
| **Qualitative Description** | **Class 1 Mentally Healthy** | **Class 2 Depressed** | **Class 3 Alcohol-Tobacco** | **Class 4 Alcohol-Tobacco-Cocaine** | **Class 5 Internalizing** | **Class 6 Bipolar** | **Class 7 Polysubstance/ Elevated Psychopathology** | **Class 8 Polysubstance /Very High Psychopathology** | **Entropy[a]** |
| Lifetime Prevalence Rates | | | | | | | | | |
| Prescription Opioid Use Disorder | 0.1% | 1.1% | 2.7% | 7.3% | 4.2% | 7.7% | 74.0% | 28.3% | 0.44 |
| Alcohol Use Disorder | 12.0% | 25.1% | 76.0% | 85.0% | 45.9% | 67.1% | 88.0% | 89.9% | 0.50 |
| Tobacco Use Disorder | 11.9% | 25.1% | 69.3% | 81.2% | 50.3% | 59.7% | 86.7% | 85.5% | 0.48 |
| Cannabis Use Disorder | 0.3% | 1.4% | 20.2% | 37.3% | 12.5% | 19.5% | 66.7% | 33.1% | 0.46 |
| Cocaine Use Disorder | 0.0% | 0.0% | 5.9% | 16.4% | 1.4% | 8.0% | 58.2% | 23.3% | 0.44 |
| Heroin Use Disorder | 0.0% | 0.0% | 0.7% | 1.2% | 0.7% | 0.6% | 22.9% | 8.4% | 0.42 |
| Stimulant Use Disorder | 0.0% | 0.3% | 3.3% | 10.7% | 0.3% | 4.5% | 52.1% | 26.6% | 0.43 |
| Sedative Use Disorder | 0.0% | 0.4% | 0.8% | 2.9% | 2.9% | 2.0% | 54.7% | 18.3% | 0.43 |
| Antisocial Personality Disorder | 0.3% | 1.4% | 5.0% | 16.5% | 4.4% | 14.1% | 25.8% | 54.0% | 0.43 |
| Bipolar 1 Disorder | 0.3% | 0.0% | 1.7% | 0.0% | 0.0% | 100.0% | 10.9% | 57.1% | 0.45 |
| Major Depression Disorder | 7.2% | 56.0% | 18.8% | 68.0% | 71.7% | 0.0% | 43.5% | 25.5% | 0.48 |
| Generalized Anxiety Disorder | 0.6% | 23.1% | 2.2% | 34.5% | 50.7% | 36.7% | 16.3% | 82.3% | 0.46 |
| Social Phobia | 0.6% | 6.7% | 1.0% | 12.4% | 45.4% | 16.1% | 6.7% | 79.4% | 0.44 |
| Panic Disorder | 0.7% | 9.8% | 2.7% | 18.0% | 55.9% | 30.2% | 15.7% | 87.2% | 0.45 |
| Agoraphobia | 0.1% | 1.5% | 0.0% | 2.5% | 45.9% | 10.6% | 4.3% | 70.0% | 0.44 |
| Specific Phobia | 2.2% | 13.5% | 4.0% | 17.3% | 47.1% | 20.3% | 11.1% | 59.6% | 0.44 |
| Postraumatic Stress Disorder | 0.4% | 15.0% | 1.9% | 35.6% | 33.8% | 39.3% | 28.1% | 77.8% | 0.45 |
| % with P-OUD Who Have Ever Received Treatment[b] | 4.7% | 22.9% | 34.7% | 8.9% | 38.2% | 35.0% | 37.2% | 29.9% | - |
| Model Estimated $n^c$ | 22056.11 | 5522.35 | 5456.41 | 1407.92 | 852.24 | 467.32 | 399.91 | 146.71 | - |
| Sample Proportion | 60.75% | 15.21% | 15.03% | 3.88% | 2.35% | 1.29% | 1.10% | 0.40% | - |

[a]Variable-specific entropy

[b]Because number of participants in each class reflect model-based estimates, the results are allowed to take on fractional values

[c]Treatment targeted to P-OUD

**Table 2**

Demographic Predictors of Class Membership

| Qualitative Description | Low-Average OUD Rates | | Elevated OUD Rates | | | Very High OUD Rates | |
|---|---|---|---|---|---|---|---|
| | **Class 2 Depressed** | **Class 3 Alcohol-Tobacco** | **Class 4 Alcohol-Tobacco-Cocaine** | **Class 5 Internalizing** | **Class 6 Bipolar** | **Class 7 Polysubstance/ Elevated Psychopathology** | **Class 8 Polysubstance/ Very High Psychopathology** |
| **Variable** | **OR** | **OR** | **OR** | **OR** | **OR** | **OR** | **OR** |
| American Indian/Alaska Native, non-Hispanic | 0.97 | 1.18 | 4.87* | 2.16 | 3.59* | 0.82 | 6.12* |
| Asian/Native Hawaiian/ Other Pacific Islander, non-Hispanic | 0.25* | 0.25* | 0.14* | 0.07* | 0.31* | 0.14* | 0.00* |
| Black, non-Hispanic | 0.48* | 0.62* | 0.61* | 0.44* | 0.85 | 0.21* | 0.41* |
| Hispanic, any race | 0.45* | 0.37* | 0.59* | 0.31* | 0.78 | 0.19* | 0.34* |
| Male | 0.27* | 3.44* | 0.88 | 0.36* | 0.84 | 1.65* | 0.65 |
| Age (−SD)[a] | 1.04 | 1.52* | 1.47* | 1.28* | 1.52* | 1.75* | 1.63* |
| Age (+1SD)[a] | 0.97 | 0.66* | 0.68* | 0.78* | 0.66* | 0.57* | 0.61* |

*Note:* Reference classes for predictors were White/non-Hispanic (for race/ethnicity) and female (for sex). The reference class for outcome was class 1 (mentally healthy class). The * mark reflects significance at the .05 level after adjusting for the false discovery rate. OR=odds ratio

[a]Significance tests for age reflect test of overall mean odds ratio; specific odds ratios were calculated by comparing the estimated odds between those associated with ±1 standard deviation in age (which reflect ages 28.10 and 63.16, respectively) compared to the estimated odds associated with the average sample age (45.63)