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The nexus of opioids, pain, and addiction: Challenges and solutions

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ABSTRACT

Pain and addiction are complex disorders with many commonalities. Beneficial outcomes for both disorders can be achieved through similar principles such as individualized medication selection and dosing, comprehensive multi-modal therapies, and judicious modification of treatment as indicated by the patient's status. This is implicit in the term "medication assisted treatment" (MAT) for opioid use disorders (OUD), and is equally important in pain management; however, for many OUD and pain patients, medication is central to the treatment plan and should neither be denied nor withdrawn if critical to patient well-being. Most patients prescribed opioids for pain do not develop OUD, and most people with OUD do not develop it as a result of appropriately prescribed opioids. Nonetheless, concerns about undertreatment of pain in the late 20th century likely contributed to inappropriate prescribing of opioids. This, coupled with a shortfall in OUD treatment capacity and the unfettered flood of inexpensive heroin and fentanyl, behavioral economics and other factors facilitated the 21st century opioid epidemic. Presently, injudicious reductions in opioid prescriptions for pain are contributing to increased suffering and suicides by pain patients as well as worsening disparities in pain management for ethnic minority and low-income people. Many of these people are turning to illicit opioids, and no evidence shows that the reduction in opioid prescriptions is reducing OUD or overdose deaths. Comprehensive, science-based policies that increase access to addiction treatment for all in need and better serve people with pain are vital to addressing both pain and addiction.

1. Introduction

Pain and addiction are complex and often intertwined disorders in which undertreated pain leads some people to illicit opioid use and some people treated for pain develop opioid use disorder (OUD). However, most opioid-prescribed pain patients do not develop OUD, and most people with OUD did not develop it while taking appropriately prescribed opioids (Brat et al., 2018; Institute of Medicine (IOM), 2011; Scholten and Henningfield, 2016; Scholten et al., 2017; Volkow and Collins, 2017; Volkow and McLellan, 2016). Although the 21st century opioid epidemic has been fueled in part by efforts to address undertreated pain, other factors contributed; including the behavioral economics of access to addiction treatment versus heroin and fentanyl cost and availability. As implied by the President's Commission Report (Christie et al., 2017), increased access to evidence-based treatment of pain and addiction and new medications could help address both the opioid epidemic and pain in America. This commentary explores commonalities across pain and addiction, and describes how public health policy and attention to market forces could address the opioid epidemic and improve pain and OUD outcomes.

2. The 21st century opioid epidemic and pain in America

The 21st century opioid epidemic has evolved to the point that overall life expectancy is declining as opioid overdose deaths escalate (Jalal et al., 2018; Joszt, 2018; Murphy et al., 2018). Concurrently, rates of chronic pain-associated suicide have increased as opioid prescribing declines (Ehley, 2018; Hoffman and Goodnough, 2019; Hoffman et al., 2016; Lewis, 2019; Nicholson et al., 2018; Petrosky et al., 2018; Ray and Hoffman, 2018). There is widespread agreement that opioids need to be used more carefully and be more judiciously prescribed (Babu et al., 2019; Inter-Agency Task Force, 2018; Volkow and Collins, 2017). But broad-stroke approaches to reducing opioid prescribing have exacerbated the problem of undertreated pain, which may be contributing to the opioid epidemic as some pain patients turn to illicit opioids (Dineen and DuBois, 2016; Hoffman and Goodnough,

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2019; Inter-Agency Task Force, 2018; IOM, 2011; Lane, 2018; Nicholson et al., 2018; Ray and Hoffman, 2018).

For example, strategies such as the Veterans Affairs' and Medicare's approaches to reducing opioid prescribing using broad reduction targets (Dineen and DuBois, 2016; Good, 2014), and the Drug Enforcement's Administration's (DEA) reduction of quotas for opioid raw materials for medicine production,[1] may have contributed to increased illicit marketing and use of heroin, fentanyl, and counterfeit materials, along with increases in overdose rates and suffering by pain patients (Ehley, 2018; HP3, 2019; Hoffman and Goodnough, 2019; Petrosky et al., 2018).

Such approaches to reducing opioid prescribing can also exacerbate disparities in quality pain management in low-income, minority, and rural populations (Friedman et al., 2019; Guy Jr et al., 2019; Healy, 2019; IOM, 2011; Jalal et al., 2018), hurting those who are already hurting the most. For example, 7-day limits on opioid prescriptions can increase monthly patient costs four-fold – disproportionately affecting low-income and uninsured populations. Harsh DEA oversight of opioid prescribers can also worsen disparities as doctors make on-the-spot prescribing decisions that are influenced by both legal liability concerns and implicit biases (Firth, 2018; Hoffman et al., 2016; Zhang, 2017).

3. Commonalities in pain and addiction that are relevant to policy

Pain and OUD often go hand-in-hand and share common factors. Both are often best addressed by programs that incorporate similar key elements, which may include medication along with attention to individual behavioral and psychosocial factors and co-morbid conditions as summarized in Table 1.

Advances in addiction science and pain management can provide the basis for more cohesive, comprehensive policies for both public health challenges (Becker et al., 2018; Meske et al., 2018; Volkow et al., 2018; Volkow et al., 2016; Volkow and McLellan, 2016). Many evidence-based approaches to address pain and OUD already exist but are underutilized; for example, the 2000 Drug Addiction Treatment Act (DATA 2000) (SAMHSA, 2018, 2019) could contribute to far greater addiction treatment access than current funding allows. The pipeline of less abusable pain medications and new drugs for OUD, both of which have been encouraged and incentivized by the FDA (Schnoll and Henningfield, 2016) and enabled by NIDA funding (Volkow and Collins, 2017; Volkow et al., 2016) could help address the opioid epidemic and shift prescribing to safer medicines. Unfortunately, many third-party payers have been reluctant to reimburse new less-abusable medicines. A broad moratorium on opioid approvals as advocated by some (Public Citizen, 2019) would further delay transformation of the opioid market to safer medicines (Coe et al., 2019).

4. Evidence-based treatment practices exist but are under-utilized

There are several fundamental principles that guide best practices in pain management and OUD treatment (Table 2); yet they are often not reimbursed, and many healthcare providers are not adequately trained in their use (IOM, 2011). The 2017 President's Commission report advocated expanded prevention and treatment interventions, greater access to naloxone, and a dramatic increase in OUD treatment access, but translation into action has languished without funding.

The most fundamental principle is that people with either condition merit a thorough diagnostic evaluation to individually tailor and guide treatment, including selection of the most appropriate medicine and instructions for safe and effective use. For some people with pain and/or opioid use disorder, this is sufficient for successful treatment and extensive behavioral support may not be necessary (Carroll and Weiss, 2017; IOM, 2011; Sigmon et al., 2015). It seems plausible that long acting depot preparations of buprenorphine and naltrexone may also reduce the need for extensive behavioral support for some people (Haight et al., 2019; Tompkins et al., 2019). For many, people with OUD and pain, however, comprehensive and multi-modal approaches are more effective than simply providing a medication (Carroll and Weiss, 2017; IOM, 2011; Vallerand et al., 2015). Acceptable individualized treatment approaches that sustain compliance and benefit the patient, regardless of whether they are FDA-approved, are advocated because they can help on an individual patient basis. These

Table 1
Factors common to etiology and prognosis of pain and opioid use disorders.[a]

Both may involve physical, behavioral, social, personality, comorbidities, genetic, environmental, and other factors that influence the disorder's expression, severity, prognosis, and patient's treatment needs.
Neither is a simple physiological disorder but typically involve emotional components vital to address to ensure treatment compliance and improve outcomes.
Both represent a spectrum of etiologies and phenotypes, despite sweeping generalizations that often made about people with pain and substance use disorders.
Treatment of pain with opioids can lead to physical dependence and withdrawal, but this does not mean that the person has developed OUD, and opioid agonist-based treatment for OUD sustains physical dependence (albeit ideally at a lower level than was occurring with illicit opioid use), but such medication use should not be considered “addictive use” or “abuse”.
There is a risk of development of OUD during pain management with opioids but the risk appears low in properly selected, prescribed, and managed patients.
Both can be stigmatized by those who “survived” without treatment or with only brief interventions.
Inadequate pain treatment may precipitate or exacerbate OUD: Inadequate pain treatment, including inappropriate medication restrictions, may precipitate opioid seeking *from both legitimate and illicit sources.*
Low income and minority persons are less likely to have access to effective treatment, may wait longer for treatment, and have fewer options.

[a] For additional information and perspectives see the following articles: (Centers for Disease Control and Prevention, 2016; Koop, 2003, 2006; Volkow et al., 2018; Volkow and McLellan, 2016).

Table 2
Commonalities in the treatment of pain and OUD.

Individualized assessment: Vital for developing the most appropriate treatment approach but may require more time and expertise than are typical of many providers and programs or covered by third party payers.
Medication Assisted Treatment (MAT) for OUD and Multimodal Treatment for Pain: Both may be treated with opioids in which experts and guidelines recommend that the medication accompany other components as per individual needs to improve outcomes and reduce unintended consequences. A distinction is that whereas medication is considered a first-line treatment for many people with OUD, for many types of pain, opioids should only be used when other treatments have failed or the pain is known to very likely require opioids (e.g., serious trauma, post-surgery, and cancer-caused pain).
Multimodal/comprehensive: The concept of MAT for treatment of substance use disorders has many parallels with what is often referred to as multimodal treatment of pain, which is often more effective than treatment that primarily involves the dispensing of a drug with little social, behavioral, or psychiatric support or attention to co-morbid conditions and vice versa.
Follow-up monitoring and intervention as indicated: Despite recognition of some types of pain as “chronic” and that OUD may also be considered a long-term, if not chronic, condition, supportive interventions beyond medications, if provided at all, are often limited to the initial treatment phase, and long-term monitoring and interventions are less typical than would be expected for other chronic conditions such as asthma, cardiovascular disease, and diabetes.

[a] For additional information and perspectives see the following articles: (Inter-Agency Task Force, 2018; IOM, 2011; Vallerand et al., 2015).

[1] The DEA has implemented large reductions and proposed further reductions for opioids available to manufacture medicines (DEA, 2018), following the “Safe Prescribing Plan” that seeks to “cut nationwide opioid prescription fills by one-third within three years.” In 2019 it would decrease quotas by an average 10%, for oxycodone, hydrocodone, oxymorphone, hydromorphone, morphine, and fentanyl. This may contribute to shortages in certain medicines that may not be equitable geographically or demographically.

may include exercise, meditation, yoga, complementary and alternative medicine, cognitive behavioral therapy, acupuncture, and dietary supplements, coupled with active patient monitoring and follow-up assessments (Inter-Agency Task Force, 2018; Vallerand et al., 2015; Volkow and McLellan, 2016).

5. Fundamentals of treatment acceptability and utilization from a marketing and behavioral economic science perspective

Among the most well accepted and behavioral science-supported marketing principles is that product seeking and use is increased when the products or services are more accessible, appealing, and affordable (Bickel et al., 2018; Bickel et al., 2017; Schwartz et al., 2019). For example, when methadone treatment clinics emerged in the 1970s, they were relatively few and far between compared to the geographic distribution of people with OUD, and many were inhospitable and unacceptable to those in need of treatment. The passage of DATA 2000, along with the approval of buprenorphine for OUD, made it possible for people to access buprenorphine from local health professionals and clinics, greatly expanding treatment access for those who found methadone clinics unacceptable (SAMHSA, 2018, 2019). Despite many innovations in naloxone delivery systems, access to nasal systems without prescription due to waivers of the prescription requirement in most states, and a greater likelihood that first responders are equipped with naloxone, the cost to consumers and first responders that has greatly increased in the past two decades has limited access to these life-saving products at a time when illicit heroin and fentanyl costs have plummeted (Hufford and Burke, 2018).[2] Cost is attributed as a major reason that many first responders are not equipped with naloxone (Crime Justice News, 2019). In short, the behavioral economics and market forces perversely favor illicit drugs over treatment – at least for low income people who do have ready access to heroin and fentanyl that be purchased for less than ten dollars per dose.

Whereas most pain in the U.S. is self-managed by over-the-counter (OTC) medicines, for tens of millions of people OTC analgesics are inadequate, and/or are associated with serious side-effects and mortality (IOM, 2011). Millions more are treated with opioids, which provide relief from their pain (IOM, 2011; Meske et al., 2018), but most do not receive the individualized assessments, multi-modal treatments, or level of monitoring recommended by recent guidelines and reviews (CDC, 2016; Inter-Agency Task Force, 2018; IOM, 2011; Vallerand et al., 2015; Volkow et al., 2016). In part, this is because economic factors and marketing approaches are not designed to achieve the fundamentals summarized in Table 3.

Table 3 summarizes some of the core cross-cutting elements that are understood from medical and consumer marketing (Kolassa et al., 2002) and supported by behavioral economics for optimal care (Bickel et al., 2018; Bickel et al., 2017; Schwartz et al., 2019). Interventions need to be attractive, accessible, affordable, and in wide variation to address broad and diverse population needs. This includes harm reduction interventions for OUD, such as needle exchange programs and naloxone access, which are often prevented by state or local policies or so highly restricted as to be of limited impact. Furthermore, policies and recommendations related to treatments for pain and OUD should always be evaluated to assess their effect on low-income and minority persons (Henningfield, 2018a, 2018b). A combination economic factors and lack of health insurance was attributed to contribute to the finding that "black patients" were approximately 35 times less likely than "white patients" to receive buprenorphine prescriptions for OUD (Lagisetty et al., 2019). Increasing naloxone costs coupled with increasing treatment demand that is outpacing treatment access is also counter to fundamental marketing principles and behavioral economics.

Table 3
Key considerations to increase the reach and diversity of people who may be helped by medicine and non-medicine-based treatments, including treatment services and behavioral programs.

Cost: Treatments must be affordable and/or include mechanisms to make them affordable across the population including low income persons.
Access: Treatments must be as readily assessible as their labeling will allow. Barriers can include geographic gaps in distribution of medicines and programs. Hidden barriers can include complicated applications, point-of-sale limitations that leave many people without convenient access, and population-specific barriers such as commutes to programs that might be less surmountable by certain populations (e.g., single-parents with young children, people with low income, ethnic minorities, and people living in rural areas or without access to public transportation).
Appeal and attractiveness: Product characteristics, labeling, marketing, and appropriately supportive and encouraging consumer information should emanate from government and professional organizations that are independent of commercial interests. The same principals apply to programs. In contrast, although expanded medication treatment as allowed under DATA 2000 has made OUD treatment programs more widely available and hospitable, many geographic areas have no certified prescribers, and many methadone program-based clinics are uninviting to many in need of help.
Professional education: Health care providers at all levels who have patient/client contact need balanced and credible information that is accepted, if not endorsed by, government and professional organizations that are independent of commercial interests.

6. Research and innovation

Many people with OUD and pain are not adequately treated by FDA approved treatments (Christie et al., 2017; Henningfield, 2018b; NIH, 2018). Research on new treatments is needed, while recognizing that the average time and cost of getting a new medication to market may exceed 10 years and 2.7 billion dollars (DiMasi et al., 2016).

For pain patients who benefit from opioids, more research is needed on minimizing development of OUD (IOM, 2011; Rosenblum et al., 2008). For people with OUD, efforts should be made to ensure ready access to existing evidence-based treatments on demand. At the same time, research should be accelerated to address the needs of those for whom currently available treatments are not effective or acceptable due to side effects or individual preferences (Henningfield, 2018a, 2018b). This includes research on behavioral management, exercise, diet, and dietary supplements such as kratom, which is used by several million people in the U.S. with many reporting use in place of opioids to relieve pain and to achieve and sustain abstinence from opioids (Grundmann et al., 2018; Swogger and Walsh, 2018).

Research is needed to better guide prescribing, minimize implicit bias among prescribers, and empower prescribers who feel trapped "between a rock and a hard place" to use evidence-based prescribing practices as opposed to simply reducing prescribing to meet arbitrary targets (Dineen and DuBois, 2016). More research is also needed on the potential for medications such as antidepressants and emerging therapies (e.g. cannabinoids, MDMA, psilocybin) to help more effectively manage pain and associated comorbid conditions, and to improve quality of life in people with these disorders (Belouin and Henningfield,

[2] Naloxone cost and access is complex and evolving with newer products costing hundreds and in the case of the electronic autoinjector, thousands of dollars. Whereas some states and cities offer vouchers for products that can provide naloxone from some pharmacies at no cost or low cost, these programs are limited geographically, and demand often exceeds supply. Recent programs to expand naloxone access including waivers to allow pharmacy sales of nasal naloxone without a prescription are very important and undoubtedly saving lives. However, a recent informal survey by the authors in Maryland revealed that nasal naloxone spray, is about $130.00 to $150.00 for a two-pack, and many stores were out of stock. In contrast, a wide a variety of heroin and fentanyl products are more readily available on "the street" for 5 to 15 dollars a dose. Shortages and high costs are also cited by many fire and police departments as limiting their availability such first responders (Crime and Justice News, 2019; Hufford and Burke, 2018).

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2018; Heal et al., 2018).

7. Conclusions

It is sobering that current opioid epidemic overdose deaths shows little sign of abatement (Ahmad et al., 2019; Jalal et al., 2018; Lopez, 2019) and that many pain patients are finding it harder to get appropriate treatment (Hoffman and Goodnough, 2019).[3] It is also disheartening that many evidence-based solutions, including greatly expanded treatment access for OUD and opioid overdose, and stronger support of multimodal therapies for OUD and pain have not been accepted politically or funded commensurate with need and projected benefit. We appeal for accelerated implementation of such approaches, along with more research to assess their impact on the opioid epidemic and pain management. This is also crucial to minimizing the risk of future epidemics. It is fundamentally the same public health approach that is applied to control infectious diseases including influenza, HIV AIDS, malaria, and polio and is eminently applicable to pain and OUD. We also believe that cohesive, comprehensive policies that better serve people with pain and make addiction treatment as accessible as addicting drugs – "for all the people" – a vision forcefully articulated by former Surgeon General C. Everett Koop (Koop, 2003, 2006) – are essential for addressing both the opioid epidemic and pain in America.

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Declaration of competing interest

In the past three years, the authors have provided consulting services to pharmaceutical developers on the evaluation and regulation of medications regarding their potential for abuse and addiction including opioids for pain management and treatments for OUD and overdose. Through PinneyAssociates, the authors also provide consulting services on cannabinoids and dietary supplements, including kratom which is used by some people to manage their OUD, and on smoking cessation and tobacco harm minimization (including nicotine replacement therapy and electronic vapor products) to Niconovum USA, Inc., R.J. Reynolds Vapor Company, and RAI Services Company, all subsidiaries of Reynolds American Inc. RAI were acquired by British American Tobacco (BAT) in July 2017. JEH co-holds a patent for a novel nicotine medication that has not been commercialized. JBA and BS are employees of Harm Reduction Therapeutics, a nonprofit entity pursing the development and approval of over-the-counter naloxone for opioid overdose; and JEH, KKG, and SHS provide support to Harm Reduction Therapeutics through Pinney Associates.

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[3] A Centers for Disease Control and Prevention report (2019) provides "provisional drug overdose death counts" that suggest that overall drug overdose deaths may have declined by a few thousand with part of the decline contributed to by reduced opioid deaths. The report describes numerous limitations of the data and the analysis, and the levels remain horrifically high, but if the effect is real it is promising and may reflect efforts in various states to improve access to OUD treatment as well as naloxone access (see additional discussion of limitations by Lopez, 2019).

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