

CHAPTER 1

HISTORICAL NOTES AND PERSPECTIVES

“The pre-eminent place in any history of drugs must be assigned to opium.”

Richard Davenport-Hines

Opium derivatives have been used continuously throughout the ages for a variety of perception-altering purposes. Their therapeutic capacity as potent analgesics has made this drug class uniquely valuable. Indeed, the capability of medical providers to meet the imperative to relieve suffering would be largely unmet were it not for these drugs. This unmatched benefit to humankind, however, has come with a price. Recreational use, and compulsive use that becomes sustained by uncontrollable cravings, can undermine public health and can be viewed (and is judged) in medical, legal, social, and anthropologic contexts. The dichotomous and sometimes paradoxical reality of the potential “good” and the unlikely but ever-lurking “bad” of opioids used in a medical context has confronted, and no less confounded, physicians for centuries.

The history of man’s relationship with opioids is replete with ambivalence and highly mixed emotions, tensions, and strained—if not downright inconsistent—attitudes and policies. During the past three decades, the medical profession has become more attuned to these issues and its awareness has been increased by the advancing knowledge of pharmacology and the disquieting recognition of the large-scale public health tragedy of needless yet treatable pain.

More recently, there also has been increased insight into the fundamental risks associated with exposure to these drugs, particularly as they relate to the genetic, psychosocial, and situational predispositions toward abuse and addiction. It is a challenging era, characterized by both growing outrage over the undertreatment of pain and an evolving clarity that our most effective treatment, the opioid drugs, will be increasingly problematic unless the risks are fully understood and managed.

The need to identify and then nurture the proper balance between expanded access and a proactive effort to limit misuse, abuse, addiction, and diversion has never been more critical. Indeed, this “principle of balance” has been invoked as the most

effective and cogent means to create positive change in this arena (table 1). Increasingly, the scientific, clinical, and regulatory communities have jointly expressed a multilateral commitment to simultaneously ensure access to the therapeutic use of opioid drugs (and to expand this use as appropriate) while addressing the potential for harm. Efforts are being made to create balanced clinical guidelines and regulatory policies. Even the most challenging clinical confounds—such as treating the known substance abuser with opioids in an effort to relieve suffering and improve functional outcomes—are undergoing fresh appraisal.

Compelling need to implement the principle of balance motivated the Federation of State Medical Boards of the United States to create *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain*. The guidelines, which

Table 1. The principle of balance in opioid use

Medical availability

While opioid analgesics are controlled substances, they are also essential medications and are absolutely necessary for relief of pain

Opioid analgesics should be accessible to all patients who need them for relief of pain

Governments must take steps to ensure adequate availability of opioids for medical and scientific purposes, including:

- Empowering medical practitioners to provide opioids in the course of professional practice
- Allowing practitioners to prescribe, dispense, and administer according to the individual medical needs of patients
- Ensuring that a sufficient supply of opioids is available to meet medical demand

Drug control

When misused, opioids pose a threat to society

Clinicians must recognize that a system of controls is necessary to prevent abuse and diversion. Although the system of controls is not intended to interfere with legitimate medical use, controls are necessary to protect public health and should be understood, and supported, by the clinical community

Minimizing risk of abuse and diversion during treatment of individual patients is part of the essential skill set needed for safe and effective clinical use of opioid drugs

are endorsed by various federal and state regulatory bodies, professional organizations, and patient advocacy groups, have been a signal event among many educational, regulatory, and policy initiatives designed to promote a balanced perspective. A recent report card on regulatory issues, published by the University of Wisconsin's Pain and Policy Studies Group ("Achieving Balance in State Pain Policy: A Progress Report Card," available at <http://www.medsch.wisc.edu/painpolicy>), describes many positive changes that have emerged from this effort but overall suggests that there is still considerable room for improvement (table 2).

The intent of this book is to help clinicians make practical sense of the varied and often conflicting pharmacologic, clinical, and regulatory issues to promote the most healthful outcomes possible for patients in pain. The aim is to improve knowledge and skills related to both the principles of prescribing and the management of risk. In this way, healthcare professionals and those they serve may benefit increasingly from the unique therapeutic potential of this drug class and fear less the undeniable, yet manageable, potential for harm.

Table 2. Number of states with policy language that has potential to impede pain management

Negative provisions	Number of states
Opioids are considered a treatment of last resort	10
Medical use of opioids is implied to be outside legitimate professional practice	14
The belief that opioids hasten death is perpetuated	15
Physical dependence or analgesic tolerance is confused with addiction	18
Medical decisions are restricted on the basis of patient characteristics	5
Medical decisions are restricted on the basis of mandated consultation	11
Medical decisions are restricted on the basis of quantity prescribed or dispensed	10
Length of prescription validity is restricted	7
Practitioners are subject to additional prescription requirements	3
Other provisions may impede pain management	15
Provisions are ambiguous	33

Adapted, with permission, from Pain and Policy Studies Group. Achieving balance in state pain policy: a progress report card. Madison, Wis: Univ of Wis Comprehensive Cancer Center, 2003. Available at: <http://www.medsch.wisc.edu/painpolicy>.

Lessons from history

The history of opioids provides context for education predicated on the principle of balance. The history dates back millennia and provides many relevant lessons. It highlights elements that are unique to our contemporary times and issues that almost eerily recapitulate the experiences of other eras. The logical place to start this history discussion is with the “ontogeny” of opioids, a class of drugs originally derived from *Papaver somniferum*. Evidence found in a Sumerian ideogram, depicting the opium poppy as “the plant of joy,” suggests that this flowering plant was domesticated for its pharmacologically active milky white juice as long as 8,000 years ago. A papyrus dated 1552 BC advises Theban physicians about the use of opium in hundreds of potions for myriad “medicinal” purposes. Arab, Greek, and Roman physicians described opiate toxicity in the 2nd century BC, and Nero, the Roman emperor, took advantage of this quality of opium by intentionally overdosing Britannicus in AD 55, taking his throne. Egyptian documents describe the use of opium for pain relief, as do Roman documents, around this same epoch.

During ancient times, consumption of opiates (a term referring to the alkaloid derivatives of opium) became routine, even commonplace, among many seemingly upstanding citizens, and there is documentation that this occurred without the pathognomonic dose escalation and dysfunction attributed to addiction. Galen, for instance, reported that the political leaders of the day could distinguish the quality of the ingredients of their opiate concoctions, reducing consumption when necessary to execute their duties.

In the 16th century, both German and British physicians commonly prescribed opium admixtures, under the rubric of laudanum, for a variety of ailments. This practice soon became associated with quackery, since it was purported to be a panacea for all ills at a time when at least some rigor in medicine was being demanded. It was also around this time that there were observations describing tolerance and physical dependence.

By the turn of the next century, 2 schools of medicine had diverged in France. In the southern regions, physicians preferred tonics, whereas northern practices influenced by Parisian schools of thought placed great reliance on bloodletting and purging. The former approach was adopted by the English physician Thomas Sydenham. He, too, used the term *laudanum* for his alcohol-opium tincture. He wrote, “So necessary an instrument is opium in the hand of a skillful man, that medicine would be a cripple without it.”

During the 17th and 18th centuries, physicians and pharmacists throughout England, France, and Germany experimented with a variety of formulations and means of administration in both humans and animals. Physical dependence, manifested by an acute abstinence syndrome, became well known, mostly in persons using opiates for what would probably be classified as mood disorders today (ie, anxiety and depressive illness). This era is marked by a substantial increase in the use of psychoactive drugs in Europe for purely experiential purposes.

Concurrently, British commercial interests expanded the opium trade from India to China. This trade became a major revenue generator and offset the trade deficit from Chinese silk, spices, and other commodities. The opium trade had a devastating effect on productivity of Chinese peasants, however, and in 1799, the emperor of China issued a proclamation that prohibited importation of opium. This ban had limited effect, because market demand exceeded the capacity of imperial rule to stop the trade.

In 1805, Friederich Wilhelm Sertürner, an apothecary's assistant in Hanover, Germany, isolated from opium a white crystalline powder that he thought would explain the sleep-inducing quality of the parent compound. He called this purified product morphium, after the Greek god of dreams and sleep, Morpheus. Apparently, Sertürner was not a disciplined scientist, and his eccentricities delayed appreciation of his discovery for more than a decade.

The Parisian pharmacist Pierre-Jean Robiquet perfected an extraction process for morphine, and morphine was soon promoted as both an analgesic and a cure for opium addiction. Commercial morphine appeared in London in 1821, and wholesale production by the German pharmacist Heinrich Emanuel Merck began a few years later.

With the development of the hypodermic syringe in the mid 19th century, morphine could be injected directly into painful areas, termed neuralgias, which was done with the thought that the injection would induce localized anesthesia.

Public concern and legislation

Early in the 20th century, growing use and abuse of opioids and other drugs in the United States led to increasing public concern and to reaction by politicians. In 1906, the Pure Food and Drug Act was passed, which gave the government the obligation of regulating drugs and establishing their safety and efficacy before their entry into the US market. This was followed in 1914 by the far-reaching Harrison Narcotics Act, which applied controls to

opioid analgesics and, among other features, prohibited physicians from prescribing opioids for addicts.

In 1919, the Supreme Court upheld this law (*Webb et al vs the United States*) and stated that a physician must not provide opioids for maintenance of an addict. Dispensing centers for maintenance were closed, driving procurement underground. Addicts who obtained drugs illegally became criminals, and drug use was increasingly viewed as being under the purview of the criminal justice system rather than the healthcare system. In 1937, the Marijuana Tax Act outlawed cannabis and heroin, adding further aspects of drug use to the criminal code.

Throughout the 20th century, efforts to stem abuse and addiction by law and regulation surged in the United States. In 1970, the Federal Controlled Substances Act increased the monitoring of the manufacturing, prescribing, and dispensing of opioids and other controlled substances. It required registration of all prescribers of controlled substances and categorized potentially abusable drugs into 5 schedules, each with different regulatory mandates. The law stipulated that drugs in Schedule II, such as morphine, could not be prescribed by telephone, nor could morphine prescriptions be refilled without a new written prescription. These federal efforts were mirrored at the state level, where a complex array of laws and regulations created further requirements for prescribers and patients and enacted an additional set of civil and criminal penalties that could be applied to those prosecuted.

This societal decision to regulate medical practice and criminalize the administration of opioid medications in some contexts led to secondary phenomena, which had effects of their own. Prescribers became increasingly concerned about the potential for investigation and sanction or prosecution. To some degree, this concern has contributed to the underuse of opioid medications. Equally important, the criminalization of opioid addiction fostered an illicit drug trade that, in turn, brought new problems, including the involvement of organized crime and violent gangs in drug trafficking. Over time, all these problems—undertreatment of pain, occurrence of opioid abuse and addiction, and criminal activities surrounding opioid trafficking—have increasingly undermined public health. Clearly, pursuant to pain management and opioid analgesia, there is a pressing need for rational and consistent policies, initial and continuing education of healthcare professionals, and application of sound principles of assessment, prescription, and management.

Conclusion

There is growing tension between clinicians' needs to support therapeutic use of opioids, to address abuse and addiction as conditions that are fundamentally medical rather than legal, and to minimize societal harm resulting from drug abuse, addiction, and trafficking. These contemporary issues reflect an iterative evolution that dates back thousands of years. With the advantage of hindsight, it is apparent that the current medical, sociopolitical, and economic issues surrounding opioid use, misuse, and abuse do not depart much from those of previous eras. A new paradigm that brings historically adversarial parties together is needed. The principle of balance supports this paradigm and has potential to inform the creation of clinical guidelines, regulations, and laws that meet the needs of patients without compromising the appropriate societal demand for control of potentially abusable substances.

Suggested readings

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