Moving beyond misuse and diversion: the urgent need to consider the role of iatrogenic addiction in the current opioid epidemic.

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Moving Beyond Misuse and Diversion: The Urgent Need to Consider the Role of Iatrogenic Addiction in the Current Opioid Epidemic

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An epidemic of drug overdose deaths has led to calls for programs and policies to limit misuse and diversion of opioid medications. Any parallel call to consider the risk of iatrogenic addiction when treating pain has been muted in comparison.

We have moved beyond questions of nonmedical use, abuse, and diversion to highlight the role of prescription opioids in causing addiction even when prescribed and used appropriately.

Unfortunately, current evidence is insufficient, and a rapid expansion of longitudinal research is urgently needed to guide clinicians in balancing the need for opioids with the risk of adverse consequences. Meanwhile, medical education should place greater emphasis on the abuse liability of prescription opioids, and providers should endeavor to attenuate risk when possible. (*Am J Public Health.* 2014;104:2023–2029. doi:10.2105/AJPH.2014.302147)

THE UNITED STATES CONTINUES to suffer from a startlingly severe epidemic of drug overdose deaths,[1–6] with approximately 46 Americans dying per day in 2010 from an overdose involving prescription opioids.[7] The increase in overdose deaths was directly paralleled by dramatic increases in the sale of opioid pharmaceuticals between 1999 and 2010.[7–13]

Attention to this health threat has grown exponentially in recent years, but discussion and interventions have focused almost exclusively on issues such as illegitimate prescribing, nonmedical use, diversion, and overdose.[3–5,7,8,10,11,13–30] These topics are important but pertain primarily to individuals who already engage in nonmedical use of opioids.

A different question is why nonmedical opioid use occurred in the first place. It is universally understood that some small proportion of individuals will intentionally misuse opioid medications for their euphoric effects, and many assume the initial decision to begin doing so is entirely volitional. Largely unaddressed is that some individuals transition to nonmedical use and addiction despite their intention to use medications only as directed and only for pain relief. To date, few articles have alluded to iatrogenic addiction in the context of the current opioid epidemic.[5,22,23,31] None have explicitly called for a disambiguated determination of the role of inadvertent iatrogenic addiction as opposed to the role of intentional misuse and diversion.

We have moved beyond widespread recognition that prescription opioids have contributed to increased fatalities and beyond interventions that bluntly restrict the supply of prescription opioids to prevent misuse and diversion. Instead, we specifically focus on the issue of iatrogenic addiction, the degree to which it is underrecognized, and the need to (1) fully characterize its contribution to the current health crisis, (2) identify patients at risk and intervene early to prevent new cases of opioid use disorders, and (3) consider the issues of acute pain treatment and unscheduled care settings in addition to the more commonly discussed issue of chronic pain management. Most importantly, we seek to remind medical providers that well-intentioned efforts to treat pain may inadvertently lead to opioid use disorders, even if patients follow medical direction precisely. We also suggest urgent steps, including a call to arms for rapid expansion in research activity and better integration of existing evidence into provider education and clinical practice.

OPIOID PRESCRIBING AND OVERDOSE DEATHS

Approximately 15.7 million people in the United States report nonmedical use of prescription drugs,[32] and in 2007, drug overdose surpassed motor vehicle accidents as the leading cause of injury death in the United States.[8] The primary substance contributing to these alarming statistics is prescription opioids.[2] Nonmedical use of prescription opioids is concerning not only because of the risk of fatal overdose but also because it often precedes injection heroin use.[26]

This epidemic was predictable. The abuse liability of opioids is well established[10,12,15,33] and a similar phenomenon occurred in the 19th and early 20th centuries, when opioids were prescribed liberally and indiscriminately for all types of pain.[34,35] Physicians undoubtedly, and in most cases unknowingly, contributed significantly to recent increases in opioid-related morbidity and mortality. However, this realization does not by itself illuminate the important question of how often and under what circumstances people have become addicted as a result of appropriate medical use as opposed to nonmedical use.

ORIGIN OF CURRENT PRACTICE IN PAIN TREATMENT

Factors contributing to increases in opioid prescribing have been detailed elsewhere.[5,12,22,25,29,36] The more permissive attitude toward opioids for pain treatment began in the 1980s, after several reports suggested a low potential for iatrogenic addiction in patients treated with opioids.[33,37,38] Eventually, a 1997 consensus statement concluded there was insufficient evidence to suggest that opioids result in iatrogenic addiction.[39] Belief in the safety of opioids proliferated

rapidly throughout the medical education system and has been reaffirmed in several articles, as recently as 2010 by a Cochrane review.[40–42] Other factors included attempts to improve pain management,[39,43] emphasis on patient satisfaction and inclusion of pain relief in patient satisfaction assessments,[44,45] aggressive marketing of opioids by the pharmaceutical industry,[28,46] and welfare and health care reform.[22]

The cumulative effect was that medical providers internalized a simple message: pain must be treated adequately, using opioids if needed, without fear of causing iatrogenic addiction.[12,15,33,39,40,47] Of note, there has been and currently remains little opportunity to alter this message in medical education, which provides minimal training on pain management or recognition of substance use disorders.[20,21,48] For example, a survey of formal pain management curriculums in Canadian universities found that, on average, medical students received 16 hours of education in pain management, whereas veterinary students received 87 hours.[49] Other studies have shown that many physicians are aware that their knowledge and confidence in pain management is insufficient, and many do not adhere to clinical guidelines when treating chronic pain.[20,21]

ACTUAL RISK OF IATROGENIC ADDICTION

There are no randomized trials and few well-designed longitudinal studies to characterize the rate of iatrogenic addiction or the circumstances by which it occurs. The evidence we do have is limited in quality, ambiguous in terminology, and conflicting in results.[25,33,38–40,47] Overall, more recent evidence tends to indicate a higher rate of iatrogenic addiction than is commonly realized.[50,51] Nonetheless, the most recent systematic review concluded, "The available evidence suggests that opioid analgesics for chronic pain conditions are not associated with a major risk for developing dependence."[40(p688)]

The general lack of consistent and reliable information has allowed competing viewpoints, both for and against the assertion that iatrogenic addiction is a frequent consequence of opioid therapy. Knowledge gaps are even more pronounced with respect to acute pain and unscheduled care settings.

Evidence to Date

Studies from the 1980s reported addiction rates after opioid treatment as low as 0.03% to 0.1% in hospitalized patients with no prior addiction history and 5% for patients with chronic noncancer pain.[37,38,52,53] In the early to mid-1990s, studies began to report addiction among patients treated with opioids for acute or subacute pain ranging from 3.8% to 27%, although these studies did not include a definition of addiction and did not specify whether addiction was iatrogenic in etiology.[47] More recent studies have suggested higher rates of opioid misuse, ranging from 3.27% to 56%, depending on specific definitions and outcome measures.[25,54] One large study found that 35% of patients treated long term with opioids met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[55] criteria for an opioid use disorder.[16]

A few studies have addressed the risk of iatrogenic addiction somewhat more directly. Opioid-naïve patients receiving an opioid prescription within seven days of short-stay surgery were 44% more likely to become long-term opioid users within one year than were those not receiving opioids,[17] and prolonged use of opioids has been associated with self-reported patient concern regarding addiction.[18] Another study found that 44% of patients in a methadone maintenance program, who also had chronic pain, reported that opioids prescribed medically for their pain had led to an addiction.[19]

Arguments Against Iatrogenic Addiction

Support in favor of prescription opioid safety is intuitively predicated on the belief that opioids carry a low risk of addiction when prescribed and used appropriately. This assertion is not entirely without merit. Pain is a significant health problem,[43,56,57] and there are some reasons to believe that opioids do not, by themselves, lead to addiction, particularly in patients without a history of substance use disorders, mental illness, or chronic pain requiring long-term therapy.[16,25,54,58–63] For example, research suggests that pain may attenuate the euphoric effects of opioids.[64] Furthermore, even if appropriate medical use provides an initial exposure to opioids, that exposure is necessary but not sufficient to cause addiction. Addiction is a complex phenomenon that includes repeated exposure to drugs with abuse liability combined with predisposing environmental and genetic risk factors.[62,63] Many patients can be prescribed high doses of opioid medications for prolonged periods without exhibiting maladaptive patterns of misuse or functional impairments caused by misuse, even after the onset of physiological dependence.[65,66]

Arguments for Iatrogenic Addiction

Despite the validity of such arguments, even pain management advocates, who led the initial charge in favor of more aggressive use of opioids, now recognize the imprudence of minimizing the addiction potential of pharmaceutical opioids.[67] First, it is difficult to believe that the parallel rise in prescriptions and associated harms is mere correlation without causation, particularly because of the inherent abuse liability of opioids.[10,12,15,33] If there is a causal relationship, it is difficult to believe that the problem is solely attributable to patients with already existing substance use disorders or that incident cases are solely the result of inappropriate prescribing or intentional misuse. Second, evidence in favor of opioid safety is determined by small and nongeneralizable samples, anecdotal reports, or surveys of provider perception.[15,33,47,50,51] Evidence of this quality certainly does not rule out the possibility of significant risk, and even if risk is very low, it would still cause significant harm because of the frequency with which opioids are prescribed. Finally, there are flaws in the argument that the risk of iatrogenic addiction can be addressed simply by modifying prescribing practices for those with a greater predisposition to addiction.[22] The lifetime prevalence of behavioral health disorders is reported to be as high as 50%,[58,59,68] yet patients without a history of behavioral health disorders may also develop iatrogenic addiction.[22] Thus, history of mental illness or substance use disorder may not provide the

sensitivity or specificity required to tailor prescribing practices.[12]

Acute Pain and Unscheduled Care Settings

The related topics of acute pain treatment and unscheduled care settings warrant special consideration. Because the probability of addiction is related to the duration of exposure,[69] it is tempting to assume that brief exposures for acute pain (e.g., emergency departments, operative intervention) have a negligible role in iatrogenic addiction, particularly compared to prolonged exposures with chronic pain management. However, there is evidence to challenge this assertion,[17,18] and there are several reasons even unscheduled care settings may contribute to iatrogenic addiction.

Acute care providers prescribe opioids frequently.[14] In the United States, there are more than 129 million emergency department visits annually,[70] and an estimated 39% of emergency department visits are for painful conditions.[71] Even if an initial exposure is insufficient to cause addiction directly, perhaps it is sufficient to trigger initial misuse that could ultimately lead to addiction. In addition, emergency departments and other safety net providers often treat patients repeatedly as patients with acute pain transition to subacute and chronic pain. They also provide care for patients with established chronic pain who experience lost or interrupted access to other care providers.

It is interesting to consider that providers of unscheduled care may be unlikely to recognize iatrogenic addiction as a direct consequence of their own care, because any adverse consequences would occur downstream. If so, it may be that iatrogenic addiction is especially underappreciated in these settings, particularly in the absence of dedicated systems to provide longitudinal outcomes data.

CURRENT MEASURES FOR THE OPIOID EPIDEMIC

Most efforts to address the current opioid epidemic have involved

1. identification of negligent prescribing practices[30];
2. pursuit of abuse-deterrent drug formulations[72,73];
3. measures to prevent misuse and diversion, such as prescription drug monitoring programs and monitoring of chronic pain treatment through urine testing, medication contracts, and mandated electronic prescribing[27,36,74];
4. expanding utilization of medication-assisted therapies[6]; and
5. overdose prevention education and naloxone distribution to prevent overdose fatalities.[22,75–78]

These interventions, although important, have been discussed elsewhere and do not directly address the problem of how iatrogenic addiction is initiated. However, simply reducing the supply of prescribed opioids available to those affected by substance use disorders, in the absence of diagnosis and treatment, can have unintended consequences, such as switching to heroin as a less expensive or more easily available alternative.[29,79]

Various other measures may have some inadvertent effect on the problem of iatrogenic addiction simply by curtailing the degree to which pain is treated (i.e., opioid amount, duration, potency, and frequency of use) and thus the extent of exposure. Recently, emergency physicians have been encouraged to limit the amount and duration of opioid medication provided by any single prescription, avoid replacing lost or stolen prescriptions, and avoid treating chronic pain or refilling opioid prescriptions.[51,80] The Joint Commission on Accreditation of Healthcare Organizations recommendations include the use of multimodal treatment plans, including psychosocial support, coordination of care, promotion of healthful behaviors, and both nonopioid and nonpharmacologic approaches. The commission also acknowledges that not all pain can be eliminated and that in some cases "the best approach may be to start with a non-narcotic."[81(p2)] There are also examples of advocacy and policymaker opposition to approval of new high-potency opioid pain medications.[31]

Several publications and practice recommendations have recently begun to reintroduce the idea of iatrogenic addiction, but only indirectly and without explicit separation from misuse and diversion. The American College of Emergency Physicians guidelines recommend consideration of the patient's risk for opioid misuse, abuse, or diversion.[82] The Joint Commission on Accreditation of Healthcare Organizations recommends that patients be educated about the potential for addiction when prescribing opioids.[81] The Federation of State Medical Boards similarly recommends providing information to patients regarding the addictive nature of opioids and the potential dangers of misuse.[74] The Food and Drug Administration approved Risk Evaluation and Mitigation Strategy for Extended-Release and Long-Acting Opioid Analgesics requires pharmaceutical companies to make training and educational materials on the safe use of opioid medications available to prescribers and patients.[83–85] Several recent publications have implied that modification of opioid prescribing practices would attenuate the problem of iatrogenic addiction,[5,22,23] and one has explicitly indicated that screening for factors that predispose individuals to substance use disorders could help prevent iatrogenic addiction.[23]

RECOMMENDATIONS FOR FUTURE ACTION

Any attempt to develop recommendations to address the issue of iatrogenic addiction in clinical practice is challenged by considerable deficiencies in the available evidence base. Hence, our primary recommendation is to expand the volume of research on iatrogenic addiction with great urgency, and research methods should be sufficiently rigorous to inform clinical practice guidelines. In addition, we need to vastly improve collaborative work across the fields of addiction and medicine to ensure that empirical evidence is transdisciplinary and translated into clinical practice and health policy.

Research

Advances in addiction science have improved our knowledge of opioid abuse liability and risk factors associated with opioid misuse and addiction, but the risk of addiction from appropriate medical use remains poorly defined. Evidence that does exist often does not transfer between siloed disciplines; what may seem obvious in the field of addiction may not be common knowledge to the professionals prescribing opioid medications for pain relief. In our clinical experience, few physicians

outside chronic pain management are familiar with the term "iatrogenic addiction," even though both words in that term are in common use separately.

The most fundamental need is for more precise determination of how frequently and under what circumstances iatrogenic addiction occurs. There is knowledge about the individual-, family-, and environment-level factors, including nonmedical use of prescription opioids, which are associated with the development of illicit drug use and addiction.[58–63,86–92] However, there is little understanding of how these and yet other unidentified factors specifically relate to iatrogenic opioid addiction. There is even less understanding of risk factors at the health care system level and how external factors, such as health care setting, prescriber specialty, type of pain, and prescribing patterns are associated with iatrogenic addiction. Characterizing the range of contributory factors would provide a foundation for further research and allow interventions to be targeted proportionally to areas of greatest need. It would also suggest which actions should be avoided to reduce the incidence of iatrogenic addiction.

Perhaps the most important intervention would be the application of tools to appropriately risk-stratify patients before prescribing opioids to manage pain. Presently, there is no available method with adequate sensitivity or specificity to do so, and inaccurate assessments promise unnecessary stigma and inappropriate exclusion from opioid therapy.[12]

After it becomes possible to accurately estimate the risk of iatrogenic addiction, there will be a need for research to guide clinicians on how to balance the risk of iatrogenic addiction with the risk of undertreated pain. Currently, there is no clear understanding of how patients or providers should balance these risks, either for individuals with an elevated risk of iatrogenic addiction or for those already suffering from the condition. For example, in cases of elevated risk, we do not know when it is appropriate to forgo opioids, use alternate dosing or abuse-deterrent formulations, or treat as needed but monitor closely. If close monitoring is adopted, we do not know how frequently this should occur, what targets should be selected (e.g., level of euphoria with appropriate use? indications of misuse?), or how best to measure these targets. When iatrogenic addiction has occurred, the best strategies for early recognition and intervention are neither characterized nor empirically tested. In particular, we do not know if, and to what extent, individuals with iatrogenic addiction might require different treatment strategies than are used for other forms of opioid addiction.

Ultimately, newly developed interventions need to be translated into practice. This will be facilitated if evidence is of high quality and developed within the settings and conditions for which the intervention is intended. It will also be vital to incorporate implementation science and effectiveness-implementation hybrid research designs to expedite the translation of empirical findings into clinical practice and public health policies.[93] Such research is inherently multidisciplinary and should include the perspectives of experts in addiction, pain, policy, public health, and ethics as well as health economists, law enforcement officials, advocacy groups, patients, and medical providers.

Education

The full range of available evidence on iatrogenic addiction has not been integrated into medical education to the same degree as has the more selected evidence initially promoted by pain advocates. We suggest several key points of desirable content.

Most fundamentally, providers need to understand the complex etiology and natural progression of opioid addiction and be reminded that appropriate medical use of prescription opioids can, in some unknown proportion of cases, initiate a progression toward misuse and ultimately addiction. The need to learn which patient characteristics are associated with developing addiction directly follows that foundation, as does the need to screen for those factors before prescribing opioid medications.[58–62,86–92] This should be differentiated from the important but different task of screening for opioid use disorders that are already present.

Providers will also need to adopt appropriate strategies for determining when and how opioids should be prescribed. This involves determining not only the risk of iatrogenic addition but also the degree to which opioids are appropriate and necessary. How opioids may be insufficient to treat or may even exacerbate pain[94–97] and may reduce functional status[24] should be understood along with more commonly recognized side effects and benefits. It is interesting that the majority of individuals with chronic pain report not using opioids, and those who do report use of opioids still indicate high levels of chronic pain.[96] Providers should also have more training in alternative approaches to managing pain, particularly in high-risk populations. These include nonopioid pain medications, mixed narcotic agonist–antagonists such as buprenorphine, and physical and occupational therapy.[22,98]

Practice

Adding nuance to current practice in pain treatment will be a delicate matter. The push to incorporate addiction risk into medical decision-making should not come at the expense of improvements in pain management. Nonetheless, it may be appropriate to forgo opioids in situations where, on the basis of the best available evidence, the risks of iatrogenic addiction may outweigh the consequences of undertreated pain. When in doubt, shared decision-making approaches may be desirable and, in the setting of chronic pain, could combine the clinical expertise of pain specialists and addiction treatment providers. In addition, alternative pain management strategies should be covered by health insurance so that providers can be reimbursed appropriately for providing these services.

When opioids are prescribed in situations of greater than usual risk, a variety of measures may be necessary. These might include alternate prescribing patterns (e.g., adjusted dosage, potency, duration), patient education on the risks of iatrogenic addiction, and serial evaluation to identify opioid use disorders at the earliest possible stage. Other adjuncts might include more generalized use of pain management contracts, which are currently used only in the context of chronic pain. In the case of patients who have already been diagnosed with a substance use disorder, medication-assisted treatment may be considered in addition to nonopioid pain management.[6]

Even when the risk of iatrogenic addiction is not elevated, providers should still be encouraged to advise patients of the risks of iatrogenic addiction and any recommendations to mitigate that risk. Providers commonly warn patients about the danger of sedation when prescribing opioids; warning about the risks of overdose and addiction should be as, if not more, important.

CONCLUSIONS

Pain relief is a core component of routine medical practice, but trends in morbidity and mortality associated with prescription opioids are alarming. Even if iatrogenic addiction occurs in only a small proportion of cases, the health consequences would still be considerable because of the absolute number of patients prescribed opioids annually. Physicians should once again become mindful that prescription opioids may lead to addiction in susceptible patients, even when prescribed and used appropriately. This recognition necessarily requires that the mission to treat pain must be balanced to at least some degree by a mission to prevent opioid abuse and addiction. Unfortunately, methods to achieve this balance are largely unknown. A true call to arms, broadly heralded across many research communities, is urgently needed to guide our response to this health emergency. ■

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This article was accepted June 22, 2014.

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G. A. Beauchamp and M. S. Lyons conceptualized the article. All authors contributed to all stages of the drafting and revision of the article.

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