

Editorial

## Opioid-Related Issues “Popping” Up Again

Howard S. Smith, MD

*“Sine papaveribus, sine opiates et medicamentis, ex lis confectis, manca et clausa, esset medicina.”*

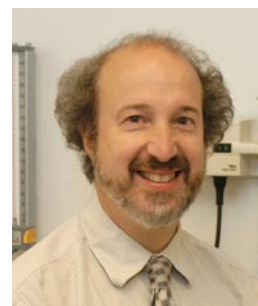
*“Without opium, without hypnotics and the medicines made from these, medicine would be helpless and crippled.” (1).*

**F**or centuries the world has appreciated the potent analgesic qualities and adverse effects/addictive qualities of opioids. Evidence of potential poppy plant use (preserved remains of cultivated poppy seeds and pods) may date back to the fourth millennium BC (2). Opium was proposed as a remedy for multiple ailments in 1552 BC in the Ebers papyrus.

Drug use in ancient central Asia is evidenced by Herodotus' fifth century BC mention of the Massagets' (a people who inhabited the northern coast of the Caspian Sea) custom of inhaling smoke from burnt poppy heads for the purpose of inducing euphoria (3).

Although there have been amazing advances in pain medicine, the age-old controversy surrounding opioids continues. Currently, opioids are accepted analgesics for cancer pain and non-cancer pain alike and the concept of “balance” best describes the optimal approach to opioid prescribing. Balance refers to assuring opioids are able to be prescribed freely when appropriate in efforts to ameliorate suffering, while at the same time spending efforts to avoid or minimize opioid diversion/misuse.

In the 1600s and 1700s, in the section on gout in *The Ancient Physician's Legacy*, the formula of Thomas Dover's famous, Dover's Powder was revealed. “Take Opium one ounce, Salt-Petre and Tartar vitriolated each four ounces, Ipocacuana one ounce. Put the Salt-Petre and Tartar into a red hot mortar, stirring them with a spoon until they have done flaming. Then powder them very fine; after that slice in your opium, grind them to a powder, and then mix the other powders with these” (1). Opium use continued to grow both for medicinal uses, and pseudo-medicinal uses (including via smoking). The publication of Thomas de Quincey's *Confessions of an English Opium-Eater* (1821–1822) brought the addictive potential of opioids (which was already known) into the main arena of international attention.



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In the United States, opioid use began to increase again after the Civil War, but the Harrison Act of 1914 dramatically restricted easy access to opioids. The medical use of opioids gradually increased in the late twentieth century with the movements of cancer pain initiatives and the early birth of palliative medicine. The decade 1990 to 1999 saw a significant increase in opioid prescription for non-cancer pain which still continues to grow.

Thus, throughout these many, many years of opioid use, the pendulum of the medical profession, society, and regulatory agencies has been swinging between opiophilia and opiophobia camps.

Based on data from the U.S. Drug Enforcement Agency (DEA) Automation of Reports and Consolidated Order System (ARCOS), which monitors opioid production and delivery to retail pharmacies, between 1997 and 2004 the amount of oxycodone, hydrocodone, and methadone delivered increased by 640%, 275%, and 903%, respectively (4).

Government data show that since 1990, there has been a progressive increase in opioid prescribing, and a concurrent increase in drug theft, drug-related emergency department encounters, and in unintentional drug overdose deaths (4). Between 1999 and 2000, deaths attributed to prescription opioids began to exceed those of heroin and cocaine (4).

Headline news coverage began to publicize stories on the terrible hazards of these "excessively prescribed" analgesics, such as Oxycontin and, more recently, methadone (4).

However, despite stories of increasing opioid misuse depicting large amounts of easily accessible opioids in the US, even in present times opioid availability/accessibility for medical use in patients with severe pain in some countries can be problematic.

In India, a million people with cancer and an unknown number of people with other incurable and disabling diseases may encounter difficulties with opioid availability. Major barriers to opioid access are complicated regulations and problems related to attitude and knowledge regarding pain relief and opioids among professionals and the public (5).

Many challenges relating to various opioid issues await scientists and clinicians alike. Although much is known regarding various opioid mechanisms of action, the "whole story" is far from certain. Opioids possess peripheral, spinal, and supraspinal actions. Most of the attention relating to supraspinal opioid analgesic actions dates back to seminal articles in 1974

and 1975 by Agu Pert and Tony Yaksh (6) about microinjections. Microinjections of morphine sulfate (20–40 micrograms) were made into various subcortical regions of the rhesus monkey brain. The effects of these injections were evaluated on the nociceptive threshold as defined by the shock titration technique (6). The results of this preliminary investigation indicate that the region of maximal antinociceptive sensitivity to morphine in the primate is the periventricular-periaqueductal gray matter (6,7).

The work of Dr. Mary Heinricher, Dr. Howard Fields, Dr. Allan Basbaum, and others described the effects of opioids, activating the *off cells* and inhibiting the *on cells* in the Rostral Medulla. However, there remains uncertainty about some of the most basic ways as to how opioids work.

### **RENEWED INTEREST IN OPIOID PRESCRIBING AND OPIOID RELATED ISSUES**

Over the past 5 years, many states have attempted to re-evaluate the need to balance protecting clinical practice while reducing opioid abuse and diversion, which in the past had been more focused on enforcement of controlled substances regulations and less on patient care. In the area of medical practice, for example, the Federation of State Medical Boards, a national organization, has drafted model regulations for the medical use of controlled substances ("Model Guidelines for the Use of Controlled Substances for the Treatment of Pain"), which have now been adopted, at least in part, by almost half of the states. These model guidelines are used by State Boards to judge the appropriateness of a therapy and should be considered by prescribers as the Federation of State Medical Boards basic approach to the structuring and documentation of opioid therapy (8).

There has been renewed interest in opioid prescribing in the US, perhaps in part due to a growing number of tools/instruments to help clinicians with "screening"/decisions/documentation related to opioid therapy. The Opioid Management Society (OMS) was started during the past decade as well as their Opioid Education Program and the *Journal of Opioid Management*. OMS is dedicated to the proper and adequate use of opioids for the control of all types of pain. Through research, education, and dissemination of leading edge information, OMS hopes to enhance the medical profession's knowledge on how to better utilize this important class of drugs. Just in 2007 – 2008, there are at least 8 mini-books or major texts

published, in press, or in the process of coming out with the next edition devoted in large part to opioids/opioid related issues (9-16). So it seems appropriate to devote this special issue of *Pain Physician* to opioids including: various routes of opioid administration, combining other agents with opioids in attempts to make them better analgesics, and matters related to the safe and optimal clinical use of opioids in interventional pain medicine in 2008.

At the end of 2007, Dworkin et al (17) updated their last published recommendations of the Neuropathic Pain Special Interest Group from 2003 (18). In the 2003 recommendations opioids and tramadol were listed as first-line medications for the treatment of neuropathic pain, however, in the 2007 recommendations they have been "cut from the starting team," and relegated to second-line therapy (except in "select clinical circumstances"). Four such circumstances which the authors list include:

- 1.) during titration of a first-line medication to an efficacious dosage for prompt pain relief,
- 2.) episodic exacerbations of severe pain,
- 3.) acute neuropathic pain, and
- 4.) neuropathic cancer pain (17).

Dworkin and colleagues (18) add that such "first-line" use of opioids should be reserved for circumstances in which "suitable alternatives cannot be identified and should be on a short-term basis to the extent possible" .

One special clinical scenario where opioids may be best reserved as second-line treatment options is painful HIV neuropathy (19). Some of the reasons given by Dworkin and colleagues for "axing opioids from the starting line-up of analgesics for neuropathic pain" include:

- a.) more frequent adverse effects than some first-line agents (20-22) (some of which may persist throughout long-term treatment) (23);
- b.) the long-term safety of opioid therapy has not been systematically studied (24,25), and preliminary evidence that long-term opioid therapy may be associated with immunologic changes and hypogonadism (26-28)
- c.) experimental data which suggest that opioid treatment may be associated with opioid-induced hyperalgesia (29-32); and

- d.) the potential for opioid analgesic misuse or addiction (17).

In the new millennium concerns regarding the addictive potential of opioids became stronger as evidenced by publications like "The Search for a Non-addicting Opioid" (33). Risk management plans were advocated in efforts to minimize opioid misuse. Opioid treatment agreements; random urine drug testing; screening processes to help determine suitability of specific patients for long-term opioid therapy; informed consent sheets for patients describing the risks, benefits, alternatives, and rules of long-term opioid therapy; unscheduled pill counts; and other strategies are currently used more often. Additionally, documentation of the patients medical condition/indications for long-term opioid therapy, with continued follow-up/assessments of the patient's 4As – analgesia, adverse effects, activities of daily living, and aberrant drug use (34) — are now strongly encouraged (with or without various documentation and/or screening tools) .

Another issue of opioid prescribing is who should be prescribing opioids for the "routine," "stable" patient on long-term therapy. Wiedemer et al. concluded that a nurse practitioner (NP)/clinical pharmacist-run clinic, supported by a multi-specialty team, can successfully support a primary care practice in managing opioids in reasonably complex pain patients (35).

Finally, health care providers should also have an appropriate "exit strategy" to gradually taper off opioids at some point if titration trials of multiple different opioids have failed to provide any significant analgesia or have worsened pain. Patients should be re-assured that they will not be abandoned and other analgesic strategies will be employed.

Opioids have for many centuries been known to have important medical uses and to also possess abuse potential. The level of comfort of practitioners related to prescribing opioids as well as the comfort of patients receiving opioids continues to be an issue even in 2008. It is hoped that increasing knowledge regarding opioids and their use may lead to a decrease in angst surrounding their prescription as well as more appropriate prescribing practices and associated documentation.

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