New Addiction Criteria: Diagnostic Challenges Persist in Treating Pain With Opioids

There has long been a tendency to consider pain and addiction as different entities, requiring radically different treatment. This tendency is partly due to the discomfort clinicians (especially specialists) feel when attempting to treat one of these problems outside the boundaries of their own expertise and experience. Yet when pain is treated medically, it is addictive drugs (notably opioids) that are often chosen, not least because of their unique efficacy for treating pain. The more these drugs are used, the more addiction surfaces as a significant accompaniment to pain, especially in the case of long-term treatment of pain symptoms.

It is often said that addiction is easy to recognize, that it rarely arises during the treatment of pain with addictive drugs, and that cases of addiction during pain treatment can be managed in much the same way as other addictions, but such generalizations grossly oversimplify the real situation. Experts have struggled for years to understand addiction, to outline its basic mechanisms, and to come up with ways to describe and define it. Even today, the Diagnostic and Statistical Manual of Mental Disorders (DSM) specifications for addiction are being rethought and rewritten, in part because previous definitions of addiction were unsatisfactory when applied to opioid-treated pain patients. Reports in the literature cite addiction rates during chronic pain treatment with opioids that range from less than 1% to as much as 50%, underlining our true uncertainty about how often addiction arises, or what addiction actually is. Patient behaviors can be variously interpreted as drug seeking, and whether or not a formal diagnosis of opioid addiction is made, there is much uncertainty about how to treat severe pain in the presence of this comorbid diagnosis. The problem is that no consensus exists about how to recognize addiction when it arises during the treatment of pain with addictive drugs—and even less agreement about how to treat it.

This issue of Pain: Clinical Updates will review the current understanding of the biological basis for addiction, the evolution of addiction definitions, and—given that the treatment of long-term chronic pain with addictive drugs can be accompanied by addiction or states akin to addiction—reflect on the diagnostic and therapeutic challenges that need to be overcome if affected patients are to be appropriately supported.

The Neurobiology of Addiction

The identification of a so-called “reward center” in the brain opened the way toward a much greater understanding of addiction. Addiction was now understood as essentially a compulsive and pathological pursuance of natural “rewards.” Anatomically, this center is the mesocorticolimbic system, comprising the ventral tegmental area,
Experts have struggled for years to understand addiction, to outline its basic mechanisms, and to come up with ways to describe and define it.

Endogenous opioids are important mediators of drug addiction, as well as other addictions such as gambling, so that opioid antagonists can occasionally be helpful for treating a number of addictions. Exogenous opioids produce addiction directly as an opioid receptor effect in the nucleus accumbens, and indirectly by decreasing GABAergic inhibition of dopamine. Exogenous opioids are highly addictive, but they do not invariably produce addiction, especially if taken under carefully controlled conditions for the treatment of pain. Likewise, other addictive substances such as alcohol can be imbied without producing addiction, leading to addiction only in susceptible individuals.

When an addictive drug is first taken it produces euphoria via a dopamine surge in the mesolimbic pathways. Opioids are capable of producing a dramatic euphoric effect, especially when injected. The more lipophilic the drug and the more rapidly it reaches the nucleus accumbens, amygdala, and hippocampus (Fig. 1). Although the common final pathways are dopamine pathways, these centers are also replete with opioid systems. The hypothesis of “reward” as the sole basis for addiction is not, however, universally accepted. Nevertheless, the mesolimbic system can be understood as a system with strong evolutionary advantages, since key survival behaviors such as maternal bonding, feeding, and sexual activity are all enabled by the hedonia, learning, or incentive salience (motivational “wanting”) produced in this center. 8 Exactly which is the primary enabling mechanism is still debated.

Figure 1

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When opioids are taken continuously for the treatment of chronic pain, the adaptations that arise are similar to

Fig. 1. Key neural circuits of addiction. Adapted with permission from Nestler.7 Dotted lines indicate limbic afferents to the nucleus accumbens (Nac). Blue lines represent efferents from the Nac thought to be involved in drug reward. Red lines indicate projections of the mesolimbic dopamine system thought to be a critical substrate for drug reward. Dopamine neurons originate in the ventral tegmental area (VTA) and project to the Nac and other limbic structures, including the olfactory tubercle (OT), ventral domains of the caudate-putamen (C-P), the amygdala (AMG), and the prefrontal cortex (PFC). Green indicates opioid-peptide-containing neurons, which are involved in opiate, ethanol, and possibly nicotine reward. These opioid peptide systems include the local enkephalin circuits (short segments) and the hypothalamic midbrain beta-endorphin circuit (long segment). ARC, arcuate nucleus; Cer, cerebellum; DMT, dorsomedial thalamus; IC, inferior colliculus; LC, locus ceruleus; LH, lateral hypothalamicus; PAG, periaqueductal gray; SC, superior colliculus; SNr, substantia nigra pars reticulata; VP, ventral pallidum. Taken from Ballantine and LaForge.6
those previously described: tolerance and dependence are expected; they determine drug need; and they may become significant forces for drug-seeking behavior. There are, however, substantial differences between the illicit drug user and the opioid-treated pain patient. Opioid-treated pain patients generally bypass the stage of positive reinforcement, and they do not necessarily present with the risk profile of the addict who initiates his or her own use (see Fig. 3).  

While the mechanisms of drug reinforcement described here are fairly well understood, what is far less obvious is how and why drug seeking becomes compulsive and thus enters the realm of drug addiction, which, unlike tolerance and dependence, is considered irreversible because affected individuals remain vulnerable to relapse even after drug cessation. Insofar as memory and learning are critical factors, drug addiction seems to result from conditioning, where repeated drug-seeking behavior is combined with drug use. Mechanisms underlying the irreversibility of such conditioning could include gene regulation and actual physical remodeling of synapses and circuits in higher centers such as the amygdala, hippocampus, and prefrontal cortex.

In pain patients, unlike illicit drug users, opioid seeking, even if it seems compulsive, may not necessarily be indicative of addiction.

**Evolution of Addiction Definitions and DSM-V**

Definitions and criteria for disease are developed in order to achieve consensus about what constitutes a particular disease state. Additionally, diagnostic terminology and coding are used both nationally and globally to determine what services and treatments are appropriate or needed and where. Consensus definitions thereby become crucial to the provision of services. Service needs have been an important driving force behind the evolution of addiction definitions, and they are again becoming an important factor, especially in the United States, where prescription opioid abuse has burgeoned and presents a huge unmet service need. There is little consensus about what constitutes dependence or addiction in opioid-treated pain patients. There are no agreed criteria, and efforts to mold DSM criteria to accommodate the state of dependence or addiction in pain patients have been largely unhelpful and even damaging.
Before the 1950s, addiction was considered a weakness of character or control, not a medical illness. At the time, understanding of addiction neurobiology was rudimentary, and the existence of endogenous opioid systems only imagined. In the 1950s, criteria for addiction were sought in order to medicalize it and facilitate treatment. The first Diagnostic and Statistic Manual (DSM) of the American Psychiatric Association, published in 1952, grouped alcohol and substance abuse under Sociopathic Personality Disturbances and did not recognize the key role of tolerance and withdrawal in drug addiction. It was not until the publication of DSM-III in 1980 that tolerance and withdrawal were included as criteria together with social and cultural factors. This edition was also the first to formally use the term “dependence” to denote drug addiction. “Dependence” is distinguished from “abuse,” which is maladaptive use without tolerance, withdrawal, or a pattern of compulsive use. The reader will readily see that the definition of these terms in DSM-III and DSM-IV (mirrored in the International Classification of Diseases) is not the same as is generally understood in colloquial English. This difference in itself produces much confusion. Over the years, many words have found their way in and out of addiction nomenclature, including the terms “habituation,” “misuse,” “abuse,” “dependence,” and “addiction.” The word “addiction” in medical definitions has been eschewed lately because of its associated stigma. What is particularly problematic about the choice of the term “substance dependence” to describe drug addiction is that it produces confusion when it comes to treating pain with opioids, because continuously treated pain patients can be expected to be dependent (i.e., have difficulty discontinuing treatment) but are not necessarily addicted (i.e., compulsively drug seeking).

New definitions for drug addiction were published by the American Psychiatric Association in May 2013 in DSM-V. Two significant changes were made in deference to the problems experienced conceptualizing dependence and addiction when they arise in opioid-treated pain patients.
The first change was to abandon the term "substance dependence," which had been used in both DSM-III and DSM-IV to denote drug addiction.17 In DSM-V, "substance dependence" has been superseded by terms such as "substance use disorder" and "opioid use disorder."

The second important change was to specify that two items are needed from the list of behaviors suggesting compulsive use (see Table I) in order to meet criteria for substance use disorder. Tolerance and withdrawal are not counted for those taking prescribed medications under medical supervision such as analgesics, antidepressants, anti-anxiety medications, or beta-blockers. For DSM-IV, three items were needed in order to meet criteria for substance dependence, and they could include tolerance and withdrawal. Thus, for continuously treated pain patients who would almost always display tolerance and withdrawal, only one behavioral criterion was needed. It was easier, therefore, for an opioid-treated pain patient to meet criteria for addiction under DSM-IV than it will be under DSM-V.

### Conceptualizing Dependence and Addiction

As this history has unfolded, we can see how radically our understanding of addiction has changed on the basis of scientific exploration (neurobiology), as well as the intellectualization of addiction as a disease worthy of treatment rather than a character flaw (development of addiction definitions and criteria). Yet, much uncertainty remains about exactly what addiction is and how best to treat it. That uncertainty is particularly problematic in the case of iatrogenic addiction (addiction arising as a direct consequence of medical treatment with an addictive drug), as reflected in efforts to develop definitions for dependence and addiction in pain patients, which remain unsatisfactory. Whereas for the illicit drug user, a pathway toward addiction (from risky initiation toward habituation, Fig. 3)18,20 can be relatively easily theorized, the pain patient presents a much less certain trajectory toward addiction. Moreover, unlike the illicit drug user who persists in usage, the pain patient who persists in usage may not be addicted.

Two major distinctions between iatrogenic and non-iatrogenic addiction are worthy of mention: differences in presentation and differences in disease progression.

### Differences in Presentation

If one looks at the behaviors listed in DSM-V (left-hand column of Table I, which are similar to behaviors listed in DSM-IV), it is easy to see that although an opioid-treated pain patient may meet these criteria, the degree to which they are diagnostic for addiction is open to interpretation. All of the behaviors are fairly common in opioid-treated pain patients, but they are usually attributed to pain rather than to addiction? Signs of compulsive use in the pain setting may be different, and one suggested scheme is represented in the right-hand column of Table I. Even accepting that these are signs of compulsive use, such behaviors are also often attributed to uncontrolled pain and not to addiction, and presentations may vary depending on a number of contextual and cultural factors. There is really no current agreement about when the compulsive behaviors seen

<table>
<thead>
<tr>
<th>Behavioral criteria used for Substance Use Disorder, Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V).19</th>
<th>Behaviors suggesting prescription drug abuse:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Failure to fulfill major role obligations at work, school or home</td>
<td>• Multiple prescribers</td>
</tr>
<tr>
<td>• Continued use in situations in which it is physically hazardous (e.g., driving)</td>
<td>• Frequent emergency room visits</td>
</tr>
<tr>
<td>• Persistent or recurrent social or interpersonal problems</td>
<td>• Multiple drug intolerances described as “allergies” and refusal to pursue nonopioid treatments</td>
</tr>
<tr>
<td>• Substance taken in larger amounts or longer than was intended</td>
<td>• Frequent dose escalations and self-dose escalation</td>
</tr>
<tr>
<td>• Persistent desire or unsuccessful effort to cut down</td>
<td>• Frequent running out of medication early</td>
</tr>
<tr>
<td>• Great deal of time spent in activities necessary to obtain substance, use substance, or recover from substance use</td>
<td>• Frequent telephone calls to clinic and early appointments</td>
</tr>
<tr>
<td>• Important social, occupational, or recreational activities given up or reduced</td>
<td>• Focusing mainly on opioid issues during visits</td>
</tr>
<tr>
<td>• Continued use despite knowledge of harm</td>
<td>• Repeated prescription loss with “classic” excuses such as the dog ate my prescription, the airline lost my baggage, the medicine was stolen</td>
</tr>
<tr>
<td>• Craving</td>
<td>Adapted from Wilsey and Fishman.24</td>
</tr>
</tbody>
</table>

Table I

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Differences in Disease Progression

It is generally accepted that patients treated continuously with opioids are likely to develop tolerance (need periodic dose escalation) and physical dependence (experience withdrawal in the case of inadequate dose). There may be exceptions, but neuroadaptations similar to the adaptations that occur during illicit opioid use can be expected during the treatment of pain with opioids. The main difference is that the behaviors that develop and become established as memories are different (Table I). Dependence is important because, as already discussed, whether or not it is part of a drug use disorder, it is a powerful driver of opioid-seeking behavior. In a pain patient, it is never clear exactly why opioids are sought. What is clear, however, is that dependence plays an important role in insistent continuation of treatment despite poor effect and may contribute to observed opioid-seeking behaviors. There is no clear demarcation between dependence and addiction in pain patients, even though there may be clarity at both ends of the spectrum (Fig. 4).

These differences in presentation and disease progression point to an urgent need both to continue our reappraisal and refinement of addiction definitions for this group of patients and to meet the current clinical challenge of how to manage and support the many patients who fall between the two ends of the pain-addiction spectrum.

Conclusion

In the United States, the popularization of chronic opioid therapy has produced three-fold increases in opioid prescribing for chronic pain, parallel increases in known cases of opioid abuse, and thousands of patients who have developed complex opioid dependence. Other developed countries have witnessed a similar, though less marked,
trend. When opioid dependence becomes complex and hard to reverse, it resembles addiction. It shares enough similarity to addiction that it requires similar treatment, made even more challenging by the coexistence of pain.

There is no easy formula that fits all patients. Even the basic decision whether to try and taper or discontinue the opioid is complex: Will maintenance work better for the patient and for the pain than abstinence? Has the dose become unacceptably high? How should tapering be achieved if this strategy is decided upon? For example, should there be a slow taper, a rapid buprenorphine taper, or a methadone taper?

Yet another vital layer of complicated treatment decision-making is how to encourage and motivate the patient through the process of optimizing treatment. Appropriate services and appropriately trained providers are in critically short supply in the United States, which is uniquely burdened because of prolific opioid use. Similarly, in the United Kingdom, although there is a publicly stated aim that addiction services should support patients regardless of their route into dependency, these services have neither the resources nor the expertise to manage emergent or worsening pain when opioids are reduced. The availability of multidisciplinary biopsychosocial care with a prominent component of self-management, generally accepted as the gold standard of care for chronic pain, has all but disappeared in the United States, although we may be beginning to see a reawakening of these approaches in the context of co-occurring pain and addiction.23 The unfortunate consequence is the continuation of the fragmented, polarized approach that often results in neglect of dependence, neglect of pain, or even loss of hope that medicine can help at all. The catastrophic result often is a resort to illicit sources of pain medication. When severe refractory chronic pain and opioid dependence arise together, the combination presents an enormous challenge to clinicians, who need to be provided with the right constructs, training, tools, and resources for collaborative work that are all needed to manage this condition.

New addiction criteria may have removed some of the confusion associated with the word “dependence,” but if anything, the new criteria have left an even bigger question mark as to how we can achieve a consensus on diagnosing opioid addiction during opioid treatment of pain so that we can appropriately recognize and treat it.23

References

Headache and other types of pain have some common characteristics concerning pain generation and chronicity. But some distinct pathophysiological processes are unique to the headache. This book explores pain mechanisms, diagnosis, and management of headache and other chronic pain through sessions of a joint symposium of IASP and the International Headache Society.

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The neurobiology and mechanisms discovered in animals often do not translate to patients with a chronic pain condition. To help researchers and clinicians develop and use models that can help translate data from animals into humans, this book presents 29 chapters by internationally recognized experts. It is a comprehensive survey of pain models at different levels, and commentaries by clinicians directly address clinical perspectives.

Price: US$130 (IASP Members: US$105)

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Price: US$85 (IASP Members: US$70)

Many people with chronic pain avoid activities they fear may cause additional pain. This book provides a guide to the treatment of pain-related fear. International experts provide practical advice on assessment, treatment goals, and graded-exposure behavioral experiments that may be easily applied in routine clinical practice. This is the definitive handbook on fear avoidance.

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