Drug repurposing for opioid use disorders: integration of computational prediction, clinical corroboration, and mechanism of action analyses

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Abstract
Morbidity and mortality from opioid use disorders (OUD) and other substance use disorders (SUD) is a major public health crisis, yet there are few medications to treat them. There is an urgency to accelerate SUD medication development. We present an integrated drug repurposing strategy that combines computational prediction, clinical corroboration using electronic health records (EHRs) of over 72.9 million patients and mechanisms of action analysis. Among top-ranked repurposed candidate drugs, tramadol, olanzapine, mirtazapine, bupropion, and atomoxetine were associated with increased odds of OUD remission (adjusted odds ratio: 1.51 [1.38–1.66], 1.90 [1.66–2.18], 1.38 [1.31–1.46], 1.37 [1.29–1.46], 1.48 [1.25–1.76], p value < 0.001, respectively). Genetic and functional analyses showed these five candidate drugs directly target multiple OUD-associated genes including BDNF, CYP2D6, OPRD1, OPRK1, OPRM1, HTR1B, POMC, SLC6A4 and OUD-associated pathways, including opioid signaling, G-protein activation, serotonin receptors, and GPCR signaling. In summary, we developed an integrated drug repurposing approach and identified five repurposed candidate drugs that might be of value for treating OUD patients, including those suffering from comorbid conditions.

Introduction
Substance use disorders (SUD) when manifested in their moderate or severe presentation are considered chronic diseases of the brain that in its most severe manifestation result in an escalating and an uncontrollable use of the drug despite its adverse consequences to the individual [1–3]. SUD are estimated to affect 10.8% of the adult population in the US [4] and account for 1.5% of global disease burden [5]. In the US overdose death associated with opioids were five times higher in 2016 than 1999, leading the US government to declare the opioid crisis a public health emergency [6]. As of now opioid overdose fatalities as well as drug fatalities in general have continue to rise in the US [7]. There are few medications for SUD and while effective they are limited by limited utilization and high relapse rates [8]. There are no approved medications to treat cocaine, marihuana, methamphetamine, benzodiazepine, or inhalant use disorders. The traditional drug discovery process for medication development is lengthy and costly [8, 9]. In addition, the very modest investment from the pharmaceutical sector in SUDs has limited the discovery of new medications to a greater extent than for other neuro-psychiatric disorders. Thus, novel strategies to evaluate the potential for repurposing existing drugs to treat SUD could accelerate access to additional medications [8, 10].

Drug repurposing is a strategy that can help identify potential new therapies for complex diseases, including...
For example, lofexidine was approved for the treatment of hypertension and was recently approved for the treatment of acute opioid withdrawal [12]. With the accumulation of relevant data in machine-actionable formats, data-driven computational approaches have been developed to automate the drug repurposing process [13–18]. However, clinically validating a promising repurposed candidate drug generated by computational algorithms remains a challenge.

We propose an integrated drug repurposing strategy that combines computational-based drug prediction, patient Electronic Health Records (EHRs)-based clinical corroboration and mechanisms of action analysis. First, we developed a phenome-driven network-based drug discovery system that prioritized repurposed anti-SUD candidate drugs. The phenotypic and genetic relationships among drugs, drug phenotypes (side effects or SEs), and genes were modeled using the novel context-sensitive network (CSN)-based modeling techniques that we previously developed [16, 19, 20, 22, 23]. Then phenome-driven network-based prioritization approaches, which we recently developed both for understanding disease mechanisms and for drug discovery [14, 16, 18, 19, 21–23], were used to prioritize repurposed candidate drugs based on their phenotypic and genetic relevance to the input disease (i.e., SUD). In our study, we significantly leveraged the context-sensitive drug side effect network that we constructed based on known drug side effects. Side effects are observable phenotypes of drugs manifested at the level of the whole-body system and are mediated by a drug interacting with its on- or off-targets through a cascade of downstream pathway perturbations. While mechanisms of action (on- and off-targets) of many drugs and the underlying molecular mechanisms of diseases remain largely unknown, we can infer novel connections between drugs and diseases (drug repurposing) based on the observed drug and disease phenotypes as well as known drug-targets and protein–protein connections [22]. Instead of directly identifying drugs that target SUD’s mechanisms, which remain largely unknown, the phenome-driven drug discovery system identifies drug candidates that share similar drug phenotypes (i.e., side effects) and/or common targets with drugs causing or treating SUD. Second, we then performed retrospective case-control studies to evaluate the clinical efficacy of promising repositioned candidate drugs using EHRs of 72.9 million patients (20% of the US population). Finally, we examined potential mechanisms of action of promising repurposed candidate drugs in targeting SUD by developing data-driven informatics approaches. The knowledge and data generated by our study (i.e., promising candidate drugs with both supporting clinical evidence and potential mechanism of actions) can set the foundation of experimental testing in animal models for SUD or for pilot testing in clinical trials.

Material and methods

Our study entailed three steps (Fig. 1): (1) We constructed a drug side effect-gene (DSEG) computational drug prediction system to prioritize drugs to treat SUD. (2) We performed retrospective case-control studies to evaluate top candidate drugs using patient EHR data. (3) We performed genetic and pathway enrichment analysis of top candidate drugs to understand their potential mechanisms of action.

Computational drug prediction

Constructing drug side effect-gene prediction system

We constructed a DSEG drug prediction system that models the interconnections among drugs, side effects, and genes using the CSN-based modeling techniques that we previously developed [19–23]. The DSEG system included two networks (Fig. 1a): (1) a drug phenotypic (drug side effects) network (DPN) and (2) a protein–protein interaction network (PPIN). DPN was constructed using drug-SE pairs from the Side Effect Resource (SIDER) database [24] and
consisted of 1430 drug nodes, 4251 SE nodes, and 145,321 drug-SE edges. PPIN was directly constructed from protein–protein interactions in STRING [25] and consisted of 17,906 gene nodes and 2,091,571 gene–gene edges. Drug nodes (899 drugs) on DPN were connected to gene nodes (1021 genes) on PPIN using drug-target associations from the DrugBank database [26].

**Prioritize anti-SUD drug candidates**

We prioritized candidate drugs using the network-based ranking algorithms that we previously used for drug repurposing, gene discovery, and gut microbial metabolite discovery for the disease [16–23, 27–29]. In brief, given an input or seeds (drug abuse, drug dependence, and drug withdrawal syndrome in our study), the ranking score for each drug on the entire network was iteratively updated by:

\[
p_{k+1} = (1 - \alpha)T^k p_k + \alpha p_0,
\]

where \(\alpha\) (\(\alpha = 0.15\) in this study) denotes the probability of restarting from the seed nodes at each step. The algorithm was iterated until convergence (\(\|p_{k+1} - p_k\| < 10^{-8}\)). We used D and G to represent DPN and PPIN, respectively. \(T\) denotes the transition matrix of DSEG network:

\[
T = \begin{pmatrix}
T_{DD} & T_{DG} \\
T_{GD} & T_{GG}
\end{pmatrix},
\]

In Eq. (2), the diagonal sub-matrices \(T_{xx}\) \((x \in \{D, G\})\) were calculated through normalizing the adjacency matrix of D and G, the off-diagonal sub-matrices \(T_{xy}\) \((x, y \in \{D, G\})\) were calculated through normalizing the adjacency matrix of the bipartite network connecting D and G.

**Evaluation**

We evaluated how the drug prediction algorithm ranked the four drugs (methadone, buprenorphine, naltrexone, and naloxxone) approved for the treatment of OUD or opioid overdose reversal. Lofexidine, an alpha 2 adrenergic agonist that was recently approved for the treatment of acute opioid withdrawal [10], was not included since it was not in the SIDER database and on the DPN. The average ranking of these four drugs among all FDA-approved drugs was calculated.

**Electronic health records-based large-scale clinical corroborations for predicted anti-SUD drug candidates**

We performed a retrospective case-control study to evaluate top repurposed candidate drugs for treating OUD using de-identified population-level EHR data collected by the IBM Watson Health from 360 hospitals and 317,000 providers across 50 states from 1999 up to August, 2020, representing 20% of the US population [30]. The EHRs are de-identified according to the Health Insurance Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act standards. After the de-identification process, the curation process normalizes the data by mapping key elements to widely-accepted biomedical terminologies [31]. Specifically, disease terms are coded using the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT), a global standard for health terms that provides the core general terminology for EHRs [32]. We have recently used this EHR database for drug repositioning for Alzheimer’s disease [23, 33] and for studying the risk and outcomes of COVID-19 in patients with SUD, mental disorders, and cancers [34–37]. The EHR data are de-identified and aggregated (not patient-level) and institutional review board review was exempt.

We used the odds of remission from OUD as the outcome measure. The status of OUD was based on the diagnosis of “Opioid dependence (disorder)” (SNOMED-CT concept code 75544000) and the outcome measure “remission of OUD” was based on the diagnosis of “Opioid dependence in remission (disorder)” (SNOMED-CT concept code 191821007). At the time of the study, there were 326,620 patients with OUD and 28,940 of whom had a record of OUD in remission. We investigated the associations between top-ranked drugs and the odds of remission from OUD.

For a candidate drug A for repurposing, we identified a study cohort of OUD patients diagnosed with drug A’s original indication. We obtained drug indication information from the National Library of Medicine DailyMed, a comprehensive and up-to-date resource of medication content and labeling as found in medication package inserts [38] and other authoritative health information sites. For example, “depressive disorder” is the initial treatment disease of citalopram. In the study cohort, the exposure group (drug group) was comprised of OUD patients with depressive disorder who were prescribed with drug A (citalopram) before remission of their OUD. The comparison group (no drug group) was comprised of OUD patients with depressive disorders but without drug A (citalopram). We compared the odds of remission from opioid dependence between the exposure group and the comparison group.

The EHR data are de-identified population-level (not patient-level) data, therefore we used odds ratios (OR) instead of regression analyses, as previously done by studies that used the Explorys EHR database [23–25, 34–37]. For a given input set of patient characteristics (e.g., age, gender, race, diagnosis, comorbidities), the Explorys Explore Cohort Discovery tool built a patient cohort by querying the...
EHR database for patients matching the inputs. Patients with missing values for the input queries were not included in the returned cohorts. The associations between candidate drugs and remission were estimated by an OR for remission comparing the exposure group versus the comparison group in which both groups suffered OUD. The adjusted odds ratios (AORs), 95% confidence intervals (CIs), and \( p \) values were calculated using Cochran–Mantel–Haenszel (CMH) method \[39\], controlling for age (adult: 18–64 years, seniors: >64 years), gender (male, female), race (Caucasian and non-Caucasian), original indication, and existing treatments for opioid dependence. A two-sided \( p \) value < 0.05 was considered as statistical significance. All analyses were done using R, version 3.6.3. Drugs with insufficient data (e.g., rarely used drugs in OUD patients) to perform the CMH analysis were excluded. Among the top 20 drugs, one drug was excluded.

**Analysis of top anti-SUD drug candidates in the context of OUD at the genetic and functional levels**

**Genetic-level analysis**

We obtained 19 OUD-associated genes from the published literature \[40–42\], including APBB2, BDNF, CNIH3, COMT, CYP2D6, DRD2, DRD4, HTR1B, KCNC1, KCNG2, OPRD1, OPRK1, OPRM1, PDYN, PENK, POMC, RGMA, SLC6A4, and TPH2. For each repurposed candidate drug, we used the STITCH (Search Tool for Interactions of Chemicals) database to obtain its associated genes. STITCH contains data on the interactions between 500,000 small molecules and 9.6 million proteins from 2031 organisms \[43\]. In this study, we used chemical-gene associations found in the human body. The scores of chemical-gene associations ranged from 100 to 999 and we used the median score of 500 as the cutoff value. For example, at cutoff score of 500, olanzapine (a top repurposed candidate) is associated with 62 genes. We identified OUD genes that are directly targeted by a candidate drug by intersecting OUD-associated genes with drug-associated genes. For example, among 62 gene targets of olanzapine, seven are OUD-associated genes (BDNF, CYP2D6, DRD2, DRD4, HTR1B, POMM, and SLC6A4).

**Functional-level analysis**

We then investigated how the repurposed anti-OUD candidate drugs are functionally related to OUD by directly targeting OUD-associated pathways. We used rich pathway information from the Molecular Signatures Database (MSigDB), currently the most comprehensive resource of 17,779 annotated pathways and gene sets \[44\], to perform pathway enrichment analysis as in our previous studies \[45, 46\]. To identify genetic pathways significantly enriched for OUD, genetic pathways were first obtained from MSigDB for each OUD gene. For each pathway, we assessed its probability of being associated with the given set of 19 OUD-associated genes as compared to its probability of being associated with the same number of randomly selected genes. The random process was repeated 1000 times and a \( t \)-test was used to assess the statistical significance. We obtained a total of 53 significantly enriched pathways for 19 OUD genes, which include G-protein activation, opioid signaling, gap junction, and serotonin receptors, among others.

Similarly, we identified genetic pathways significantly enriched for each candidate drug. Genetic targets of each candidate drug were obtained from the STITCH database. For each drug-targeted gene, its associated pathways were obtained from the gene–pathway pairs form the MSigDB database. For each pathway, we assessed its probability of being associated with the given set of drug-associated genes as compared to its probability of being associated with the same number of randomly selected genes. For example, a total of 317 pathways were significantly enriched for the set of 62 olanzapine-associated genes, which include 41 of the 53 OUD-associated pathways. For each repurposed candidate drug, we identified OUD pathways that are also significantly enriched for the drug by intersecting drug-associated pathways with OUD-associated genes and pathways.

**Results**

**Our drug prediction system ranked approved SUD treatments highly**

Table 1 lists the ranks (in top percentage) for the four medications used clinically to treat OUD and opioid overdose reversal (naloxone). Our system prioritized these four drugs within the top 3.4% among 1430 FDA-approved drugs on the network.

Table 2 shows the top 20 predicted drug candidates for SUD. Overall, 17 out of 20 are implicated as SUD treatments through different sources, including FDA drug candidates.
Table 2 Top 20-ranked repurposed drug candidates.

| Rank | Drug       | Original Indication     | Evidence                                                                 |
|------|------------|-------------------------|--------------------------------------------------------------------------|
| 1    | Pregabalin | Diabetic neuropathic pain | NCT00142883                                                           |
| 2    | Fentanyl   | Pain/acute pain          |                                                                          |
| 3    | Morphine   | Pain/acute pain          |                                                                          |
| 4    | Oxycodone  | Pain/acute pain          | NCT00218374                                                           |
| 5    | Hydromorphone | Pain/acute pain      | NCT00218361                                                           |
| 6    | Citalopram | Depression               | NCT01535573                                                           |
| 7    | Ziprasidone | Schizophrenia            | PMID24628830                                                          |
| 8    | Atomoxetine | ADHD                    | NCT01498549                                                           |
| 9    | Tramadol   | Pain                     | NCT00301210, NCT01188421, NCT00142896, NCT03365817                     |
| 10   | Bupropion  | Depression               | NCT02111798                                                           |
| 11   | Mirtazapine | Depression              | NCT02541526, NCT00249444, NCT0322309, NCT00732901                     |
| 12   | Cortisol   | Rheumatoid arthritis     | NCT00759005, NCT01718964                                              |
| 13   | Naltrexone | OUD                      | FDA-approved                                                            |
| 14   | Tapentadol | Pain                     | NCT00687713                                                           |
| 15   | Amphetamine | ADHD                    | NCT00421603                                                           |
| 16   | Methylprednisolone | Rheumatoid arthritis |                                                                          |
| 17   | Triazolam  | Insomnia                 | NCT00218166                                                           |
| 18   | Olanzapine | Schizophrenia            | NCT02643355                                                           |
| 19   | Topiramate | Seizures                 | NCT00396734, NCT00421603                                              |
| 20   | Fluoxetine | Depression               | NCT00142779                                                           |

NCT: SUD drugs from clinical trials. PMID: SUD drugs from biomedical literature.

Fig. 2 Odds ratios of remission from opioid dependence and the corresponding 95% CI of 10 of top 20-ranked drugs. Triazolam was excluded due to insufficient cases for patients with opioid dependence.

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CIs of remission from OUD for the 19 top candidate drugs. Triazolam was excluded due to insufficient cases for patients with OUD. Naltrexone, an FDA-approved OUD treatment, has the highest effects on remission from OUD. Specifically, we studied OUD patients who were not prescribed methadone or buprenorphine. In this cohort, those who have prescribed naltrexone had odds of remission nearly 4.00 times as compared to those not prescribed naltrexone (AOR: 3.54, 95% CI: [3.31,3.69], p value < 0.0001), adjusting for age, gender, and race. This result supports the validity of the EHR-based evaluation of clinical efficacy of candidate drugs for treating OUD.

For the remaining 18 drugs, eight had an AOR of remission significantly higher than 1.0. Olanzapine, a drug approved to treat schizophrenia, has the highest AOR of remission from OUD. Specifically, we studied patients with OUD and schizophrenia but not prescribed methadone, buprenorphine, or naltrexone. In this cohort, OUD patients who were prescribed olanzapine had odds of OUD remission nearly 50% higher compared to patients not prescribed olanzapine (AOR: 1.90; 95% CI [1.66,2.18], p value < 0.0001), adjusting for age, gender, and race. Three antidepressants (bupropion, mirtazapine and atomoxetine) had odds of OUD remission nearly 2.00 times compared to patients not prescribed these antidepressants (AOR = 1.31–1.46), p value < 0.0001; 1.37 [1.29–1.46], p value < 0.0001; 1.48 [1.25–1.76], p value < 0.0001, respectively).

The prescription of opioid analgesics was negatively associated with OUD remission. For example, patients who were prescribed morphine had odds of remission 16% lower compared to patients with no prescription of morphine (AOR: 0.84; 95% CI [0.76,0.92], p value < 0.0001). These results show that opioid analgesics can aggravate OUD. Interestingly, we found that tramadol was the only opioid analgesic positively associated with OUD remission (AOR: 1.51; 95% CI [1.38,1.66], p value < 0.0001). Tramadol has a lower risk of addiction compared to other opioid analgesics [48] and previous studies support benefits in the management of opioid withdrawal symptoms and long-term OUD treatment [49, 50]. Our findings alongside the prior studies in the literature support further evaluation of tramadol for OUD treatment, including treatment of comorbid OUD in pain patients.

### Analysis of repurposed candidate drugs in the context of OUD at the genetic and functional level

We analyzed how each of the five promising drugs (reducing OUD relapse) (Fig. 2) relates to OUD at the genetic and functional level. At the genetic level, each candidate drug directly targets multiple OUD-associated genes. For example, olanzapine targets a total of 62 genes, among which seven genes are implicated in OUD. Tramadol targets 16 genes, of which five are OUD genes, including three opioid receptors (OPRD1, OPRK1, and OPRM1) (Table 3).

While each candidate drug is associated with higher odds of OUD remission based on EHR analysis, these drugs target different aspects of OUD and OUD genes as shown in Table 3. The complete list of OUD- and drug-associated genes are in Supplementary file S1.

We then analyzed how these candidate drugs are functionally involved in OUD. We identified 53 genetic pathways that are significantly enriched for the 19 OUD-associated genes. The top enriched OUD pathways are opioid signaling, G-protein activation, gap junction, potassium channels (full list is in Supplementary file 2). We identified significantly enriched pathways for each candidate drug and the shared pathways between the drug and OUD. As shown in Table 4, each candidate drug targets multiple OUD-associated pathways. For example, 317 pathways are significantly enriched for olanzapine, among which 41 are also significantly enriched for OUD (77% of 53 OUD pathways) including G-protein activation, serotonin receptors among others. A total of 42 pathways are significantly enriched for tramadol, among which 24 were OUD-associated pathways (45% of 53 OUD pathways) including G-protein activation, serotonin receptors, opioid signaling among others. The full list of OUD-associated pathways targeted by each candidate drug is in Supplementary file S2.

### Discussion

We developed an integrated drug repurposing strategy for OUD that is applicable to other SUDs. The approach combined computational drug candidate prediction, EHRs-
Drug repurposing for opioid use disorders: integration of computational prediction, clinical... based clinical corroboration, and mechanisms of action analysis using genetic, genomic, phenotypic, and patient EHR data. We identified one opioid analgesic (tramadol), one antipsychotic (olanzapine), two antidepressants (mirtazapine and bupropion), and one selective norepinephrine reuptake inhibitor (atomoxetine), that might be of value in

| Drug          | Total (n) | Shared (n) | Top 10 pathways                                                                 |
|---------------|-----------|------------|---------------------------------------------------------------------------------|
| Atomoxetine   | 42        | 16         | Xenobiotics                                                                     |
|               |           |            | Voltage gated potassium channels                                                |
|               |           |            | Cytochrome P450—arranged by substrate type                                      |
|               |           |            | Phase 1—functionalization of compounds                                           |
|               |           |            | Neuroactive ligand–receptor interaction                                          |
|               |           |            | Biological oxidations                                                           |
|               |           |            | Posttranslational regulation of adherens junction stability and disassembly     |
|               |           |            | Potassium channels                                                              |
|               |           |            | SHP2 signaling                                                                  |
|               |           |            | Neurotrophic factor-mediated Trk receptor signaling                              |
| Bupropion     | 305       | 21         | Serotonin receptors                                                              |
|               |           |            | Xenobiotics                                                                      |
|               |           |            | Amine ligand-binding receptors                                                   |
|               |           |            | Cytochrome P450—arranged by substrate type                                       |
|               |           |            | Opioid Signaling                                                                |
|               |           |            | Phase 1—functionalization of compounds                                           |
|               |           |            | Class A/1 (Rhodopsin-like receptors)                                             |
|               |           |            | Neuroactive ligand–receptor interaction                                          |
|               |           |            | Biological oxidations                                                           |
|               |           |            | Posttranslational regulation of adherens junction stability and disassembly     |
| Mirtazapine   | 93        | 24         | Serotonin receptors                                                              |
|               |           |            | Repression of pain sensation by the transcriptional regulator DREAM             |
|               |           |            | Xenobiotics                                                                      |
|               |           |            | Regulation of ck1/cdk5 by type 1 glutamate receptors                            |
|               |           |            | Amine ligand-binding receptors                                                   |
|               |           |            | G alpha (1) signaling events                                                     |
|               |           |            | Cytochrome P450—arranged by substrate type                                       |
|               |           |            | G alpha (1) pathway                                                             |
|               |           |            | Phase 1—functionalization of compounds                                           |
|               |           |            | Class A/1 (Rhodopsin-like receptors)                                             |
| Olanzapine    | 317       | 41         | G-protein activation                                                             |
|               |           |            | Androgen biosynthesis                                                            |
|               |           |            | Serotonin receptors                                                              |
|               |           |            | Repression of pain sensation by the transcriptional regulator DREAM             |
|               |           |            | Xenobiotics                                                                      |
|               |           |            | Regulation of ck1/cdk5 by type 1 glutamate receptors                            |
|               |           |            | Synedcan-3-mediated signaling events                                             |
|               |           |            | Amine ligand-binding receptors                                                   |
| Tramadol      | 42        | 24         | G-protein activation                                                             |
|               |           |            | Serotonin receptors                                                              |
|               |           |            | Repression of pain sensation by the transcriptional regulator DREAM             |
|               |           |            | Xenobiotics                                                                      |
|               |           |            | Amine ligand-binding receptors                                                   |
|               |           |            | G alpha (1) signaling events                                                     |
|               |           |            | Cytochrome P450—arranged by substrate type                                       |
|               |           |            | Opioid Signaling                                                                |
|               |           |            | Peptide ligand-binding receptors                                                 |
|               |           |            | Phase 1—functionalization of compounds                                           |
improving outcomes in OUD patients, including those suffering from comorbid conditions.

Our study shows that patients with schizophrenia and OUD who were prescribed olanzapine had higher odds of OUD remission than individuals without olanzapine (AOR = 1.90). Olanzapine is an antipsychotic drug that acts as an antagonist at dopamine D1 and D2 receptors, 5H2A and 5H6 serotonin receptors, H1 histamine receptors, adrenergic alpha one receptor, and muscarinic M1–M5 receptors [51]. In our study, we showed that olanzapine directly targets 7 of 19 OUD-associated genes, including BDNF, CYP2D6, DRD2, DRD4, HTR1B, POMC, and SLC6A4. Based on pathway enrichment analysis, olanzapine significantly targets 41 of the 53 OUD-associated pathways (77%). Some of the pathways, such as G-protein activation, serotonin receptors, neuroactive ligand–receptor interaction, and GPCR signaling are known to be involved in opioid addiction [52, 53].

In our analysis, patients with pain and OUD who were prescribed with tramadol had higher odds of OUD remission than individuals without tramadol (AOR = 1.51). Tramadol is a prodrug whose metabolite (O-desmethyltramadol) acts as an opioid agonist and a serotonin-norepinephrine reuptake inhibitor [54]. Tramadol is widely used as an analgesic and is believed to be less addictive than other equipotent opioid analgesics. The increased odds of OUD remission, we observed when tramadol was prescribed to patients with comorbid pain identifies it as another opioid agonist potentially beneficial for OUD treatment. Consistent with this, studies have reported the benefit of Tramadol use for opioid detoxification [55]. Intriguingly whereas the prescription of opioid analgesics was associated with decreased risk for OUD remission, the prescription of tramadol showed the opposite association. In this respect, tramadol might be particularly useful in the management of pain patients suffering from OUD. Our analysis of genes and genetic pathways targeted by tramadol show that tramadol directly target OUD-associated genes and opioid receptors (CYP2D6, OPRD1, OPRK1, OPRM1, and SLC6A4). Among 42 pathways significantly enriched for tramadol, 24 were OUD-associated pathways (45% of 53 OUD pathways) including G-protein activation, serotonin receptors, opioid signaling, GPCR signaling among others. These potential mechanisms of action of tramadol suggest tramadol may help treat OUD in general and not only in OUD patients with pain.

Two antidepressants (bupropion and mirtazapine) and one selective norepinephrine reuptake inhibitor (atomoxetine) that also has antidepressant properties were identified as anti-OUD candidates. Inasmuch as depression is frequently comorbid with OUD and contributes to relapse this could be a mechanism for improving outcomes in OUD. Most notable is bupropion, a blocker of dopamine and norepinephrine transporters and an antagonist at various nicotine receptors including the alpha 4 beta 2 receptor associated with the rewarding effects of nicotine [56], since it is an approved treatment for smoking cessation. Furthermore, preclinical studies have reported that bupropion prevented the development of tolerance to opioids and the emergence of withdrawal symptoms [57]. Our analysis shows that bupropion directly targets multiple OUD-associated pathways including serotonin receptors, opioid and GPCR signaling, neuroactive ligand–receptor interaction, which suggests that bupropion may also be beneficial in OUD treatment.

Mirtazapine enhances noradrenergic and presumably dopaminergic signaling through its antagonistic effects at serotonin receptors (5HT2 family) and alpha 2 adrenergic receptors. Preliminary evidence has shown a therapeutic benefit of mirtazapine in the treatment of patients with methamphetamine use disorder alone or when combined with naltrexone [58]. Our genetic and pathway analyses showed that mirtazapine directly target five OUD-associated genes (CYP2D6, DRD2, DRD4, OPRK1, and SLC6A4) and 24 OUD-associated pathways including serotonin receptors, G alpha signaling, GPCR signaling, and GAP junctions, among others.

Atomoxetine is a selective norepinephrine (noradrenaline) reuptake inhibitor for the treatment of attention-deficit hyperactivity disorder (ADHD) [59, 60]. It is a highly selective and potent inhibitor of the presynaptic noradrenaline transporter and could be of use in the treatment of depression associated with OUD as a monotherapy or as an augmentation agent [61]. Preclinical studies have shown that atomoxetine attenuated stimulant self-administration perhaps by modifying the reinforcing properties of stimulants [62]. Our EHR-based analysis showed that atomoxetine is associated with significant OUD remission in patients with ADHD and OUD. In addition, atomoxetine directly targets three OUD genes (BDNF, CYP2D6, and SLC6A4) and 16 of the 53 OUD pathways including potassium channels, neuroactive ligand–receptor interaction, and chemical synapsis.

One important finding is that all five candidate drugs directly target multiple OUD genes and pathways, suggesting that these drugs may treat OUD in the general population and might be particularly beneficial in patients with comorbid conditions (pain, depression, schizophrenia, ADHD). In addition, these drugs target different OUD genes and pathways, suggesting that combinations of these drugs may have synergistic efficacy in treating OUD.

Our study has several limitations. First, we used patient EHR data to corroborate top-ranked anti-OUD candidate drugs generated by the network-based prediction algorithm. Patient EHR data were collected for clinical convenience and billing, not for research purposes. Though EHR data have been widely used for research purposes, they have inherent limitations including under-diagnosis, over-diagnosis, or mis-
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