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Long-Acting Opioids: A Second Glance

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OxyContin®, mistakenly considered a panacea for chronic pain patients, is being repositioned on drug formularies across the nation, most commonly with the implementation of prior authorization requirements. This drive is multi-factorial. First, OxyContin®'s potential for abuse and diversion and reports of fatal overdoses have caught the attention of the public media, healthcare policy makers, and state and federal agencies (1). Second, no evidence exists to support claims that OxyContin® provides superior analgesia or is better tolerated than other opioids (2). Finally, when comparing equianalgesic doses, OxyContin® is the most costly (Table 1).

Table 1: Cost Comparison of Long-Acting Opioids

Generic	Brand	Dose	Cost* / yr ($)
Methadone	generic	10 mg q8h	237
Morphine, ext. release	generic	60 mg q12h	2,381
Morphine, ext. release	Oramorph SR®	60 mg q12h	2,645
Morphine, ext. release	MS Contin®	60 mg q12h	2,779
Morphine, ext. release	Kadian®	60 mg q12h	2,849
Fentanyl, transdermal	Duragesic®	1 50mcg patch q72d	2,920
Oxycodone,ext. release	OxyContin®	40 mg q12h	3,287

*AWP-13% or MAC

Therefore, OxyContin® is now being reserved for patients who have a documented history of intolerance or failure with other long-acting opioids. Meanwhile, providers continue to be confronted with the considerable challenge of treating patients with chronic, intractable pain (moderate to severe pain requiring continuous analgesia for an extended period of time). Providers who had become familiar and comfortable with prescribing OxyContin® are being asked to prescribe alternatives. The following is intended to provide practical considerations in the use of alternative long-acting opioids (extended-release morphine, transdermal fentanyl, and methadone) in the setting of chronic, intractable pain.

Extended-Release Morphine

Morphine is the gold standard for treating pain and often considered first-line. Advantages include its long history of use and commercial availability in a variety of dosing forms. It can be easily titrated from a short-acting to a long-acting preparation. This practice allows patients and providers to determine daily dose-requirements and adjust doses according to pain relief goals prior to initiating long-term therapy.

In the setting of severe renal dysfunction, morphine metabolites can accumulate and increase the risk of adverse effects, particularly in the elderly. Drug doses should be decreased and/or dosing intervals increased if creatinine clearance < 30 mL/min. In patients with renal failure, alternative opioids may be more appropriate. When switching from one branded product to another, different doses may be required to produce an equivalent level of pain control. Generic extended-release morphine, MS Contin®, and Oramorph SR® are preferred agents. Kadian® is more expensive and offers little advantage over the others.

Methadone

Methadone is a good agent for chronic pain, but is challenging to use because of variability in potency and delayed accumulation. Yet the phenomenon of delayed drug accumulation and time to reach steady state is ideal in chronic pain, in which the goal is not rapid analgesia, but rather gradual improvement in pain and functioning. Of the long-acting opioids, methadone is the most cost-effective and offers several additional advantages: 1) gradual onset and delayed withdrawal symptoms if discontinued abruptly, 2) the ability to be delivered down an NG tube, 3) because methadone is in a distinct class of opioids, it may be used in patients with hypersensitivity to morphine and its derivatives, and 4) a low rate of drug escalation and drug seeking.

With careful and conservative dosage titration and patient monitoring, methadone can be used safely and effectively (5). Cross-tolerance to morphine is incomplete and patients may ultimately require 1/10th to 1/20th of the previous morphine dose (3). Because the best dosing strategy has not been established, treatment must be individualized and a conservative approach is recommended. In opioid-naïve patients, doses of 2.5 to 5 mg every 8 hours are recommended. In rare circumstances, particularly in patients on high dose morphine equivalents > 300 mg per day, 10 mg q 8 hours may be necessary. Steady state serum levels typically are not achieved for 5 to 7 days after initiation or a dose change. Therefore, delayed analgesia and sedation may occur and dose increments should occur no more frequently than every 5 to 7 days. Once a stable dose has been established, the frequency of follow-up can often be reduced (4). The VA has developed dosing strategies based on the desired rapidity of conversion and prior exposure to opioids and can be accessed at http://www.vapbm.org.

Over three decades of research has established the safety of methadone. In some patients, methadone may cause less constipation than morphine. Methadone is susceptible to several significant drug interactions: phenytoin, carbamazepine, rifampin, barbiturates, and a few antiretrovirals induce methadone metabolism necessitating methadone dose increases or doses larger than anticipated. The "azole" antifungals, e.g. fluconazole, and the SSRI and tricyclic antidepressants may increase methadone levels and a dose reduction may be necessary.

Transdermal Fentanyl

Transdermal fentanyl is not recommended as first-line opioid therapy due to difficulties with dose titration and cost. It is best reserved for patients who have experienced intolerance to morphine or methadone, such as severe nausea and vomiting or hallucination and confusion in the elderly. Advantages are ease of compliance and infrequent dosing. It is particularly useful in patients who are unreliable or who cannot take oral medications, and like methadone, in patients with hypersensitivity to morphine.

The following points should be considered when prescribing transdermal fentanyl. Its relative potency to other opioids has not been definitively established. The conversion recommendations in the product labeling may

result in under-dosing. There is a lag time between skin absorption and steady-state drug levels. The onset of action is typically 6-12 hours and dosage titration should occur no more frequently than every 48 to 72 hours. The manufacturer does not recommend cutting patches in half because controlled drug delivery cannot be ensured. In addition, direct heat near the area of application and fever can increase drug release and cutaneous absorption. Finally, reports of fentanyl abuse are emerging. Fentanyl is available in sufficient amounts for abuse from the patch after 3 days of therapeutic use. Abuse and subsequent adverse events due to ingestion of contents, application of multiple patches cutaneously, attempts to inject the solution, and volatilization and inhalation have been reported (6). All patches should be folded with adhesive sides together and carefully disposed of immediately after removal and discontinuation of use (7).

Opioid Conversion

Many dose conversion tables are available, yet it is not known which, if any, is better and more consistent than another. When using equianalgesic dose tables, the following should be taken into consideration: 1) Most conversion ratios are based on small, single-dose studies not designed to assess equianalgesic doses and may not apply to patients receiving repeated doses of opioids; 2) Confidence intervals for ratios are wide suggesting a large inter-patient and intra-patient variability; and 3) Several studies suggest there is a lack of a bi-directional relationship among ratios (8). For example, the ratio suggested for conversion of morphine to methadone may not universally apply when switching from methadone to morphine. These factors and others highlight the need for close, individual monitoring of patients when converting among opioids. Providers should use a conversion table they are most comfortable with, along with an overall conservative approach (9). Table 2 has been adapted from the American Pain Society (9).

Table 2: Equianalgesic Doses and Starting Doses (9)

Drug	Equianalgesic Dose	Starting Dose for Opioid-Naïve Adult
Extended Release Morphine	30	15 mg q12h
OxyContin	20	10 mg q12h
Methadone	20 (acute) 2 - 4 (chronic)	2.5-5 mg q8h
Fentanyl	25 mcg/h ≈ 45 mg/d[7]	25 mcg/h q72h

General Considerations

Concerns regarding under-treatment of chronic pain have captured the attention of patient advocacy groups, policy makers, and JCAHO. Misconceptions of opioid laws, negative social stigma, lack of payment for specialized pain management services, and a paucity of formal provider education confound the issue. In Oregon, the Intractable Pain Act (ORS 677.470-485) assures that patients with chronic, intractable pain receive proper assessment, documentation and management of pain; receive assessment and recommendations by a physician specializing in the body area in which the pain is located (e.g. gastroenterologist for abdominal pain); and sign a material risk notice regarding controlled substances (10). Although, not required, signed pain contracts, that outline patient and physician expectations, are also recommended.

In carefully selected patients and when prescribed thoughtfully, opioids can provide significant benefit in chronic, intractable pain states. Yet, opioids are not recommended first-line, nor are they universally effective. There is no type of pain or patient group that is inherently or universally responsive to opioids. The initiation of opioid therapy should, therefore, be undertaken in the context of a therapeutic trial. Although they often do not provide complete pain relief, opioids should produce graded analgesia with increasing doses. Failure to achieve this by 4 weeks should prompt evaluation of compliance or drug diversion. In the absence of such, it is probable that the pain is not responsive to opioids, and discontinuation should be considered. In opioid-responsive patients, opioids are not recommended as primary or sole therapy. Non-opioid analgesics such as acetaminophen, salicylates, and NSAIDs as well as adjuvant analgesics like tricyclic antidepressants and anticonvulsants can provide added analgesia and a dose-sparing effect when used in concert with opioids. In chronic pain, it is important to add analgesics sequentially, not concomitantly, with sufficient time to evaluate the benefit of one drug, prior to adding another.

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DEPAKOTE ER® for DEPAKOTE® Errors Noted

The Oregon RetroDUR Council has noted several cases where it appears patients have inadvertently had Depakote® products switched. According to the Institute For Safe Medication Practices (ISMP), at http://www.ismp.org , this medication error has been reported nation wide. ISMP gives the following recommendations:

Problem: Depakote ER® (divalproex sodium extended release) is a new tablet formulation of extended release divalproex sodium for migraines. Maximum frequency of administration is once daily. Depakote® (divalproex sodium delayed release), an enteric coated product, can be taken more than once daily. The two formulations are not substitutable. Dosing errors have been reported when the two drugs have been mixed up.

Recommendation: Educate staff about the different dosing schedules and indications for both formulations. Initiate a computerized alert to remind about potential mix-ups. Design computer mnemonics to prevent the drugs from appearing on computer screen simultaneously (or place appropriate alerts on the screen). Be wary of verbal orders since "ER" could sound like "DR," which has been used unofficially for the delayed release product.

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