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GUEST EDITORIAL

The importance of buprenorphine research in the opioid crisis

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Abstract

With the urgency to treat patients more effectively for opioid use disorder in the midst of the opioid epidemic, a key area for precision medicine is to improve individualized medication-assisted treatment for opioid use disorder. The expansion of medication-assisted treatment is a key to reducing illicit opioid use, preventing opioid overdose deaths, and reducing the comorbidities and societal impacts of opioid use disorder. The most common medication for opioid use disorder will soon be buprenorphine. Research to date shows the successful impact of buprenorphine treatment, including the pharmacogenomics of buprenorphine response and treatment efficacy. Buprenorphine is also a promising treatment for depression and anxiety, and neonatal opioid withdrawal syndrome (NOWS). However, the rates of success with medication-assisted treatment for opioid use disorder, particularly at the beginning of treatment, still show many individuals relapsing to illicit opioid use. With the scope of the opioid crisis, there is an urgent need for expansion of buprenorphine treatment research to provide critical information for improving outcomes of opioid use disorder. Implementing the best strategies for opioid use disorder treatment is of dire urgency and will save lives.

Opioid use disorder and opioid substitution therapy

The opioid addiction crisis is ongoing, with the majority of those with opioid use disorder (OUD) having started with prescription opioids [1]. Every day more than 115 people die from opioid-involved overdose in the US, with the greatest percentage of those deaths involving prescription opioids [2]. Beyond overdose, there are significant impacts from OUD, including the burden of addiction on individuals and society. These burdens include significant individual comorbidities, economic loss (e.g., emergency health care utilization [3]), impacts on children through neonatal opioid withdrawal syndrome (NOWS) [4], the destructive effect of OUD on families, and impact within the U.S. legal and criminal justice system [5]. Many medical providers are now prescribing opioid-free treatment modalities (particularly for chronic pain) to prevent future addiction to opioids; however, there remain millions of people affected by OUD. OUD is a chronic disease that can be compared to other chronic health conditions, such as diabetes and heart failure. Thus treatment for OUD is now being considered for extended periods [6].

Research has shown that treating OUD through medication-assisted treatment (MAT) with opioid substitution therapy (OST) leads to decreased mortality rates and improved outcomes [7]. The current FDA-approved treatments for OUD frequently consist of OST with medications, such as methadone and buprenorphine. OST medications act as agonists at the mu-opioid receptor (MOR), which is the primary target of addictive opioids. Methadone is a full MOR agonist. Buprenorphine is both a partial MOR agonist and a kappa-opioid receptor (KOR) antagonist.

Opioid substitution therapy through buprenorphine

Buprenorphine is quickly becoming the most important OST for OUD, because of its availability in primary care

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settings, accessibility for patients, and more favorable safety profile [8]. In the United States, buprenorphine is frequently compounded in sublingual tablets with naloxone to discourage patients from misusing the crushed tablet. The medication does not require daily observed dosing like methadone and is available in extended release formulations. All these factors can reduce access hurdles for some patients to OST and support greater adherence to therapy. However, a considerable limitation in access to buprenorphine-based OST remains due to the number of physicians who can prescribe buprenorphine. A Drug Enforcement Agency (DEA) waiver is available for the prescribing of buprenorphine to treat OUD. Clinicians have to complete 8 hours of training to obtain the waiver to prescribe buprenorphine for OUD. Mid-level practitioners, such as physician assistants and nurse practitioners, must have 24 hours of training. Thus, there are limitations for clinicians with already full schedules due to the time requirements for obtaining the waiver. There are other barriers, including concerns from providers about not having the skills to treat OUD even if cleared to prescribe buprenorphine, concerns about the lack of psychosocial and mental health support available for OUD patients, misconceptions about the value of OST, lack of training in addiction treatment, and misconceptions about addiction [9, 10]. It is also important to note another caveat to the improved accessibility of buprenorphine by patients, as there are health disparities in access to buprenorphine. For example, individuals in predominantly white, higher-income areas of New York City as of 2007 were more likely to have access to buprenorphine than low-income, predominantly African–American and Hispanic areas [11].

Improving successful opioid substitution therapy

While the treatment of OUD with OST improves outcomes compared to no treatment, there is a wide range of the overall success of OST, depending on what time period is being reported. Two recent reports indicated that ~40% of patients treated with buprenorphine were retained in OST treatment for 1 year [12, 13]. There are some known demographic, socioeconomic, and psychosocial contributors to the retention of individuals in MAT, based mostly on research in methadone-based OST. These contributors include depression, stress, employment status, association with other drug users, and stability of personal relationships [14]. Schizophrenia, bipolar disorder, and alcohol abuse or dependence have also been found to predict relapse rates during treatment [15]. Anxiety has been associated with opioid positive urine drug screens during methadone OST [16]. Anxiety and substance use, specifically alcohol and benzodiazepines, have also been identified as predictors of relapse during buprenorphine treatment [17]. In one study of buprenorphine treatment, dropout was associated with age, ethnicity, hepatitis C infection, and employment status [18].

Precision medicine characterizes individual variability in genes and environment for improving individualized treatment response. Precision medicine principles can be applied in order to improve OST/MAT outcomes. Expanding our understanding of the key factors that contribute to OST success for each patient, including psychological, socioeconomic, environmental, and genetic factors, in longitudinal research provides a way to better target for each patient the level and types of support most critical to successful OST adherence. No study thus far has investigated the impact of combinations of these factors on the efficacy or effectiveness of OST in a real-world setting. Precision medicine will help identify if other medications (e.g. methadone or naltrexone), increased patient monitoring, and/or employing different behavioral therapies will better support successful OST and MAT for specific patients at increased risk of relapse. Further, through the use of longitudinal clinical data, there is an opportunity for better predictions of the long-term health outcomes of individuals.

Precision medicine also includes the use of genetic data, through genetic biomarkers that correlate with increased or decreased risk of outcomes. It will be important to use pharmacogenomic analyses in buprenorphine treatment to identify genetic variation that corresponds with efficacy in treatments for OUD. Efficacy can be defined as either reduction in drug use or prevention of relapse, and there are a series of studies that have used this pharmacogenomics approach in the treatment of nicotine and alcohol use disorders [19–25]. Several studies have also identified variants associated with either the dose or serum concentration of methadone [26–32]. Metabolism of buprenorphine is variable among individuals suggesting a similar genetic etiology. Buprenorphine is metabolized by CYP450 enzymes, and research has well characterized the impact of genetic variation for CYP450 enzymes for other drug response [33–35]. Genetic variation impacting pharmacokinetics and pharmacodynamics for buprenorphine will likely be important for treatment outcomes, although there is no published research identifying polymorphisms associated with buprenorphine dose or serum concentration [36]. There have been some studies of the pharmacogenetics of buprenorphine efficacy, implicating *OPRD1, SLC6A3, SLC6A4*, and *COMT*; however, far more research must be done in larger sample sizes for further discovery [23, 24, 37, 38]. There is also the unexplored area of the pharmacogenomics of adverse reactions to buprenorphine [36]. Thus, there is a great potential for determining prospective genetic biomarkers to identify patients who will benefit the most from

buprenorphine-based OST, and, conversely, patients at greatest risk of relapse who would benefit from additional treatment strategies to support recovery. It is important to note that the pharmacogenomics research to date has been in those of both European and African ancestry, and that ongoing research needs to continue across multiple ancestries, including expanding across Hispanics and other ethnic groups, so that pharmacogenomic biomarkers are well characterized across ancestry.

Resources for improving precision medicine for buprenorphine-based ost

To obtain sufficient cohorts of patients for expanded research into buprenorphine-based OST, a valuable resource will be health care systems with longitudinal electronic health record data (EHR) data and, when possible, these EHRs coupled with genetic data. There is existing research showing the utility of using clinical data for addiction research. For instance, patients' clinical data have shown relevant changes up to 2 years before opioid overdose, which supports using the longitudinal clinical data of patients for relapse prediction [39]. Vivolo-Kantor et al. characterized the rates of overdose using emergency department data and hospital billing data from July 2016 to September 2017, noting increase in overdose across that time period as well as the variability in location of these events, varying by region and urbanization level [40]. Hasegawa et al. evaluated emergency department visits for opioid overdose [41]. They determined that frequent emergency department visits were associated with higher likelihood of future hospitalizations and near-fatal events. These are examples of information that could be used within health care systems to identify individuals with greatest need for intervention, potentially intervening far before overdose events. Further, research has shown that buprenorphine treatment started in the emergency room, with a direct 'warm handoff' to MAT clinics, increases engagement in formal addiction treatment [42]. For many patients this was their first treatment contact.

There are specific health system characteristics, that if present, will support the discovery of the most robust insights into key contributors to successful OST and support productive large-scale research. This includes health systems that have a substantial commitment to high-quality MAT for OUD, with psychosocial supports of drug counseling and case management encouraging continued patient retention. Health care systems with a decade or more of EHR data across primary and speciality care are also important, as EHR data provides inroads to multifaceted analyses of patient characteristics without time- and resource-consuming data collection. Health care systems that have digitally accessible ways of obtaining more information from patients, such as web portals for collecting patient responses, are also critical for facilitating collection of additional highly structured questionnaire data to further improve patient characterization for research. Medical systems taking care of large stable populations of OUD patients of diverse ancestries, as well as a wide range of ages including pregnant women and children, are possible within areas hardest hit in the US with the opioid epidemic. Health care systems with strong research infrastructure, including biorepositories, also provide a further strength for robust OST research. Other features that can contribute to robust research include embedded psychiatry residents cross-training within MAT clinics, with full time pharmacist involvement and system oversight. Health care systems with close relationships to local organizations are also important, as they are well connected to the larger environment in which patients are treated. This includes drug and alcohol counseling agencies, community mental health providers, county authorities, law enforcement, and pharmacies, which are integral to successful OST. Warm hand-offs of patients in general, including incorporating obstetric providers for concurrent MAT and pre-natal care, will also capture more data from OUD patients before and during OST.

An example health-care system for expanding buprenorphine OST research

One health care system that meets most of these criteria for expanded precision medicine research in OST is Geisinger, the largest health care provider in central Pennsylvania, which has now expanded into New Jersey. Geisinger is a primary and specialty care provider, and implemented an EHR in 1996. The Geisinger patient population is geographically stable, so longitudinal EHR data are common in this health system. Pennsylvania is one of the states most impacted by the opioid abuse epidemic across the United States: at least 10 Pennsylvanian's die every day from opioid overdose [43]. Hospital admissions for opioid overdose have nearly quadrupled since 2010 in Pennsylvania.

There have been limited numbers of addiction support providers in rural areas, such as the rural central Pennsylvania areas covered by Geisinger. There are also few primary care practitioners with training in addiction treatment. To address the opioid epidemic, Geisinger has opened three MAT clinics in 2017–18, with a fourth to soon be opened. In the first 8 months of 2018, 848 unique OUD patients were treated in these MAT clinics. Geisinger uses a hub and spoke model for deploying MAT clinics [44], where a centralized addiction specialist team works with primary care practitioners acting as "spokes". With this structure, there can be a rapid expansion of access to high-quality MAT, including quantitative buprenorphine and

buprenorphine metabolite monitoring, referral and follow-up with psychosocial supports from licensed drug and alcohol counselors, primary care physician support, structured prescribing intervals, rigorous diversion control policies, and pharmacist oversight for contraindicated medications. The MAT clinics employ witnessed dosing of buprenorphine with serial drug level monitoring for diversion control. Geisinger also is pursuing the eventual elimination of co-prescribing of contraindicated and concerning abusable medication, with a 90% reduction of this kind of prescribing. The hub and spoke model addresses many of the hurdles described for primary care providers by providing resources for patients and their primary providers beyond OST prescriptions. These MAT clinics can reduce the number of overdose deaths for treated patients, minimize the risk of diversion, and decrease the risk of relapse.

Geisinger MAT clinics provide comprehensive addiction evaluations, including use of the Addiction Severity Index embedded in the EHR, a critical asset for precision medicine OST research. Additionally, withdrawal assessment for alcohol (CIWA), and clinical opiate withdrawal scale (COWS) scores are recorded. This information is being integrated into the EHR at the beginning of care, and then updated every 6 months. These EHR data support logical prescribing levels for buprenorphine, critical measures of patient acuity, and provide information flow between the hub of the MAT treatment and the spokes (primary care providers and addiction treatment coordinators) via the EHR. These EHR data are thus a valuable opportunity for de-identified research within these records.

In terms of genetic data, the MyCode Community Health Initiative at Geisinger is a biorepository that will have more than 200,000 individuals with whole-exome sequencing and whole-genome array based genotyping in parallel. There is already a focus on consenting patients for MyCode within the MAT clinics for expanding the use of genomic data in addiction research. This genetic data coupled with the data collected as a part of general patient care as well as within addiction treatment at Geisinger will be a rich resource for pharmacogenomic analyses of buprenorphine response and adverse events.

Other health system resources with these optimal characteristics may also include the Kaiser Permanente, the Million Veteran Program and Vanderbilt University Medical Center. This list is not meant to be exhaustive, but illustrative.

Improving translation of research findings to clinical practice

While it is critical to expand research into key factors to improve precision medicine of OST, it is also important to identify the best strategies for bringing research findings to addiction care so that information that can improve patient outcomes can be utilized more quickly. The translation from discovery in research to updates in clinical practice is often slow, taking upwards of 17 years [45]. The implementation of pharmacogenomic findings in general into clinical care of patients has been slow [46]. With the ongoing OUD crisis, it is critical to develop an understanding now of the best strategies for widespread dissemination of interventions [47]. Methods of implementation science can be used to understand barriers and facilitators to implementation into care, and better understand organizational readiness to implement change. By applying implementation science, discovery of useful pharmacogenomics and clinical information can be quickly incorporated into clinical care, ensuring the success of bringing precision medicine principles to OST for successful MAT. Patients' and healthcare professionals' positive attitudes and beliefs toward utilizing and receiving pharmacogenomic results have been well-documented [48–50]. What are not known are the factors that facilitate and hinder a healthcare system's ability to successfully implement pharmacogenomic testing and the use of other clinical and demographic factors to improve the care of patients undergoing OST with buprenorphine. This is a beneficial area of research.

Expansion of buprenorphine for treatment of mood and anxiety disorders

In addition to the importance of elucidating the role of buprenorphine as OST, and the importance of precision medicine for buprenorphine treatment, there is also an important area of research to be pursued in better understanding the antidepressant and anxiolytic effects of buprenorphine, and the impact of those factors on therapeutic response. There are high rates of co-morbidity of OUD with anxiety and mood disorders, and the antidepressant effects of buprenorphine at low doses may prove critical in improving OST and MAT outcomes, since depression is associated with continued use during treatment [14].

There are now are multiple preclinical rodent studies which demonstrate that chronic administration of relatively low doses of buprenorphine have antidepressant and anxiolytic effects [51–54]. This effect of buprenorphine is attributed to its high affinity kappa-opioid receptor (KOR) antagonism, as other KOR antagonists have similar effects [55]. The buprenorphine antidepressant activity in the forced swim test in mice is absent in *OPRK1* (the gene encoding KOR) gene null mutants [53]. However, in the novelty-induced hypophagia test in mice, the antidepressant effects of buprenorphine were absent in *OPRM1* null mutants but

retained in *OPRK1* null mutants [56]. Thus, the buprenorphine MOR and KOR activities may both be relevant to its effects on rodent models of anxiety and depression.

In humans, a study by Bershad et al. found buprenorphine dampens the response to stress [57]. Trials of buprenorphine in depression are promising. In an open label, 8-week, flexible dose study of 15 older persons with treatment-resistant depression, Karp et al. [58] noted improvements over baseline depression ratings after 3 weeks of low dose buprenorphine, where daily doses ranged from 0.2 to 1.6 mg. In a double-blind, placebo-controlled trial, Fava et al. [59] reported significant improvements over baseline depression ratings among adults with treatment-resistant depression when treated with 2 mg buprenorphine combined with a mu antagonist, samidorphan (2 mg), as an add-on to existing antidepressant therapy. In subsequent phase III double blind trials, the Alkermes compound ALK 5461 (buprenorphine + samidorphan) showed promising antidepressant activity, resulting in an FDA new drug application by Alkermes. However, it is important to note that details of the trials have not yet been published in peer-reviewed format. It is noteworthy that the efficacious anxiolytic and antidepressant doses of buprenorphine are ~1/10th the doses used to treat OUD.

With the promising evidence of the anxiolytic and antidepressant activity for buprenorphine, important research questions have been raised. For example, what are the buprenorphine transcriptomic and proteomic profiles that convey the antidepressant and anxiolytic activity? And are these profiles similar to those of serotonergic or noradrenergic antidepressants? Which neural pathways are involved in these activities of buprenorphine, and how similar are these pathways to those of serotonergic or noradrenergic antidepressants? Are there pharmacogenetic, biomarker, and or/clinical profiles of responders to the antidepressant and anxiolytic activity of buprenorphine?

Buprenorphine treatment for neonatal opioid withdrawal syndrome

Another important area of research is the treatment of neonatal opioid withdrawal syndrome (NOWS), a series of conditions newborns have when going through withdrawal from opioids they were exposed to in the womb. Kraft et al. [60] documented that buprenorphine was a superior treatment for NOWS, compared to the standard treatment of morphine. In their double blind clinical trial, 63 term infants with NOWS were randomized. The buprenorphine-treated group ($n = 33$) had a shorter mean hospital stay (21 versus 33 days, $p < 0.001$) and a shorter duration of pharmacotherapy for NOWS (15 versus 28 days, $p < 0.001$). It can be expected that buprenorphine will be adopted as a standard treatment for NOWS, given these highly significant benefits. There are a series of questions to be answered through research, which will be critical to using buprenorphine in treatment of NOWS. For example, what are the developmental effects of perinatal buprenorphine exposure, and how do they differ from those of morphine, short and long-term? What differences in outcomes do we identify in the use of buprenorphine for NOWS when compared to adult buprenorphine exposure? Are there key contributors to NOWS buprenorphine response, whether they be pharmacogenetic or clinical?

Conclusions

Buprenorphine is a critically useful medication in opioid crisis. Expanded precision medicine research into the environmental and genetic characteristics of patients most likely to benefit from buprenorphine treatment of OUD is urgently needed to improve therapeutic responses. Implementation research guiding health systems on mechanisms to bring these findings quickly into the clinic are equally important. If research expands and focuses in these areas there is the potential for improving long-term outcomes and saving lives. An additional promising area of investigation is precision medicine of the anxiolytic and antidepressant activities of buprenorphine. Understanding the antidepressant and anxiolytic aspects of buprenorphine may help reduce the suicide rate, by providing an alternative pharmacotherapy for treatment-resistant depression.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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