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The Doctor's Dilemma: Opiate Analgesics and Chronic Pain

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Opiates are utilized routinely and effectively as a short-term analgesic treatment for a variety of acute pain conditions such as occur following trauma, and for patients with painful terminal diseases such as cancer. Because opiate analgesics are highly addictive substances, their use in the treatment of chronic nonmalignant pain remains controversial.

Opiates have been used for centuries and remain to this day the most potent and reliable analgesic agents (Pasternak, 2011). They are used routinely and effectively for the treatment of acute severe pain following trauma, extensive burns, or surgery. They are also used for patients with painful terminal diseases such as cancer. In these time-limited situations, the efficacy of opiates is extensively documented and broadly accepted. In fact, their use has recently grown, in part because providing adequate pain relief is now considered an important standard of care and is required by law in some states. Beyond potent analgesia, opiates reduce anxiety and produce mild sedation and a palpable sense of well-being, often to the point of euphoria. These are an unmitigated benefit for patients who would otherwise have to endure the pain and suffering of acute or terminal medical conditions. While there is no debate over the short-term use of opiates, their use for chronic nonmalignant pain is controversial, and there is growing reluctance among some physicians to prescribe them. The problem is that the most powerful opiate analgesics are also the most liable to cause abuse and addiction.

Opioids are defined by their actions at one of the family of opioid G protein-coupled receptors (GPCRs). There are four known opioid receptors (mu [μ], delta [δ], kappa, and the nociceptin/orphanin peptide receptor); however, only agonists at μ consistently produce potent analgesia, and drugs activating μ (e.g., heroin, morphine, and oxycodone [OxyContin]) are also the most commonly abused (Koob and Le Moal, 2006; Pasternak, 2011). Despite decades of research, pharmaceutical companies have been unable to design opioid ligands that retain high analgesic potency but with reduced abuse potential. Furthermore, there are currently no nonopioid analgesics with either the broad range of analgesic efficacy or the potency of μ agonists. This lack of progress in new drug development is particularly daunting in view of the growth of our understanding of the mechanisms of pain and of opioid receptor function. The inability to uncouple powerful analgesia from addictive potential is a barrier to resolving the current dilemma about opiate use for chronic pain. In some ways, dissolving the bond between potent analgesia and addiction is the holy grail of pain research. One could argue that if a drug were found that was potent across a broad range of painful conditions, was not addicting, and to which patients did not develop tolerance, pain would cease to be a significant medical problem. Meanwhile, the debate continues over when and how to use opiate analgesics.

Those practitioners who favor broader acceptance of use for chronic nonmalignant pain (e.g., low back pain, neuropathic pain) argue that it is unconscionable to withhold adequate treatment from any patient complaining of severe pain, whatever the cause. Furthermore, they assert that addiction is rare when opioid analgesics are used appropriately (e.g., Edlund et al., 2007). Lined up against them are those who argue that addiction is a significant risk and is common among pain patients treated with opiates. For example, Ballantyne and LaForge (2007) suggest that long-term treatment of chronic pain patients with opiates has contributed to the recent increase in opiate abuse and addiction. Unfortunately, the heat of the argument is sustained by the lack of solid evidence on either side. Both sides claim the moral high ground, and an ongoing appeal to ethics instead of scientific evidence clouds the essential issues and prevents consensus on the appropriate use of opiates in chronic pain.

The decision about long-term opiate prescribing is further complicated by the substantial increase in people diverting and abusing prescription opiate analgesics. Figures from the Substance Abuse and Mental Health Services Administration (SAMHSA) raise significant red flags; for example, "In 2009, an estimated 3.1 million persons aged 12 or older used an illicit drug for the first time within the past 12 months." About 17% (~500,000 people) initiated illicit drug use with pain relievers (http://oas.samhsa.gov/NSDUH/2k9NSDUH/2k9Results.htm). In addition to their addictive potential, high doses of potent opiate analgesics cause profound respiratory depression, the leading cause of death from these drugs. Because of this, the problem of opiate diversion has been dramatically magnified by the parallel growth of emergency room visits and deaths due to prescription opiate overdose (http://oas.samhsa.gov/2k10/DAWN016/OpioidEdHTML.pdf). The increase in overdose deaths has led to media headlines and increased social

concern (http://www.nytimes.com/2011/01/06/health/06drugs.html). This in turn has provoked law enforcement efforts to disrupt and punish diversion. While the effectiveness of law enforcement approaches to this problem is debatable, these well-meaning efforts further complicate physician decisions. In addition to concerns about contributing to addiction, many fear investigation, censure, or even arrest for prescribing these drugs. Law enforcement efforts to stem illegal diversion of prescription medications have very likely shifted the balance in the medical community back toward underprescribing opiates. At this point, it is unclear whether the increased fear among physicians of creating an addict or being investigated by law enforcement has hurt more individuals, because their pain relief is inadequate, or has helped more, by reducing access to a potentially addictive substance.

How Likely Is Opioid Addiction in Chronic Pain Patients?

To what extent is physician prescription of pain killers to pain patients responsible for the epidemic of prescription pain-killer abuse? The answer is not straightforward. Prescription opiate abuse is not rare, but from the same SAMHSA report mentioned above, statistics suggest that of those abusing pain relievers, most (~70%) got them illicitly. Less than 20% got the drugs directly through a prescription from a doctor. This suggests that while diversion and illicit use are real, the great majority of individuals abusing opioids (usually young people) are getting "high" by taking grandma's OxyContin, stealing them, or buying them from their friends or relatives and do not get them by prescription from an MD.

Some illicit users overdose and show up in emergency rooms or wind up dead from respiratory depression. Clearly, the problem is serious from both a social and medical standpoint. On the other hand, most people who come to a physician with a pain complaint have a valid problem that deserves treatment. Furthermore, there is evidence to suggest that treating previously drug-naive chronic pain patients with opioids is associated with a very low risk of addiction. For example, Edlund et al. (2007) prospectively studied over 15,000 veterans who were not on opioids before the study period. The subjects were started on opiate analgesics for pain and maintained on the medications for at least three months. Only 2% developed opioid abuse. Although another study indicated an overall greater incidence of opioid abuse (~6%) in individuals treated for pain (Pletcher et al., 2006), most of the abusers had used illicit drugs (mainly amphetamine) prior to opioid treatment. Importantly, neither study reported any cases of opiate addiction, only abuse. This distinction is important because substance abuse is much more common than true addiction, and its definition is influenced by social, cultural, and legal factors that are independent of the medical (or, for that matter, scientifically addressable) issues. For example, any recurrent illicit use of a substance that affects job, school, or interpersonal function could be considered abuse (e.g., habitually taking a roommate's prescription opiate medication). Addiction/dependence is characterized by preoccupation with obtaining and taking the drug and a high frequency of use despite obvious social, medical, legal, and/or economic harm. The clinical studies referred to above indicate that opiate addicts and pain patients are largely separate populations and that opiate addiction due to appropriate medical management of pain is rare. However, the doctor's decision for any given patient is still influenced by the widespread diversion of prescription opiate pain killers, because in many cases it is difficult to know who is faking a pain complaint to get a prescription. That said, the person who is lying to get a drug is already a drug abuser, and so the prescribing physician is not creating a new addict or abuser.

The rarity of addiction when opiates are used to treat pain is counterintuitive, because the relief of pain itself produces reward independently by negative reinforcement (King et al., 2009). However, consistent with the clinical evidence, animal studies using the conditioned place preference paradigm have demonstrated that morphine is actually less rewarding in the presence of ongoing pain (e.g., see Betourne et al., 2008). Somehow, the presence of ongoing pain appears to lower rather than increase the risk of opiate addiction.

Are Chronic Pain Patients Harmed by Withholding Opiate Pain Killers?

Despite what appears to be a low risk of addiction in naive, chronic pain patients, it is reasonable to ask how much harm is actually done to patients with chronic pain by withholding opiate analgesics. Are these drugs effective in this situation, and if so, how long do they remain effective? In fact, opiates do produce effective analgesia when used acutely in patients with chronic pain (Kalso et al., 2004), and analgesic effectiveness can be sustained for up to eight weeks. However, there are no studies confirming their effectiveness beyond two months, and the mean pain reduction in the short term is also modest (Kalso et al., 2004). There are other reasons to be cautious when committing a patient to long-term opioid use. One is that animal studies suggest that dependence and worsening of pain are possible with prolonged use of μ agonists. A second potential issue is analgesic tolerance to opioids. Although this has not been demonstrated in the clinical situation, opioid dose escalation to maintain analgesia is not uncommon. Furthermore, analgesic tolerance has been consistently observed in animal studies (e.g., see Chang et al., 2007). In addition, at least mild physical dependence can be demonstrated in most individuals treated with μ agonists. Whether or not physical dependence is a clinically significant problem in patients with chronic pain is unknown. However, animal studies show that opioids can induce a state of hyperalgesia that could complicate pain management. Sometimes, hyperalgesia can develop even when opioid administration is continued (e.g., see Ossipov et al., 2005; Gardell et al., 2006), and there is suggestive evidence that this may occur in pain patients on daily opiate therapy (Cohen et al., 2008).

Despite the lack of convincing data for long-term efficacy and the growing problem of prescription abuse, many physicians prescribe opiate analgesics for patients with chronic nonmalignant pain. The reasons are complex, but in the end, alternative approaches to pain management often fail and, as mentioned above, opiate analgesics are usually effective at the onset of treatment. While short-term benefit is likely, more evidence

is needed to guide the decision about prescribing opiates in the long term for chronic pain patients. One useful response to this uncertainty is to have official or semiofficial guidelines for opiate use in chronic nonmalignant pain patients. In fact, the State of Washington has published a set of reasonable patient assessment and care guidelines for the use of opioids for chronic nonmalignant pain (http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf). These include limiting the dose and amount prescribed; using urine testing for illicit drug use and treatment compliance; and asking about alcohol, tobacco, and drug abuse history prior to initiating treatment.

If abuse does ensue, there are ways to minimize the associated harm. The most serious adverse consequences of opiate addiction are typically related to (1) the criminalization of possession and the cost of buying the drugs (which can lead to other illegal activity); (2) the uncertain purity, dose, and potency leading to overdose; and (3) infections transmitted by shared needles. The problems of infection, purity, and uncertain dose are mitigated if the drugs are obtained by prescription, taken orally, and used only by the person who obtains the drug. While there is always risk of diversion and overdose, opioid addicts on supervised opioid maintenance therapy can be freed of the need to pay for their habit and can sometimes return to a relatively normal life. Thus, like chronic pain, opioid addiction, if not currently curable, can be managed to minimize harm to the addict and to society. Interestingly, the two most widely accepted "medications" for opiate maintenance therapy are methadone (a potent μ agonist with very slow pharmacokinetics) and buprenorphine (a partial agonist at μ), both of which have been used effectively to treat pain. If the treatments for pain and addiction are the same, there is no reason for the patient to lie about why he or she wants the opiate prescription. This openness could lead to an overall improvement in therapeutic outcomes. Interestingly, a small but growing number of physicians are trained in both pain management and addiction medicine. This combination of skills may be optimal for long-term management of pain with opiate medications.

On the Horizon: Exploiting the Cell Biology of Opioid Receptors to Enhance Analgesia

Although chronic pain does respond at least temporarily to opiate drugs, as mentioned above, there is both animal and human evidence that tolerance and dependence limit their effectiveness. Consequently, for many chronic pain patients, the treatment options are limited. The public is entitled to ask, what have we gotten in return for the millions we have spent on pain research? Can we dissolve the bond between potent pain relief and drug dependence/abuse?

There are some glimmers of hope. The binding of different ligands for the same receptor may activate distinct downstream signaling pathways in different cells, and some of these signaling pathways activate compensatory mechanisms that oppose the initial agonist effect (Pasternak, 2011). For example, following ligand binding, signaling is reduced in many GPCRs, including the μ receptor, by removal of the receptor from the plasma membrane through internalization. This requires phosphorylation of the receptor by GPCR kinases and interaction with β-arrestin (von Zastrow, 2010). Some μ ligands, e.g. morphine, activate G protein signaling but are typically much less effective in inducing β-arrestin signaling and receptor internalization. In this situation in some cells, morphine continues to signal, triggering compensatory cellular mechanisms that oppose key cellular actions of the μ agonist that regulate membrane excitability. Furthermore, when morphine is subsequently removed by washout or through administration of an antagonist, the compensatory processes dominate, producing actions opposite to those originally triggered by morphine and manifesting as increased responsiveness to noxious stimuli. Consistent with this idea, mice with a genetically modified μ that can be efficiently internalized by morphine binding show dramatically reduced tolerance and dependence (Kim et al., 2008). This raises the possibility that drugs targeted to specific signaling pathways might alleviate pain symptoms yet lack the addictive properties of the current opioid analgesics.

Another promising line of research is the study of μ/δ interactions. Although opiate analgesics initially act primarily at μ, repeated administration of a μ agonist can activate a δ-mediated opposing process. δ knockout mice do not develop morphine tolerance, and δ antagonists can prevent morphine tolerance. Synthetic bivalent molecules with a μ agonist at one end and a δ antagonist at the other show enhanced analgesia and reduced tolerance (Daniels et al., 2005). Importantly, examination of a series of such bivalent compounds with increasing separation of the μ agonist and δ antagonist moieties demonstrated that they must be separated by a critical distance for optimal efficacy. This suggests that the bivalent compounds work best when the two receptors are in spatial proximity. Perhaps most exciting, the study authors report that the bivalent compounds retain analgesic potency but are significantly less rewarding (Lenard et al., 2007).

In summary, although opiate analgesics are potent for a variety of time-limited painful conditions, the duration of their efficacy has only been established for up to two months. Animal studies indicate that tolerance and dependence are common with repeated opioid use, and both animal and human studies indicate that long-term administration of opiate analgesics can actually worsen pain. Because of this, significant caution should be exercised in initiating therapy for patients with chronic nonmalignant pain. On the other hand, although the potential is there, addiction is actually quite rare in patients treated appropriately for pain. In fact, the presence of pain appears to provide a protective action against the rewarding effects of opiates. The real problem for the treating physician is that diversion of prescription pain killers for recreational use is growing, yet for many patients with chronic nonmalignant pain, there is currently no better treatment alternative than opiate analgesics. The scientific challenge is to design a drug that retains high analgesic potency with reduced potential for tolerance, dependence, and addiction. The good news is that studies of membrane receptor trafficking, signaling, and interaction and in the chemistry of bifunctional molecules suggest that this long-standing goal may yet be achieved.

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