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STATE OF THE ART AND SCIENCE
Long-Term Opioid Treatment
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For many physicians the prospect of opioid prescription evokes a visceral reaction that is perhaps unique among medications. While other commonly prescribed medications that do not induce such feelings may be arguably more toxic or have narrower therapeutic indices (e.g. insulin or digoxin), the risks associated with long-term opioid use for pain from conditions other than cancer should not be underestimated. The development of tolerance, the potential for abuse and misuse, and a lack of understanding as to the indications for use all contribute to physician angst. Over the last 2 decades, changing perspectives in the U.S. regarding opioid prescription have followed advances in basic science, as well as hard-learned clinical experience.

Tolerance
The development of physiologic tolerance can be expected following repeated exposure to exogenous agents that occupy receptor sites normally responsive to endogenous substances. The body attempts to maintain homeostasis by reducing the number and sensitivity of receptors. In the case of opioids given for analgesia, mu-opioid receptors (so named for their prototypical agonist, morphine: mu) that normally respond to endogenous endorphins become phosphorylated, making them less responsive. Ultimately they are internalized by endocytosis, decreasing their number and the physiologic response to the exogenous opioid. The natural tendency of clinicians, then, is to increase the dose, hoping to achieve the response that was previously experienced. Unfortunately, the success of such a dose escalation strategy may be hindered by the repetition of the physiological reaction. This response is unpredictable and varies considerably by person [1].

Tolerance can develop surprisingly rapidly, even in cases of acute pain; clinical evidence of tolerance can be seen within just a few weeks. Moreover, the apparent need to maintain long-term opioid therapy following an acute injury is not a rare phenomenon. While the severity of injury and anticipated duration of rehabilitation are important factors in the transition to chronic pain, they may account for only half the expected variability in the need for long-term opioid therapy [2]. Affective pain components, self-perceived risk of addiction, prior opioid exposure, and genetic and other influences may all play prominent roles. Most importantly, the development of tolerance is by no means equivalent to addiction. Dose escalation due to tolerance is common and not necessarily directly related to the development of an obsession for the procurement and compulsive use of the drug, hallmarks of addiction.

Addiction, Abuse, and Misuse

The distinction between tolerance and addiction should be emphasized; most opioid-tolerant patients do not exhibit signs of addiction. Once again, individual variability characterizes the development of addiction, making outcome prediction difficult [3], but some features are associated with increased risk for addiction: increasing dose requirement, younger age, preexisting mental health disorders, and prior substance abuse [4]. Significantly, aberrant behaviors have been observed in nearly a quarter of patients taking opioids for noncancer low back pain in the U.S. [5]. The current widespread use of opioids for chronic noncancer pain created a need for vigilance in identifying patients who are abusing (unlawful use or use despite harm to the user) or misusing (use other than as prescribed) opioid medication.

Fear of Tolerance and Addiction

The unpredictability of patients' responses to opioid treatment fuels the fear of iatrogenically induced addiction, which historically has caused doctors to limit open-ended opioid prescriptions for patients with noncancer pain. Yet the undertreatment of pain is itself detrimental and in fact can lead to pseudoaddiction. Patients subjected to perpetual undermedication continually request dose escalation due to poor analgesic effect. Or, fearing addiction, they avoid taking the prescribed medication on a time-contingent basis [6], instead holding off until the pain is intolerable, then having difficulty "catching up" to the pain. Thus both physicians and patients contribute to this pseudoaddiction effect.

In response to the undertreatment of pain, the American Pain Society (APS) issued a 1997 statement encouraging judicious use of opioids and even suggesting that tolerance was rare [7]. Over the next decade it became apparent that the pendulum, particularly in the U.S., had swung too far and that tolerance is natural, common, and necessary to consider. The recommendations from the APS have subsequently been revised to reflect the clinical importance and frequency of tolerance development to opioid therapy [8].

Indications

Identifying patients who may be appropriate candidates for long-term opioid treatment goes beyond screening for addiction and abuse potential. Some pain states are relatively less responsive to opioids. This lack of efficacy results in relative undertreatment, which can lead to dose escalation. Phenotypic switching from opioid-predominant mechanisms to noradrenergic predominance has been observed preclinically following nerve injury [9]. This may contribute to the long-held impression that neuropathic pain responds poorly to monotherapy with mu-agonist opioids. On the other hand, combination therapy, in which opioids are combined with agents that have complementary, nonopioid-mediated mechanisms of action, especially anticonvulsants or antidepressants, has been useful in some neuropathic pain states [10].

Recent Developments

Targeting multiple receptors. Some opioids have additive or even synergistic effects because they combine nonopioid-mediated pain pathway activity with mu-opioid agonism: a dual mode of action in a single drug. One advantage of such drugs is the avoidance of drug-drug interactions (DDI). Methadone, in addition to having mu-opioid agonist effects, interacts with other receptors as well, including the N-methyl-D-aspartate (NMDA) receptors on ionotropic calcium channels. While this effect may make it a relatively better opioid choice for neuropathic pain than pure mu-opioid agonists, its long and variable elimination half-life, especially in the elderly—as well as other challenges, such as QTc prolongation and CYP3A4 metabolism—make it difficult to titrate safely. A somewhat newer agent, tapentadol, exhibits both mu-opioid agonism and synergistic norepinephrine reuptake inhibition in a single molecule with a low potential for DDI [11]. An extended-release preparation is available and approved for chronic use.

Newer formulations. The recommendations for using long-acting opioid formulations in chronic noncancer pain are controversial. While having to take medication only once or twice daily would be expected to improve compliance, the overall results on outcomes when compared to less expensive short-acting immediate release preparations remain a subject of debate. The major advantage of the long-acting formulations may lie in improvement in quality-of-life measures [12]. Transdermal delivery systems can provide less dramatic swings in blood levels, reducing euphoric effects and providing sustained analgesic levels of opioid [13].

Opioid formulations that include opioid antagonists induce withdrawal when oral tablets are misused by being taken intravenously. These formulations have been only partially successful in reducing abuse liability. The combination of buprenorphine with naloxone is a notable exception and is used to treat opioid addiction. The partial agonist, buprenorphine, which is less efficacious at the mu-opioid receptor than pure agonists such as morphine, reduces cravings without inducing withdrawal or appreciable euphoria.

Rotation and combination. Patients taking opioids even for a few weeks can not only become tolerant but can suffer withdrawal as well, though they are clearly not addicted. In an effort to deal with increasing tolerance with long-term opioid use, opioid rotation has been widely recommended and practiced clinically. While there is little evidence to support this practice [14], one can hypothesize that switching from one opioid to another might exploit subtle differences in opioid receptor subtype activation patterns [15]. Even though the mu-opioid receptor is encoded by a single gene, alternative splicing results in multiple variations in the intracellular portion of the receptor. This results in considerable variety in activation patterns and may provide a scientific rationale for both opioid rotation and the synergistic combination of two opioids given concurrently.

Conclusion

Future developments in opioid management can be expected as we learn more about the basic science of opioid analgesia generally and effective methods of glial cell modulation specifically. The development of tolerance, opioid-induced hyperalgesia, and perhaps even addiction share a common factor: altered central immune signaling [1]. By increasing knowledge about analgesia and glial cell modulation we may be able to demystify opioid management of chronic noncancer pain, lessen the stigma associated with opioid medication use, improve patient selection, and, ultimately, improve patient outcomes.

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