CHAPTER 8
PAIN AND CHEMICAL DEPENDENCY

The relationship between medical use and abuse of opioids cannot be clarified without a precise characterization of terms. Confusion about physical dependence, tolerance, and addiction augments the fear of opioid analgesic use and contributes to a physician's reluctance to prescribe opioids and a patient's reluctance to take the medications. Conversely, failure to understand the characteristics that truly constitute addiction or other forms of problematic drug-related behavior may hinder recognition of the syndrome when it does occur in the clinical setting.

Tolerance

As described previously, tolerance is a pharmacologic property of opioid drugs defined by the need for increasing doses to maintain effects. It is a complex phenomenon that may include both physiologic changes and learning (known as pharmacologic and associative tolerance, respectively). Opioid tolerance is assumed to primarily involve changes in the mechanisms initiated after binding of the drug to the receptor. Recent research has elucidated a mechanism that involves the *N*-methyl-D-aspartate (NMDA) receptor and can be reversed by NMDA receptor blockers. Other processes, such as changes in second messengers unrelated to the NMDA receptor and a change in receptor number, also may be involved. Tolerance may develop to any opioid effect, and both the rate of development and the degree of tolerance varies from effect to effect and from individual to individual.

Although tolerance is commonly portrayed as a potential problem during long-term therapy, tolerance to adverse effects actually is a favorable phenomenon. This type of tolerance allows dose escalation to levels associated with improved analgesia.

Tolerance to analgesic effects can occur and, theoretically, could be a major impediment to the clinical use of opioid drugs. In the clinical setting, however, the need for dose escalation has several potential drivers, only one of which is tolerance. Progression of disease (leading to greater nociception), a change in pain mechanism (eg, a shift over time from a predominating nociceptive mechanism to a predominating neuropathic mechanism), and psychologic processes that lead to increased pain all

may result in declining efficacy and a need to increase the dose to maintain analgesia. The need for dose escalation can be ascribed to tolerance only if an alternative explanation cannot be discerned. This occurrence appears to be uncommon in most clinical situations.

Patients who benefit from opioid therapy for a prolonged period often have stable doses for very prolonged periods. Those who experience worsening pain from time to time may require temporary dose escalation to maintain effects. At least for this subpopulation, tolerance does not preclude effective long-term therapy.

Tolerance must be distinguished from both physical dependence and addiction. Although tolerance to the positive psychic effects of a self-administered drug has been perceived as an element in the genesis of addiction, patients who receive opioids for pain do not commonly express significant effects of this type, and the development of tolerance to any mood effect rarely influences the course of therapy. In short, addiction can occur without evidence of tolerance, and tolerance can be inferred in the clinical setting without any of the behavioral problems consistent with abuse or addiction.

Physical dependence

Physical dependence is also a pharmacologic property of opioids as well as other medications, defined by the occurrence of an abstinence syndrome after abrupt dose reduction, a decreasing blood level of the drug, or administration of an antagonist. Some degree of physical dependence is usually produced with very little opioid exposure, and neither the opioid dose nor the duration of administration required to produce clinically significant physical dependence in humans is known. Therefore, most practitioners assume that the potential for an abstinence syndrome exists after opioids have been administered regularly for only a few days. Physical dependence is not problematic as long as patients are instructed not to abruptly discontinue therapy after long-term use and no antagonist drugs are administered.

The distinction between physical dependence and addiction has been a source of confusion for patients and clinicians alike. It is probably true that individuals who are predisposed to addiction and begin compulsive drug use to feel a positive psychic effect may make the transition and have compulsive use maintained by a need to avoid uncomfortable withdrawal. However, this phenomenon should not be taken as evidence that physical dependence itself results in addiction. In medically ill populations using opioid analgesics on a regular basis, physical dependence is common

but addiction is rare, and uncomplicated discontinuation of opioid therapy can be achieved easily if a tapering schedule is used when cessation is indicated.

A patient who is presumed to be physically dependent should never be labeled an addict. Misuse of the latter term reinforces the stigma associated with opioid therapy and should be abandoned. Likewise, referring to the patient as dependent should also be discouraged, since it creates confusion between physical dependence and the type of psychologic dependence that is associated with addiction.

Abuse and addiction

During the past half century, numerous definitions for abuse and addiction have been developed. Each definition has generated criticism, and each has been followed by an attempt at some later time to redefine the construct. Until recently, all definitions emerged from the field of addiction medicine, without input from pain specialists.

According to one definition, the term *drug abuse* should apply to the use of any drug that is outside of accepted norms. Although it is true that normative behavior reflects culture and is not constant, this definition has utility in the clinical setting. It labels any use of an illicit drug and any misuse of a prescribed drug (use in a manner not intended by the clinician) as abuse.

In a more complex definition, the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition text revision (*DSM-IV-TR*), classifies substance abuse as 1 of 2 psychoactive substance use disorders and defines it as a maladaptive pattern of drug use that results in harm or places the individual at risk. Considered broadly, this definition and the one discussed before it describe very similar phenomena.

Early definitions of addiction developed by expert committees of the World Health Organization were problematic because they included tolerance and physical dependence as cardinal signs of addiction. These criteria clearly do not apply to patients who receive a drug for medical indications.

The *DSM-IV-TR* does not include the term *addiction* but defines a syndrome of psychoactive substance dependence under the category of psychoactive substance use disorders. This diagnosis is characterized by a maladaptive pattern of drug use that persists for at least 1 month and includes at least 3 of 9 criteria. Although the criteria include descriptions of craving, compulsive use, and use despite harm (which could be used to establish the diagnosis of addiction in the absence of any other criteria), they also refer to

tolerance and physical dependence. These ambiguities have led to criticisms of this definition by pain specialists.

Recently, the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine established a task force that created consensus definitions of addiction, physical dependence, and tolerance (table 22). The definition of addiction states that the syndrome is a psychologic and behavioral disorder that has a genetic substrate and is characterized by drug craving, compulsive use, a strong tendency to relapse after withdrawal, and continued use despite harm to the user or those around him or her. This definition appropriately focuses on behavior as the relevant assessment for the diagnosis of addiction, rather than on phenomena related to tolerance or physical dependence.

Pseudoaddiction

In clinical practice, the diagnosis of addiction involving use of a pharmacotherapy may be particularly challenging, because the drug in question is legal and prescribed for an appropriate medical condition. This challenge is underscored by a phenomenon that has been termed *pseudoaddiction*. Pseudoaddiction refers to the development of abuselike behaviors that are driven by desperation surrounding unrelieved pain and are eliminated by measures that relieve the pain, such as an increase in medication dose.

The term pseudoaddiction was originally coined on the basis of observations of patients with cancer pain. It referred

Table 22. Terminology of substance abuse
Tolerance
A state of adaptation in which exposure to a drug induces changes that result in diminution of 1 or more of the drug's effects over time
Physical dependence
A state of adaptation that is manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, a decreasing blood level of the drug, and/or administration of an antagonist
Addiction
A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include 1 or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving

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specifically to behaviors such as drug-seeking and expressions of distress. Over time, however, it has been applied to all populations with chronic pain and sometimes used to describe behaviors that are highly problematic, such as the acquisition of street drugs to treat a pain problem.

In ascribing more overt and potentially harmful drug-related behaviors to pseudoaddiction, there is a risk of ignoring a concurrent addiction. This risk is a serious concern. It is important to recognize that addiction and pseudoaddiction can coexist and that the report of unrelieved pain does not give license to behaviors that are inappropriate or illegal. Even if the term pseudoaddiction is applied, it is necessary to gain control over behaviors that place the patient, the physician, or others at risk.

Aberrant drug-related behavior

The dual phenomenon of addiction and pseudoaddiction, either of which may explain a set of drug-related behaviors, indicates that problematic behaviors in the clinical setting have a differential diagnosis (table 23). In addition to addiction and pseudoaddiction, problematic behaviors may reflect a variety of other psychiatric disorders, family disturbances, or possibly even criminal intent. For some patients with psychiatric disorders and some with high distress but no clear psychiatric diagnosis, inappropriate opioid use may reflect self-medication (sometimes called chemical coping) or an effort to communicate anger or misery. Appropriate treatment requires a proper diagnosis based on a detailed assessment.

The concept of aberrant drug-related behavior has been developed to explore the observation that drug-related behav-

Table 23. Differential diagnosis of aberrant drug-related behavior
Addiction
Pseudoaddiction
Other psychiatric disorder
Axis I disorder (eg, anxiety disorders, major depression)
Axis II disorder (eg, personality disorders such as borderline personality, sociopathic personality)
Encephalopathy (eg, associated with medication toxicity)
Other psychosocial/emotional issues (eg, family discord, financial worries, work-related discontent, “rebellion”)
Recreational use (eg, experimentation, pleasure, escape, peer pressure)
Criminal intent

iors, and the meaning of these behaviors, vary greatly from individual to individual. In the clinical setting, aberrant drug-related behavior is synonymous with other terms, including problematic behavior, misuse and abuse behaviors and nonadherence behavior. It refers to the phenomenon of drug-related behavior that is inconsistent with the expressed intentions of the prescriber.

Aberrant drug-related behavior exists on a continuum. Some behaviors are very worrisome and probably quite suggestive of an addiction; others are less worrisome and may reflect other causes (table 24). Routine evaluation of patients using opioids must include monitoring for the development of these behaviors. Should problematic behaviors occur, the assessment must yield information that supports a specific diagnosis and facilitates an appropriate therapeutic response.

Table 24. Behaviors suggestive of addiction

Behaviors probably more suggestive of addiction

- Selling prescription drugs
- Forging prescriptions
- Stealing or “borrowing” drugs from others
- Injecting or inhaling (snorting, smoking) oral formulations
- Obtaining prescription drugs from nonmedical sources
- Concurrently abusing alcohol or illicit drugs
- Having multiple dose escalations or other nonadherence with therapy, despite warnings
- Repeatedly “losing” prescriptions
- Repeatedly seeking prescriptions from other clinicians or from emergency department staff without informing prescriber or after warnings to desist
- Showing evidence of deterioration in ability to function at work, in the family, or socially that appears to be related to drug use
- Repeatedly resisting changes in therapy, despite clear evidence of adverse physical or psychologic effects from the drug

Behaviors probably less suggestive of addiction

- Aggressive complaining about the need for more drug
- Drug hoarding during periods of reduced symptoms
- Requesting specific drugs
- Openly acquiring similar drugs from other medical sources
- Having unsanctioned dose escalation or other nonadherence with therapy on 1 or 2 occasions
- Using the drug, without approval, to treat another symptom
- Reporting psychic effects not intended by the clinician
- Resisting a change in therapy associated with “tolerable” adverse effects with expressions of anxiety related to the return of severe symptoms

The diagnosis of aberrant drug-related behavior, and subsequent control and monitoring should opioid therapy be continued, may require the input of a professional skilled in addiction medicine. Referral should be considered if the issues raised by the patient are beyond the skills of the prescriber.

Suggested readings

Definitions related to the use of opioids for the treatment of pain: a consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. 2003. Available at: http://www.ampainsoc.org/advocacy/opioids2. Accessed Dec 30, 2003

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