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The Phenomics and Genetics of Addictive and Affective Comorbidity in Opioid Use Disorder

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Abstract

Opioid use disorder (OUD) creates significant public health and economic burdens worldwide. Therefore, understanding the risk factors that lead to the development of OUD is fundamental to reducing both its prevalence and its impact. Significant sources of OUD risk include co-occurring lifetime and current diagnoses of both psychiatric disorders, primarily mood disorders, and other substance use disorders, and unique and shared genetic factors. Although there appears to be pleiotropy between OUD and both mood and substance use disorders, this aspect of OUD risk is poorly understood. In this review, we describe the prevalence and clinical significance of addictive and affective comorbidities as risk factors for OUD development as a basis for rational opioid prescribing and OUD treatment and to improve efforts to prevent the disorder. We also review the genetic variants that have been associated with OUD and other addictive and affective disorders to highlight targets for future study and risk assessment protocols.

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Keywords

opioids; comorbidity; genetics; phenomics; OUD

Introduction

The U.S. opioid epidemic remains a major public health problem and more than 130 people die each day from opioid-related overdoses (National Institute on Drug Abuse, 2019). It also represents a major economic burden, with misuse of prescription opioids alone resulting in an annual U.S. cost of $78.5 billion. Although approximately one-third of this expense ($28.9 billion) is attributable to increased health care costs and medication-assisted treatment (MAT) programs (Florence *et al.,* 2016), the remaining two-thirds are due to criminal justice-related costs and lost productivity from both nonfatal and fatal consequences of opioid use. Although initially the opioid epidemic in the U.S. was fueled by prescription opioid analgesics, it has now shifted into more use of illicit and/or more potentially deadly opioids like heroin and fentanyl (Pergolizzi *et al.,* 2018). Given the combined loss of life and financial cost of the opioid epidemic, it is important to understand the risk factors for opioid use, misuse, and opioid use disorder (OUD).

Estimates of the percentage of individuals with pain who are exposed to opioid medication and who develop problematic opioid use, dependence or addiction varies widely. Current opioid misuse is estimated to occur in 21.7% to 29.3% of individuals exposed to opioids (Vowles *et al.*, 2015). The comparable rates for developing current OUD following opioid exposure are between 8% and 12% (Vowles *et al.*, 2015), while the rates for developing lifetime opioid use disorder (OUD) are between 34.9% and 41.3% (Boscarino *et al.*, 2011, 2015). The wide range of estimates for these phenotypes reflects the difficulty in accurately ascertaining them, in part due to the lack of consistent definitions for terms like misuse, abuse, dependence, and addiction; variation in their severity; current vs. lifetime timeframes; and the various indications for which opioids have been prescribed (Boscarino et al. 2011, Boscarino et al. 2015, Cheatle 2016). Despite the range of estimates, it is clear that a large proportion of individuals treated with opioid analgesics are at risk for developing problematic opioid use behaviors. Thus, a better understanding of factors contributing to problematic opioid use can help in both the prevention and treatment of OUD and its associated risk of overdose and death,

The risk factors associated with the development of OUD include co-occurring psychiatric disorders (PDs) and other substance use disorders (SUDs), genetic variation, and environmental stressors, which may include chronic pain and past adverse experiences (Boscarino *et al.,* 2015; Barry *et al.,* 2016; Berrettini, 2017; Rogers *et al.,* 2019). These factors can act additively or synergistically to increase OUD risk. Moreover, a genetic predisposition for OUD can be shared (i.e., through pleiotropy) with other PDs and SUDs (Hu *et al.,* 2018).

In this review, we first discuss the prevalence of co-occurring PDs, principally focusing on mood disorders (MDs), and SUDs in individuals with problematic opioid use or OUD. We also explore the shared genetic factors that may underlie this and other comorbidities. By

highlighting the common comorbidities and the shared genetic architecture of these phenotypes, we hope to promote better opioid prescribing and OUD treatment practices and enhance prevention efforts.

Review Methods

To identify the relevant literature, we used Google Scholar bots with the terms “opioid abuse,” “opioid comorbid association depression,” and “opioid GWAS.” In addition, we performed detailed literature searches in Google Scholar using terms including “opioid comorbidity,” “psychiatric opioid comorbidity,” “opioid GWAS,” “SUD comorbidity,” “SUD GWAS,” and “opioid neuroticism association,” focusing on literature published over the past 10 years. We included research articles and reviews with relevant results or discussion. We also reviewed the reference lists of the articles that were initially identified through literature searches to locate additional articles that we may have missed initially. This search strategy resulted in the inclusion of work older than 10 years, but it filled a significant gap in the narrative of the review. For the compilation of the findings (see Supplementary Table 1), we consulted GeneCards – The Human Gene Database (genecards.org; Stelzer *et al.*, 2016) to catalog loci in which single nucleotide polymorphisms (SNPs) have been associated with opioid-related phenotypes, including opioid dependence and OUD; other SUDs; and associated PDs.

Origins of Comorbidity

Martins et al. (2012) outlined three overlapping hypotheses of how comorbidity between OUD and PDs develops (Figure 1). The “self-medication” hypothesis postulates that individuals develop OUD as a result of repeated opioid use to relieve symptoms associated with established PDs (Khantzian, 1985). The “precipitation hypothesis” postulates that OUD and OUD withdrawal (Vorspan *et al.,* 2015) result in shifts in behavior and alterations in neural plasticity that lead to the development of PDs. Finally, “shared vulnerability” includes common underlying genetic and/or environmental factors associated with both OUD and a PD give rise to both conditions. Although there is support in the literature for all three of these hypotheses (Emrich *et al.,* 1982; Swendsen, 2000; Krueger *et al.,* 2001; Kendler *et al.,* 2003; Saitoh *et al.,* 2004; Brady and Sinha, 2005; Martins *et al.,* 2012), in general, pre-existing PDs (“self-medication”) and genetic liabilities/personal histories (“shared vulnerability”) appear to be the most robust predictors of OUD (Brooner, 1997; Brady and Sinha, 2005; Barry *et al.,* 2016). Nevertheless, psychiatric symptoms arising from previous opioid use (“precipitation”) should not be ignored, as individuals may use opioids to alleviate incident mood or anxiety symptoms, thereby initiating a cycle of opioid use and dependence (Fatséas *et al.*, 2010; Dell’Osso *et al.*, 2014).

The development of comorbidity between OUD and other SUDs mirrors the development of psychiatric comorbidities. Individuals in withdrawal from one substance may begin to use another substance in an attempt to mitigate the negative effects or to increase the overall effect of pain relief – mirroring “self-medication” (Kaufman, 1976a, 1976b; Darke and Ross, 1997; Manchikanti *et al.*, 2006; Rogers *et al.*, 2019). Akin to “precipitation” in PDs, SUD comorbidities can also arise via “gateway” mechanisms in which the use of one drug

leads to the use of another, more potent, one (Kaufman, 1976b). There are three interrelated gateway conditions: “sequencing,” “association,” and “causation” (Kandel and Faust, 1975; Fiellin *et al.*, 2013). In sequencing, a static relationship exists between two substances, with one initiated before the other, while in association the use of two substances is begun at the same time. Finally, in causation, the act of initiating one substance results in the initiation of another substance (Fiellin *et al.*, 2013). Indeed, prior misuse of other substances is common among patients with OUD, with 34–68% of individuals initiating opioid use after experimenting with or becoming addicted to one or more other substances (Ives *et al.*, 2006; Fiellin *et al.*, 2013; Arterberry *et al.*, 2016; Rajabi *et al.*, 2019). Regardless of which gateway mechanism(s) is operative, use of the first substance can, and often does, persist despite the individual’s taking up a second drug, resulting in mixed or polydrug use disorders (Rogers *et al.*, 2019). Finally, with shared vulnerability, multiple SUDs can arise through genetic pleiotropy. This shared propensity can be explained by the “common factor model” in which genetically influenced developmental trajectories and shared genetic liabilities exist for multiple substances (Morral *et al.*, 2002; Cleveland and Wiebe, 2008).

Co-occurring substance use and PDs is common. Barry et al. (2016) found that more than half of individuals with OUD met lifetime criteria for at least three psychiatric or non-opioid SUDs. There is evidence that common physiological mechanisms underlie this comorbidity. The neurotransmitters dopamine, gamma-aminobutyric acid (GABA), and glutamate and their respective receptors are commonly involved in both SUDs and PDs (Gómez-Coronado et al. 2018). Moreover, several biological processes, including oxidative stress, immune responses, and inflammation, are common to both SUDs and PDs. These common physiological processes can be partially explained by correlated genetic vulnerabilities. Understanding these genetic correlations could greatly improve our ability to detect individuals at risk for OUD and PDs and improve the treatments available to them.

OUD and Co-Occurring Mood Disorders

SUDs occur at frequencies higher than expected in individuals with almost all PDs (Lappalainen, 2004) and an estimated 45–56% of OUD patients have at least one PD (Brooner, 1997; Kidorf *et al.*, 2004; Sullivan *et al.*, 2005; Barry *et al.*, 2016). In addition, the presence of co-occurring disorders commonly is associated with higher rates of opioid use and lower rates of MAT program adherence (Sullivan *et al.*, 2006; Grattan *et al.*, 2012; Smith *et al.*, 2017; Litz and Leslie, 2017), increasing the risk of opioid relapse by 80% (Clark *et al.*, 2015). The adverse effects of comorbidity are proportional to the number of comorbid PDs (Edlund *et al.*, 2010; Liao *et al.*, 2017). For example, in a survey of randomly selected individuals, those with one or two comorbid PDs had five times the odds of opioid use, while individuals with three or four such disorders had a nine-fold increased odds of opioid use (Sullivan *et al.*, 2005). Further, the presence of OUD and a least one comorbid PD increases the likelihood of having another comorbid SUD (Kidorf *et al.*, 2004). The majority of studies in the literature on psychiatric comorbidity with OUD involve MDs (Brooner, 1997; Kidorf *et al.*, 2004; Ahmadi *et al.*, 2004; Sullivan *et al.*, 2005; Barry *et al.*, 2016), consistent with the disorders’ shared neurobiology and phenomenology (Lutz and Kieffer, 2013).

Depression

In a review of the prevalence of comorbid PDs in opioid-dependent patients worldwide, the average rates of current and lifetime depression were estimated to be 13.4% and 25.4%, respectively (Strain, 2002). Among patients in a buprenorphine (BUP) treatment program, 19% had a current diagnosis of depression and 24% reported having had a previous depressive episode (Savant *et al.*, 2013). In a Chinese population of methadone (MET)-maintenance patients, the prevalence of depression was 38.3% (Yin *et al.*, 2015). Similarly, in a U.S. population of prescription opioid users, the prevalence of depression was 30.1%, nearly quadruple that of non-opioid users (8.4%) (Sullivan *et al.*, 2005). Among individuals entering a treatment research program for co-occurring chronic pain and OD, current depression was present in 40% of both individuals dependent on heroin and those dependent on prescription opioids, with lifetime rates of 52% and 47%, respectively (Barry *et al.*, 2016). In a study of U.S. college students who engaged in recreational prescription opioid use, 59% had symptoms of major depression (Davis *et al.*, 2020).

Depression is commonly cited as an important risk factor for the development of OUD and is associated with negative opioid use outcomes. Patients treated with opioids for chronic non-cancer pain (CNCP) are significantly more likely to exhibit symptoms of depression than those who do not receive opioids (43.6% vs. 26.8%, $p < 0.001$) (Goesling *et al.*, 2015). Similarly, individuals who screen positive for depressive symptoms or have a diagnosis of depression are 3.63 times (95% CI = 1.71–7.70) more likely to be diagnosed with OUD, with the severity of the depression significantly associated with the odds of opioid misuse (OR = 3.71, 95% CI = 1.01–13.76) (Feingold et al. 2018). In the United States between 2011 and 2015, a 1% increase in self-reported depression diagnoses was associated with a 26% increase in opioid-related overdose deaths (Foley and Schwab-Reese, 2019). In an adolescent population, a major depressive episode was significantly associated with nonmedical prescription opioid use (OR = 1.51, 95% CI = 1.37 – 1.67) and opioid abuse/dependence (OR = 2.18, 95% CI = 1.77 – 2.70) (Edlund *et al.*, 2015). Litz and Leslie (2017) also determined that OUD patients with MD or bipolar disorder [BPD]) were significantly less likely to continue BUP MAT (OR = 0.805, 95% CI = 0.651 – 0.994). The presence of multiple comorbid PDs (including depression and BPD) also increased the propensity for risky behaviors in heroin users, including unprotected sex, sharing of injection needles, and opioid overdose, likely contributing to the higher rates of HIV, hepatitis, and sexually-transmitted diseases among regular heroin injectors with depression compared to those with no history or symptoms of depression (Williams *et al.*, 2017). Finally, among opioid-naïve patients undergoing surgery, lifetime depression was associated with the subsequent long-term use of opioid analgesics (OR = 1.46, $p < 0.001$) (Leroux *et al.*, 2019).

In considering the co-occurrence of depression and OUD, it is important to distinguish between independent depression (that which arises outside of the context of opioid abuse) and depression that occurs in temporal proximity to heavy opioid use or OUD (i.e., substance-induced depression). Dakwar et al. (2011) found no significant difference in the proportion of opioid-dependent individuals with independent depression and those with substance-induced depression. However, independent depression is a robust predictor of OUD and should be considered a risk factor for the disorder among patients receiving opioid

analgesics (Feingold *et al.*, 2018). On the other hand, substance-induced depression has important implications for OUD patients who are receiving MAT, as such comorbidity can increase craving, drug-seeking, and the risk of relapse (Tiet and Mausbach, 2007). Notably, continued postoperative opioid use is associated with significantly increased odds of new-onset depression (OR = 2.08, 95% CI = 1.74–2.49) (Wilson *et al.,* 2019).

Neuroticism

Neuroticism (NEU) is one of the "Big Five" personality traits and is characterized by a tendency to feel negative emotions and a vulnerability to stress (McCrae and John, 1992). The link between high NEU scores and pain is well established (Cheng and Furnham, 2013; Yadollahi *et al.*, 2014; Krok and Baker, 2014; Shivarathre *et al.*, 2014; Bucourt *et al.,* 2017; Chang *et al.*, 2017) and is a robust predictor of the onset and burden of disease (Sutin *et al.*, 2013; Weston *et al.*, 2015). The link between NEU and disease burden is also evident in the OUD literature. In a 10-year follow-up study of older individuals administered prescription opioids, NEU was associated with both a higher risk of persistent pain (OR = 1.44, 95% CI = 1.38–1.51) and greater use of opioid medication (OR = 1.21, 95% CI = 1.14–1.29) (Sutin *et al.*, 2019). NEU score was also a significant indicator of chronic severe pain in patients in methadone maintenance therapy (MMT) ($p < 0.001$, OR = 1.60, 95% CI = 1.27–2.12) (Koh and Othman, 2019). High NEU scores are consistently observed among heroin users (Patalano, 1998; Brooner *et al.*, 2002; Kornør and Nordvik, 2007) alongside greater impulsivity, insecurity, and lower emotional stability, sociability, and ego strength (Patalano, 1998). NEU was also associated with risk of opioid relapse in a one-year follow-up study of OUD patients in a Polish sample (Betkowska-Korpała, 2012), while individuals who remained in MAT and/or remained abstinent from opioids had low or normal NEU scores (Trémeau *et al.*, 2003; Betkowska-Korpała, 2012).

It has been suggested that the link between NEU and relapse reflects emotion-focused coping in which individuals attempt to react to a stressor, in this case opioid addiction, by changing their thoughts or feelings about the stressor through positive thinking or self-criticism (Matthews and Campbell, 1998; Delié *et al.,* 2017). Emotion-focused coping was found to be less useful when dealing with a stressful situation than task- or problem-focused coping (Matthews and Campbell, 1998).

OUD and Polysubstance Use

Polysubstance use and comorbid SUDs are extremely common among individuals with OUD and their prevalence is positively correlated with opioid misuse, withdrawal, and overdose. Data from the 2016 National Survey on Drug Use and Health (NSDUH) indicate that the prevalence of polysubstance use is as high as 92.9% among individuals who use opioids other than prescribed and it increases with the severity of opioid exposure (Winkelman *et al.*, 2018). Polysubstance use was observed in 45.5% of individuals who were prescribed opioids but did not misuse them, 68.0% of those who misused opioids, 82.7% of those with diagnosed OUD, and 92.9% of heroin users. Among heroin users, nearly half (40.9%) commonly used three or more additional drugs and nearly one-third (30.0%) used two other drugs. In the 2015 Global Drug Survey (GDS), which included the United States,

United Kingdom, Germany, France, and Australia, the rates of polysubstance use among individuals self-reporting opioid misuse and abuse ranged from 40.1% to 67.2%, with males, unemployed individuals, and those with less education being at greater risk for use/dependence (Morley *et al.*, 2017). In this international comparison, polysubstance use was universally and significantly associated with the prevalence of misuse (OR = 4.36, 95% CI = 3.29–5.93) and abuse (OR = 6.49, 95% CI = 4.0–10.48) of prescription opioids. Even though the rates of reported opioid misuse and abuse in the U.S. sample were higher than any other country (28.2% and 27.7%, respectively compared to misuse as high as 27.5% [Germany] and abuse as high as 21% [U.K.]), the results of this study show that comorbid polysubstance use with OUD is a global issue. Among CNCP patients from the Department of Veterans Affairs (VA), Edlund et al. (2007) found that non-opioid substance abuse comorbidity was most strongly associated with opioid abuse and dependence (OR = 2.34), while the association with a comorbid mental health disorder was more modest (OR = 1.46). Among heroin injectors both within and outside of MAT programs in Australia, polysubstance abuse was the greatest risk factor for both negative health outcomes (injection-related risks and injuries) and criminal activity (Betts *et al.,* 2016).

As with comorbid PDs, comorbid SUDs can begin before, during, or following the onset of OUD. Savant et al. (2013) found that the rate of comorbidity of at least one lifetime SUD diagnosis with OUD was 70%, while the comorbidity with a current diagnosis was 16%. Similar results were observed by Barry et al. (2016), who found that the lifetime prevalence of any non-opioid SUD was 88.3% in heroin users and 69.8% in prescription opioid abusers, with current rates being 39.0% and 27.9%, respectively. This high rate of comorbidity of lifetime SUDs provides evidence for the “gateway” hypothesis of multi-morbidity and reinforces the clinical relevance of taking a drug use history to predict opioid use (Ives *et al.*, 2006; Hooten *et al.*, 2015). Finally, co-occurring disorders can have deleterious effects on the health of individuals in MAT programs and should be identified and treated as part of a comprehensive approach to OUD treatment.

Nicotine

Nicotine, in any form, is consistently the most commonly used comorbid substance among opioid-dependent individuals, with a prevalence reported to be as high as 98% (Clemmey, 1997; Best *et al.*, 1998; Chun *et al.*, 2009; Pajusco *et al.*, 2012). In MET-treated patients, the prevalence of smoking is three to four times that of the general population (Clemmey, 1997). The extremely high comorbidity rate may be partially explained by persistent withdrawal symptoms among patients being treated with MET or other opioid agonists. In opioid agonist maintenance clinics, the prescribed dosage of agonists like MET and BUP rarely account for either metabolic differences among patients or potential drug interactions (Trujols *et al.*, 2012). Thus, many patients experience physical and/or psychological symptoms that persist despite agonist treatment. Indeed, patients who reported that their MET doses were not adequate for symptom relief results in an increase of smoking behavior (Tacke *et al.*, 2001). Smoking may also enhance the effects of other substances, including MET. It has been suggested that MET patients smoke for one or more of three reasons: it makes taking other drugs and MET more enjoyable; it shares the same cues and withdrawal symptoms as harder drugs, making smoking highly addictive; and it is viewed as having

fewer acute negative side effects than “harder” drugs, making it more acceptable (McCool and Richter, 2003). These factors may help to explain the high rates of smoking initiation among OUD patients. Moreover, nicotine dependence among individuals in treatment for OUD leads to significantly higher rates of smoking-related morbidity and mortality and has been linked to poorer treatment outcomes (e.g., a higher rate of relapse; Burling et al. 2001; Hurt 1996; Lemon et al. 2003; McCarthy et al. 2002). Smoking is also associated with heroin use and addiction. In an Australian sample, 94% of heroin users smoked (Darke and Hall 1995). Similarly, In an Italian sample, 97.2% of heroin-addicted individuals were smokers (Pajusco et al. 2012).

Nicotine dependence is also an important risk factor for the development of OUD. Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), show that an early-onset of cigarette use is significantly associated with the initiation, re-initiation, and persistence of opioid use (ORs = 1.40–1.61) (Arterberry et al. 2016). In a meta-analysis of 175,063 individuals from North America, Asia, and Europe, Rajabi et al. (2019) reported that smoking more than doubled the odds of opioid use (OR = 2.51, 95% CI = 1.91–3.28), with the odds of OUD among smokers more than 8-fold those of non-smokers (OR = 8.23, 95% CI = 3.07–22.09). Thus, lifetime and current smoking status should be considered by clinicians to be significant risk factors for OUD. Circumspection in prescribing opioids to individuals who smoke could help to reduce the iatrogenic risk of OUD. Among individuals with OUD, the availability of a wide variety of effective treatments for smoking cessation argues for combining treatment for smoking with that for OUD.

Alcohol

The prevalence of alcohol use disorder (AUD) among individuals with OUD ranges from 7% to 46% (Strain, 2002; Sullivan *et al.*, 2005, 2006; Hartzler *et al.*, 2010; Barry *et al.*, 2016; Hser *et al.*, 2017), often significantly higher among both individuals who use prescription opioids other than prescribed and those who use illicit opioids than in the general population (Maremmani *et al.*, 2007). Regardless of when AUD develops among individuals with OUD, it is associated with poorer treatment outcomes and higher rates of overdose-related morbidity and mortality (reviewed in Witkiewitz and Vowles 2018). Because both alcohol and opioids are central nervous system depressants, in combination they can be lethal (White and Irvine, 1999). Notably, the concomitant use of alcohol and opioids can also disrupt pain signaling in the brain, interfering with the treatment of chronic pain (Egli *et al.*, 2012).

The risk of comorbidity of AUD and OUD appears to be bidirectional. Among CNCP patients, those who used opioids other than prescribed were 2.6 times (95% CI = 1.12–6.26) more likely to have past or current AUD than individuals who use opioids as prescribed (Ives et al. 2006). Additionally, using the MarketScan claims database, Landsman-Blumberg et al. (2017) observed that, among CNCP patients, those with AUD were significantly more likely to overdose on opioids ($p < 0.001$). Akin to cigarette use, data from the NESARC show that early-onset of an AUD significantly increased the odds of initiating (OR: 1.38, 95% CI = 1.16–1.63), re-initiating (OR: 2.03; 95% CI = 1.32–3.12), and persisting in (OR: 1.72; 95% CI = 1.25–2.36) opioid use (Arterberry *et al.*, 2016). As with smoking, the risk of

developing OUD could potentially be reduced by clinicians' circumspection in prescribing opioid analgesics to patients who with AUD.

Cocaine

Cocaine use disorder (CUD) is also prevalent among individuals with OUD and in MMT patients. Among Spanish heroin users, 62.3% were shown to use cocaine (Barrio et al. 1998). More recently, in a U.S. population of heroin users, 74% and 88% reported lifetime use of crack and cocaine, respectively (Bobashev et al. 2018). Similarly, in the U.S., the prevalence of cocaine use among MMT patients has been found to be as high as 75% (Grella *et al.,* 1995; Tzilos *et al.,* 2009). Because methadone, an opioid agonist, has no effects on cocaine reinforcement, many individuals in MMT programs seek out the effects of cocaine to get high.

Because there are no medications with consistent evidence of efficacy in treating CUD (Shorter et al. 2015), psychosocial treatment is the cornerstone in treating MMT patients who use cocaine. One approach for which there is consistent evidence of efficacy in reducing cocaine use is contingency management (Higgins et al., 1991; Blanken et al., 2016; Knapp et al., 2007; Lussier et al., 2006; Minozzi et al., 2016).

In addition to cocaine use and CUD being highly comorbid with OUD, a study of CNCP patients who used opioids other than prescribed showed them to be 4.3 times (95% CI = 1.76–10.4) more likely to have a past CUD than controls, with 40.3% of patients who used opioids other than prescribed testing positive for cocaine or amphetamines (Ives *et al.*, 2006). Further, among these patients, a past history of CUD was the strongest predictor of opioid misuse (Ives *et al.*, 2006). Among a cohort of patients treated with opioids, those illustrated problematic use the drugs reported significantly more years of lifetime cocaine use than those who used them as prescribed ($p < 0.002$) (Knisely *et al.*, 2008).

Cannabis

Cannabis use disorder (CaUD) also commonly co-occurs with OUD, with 22% of current users of heroin and 20% of current users of prescription opioids reporting lifetime CaUD (Barry *et al.*, 2016). CaUD, both alone and in combination with other disorders, increases the risk of developing OUD. Among young adults, a history of CaUD was associated with subsequent prescription opioid abuse in both males (OR = 2.52, 95% CI = 2.22–2.85) and females (OR = 2.34, 95% CI = 2.07–2.66) (Fiellin *et al.*, 2013). Similarly, early-onset CaUD was associated with the re-initiation (OR = 2.92, 95% CI = 1.85, 4.59) and persistence (OR = 3.11; 95% CI = 2.21, 4.39) of opioid abuse and the frequency of cannabis use predicted opioid use, initiation, and re-initiation (Arterberry et al. 2016). In U.S. population data, CaUD was significantly associated with a higher incidence of nonmedical opioid use (OR = 3.13, 95% CI = 1.19–8.23, including nonmedical prescription opioid use (OR = 2.62, 95% CI = 1.86, 3.69), and OUD (OR = 2.18. 95% CI = 1.14, 4.14) (Olfson et al. 2018). The presence of both CaUD and AUD significantly increased the risk of opioid misuse among opioid-using adults with chronic pain (Rogers *et al.,* 2019).

The Genetics of OUD Comorbidity

As discussed previously and illustrated in Figure 1, psychiatric comorbidities can develop as a result of three, non-mutually exclusive mechanisms: self-medication, precipitation, and shared vulnerability (Martins et al. 2012). Under the umbrella of shared vulnerability genetic and epigenetic contributors to comorbidity contribute to self-medication and precipitation. Thus, individuals can self-medicate symptoms of a PD, the etiology of which is partly genetic (Mullins *et al.*, 2019; Shen *et al.*, 2020) or develop an incident PD in the context of a genetically influenced SUD (Langbehn *et al.*, 2003; Kendler *et al.*, 2003). Further, multiple comorbidities can exist through pleiotropy, in which there is shared genetic variation that leads to multiple PDs and/or SUDs (Wetherill *et al.*, 2015; Hu *et al.*, 2018; Foo *et al.*, 2018; Pasman *et al.*, 2018). Indeed, significant genetic correlations have been identified between many SUDs and PDs [e.g., AUD and depression (Edwards et al. 2012; Foo et al., 2018), CUD and Tobacco Use Disorder (TUD; Sadler et al., 2014), CaUD and depression (Pasman et al., 2018), AUD and PDs/SUDs: (Walters et al., 2018; Kranzler et al. 2019), and TUD and schizophrenia (Erzurumluoglu et al., 2019)]. These findings highlight the complex nature of the shared vulnerability among SUDs and between SUDs and PDs.

Multiple candidate gene studies and a limited number of genome-wide association studies (GWAS) of OUD have identified risk or protective variants. The genes implicated in these studies include *OPRD1* (which encodes the δ-opioid receptor) and *OPRM1* (which encodes the μ-opioid receptor), and genes involved in calcium- (*PITPNM3, PPP3CA*) and potassium-related cellular effects (*KCNG1*, and *KCNG2*) (Mayer *et al.*, 1997; Zhang *et al.*, 2008; Nielsen *et al.*, 2010; Crist *et al.*, 2013; Gelernter *et al.*, 2014; Hancock *et al.*, 2015; Zhou *et al.*, 2020). Other genes associated with OUD include *RGMA, MCOLN1, PNPLA6, CNIH3*, and *DDX18* (Nelson *et al.*, 2016; Cheng *et al.*, 2018, 2020). Significant advances have also been made in the genetics of fentanyl sensitivity (Fukuda et al., 2009; Ide et al., 2014; Mieda et al., 2016; Muraoka et al., 2016; Nishizawa et al., 2018; Takahashi et al., 2018) and MET metabolism (Kharasch and Stubbert, 2013; Levran *et al.*, 2013; Marie-Claire *et al.*, 2016; Yang *et al.*, 2016), as well as the epigenetics of OUD (Li *et al.*, 2015; Browne *et al.*, 2020). The genes, variants, and pathways implicated in these studies may also be relevant to other SUDs and PDs.

There have also been several studies that demonstrate pleiotropy of loci associated with either OUD phenotypes or other SUDs or PDs. In a study investigating the potential roles of rare variants (RVs) in N-methyl-D-aspartate (NMDA) glutamate receptors in substance dependence, Xie *et al.* (2014) identified 11 RVs that were significantly associated with opioid dependence in African Americans ($p = 0.0008$), including *GRIN2B* ($p = 0.0009$) and *DISC1* ($p = 0.001$), where two SNPs were significant: rs139667828 and rs61737326. In a sample of Polish individuals Fudalej *et al.* (2016) found a significant association the *DISC1* SNP rs2738888 and OD, with the C allele also appearing to be protective against suicidality. *DISC1* has been associated to a number of PDs, most notably schizophrenia (SCZ), BPD, and depression (Millar *et al.*, 2000; Brandon and Sawa, 2011; Porteous *et al.*, 2011).

Recently, a GWAS of 41,176 individuals, comprising 4,503 opioid-dependent cases, 4,173 opioid-exposed controls, and 32,500 opioid-unexposed controls showed that the SNP

rs9291211 was associated with opioid exposure (Polimanti *et al.*, 2020). This variant is located in *BEND4*, which regulates the transcriptomic profile of *SLC30A9*. Both of these genes have been associated with neuroticism (Kichaev *et al.*, 2019) and depression (Wray *et al.*, 2018). In addition, associations with rs9291211 and alcohol consumption, neuroticism, depression, anxious feelings, and the use of dietary supplements were identified in a phenome-wide scan in the UK Biobank (Polimanti *et al.,* 2020). This study also showed an association of opioid exposure with *SDCCAG8,* which has been previously associated with risk-taking behaviors (Karlsson Linnér *et al.,* 2019), schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), and educational attainment (Lee *et al.,* 2018).

Significant genetic correlations between several OUD-associated traits and both PDs and SUDs have been identified in GWAS. A GWAS of 79,729 European American individuals (8,529 confirmed cases of prescription OUD and 71,200 controls) from the Million Veteran Program (MVP), the Yale-Penn dataset and the Study of Addiction: Genetics and Environment showed significant genetic correlations of OUD with 83 other traits, including substance-related traits and psychiatric illnesses (Zhou *et al.,* 2020). Specifically, significant positive correlations were observed between OUD and smoking behaviors, alcohol dependence and related behaviors, attention deficit/hyperactivity disorder (ADHD), major depressive disorder, schizophrenia, and neuroticism (Zhou *et al.*, 2020). Polimanti *et al.*, (2020) found that a polygenic risk score (PRS) based on a GWAS of risk tolerance (Karlsson Linnér *et al.*, 2019) was positively associated with both opioid exposure and opioid dependence. They also found that a PRS based on a GWAS of neuroticism was positively associated with opioid dependence, but not opioid exposure. Taken together, these results illustrate that different associations can be uncovered using different samples, traits, and analytic methods. Both genetic correlation and the use of PRS can be expected to provide additional insights into the genetic pleiotropy of OUD and both other SUDs and PDs.

A potentially useful resource in this effort is the Alcohol, Nicotine, Cocaine, and Opioid Dependence Gene Database (Hu *et al.,* 2018; ANCO-GeneDB; https://bioinfo.uth.edu/ancogenedb/). This freely available tool for research on the genetics of co-occurring SUDs is comprised of information from GWAS, PheWAS, PubMed, and direct experimentation, along with data from indirect sources including drug interactions, gene expression assays, and tissue-specific enrichment analyses. Although the data in ANCO-GeneDB show no overlap among SNPs across the four phenotypes, at the genic level, a total of 151 genes are shared across all phenotypes and 42 genes are shared by opioid and nicotine dependence. The next greatest overlap is among alcohol, nicotine, and OD, with a total of 71 genes. This is consistent with epidemiological evidence that these disorders commonly co-occur. Overlap between opioid dependence and either alcohol or cocaine dependence was lower, with 15 and 9 genes in common, respectively. Another approach to understanding the pleiotropy in opioid-related traits is highlighted in a recent review by Sumitani *et al.*, (2020), which curated polymorphisms in genes associated with human pain sensitivity, opioid sensitivity and/or addiction. The review illustrates the interrelated genetic basis for these three phenotypes and suggests that personalized opioid analgesic strategies can be developed for treating pain.

There is currently no database like ANCO-GeneDB that links PDs with SUDs. Such a database could substantially improve research on the comorbidity of these disorders. To highlight the shared genetic variation of OUD with PDs and other SUDs, we catalogued SNPs in 71 genes that have been associated, principally in GWAS, with opioid-related phenotypes and at least one other SUD or PD (Supplementary Table 1). The list was compiled using GeneCards – The Human Gene Database (genecards.org; Stelzer *et al.*, 2016). It shows that the phenotypes that overlap most with opioid-related traits are nicotine/smoking-related ones, which appear in 39% of the SNP/gene entries. This is followed by schizophrenia (SCZ; 31% of entries) and depression (20% of entries). Some other notable phenotypes that overlap with opioid-related phenotypes are measures of wellbeing (17%), alcohol dependence/consumption (13%), ADHD (11%), risk taking (10%), and anxiety (6%). Figure 2 summarizes these results.

Among the SNPs that have been catalogued, only one is common to both an opioid phenotype and a PD/SUD phenotype: rs4606, an exonic SNP in the *RGS2* gene (Regulator of G-protein signaling 2), whose G allele is associated with both opioid dependence (Kaski, 2019) and GAD (Dunn *et al.,* 2014). This variant has also been associated with panic disorder and several other personality disorders (Leygraf *et al.,* 2006; Smoller *et al.,* 2008; Koenen *et al.,* 2009; Otowa *et al.,* 2011).

The rates of association that appear in the table are generally consistent with the comorbidity rates observed in the literature. Consistent with the most common overlap of loci associated with opioid-related phenotypes and loci associated with smoking-related phenotypes is the high prevalence of nicotine dependence among opioid-dependent individuals. The table highlights how shared genetic liability corresponds to the comorbidity seen in clinical settings. Moreover, the SUD and PD phenotypes shown in the table are potential indicators of risk for OUD. However, this is likely just the tip of the iceberg. Understanding the genetic architecture of co-occurring disorders will require large multi-population GWAS samples that provide adequate power and represent key non-European population groups, as most of the genetic research in this area has focused predominantly on European-ancestry individuals. However, there is much complexity that must be accounted for, as a recent study showed that the predictive accuracy of PRS, even within a single ancestral population, can differ significantly when considering characteristics such as the socio-economic status, age, or sex distributions of the groups in which the GWAS and the prediction were conducted, as well as the study design (Mostafavi *et al.*, 2020).

Limitations of this Review

In this review we explored the prevalence of OUD comorbidities, which showed that several PDs and SUDs are robust risk indicators of opioid misuse and abuse. We also illustrated the complex nature of the literature on the genetics of OUD comorbidity. The review is limited by the available literature, which is fragmentary. For instance, the literature does not permit a temporal assessment of comorbidity during the evolution of the opioid epidemic, primarily in the U.S, from prescription opioid analgesics to more deadly, illicit opioids like heroin and fentanyl. As more research becomes available, future reviews should focus on this developmental perspective as the potential for negative outcomes has greatly increased over

time and new causal links and associations regarding the use of illicit opioids could be uncovered. Additionally, there is limited information provided in most studies of the temporal order of onset of OUD and comorbid disorders. The temporal sequencing of disorders has important implications for etiology and should be given greater attention in studies of comorbidity.

The complex nature of the genetics of OUD comorbidity was illustrated in two recent publications [Zhou *et al.* (2020) and Polimanti *et al.* (2020)]. These studies underscore the effects of different sample ascertainment, trait definition, and analytic approach. However, new discoveries are to be anticipated, as ever-larger study samples become available, substantially increasing the power to detect genetic associations, and novel methods are applied to identify the causal variants and effector genes uncovered by GWAS. Despite its limitations, this review of the available literature on the genetics of OUD comorbidity provides a framework within which new findings can be interpreted.

Conclusion

In this review, we have highlighted the abundant evidence that OUD is commonly associated with a variety of other SUDs and PDs. However, despite this, and the recognition that clinically it is important to assess comorbidity in patients with OUD, there has been relatively little research aimed at understanding the common genetic risk factors that may underlie these phenotypes. Further, there is little information on the genetic basis of OUD among populations other than those of European ancestry, particularly a paucity of data from GWAS.

There is evidence that recent efforts to limit opioid prescribing for pain, particularly high-dose therapies, offers the prospect of reducing the opioid epidemic. However, the reduction in prescribed opioids has been accompanied by increased use of illicit opioids. Thus, there remains a pressing need for a greater understanding of the root causes of OUD and the factors contributing to its risk, including comorbid disorders, to permit identification and intervention with individuals most susceptible to misusing opioid drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

Dr. Kranzler is a member of an advisory board for Dicerna Pharmaceuticals; is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which in the past three years was supported by AbbVie, Alkermes, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, Pfizer, Arbor, and Amygdala Neurosciences; and is named as an inventor on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018.

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Highlights

- Smoking-related phenotypes represent the most common comorbidities and risk indicators of Opioid Use Disorder.
- Among genes associated with opioid-related phenotypes, smoking-related associations were the most common phenotype overlap observed.
- The rates of association that appear among genes associated with opioid-related phenotypes are generally consistent with the comorbidity rates of psychiatric disorders observed in the literature.
- This review highlights the importance of multi-disorder comorbidity in both identifying and treating those prone to OUD. Additionally, it identifies many loci that may have roles in OUD comorbidity.

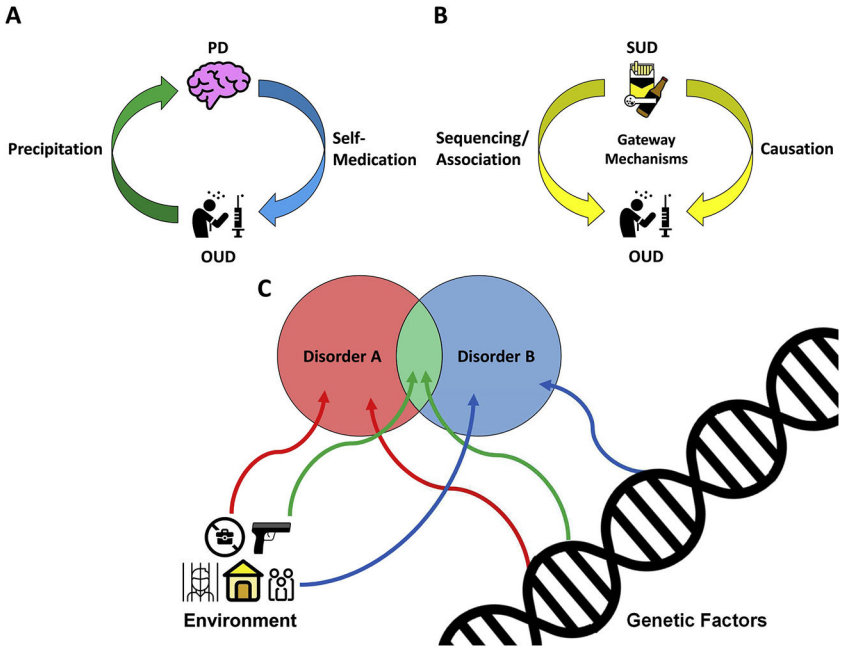

Figure 1:

Illustrations depicting different origins of OUD comorbidity. A.) OUD and psychiatric disorder comorbidities can arise via precipitation and self-medication. In precipitation, the ongoing use of opioids can result in the development of psychiatric disorders. In self-medication, individuals may begin to use opioids to alleviate the symptoms associated with pre-existing psychiatric disorders. B.) OUD and substance use disorder comorbidities can arise via sequencing and association as well as causation. In sequencing and association, relationships exist between the use of one substance and the use of another. In causation, using one substance ultimately leads to the use of another, usually more potent one. C.) Both the environment and genetic factors can lead to comorbidity. Related disorders regularly share common risk factors. However, some risk factors are unique to certain disorders. Red and blue arrows indicate factors that are unique to disorders A and B, respectively, while green arrows represent shared factors that are common to both disorders.

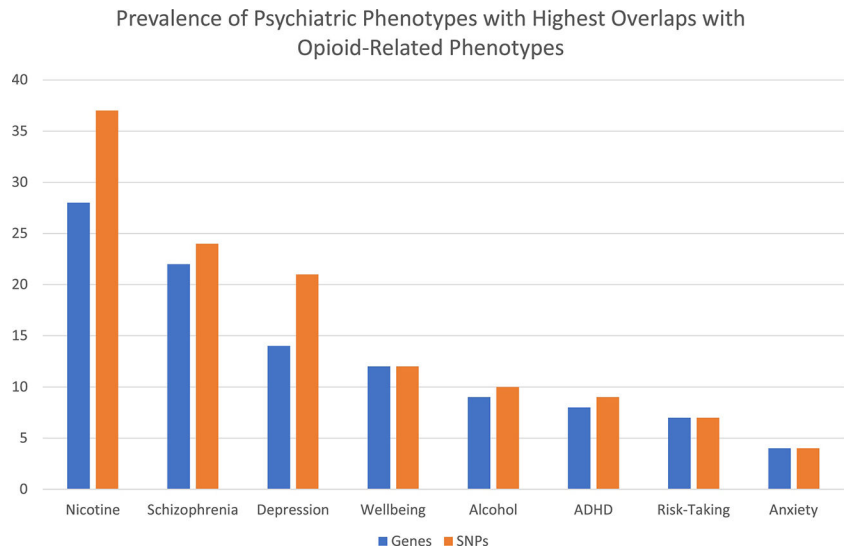

Figure 2:

Bar graphs illustrating the prevalence, measured in number of genes (blue) and SNPs (orange), of psychiatric phenotypes with the highest overlaps with opioid-related phenotypes found in Table S1.