

Opioids: Myths versus Reality, Calling All Physicians

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Introduction

The dramatic rise in the use of opioids and the recent plethora of lay as well as scientific reports of a need to curb opioid addiction due to overdoses and deaths associated with these drugs, indicates to us it is time to briefly review how opioids are used, and whether the use is appropriate.

History of Opioids

No drugs, more than opioids, have been the object of human fantasy since the dawn of human civilization. Opioids' ability to produce profound euphoria and their ability to abolish pain has kindled the imagination of humans for six thousand years. When we examine opioids and their use in the unemotional light of scientific knowledge, it is apparent that the history of opioid use is littered with the juxtaposition of ingenuity and hubris, foresight and complacency, wisdom and foolishness, scientific progress and social disenchantment. The use of opium (*Papaver somniferum*) by humans predates written history. Images of opium poppies have been found in Sumerian civilizations; poppy seeds have been found in Neolithic settlements in what is now Western Europe. In more modern times, Sydenham lauded the virtues of opium. He said "among all the remedies it has pleased almighty God to give man to relieve his suffering none is so universal and as efficacious as opium". Friedrich Serturmer isolated the active ingredient of opium in the 19th century. He called it morphium for the Greek God of sleep or dreams. When Thomas De Quincey published his autobiographical account of opiate addiction "Confessions of an English Opium Eater," he essentially started the love/hate relationship of many western societies with opium.

The 19th century saw opium wars, as opium became one of the most fought over commodities in British Empire. In the late 1800's and early 1900's the extensive use of morphine by the United States working class led to the Harrison anti-narcotic act which taxed opium and derived opium products and led to the significant reduction of opioid use [1]. In 1900 Dr. John Witherspoon delivered a speech to American Medical Association warning of the perils of opium addiction. He said, "Save our people from the clutches of this hydra headed monster which stalks abroad through civilized world wrecking lives and happy homes, filling our jails and lunatic asylums and taking from these unfortunates the precious promise of eternal life." In 1941 an article in JAMA condemned the use of narcotics even in terminal cancer because of the fear of addiction [2].

Distribution of Opioids in Recent Times

Knoll Pharmaceutical Company developed hydrocodone in the 1920's, but in a controversial decision, the US FDA, in 1971 permitted hydrocodone to have a split Schedule, in which pure hydrocodone was a Schedule II narcotic; hydrocodone combined with acetaminophen was a Schedule III narcotic. Schedule III narcotics could be prescribed over the telephone and did not require "triplicate" prescriptions, thereby greatly facilitating the prescribing of opioids by US physicians. At around the same time, a feeble statistic from a paper by Porter and Jick (1980) was trotted out by the U.S. medical establishment which claimed that addiction rates in hospitalized patients prescribed opioids was 0.03 percent [3]. In the nineties Purdue Pharmaceutical Company

began marketing the potent opioid OxyContin. Purdue Pharmaceutical Company promoted OxyContin to general practitioners who had little training in the treatment of serious pain or in recognizing signs of drug abuse in patients. In May 2007 Purdue Pharmaceutical Company paid \$634.5 million in fines for claiming the drug was less addictive and less subject to abuse than other pain medications [4]. Another impetus in increase in opioid use appears to be a proclamation by in 2001 the Joint Commission of Accreditation of Healthcare Organizations in the United States that pain assessment be the "fifth vital sign," despite the fact that pain is a symptom not a sign. This pronouncement ushered in a culture of markedly increased opioid use by western physicians.

As a result, the use of opioids in developed countries has exploded. The University of Wisconsin and The World Health Organization study demonstrates the rather large increase in the distribution of opioids beginning in 1980 through 2010 [5]. For example, globally, opioid distribution in 1980 was 1.82 in Morphine Equivalence milligrams per person per year (MEMgPPPY) and by 2010; it had increased to 58.11, a 3,193 percent increase. In the United States opioid distribution was 22.6 in 1980, and by 2010 it had increased to 693.45 a 3,053 percent increase. In Japan in 1980 it was 0.26 and by 2010 it was 26.38. The dramatic increase in opioid use from 1980 through 2010 is hypothesized to indicate better access to opioids, particularly in developed countries, although indiscriminate excessive utilization of opioids is a distinct possibility.

While the use of opioids has dramatically increased in "developed countries" many people in underdeveloped countries do not have access to opioids even for cancer pain, and they unfortunately die in severe pain. In India opioid consumption in 2010 was merely 0.24-1 [1]. The world's most populous countries have very poor availability of opioids for pain relief and consequently in each China, India, Indonesia, Nigeria, Russia, and South Africa at least 100,000 people die every year while suffering with significant unrelieved pain from cancer or HIV/AIDS related terminal illnesses. The combined suffering due to lack of opioid pain medication world-wide is staggering. The World Health Organization estimates that each year tens of millions of people suffer untreated moderate to severe pain including 5.5 million terminal cancer patients and 1 million patients in the last phases of HIV/AIDS. This lack of access to opioids in the underdeveloped countries is reprehensible, especially in view of the fact that 50 years ago the world community adopted the 1961 Single Convention on Narcotic Drugs which stated that narcotic drugs are "indispensable for the relief of pain and suffering."

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Received May 09, 2013; **Accepted** June 17, 2013; **Published** June 20, 2013

Citation: Mehendale AW, Goldman MP, Mehendale RP, Rana K (2013) Opioids: Myths versus Reality, Calling All Physicians. J Palliative Care Med 3: 151. doi:10.4172/2165-7386.1000151

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Lay Press and Regulatory Response in the USA to Opioid Epidemic

Indeed, in the 21st century there has been a chorus of lay reports because the dramatic increase in the use of opioids has resulted in overdoses, deaths, diversion and addiction. For example, the New York Times cited 15,000 deaths in 2008 versus 4,000 deaths in 1991 associated with opioid use and called for a national monitoring program and tighter control of opioids [5-7]. The United States Centers for Disease Control (CDC) observed that about 12 million Americans age 12 or older reported non-medical use of prescription "pain killers" in 2009. They also cited that half a million emergency department visits in 2009 were due to people misusing or abusing prescription "pain killers." The CDC also estimated that enough opioids were sold in 2010 in the United States to give every American adult a 5 mg Hydrocodone tablet every four hours for a month [8,9]. While this manuscript was being submitted for publication, the FDA's Drug Safety and Risk Management Advisory Committee voted 19 to 10 in favor of reclassifying changing hydrocodone-containing compounds from Schedule III drugs under the Controlled Substances Act to Schedule II [10,11]. The change must be approved by the FDA and the DEA to take effect.

Building on these data, we reach some startling observations and conclusions about the world wide use of opioids. For example, our review suggests there appears to be a disregard of scientific evidence in the use of opioids. It appears that opioids are over utilized in Chronic Non Terminal Pain (CNTP) patients and underutilized in Terminal Pain (TP) patients.

Efficacy of Opioids in CNTP Patients

It is worthwhile to review the effectiveness of opioids in CNTP. Studies indicate that the benefits of opioids in CNTP are minimal at best [12-16]. A review of 16 studies indicated that the analgesic efficacy of opioids for CNTP was adequate, although the effect on improvement of functioning was not robust. Unfortunately, in 14 out of 16 studies reviewed, the duration of opioid therapy was less than 32 weeks, a far lower duration than most people placed on opiates in the setting of CNTP. Martell et al. [14] concluded that the effectiveness of opioids for periods lasting 16 weeks or longer was unclear. In a meta-analysis of 11 studies which examined the benefits of various opioids, they found weak evidence of efficacy in a very small subset of patients. An assessment by the American Society of Interventional Pain Physician (ASIPP) suggests the long-term effectiveness of opioids is limited due a lack of long-term (greater than 3 months high quality studies). Additionally, they observed that non-therapeutic use of opioids in this population is extensive [17]. The most charitable conclusion one may draw from these results is that the benefits of long-term opioid use in CNTP are very minimal at best. Additionally these benefits appear to be occurring in tightly controlled research settings which are nearly impossible to replicate in a busy day to day clinical practice.

Use of Opioids in TP Patients

An examination of the use of opioids in the treatment of TP requires a review of the ethical principle of double effect which at once both guides and hampers the use of opioids in this patient group. Double effect simply means an action with both good and a bad effect is ethically permissible if the following conditions are met: 1) the action itself must be morally good; 2) only the good effect is intended; 3) the good effect must not be achieved by the way of bad effect; 4) the good effect must outweigh the bad result. Unfortunately, the basic premise of this double effect principle may be unsupported by scientific evidence. When we utilize opioids in terminal pain patients our intention is to relieve

the pain, but we inherently also accept the unsupported assumption that opioids may hasten death through respiratory depression. To date there is no clear data which suggests that opioids when properly used hasten death by respiratory depression. This principle of double effect in palliative care medicine has been one of the biggest barriers to proper use of opioids in TP patients. Most physicians, not experienced in palliative care, undertreat TP patients because of the fear of causing the patient's death due to opioid treatment. Further treatment of this important matter may be found in the authoritative review by Susan Anderson Fohr [17] for the International Association for Hospice and Palliative Care [18].

Obviously an excessive dose of opioids can and will cause respiratory depression. The risk of respiratory depression is greatest when opioids are first begun, as tolerance to this respiratory side effect develops rapidly. Also, patients in pain respond differently to opioids than do persons who are without pain, and pain acts as an antagonist to the respiratory depressant effect of opioids. As the pain increases, the opioid dose necessarily increases as does the tolerance to the respiratory depressant effect. Although tolerance to the analgesic effect occurs, analgesia can still be obtained by the upward titration of the opioid dose because there are parallel curves for development of tolerance to analgesia and respiratory depression.

The belief that opioids induce respiratory depression comes from many sources. One body of literature includes the use of opioids in drug addicted individuals, patients with acute post-operative pain, and volunteers without pain who receive a single opioid dose. This literature clearly establishes that opioids can lead to respiratory depression. However, this data is not relevant to TP patients. Walsh et al. found that chronic ventilator failure appears to be neither common nor severe when oral morphine is used to treat pain in TP patients [19]. Grond et al. [19] treated 401 patients using World Health Organization's (WHO) cancer pain guidelines. They concluded that when opioids are used according to WHO guidelines they are efficacious, and safe for relief of cancer pain until death [20]. The threshold for respiratory depression is always above the sedative threshold which is above the analgesic threshold. Silverman and Croker [20] found that respiratory depression is not clinically significant when patients are treated with oral narcotics [21]. According to Bonica [21], with proper titration, clinically significant respiratory depression does not occur because pain is a powerful respiratory stimulant and counteracts narcotic induced depression [22]. Clemens et al. [22] found "no higher risk of respiratory depression and increase in T CPA CO₂ in opioid-naïve palliative care patients, compared to patients pretreated with strong opioids, during symptomatic therapy of dyspnea with strong opioids." There are many more studies like this that suggest that respiratory depression is rare in TP patients treated with opioids.

Conclusions

Although for the past 6,000 years human civilization has been utilizing opioids to relieve pain and suffering, its use has been mired in a cloud of assumption, superstition, and a lack of scientific rigor and understanding. When used properly, opioids have the capacity to relieve pain and suffering, but when used improperly, as seen recently in the United States, it leaves a wake of destruction built upon an epidemic of overdose, diversion, addiction, and death.

The use of opioids in acute pain has never been controversial. Opioids, for the treatment of acute pain from surgery and trauma are indispensable; however a recent marked increase of opioid use in CNTP in "developed countries" is not justified based on the available scientific evidence. On the other hand, the perpetuated myth of double effect that

has been touted as an ethical principle in palliative pain patients may not be applicable simply because there are no data that opioids hasten death by respiratory depression when properly used. This false belief has led to the culture of under-treatment of TP patients with opioids.

Acknowledgements

The authors would like to thank Barbara Tims of Texas Medical Association Library Services, Janine Marino of Phoenix Medical Associates, and Nicholas Mehendale, a student at University of Texas at Austin in preparation of this manuscript.

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