Overview of Oral Modified-Release Opioid Products for the Management of Chronic Pain

Celene M Amabile and Bill J Bowman

OBJECTIVE: To evaluate pharmaceutical and pharmacotherapeutic differences in oral opioid modified-release products used in the management of chronic pain.

DATA SOURCES: Searches of MEDLINE (1966–May 2006) and an extensive review of peer reviewed journals were conducted using the key search terms opioid, morphine, hydromorphone, and oxycodone. Supplemental information was gathered through the American Pain Society, and limited but relevant information was obtained from manufacturers’ labeling.

STUDY SELECTION AND DATA EXTRACTION: All articles identified from the data sources were evaluated. Information deemed relevant was included for this review if it introduced new or well supported concepts or clarified clinical practice issues.

DATA SYNTHESIS: The recognition and treatment of pain has become a major focus of healthcare professionals. The Joint Commission on Accreditation of Healthcare Organizations mandates compliance with recommended standards, outcome measures, and other initiatives. A general review of pain management and pharmacokinetic parameters are included.

CONCLUSIONS: Oral modified-release products have enabled patients to better maintain pain control due to convenient dosing intervals and sustained blood concentrations. The differences between available oral modified-release products are half-life, cost, and formulation (excipients and drug-release properties).

KEY WORDS: hydromorphone, morphine, opioid, oxycodone.


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The recognition and treatment of pain have become a major focus of healthcare professionals. Opioids have become the drugs of choice for the treatment of moderate-to-severe chronic pain. The American Pain Society noted that, in most cases, the preferred route of delivery for opioids is oral administration because of its flexibility, convenience, and ability to maintain relatively steady blood concentrations. For chronic pain, around-the-clock therapy provides the most effective analgesia and results in the fewest adverse drug effects (ADEs). However, this dosing regimen often requires frequent administration, especially for agents with a short elimination half-life. The inconvenience associated with frequent dosing may be overcome by using modified-release drug products. These formulations may also ensure uninterrupted sleep and allow patients to focus on their daily activities rather than on their pain, which facilitates adherence and optimizes therapy. Therefore, oral modified-release opioid products have become the standard of care for the management of moderate-to-severe chronic pain.
This review focuses on the oral modified-release opioid products currently used to treat moderate-to-severe chronic pain: morphine (Avinza, Kadian, Oramorph, MS Contin) and oxycodone (OxyContin). These products vary in regard to their active ingredient, dosage form, mechanism of drug release, dosing frequency, pharmacokinetic profile, and cost. To effectively manage chronic pain, healthcare providers must have a complete understanding of this class of drug products. Modified-release opioid formulations have also been designed for other forms of administration (eg, transdermal fentanyl), and some oral modified-release opioid products are delivered via alternate routes (eg, rectal administration of MS Contin tablets); however, this review focuses on orally administered products. Palladone (hydromorphone), which was recently withdrawn from the market due to safety concerns, and miscellaneous products in development are included in the discussion.

The delivery systems discussed here have been designated as extended-release, controlled-release, or sustained-release. However, these terms do not have specific definitions and have been used inconsistently within other published reports. One needs to examine each product to determine its exact mechanism of drug release. The formulations in this review are generally referred to as modified-release products.

General Review of Opioid Analgesics

MEDICINAL CHEMISTRY AND PHARMACOLOGY

The opium poppy, Papaver somniferum (Papaveraceae), is one of the oldest and most prevalent sources of opioid analgesics, which have been used medicinally since the beginning of recorded history. The most important therapeutically active compounds found in the opium poppy are the alkaloids codeine and morphine (Figure 1A). Oxycodone, hydrocodone, and hydromorphone are semisynthetic derivatives of these compounds, resulting from minor chemical modifications with the characteristic phenanthrene nucleus of the natural opioids remaining intact (Figure 1B and 1C). Other opioids, such as meperidine, fentanyl, methadone, and propoxyphene, are classified as synthetic opiate agonists and lack the characteristic morphinan nucleus (Figure 1D). All of these opioid analgesics modify sensory and affective aspects of pain by binding to and activating µ-opioid receptors in the central nervous system (CNS). The pharmacologic effect of these agents is similar to that of the endogenous endorphin peptides.

PHARMACOKINETICS AND PHARMACODYNAMICS

Opioids are primarily metabolized by the liver through dealkylation, conjugation, hydrolysis, and oxidation, and their resulting metabolites undergo renal excretion. Opioids such as codeine, meperidine, and propoxyphene have pharmacologically active metabolites. Therefore, both hepatic and renal impairment may significantly influence the clinical effects of many opioids. Drug interactions also occur with some opioids. For example, codeine, oxycodone, and hydrocodone are major substrates of CYP2D6; therefore, the blood concentrations of these opioids may be affected by agents that inhibit or induce this enzyme.

All of the µ-opioid agonists have different pharmacokinetic properties, but all are pharmacodynamically similar. Blood concentrations of opioid agonists do not directly predict analgesic response. However, an increase in

Figure 1. Chemical structures for (A) morphine, (B) oxycodone, (C) hydromorphone, and (D) fentanyl. The structures of morphine, oxycodone, and hydromorphone contain the characteristic phenanthrene ring system of the natural and semisynthetic opioids.
dose typically results in greater analgesia with no limit to the effect.\textsuperscript{14} Therefore, these agents do not have a defined maximum dose, and the “ceiling” to analgesic effectiveness is imposed only by ADEs, which also increase with dose.\textsuperscript{14} Effective opioid blood concentrations are dependent on several factors including a patient’s age, medical condition, and previous opioid use.\textsuperscript{12,13} The minimum effective concentration varies greatly, and dosing should be based on clinical evaluation of the patient to achieve an optimal balance between therapeutic pain control and ADEs.\textsuperscript{12-14}

**Equianalgesic Dosing**

There is considerable individual variability in the analgesic response to opioids and the development of ADEs.\textsuperscript{15} Patients who experience insufficient analgesia or excessive ADEs with one opioid are often switched to another in an effort to improve clinical response. Clinicians refer to equianalgesic dosing charts to compare opioid regimens between oral and parenteral routes and/or between different opioids (Table 1). Several considerations should be incorporated into the clinical utilization of opioid conversion tables. First, these tables are often estimates based on single-dose parenteral studies. Second, there is considerable interpatient variability in the efficacy and safety response to opioids due to tolerance and cross-tolerance, pharmacokinetic and pharmacodynamic variability, use of coanalgesics and other CNS-active medications, and psychological variables. Third, clinicians should always use the same equianalgesic table to standardize their dose calculations between different opioids, which can minimize the risk of dose conversion errors. It is also important to remember that, if the equianalgesic table (Table 1) is used as a reference for switching patients from one opioid to another, there is not complete cross-tolerance. In other words, switching a patient from intravenous hydromorphone to intravenous morphine at equianalgesic doses may be an overestimate. The tolerance that developed while the patient was receiving hydromorphone is not the same level of tolerance that would be demonstrated when the patient is switched to morphine.

The manufacturer’s package inserts for the modified-release preparation of oxycodone (OxyContin) also contains a conversion table based on multiplication factors (Table 2).\textsuperscript{12} This table has not been verified in well controlled, multiple-dose trials and underestimates the conversion of opioid dosages compared with the chart shown in Table 1. It is also important to note that the dosing factors shown in Table 2 can be used only when converting from an opioid to OxyContin (i.e., not between the other opioids within the table). For example, a daily oral morphine dose can be converted to an equipotent OxyContin dose using the figures in Table 2, but morphine cannot be converted to meperidine using this table.

**CROSS-ALLERGINICITY**

The classification of opioid analgesics may be based on 3 different schemes: (1) analog class (phenanthrene, phenylpiperidine, diphenylheptane), (2) chemical source (natural, semisynthetic, synthetic), and (3) the presence or absence of a morphine-related chemical structure with a 6-hydroxyl group. The phenanthrene analog class consists of morphine, codeine, hydromorphone, oxycodone, and hydrocodone. Meperidine and fentanyl are in the phenylpiperidine class; methadone and propoxyphene are in the diphenylheptane class. Morphine and codeine are the 2 naturally occurring opioids, while hydromorphone, oxycodone, and hydrocodone are semisynthetic. Meperidine, fentanyl, methadone, and propoxyphene are synthetic opioids. Codeine is the only opioid that has a morphine-related chemical structure that includes a 6-hydroxyl group.

True allergic and anaphylactic reactions to opioid analgesics are rare, and the risk of cross-sensitivity is low even between the natural and semisynthetic compounds. Available reports suggest that reactions to opioids are most often related to nonimmunologic effects (histamine release, improper dosing, or concomitant medications), and none of these cases describes cross-sensitivity.\textsuperscript{16} Histamine release has been linked to urticaria, pruritus, and sneezing in pa-

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**Table 1. Equianalgesic Dosing Chart\textsuperscript{16}**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Equianalgesic Dose (mg)</th>
<th>Oral</th>
<th>Parenteral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>20 (acute)</td>
<td>10 (acute)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2–4 (chronic)</td>
<td>2–4 (chronic)</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>300 (not recommended)</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>200</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>130–200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2. Multiplication Factors for Conversion to Oral OxyContin\textsuperscript{12a}**

<table>
<thead>
<tr>
<th>Prior Opioid</th>
<th>OxyContin Conversion Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.5</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>4</td>
</tr>
<tr>
<td>Methadone</td>
<td>1.5</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.1</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
</tbody>
</table>

\( \text{Conversion Factor} = \text{mg/day of prior opioid} \times (\text{conversion factor}) \) = \text{mg/day of OxyContin}. 

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patients receiving opioids. There are no clear guidelines for patients with a reported opioid allergy. It is best to evaluate each case individually and is most often safe and necessary to administer an opioid from a nonrelated source (semisynthetic vs naturally occurring). Most of the histamine release causes pruritus, which can be treated with around-the-clock antihistamine administration prior to administering opioid doses. Since most patients develop tolerance to the pruritus, the antihistamines can be discontinued when that occurs. In some cases, changing to a different opioid may be necessary due to pruritus refractory to antihistamines.

**ADVERSE DRUG EFFECTS**

The ADEs of opioids result from the binding and activation of μ-opioid receptors throughout the body (eg, CNS, gastrointestinal [GI] system). Opioids have a low incidence of organ toxicity, and the most common opioid-induced ADEs include sedation, confusion, pruritus, nausea and vomiting, respiratory depression, and constipation. After repeated dosing, patients usually develop tolerance to opioid ADEs such as sedation, pruritus, and nausea and vomiting.15 Tolerance to respiratory depression is variable because this ADE is also dose related. For example, opioid-naïve patients are at a higher risk of experiencing respiratory depression; however, a patient receiving chronic opioid therapy may also experience this ADE if a significantly higher dose is administered. In general, patients do not develop tolerance to opioid-induced constipation. The general approaches to managing opioid-induced ADEs include trying a different drug, changing the dose or route of administration, adding a drug that counteracts the effect, and considering nonpharmacologic actions.

**Oral Modified-Release Opioid Products**

Since all of the μ-opioid receptor agonists of choice for the treatment of moderate-to-severe chronic pain (morphine, hydromorphone, fentanyl, methadone, oxycodone) have the same mechanism of action, their physiochemical and pharmacokinetic characteristics are more critical in determining the appropriate route of administration and product formulation to be used.1,2,7 For example, the short elimination half-life of opioids such as morphine, hydromorphone, and oxycodone require that these agents be administered frequently to achieve around-the-clock analgesia, which makes them excellent candidates for modified-release formulations. Conversely, methadone is a long-acting opioid (elimination half-life ~30 h) and does not require frequent dosing. Fentanyl undergoes significant first-pass metabolism and lacks sufficient bioavailability after oral administration.

Pharmacokinetic processes such as distribution, metabolism, and excretion are difficult to manipulate consistently and predictably so as to prolong the in vivo duration of action of a therapeutic agent.2 Therefore, the only effective way of controlling blood concentration profiles is to design product formulations that modify the absorption of active ingredients into the body. Table 3 lists the brand name modified-release opioid products available for the oral treatment of pain.1,2,13,17-19 Generic, AB-rated products are also available for MS Contin controlled-release tablets (15, 30, 60, 100, 200 mg) and OxyContin controlled-release tablets (10, 20, 40, 80 mg). All of these brand name and generic products are categorized as Schedule II controlled substances.

All of the products listed in Table 3 may be taken without regard to meals. However, they are sensitive to alterations that destroy their modified-release mechanisms. Therefore, these products should be swallowed whole (ie, not broken, chewed, crushed, or dissolved) due to the risk of rapid opioid release and absorption of potentially fatal doses. For patients experiencing difficulty swallowing, capsule products such as Avinza and Kadian may be opened and their entire bead contents sprinkled onto applesauce immediately prior to administration.13,17 The applesauce should be room temperature or cooler, and the entire amount should be consumed without chewing, followed by rinsing and swallowing with water to ensure that all beads are ingested. The prescribing information for Kadian also indi-

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**Table 3. Available Oral Modified-Release Opioid Products**1,2,13,17-19

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage Form</th>
<th>Strength</th>
<th>Dosing Frequency</th>
<th>F (%)</th>
<th>Time to Steady-State (days)</th>
<th>Wholesale Acquisition Cost* ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate</td>
<td>extended-release capsules</td>
<td>30, 60, 90, 120 mg</td>
<td>24 h</td>
<td>&lt;40</td>
<td>2–3</td>
<td>5.12</td>
</tr>
<tr>
<td>Avinza</td>
<td>sustained-release capsules</td>
<td>20, 30, 50, 60, 100 mg</td>
<td>12–24 h</td>
<td>20–40</td>
<td>2</td>
<td>8.88</td>
</tr>
<tr>
<td>Kadian</td>
<td>sustained-release capsules</td>
<td>15, 30, 60, 100 mg</td>
<td>8–12 h</td>
<td>40</td>
<td>1–2</td>
<td>1.92</td>
</tr>
<tr>
<td>Oramorph</td>
<td>controlled-release tablets</td>
<td>15, 30, 60, 100, 200 mg</td>
<td>8–12 h</td>
<td>40</td>
<td>1</td>
<td>6.20</td>
</tr>
<tr>
<td>MS Contin</td>
<td>controlled-release tablets</td>
<td>10, 20, 40, 80, 160 mg</td>
<td>12 h</td>
<td>60–87</td>
<td>1–1.5</td>
<td>5.53</td>
</tr>
</tbody>
</table>

F = bioavailability.

*Prices based on morphine 120 mg daily and rounding to the nearest tablet or capsule size according to equivalent dosing.
icates that the entire capsule contents may be administered through a 16 French gastrostomy tube. The prescribing information for Avinza makes no such mention. However, instructions for G-tube administration can be obtained from the manufacturer (telephone 888/828-4692).

In overdose situations, modified-release delivery systems may continue to release their active ingredients; therefore, the management of an overdose should be monitored accordingly. Evacuation of the gastric contents may be required to eliminate unabsorbed drug. In addition, some of the excipients used to prepare oral modified-release opioid products, particularly talc, may lead to serious complications if these products are parenterally abused.

**AVINZA EXTENDED-RELEASE CAPSULES**

Avinza extended-release capsules contain morphine sulfate in both immediate and extended-release beads that are 1–2 mm in diameter. The advantage of such a combination is that the immediate-release component achieves plateau morphine concentrations within 30 minutes while the extended-release component maintains these plasma concentrations throughout the 24 hour dosing interval, which is longer than most other oral modified-release opioid products are able to achieve. The SODAS (Spherical Oral Drug Absorption System) is used to produce the extended-release component of the product. The extended-release beads are prepared using sugar/starch spheres upon which a drug/excipient layer is coated, followed by an ammonio-methacrylate copolymer coating (Figure 2A).

After administration and rapid dissolution of the hard gelatin capsule shell, the permeability of the ammonio-methacrylate copolymer coating allows GI fluid to enter the beads and solubilize the drug. The entrance of GI fluid is mediated by fumaric acid, which acts as an osmotic agent and local pH modifier within the drug/excipient layer. As a result, drug release is independent of the pH of the surrounding GI environment. After dissolving, morphine may then diffuse out of the beads at a predetermined rate. This entire process prolongs the in vivo dissolution of the drug and extends its absorption into the body. The immediate-release beads are formed by utilizing the same sugar/starch core and drug/excipient layer, without the rate-limiting polymer coating, and contain approximately 10% of the respective dose. Dosing is limited to no greater than 1600 mg/day due to fumaric acid levels that may, theoretically, result in renal toxicity; however, fumaric acid has poor oral bioavailability.

**KADIAN SUSTAINED-RELEASE CAPSULES**

Kadian sustained-release capsules contain morphine sulfate in identical polymer-coated, sustained-release pellets; the product does not contain an immediate-release compo-
in a simple matrix system instead of a polymer-coated reservoir (Figure 2B). This allows for the preparation of tablet dosage forms rather than capsules. The drug and any additional excipients are uniformly blended with a hydrophilic polymer (hydroxypropyl methylcellulose) and then compressed into tablets. Upon ingestion, GI fluid penetrates the tablet and hydrates the hydrophilic hydroxypropyl methylcellulose matrix, causing it to swell and form a viscous gel layer. The gel layer controls both the diffusion of water into the system and the diffusion of drug out of the system. Over time, this layer begins to break down and dissolve. As this occurs, water penetrates deeper into the matrix, forming a new viscous gel layer. This process continues until the entire hydrophilic matrix is dissolved. The gel matrix effectively traps the active ingredient and slows its release, which may occur by diffusion through the gel layer or erosion of the gel matrix itself.

**MS CONTIN CONTROLLED-RELEASE TABLETS**

MS Contin controlled-release tablets contain morphine sulfate in a dual-control polymer matrix (Contin) that consists of a hydrophilic polymer (hydroxypropyl methylcellulose) and a hydrophobic polymer (hydroxyethyl cellulose). To prepare these systems, the drug is blended with the hydrophilic polymer, selectively hydrated with a polar solvent, and fixed with a higher aliphatic alcohol. The partition coefficients of the active ingredient with the hydrophilic and hydrophobic components of the formulation control the release of drug from the tablet. The hydrophobic content is used to slow the diffusion of drug into the aqueous phase, which limits diffusion into the GI tract and absorption into the body. These hydrophilic/hydrophobic relationships are used to provide a more constant and predictable release of drug from the system than that achieved with Oramorph.

**OXYCONTIN CONTROLLED-RELEASE TABLETS**

OxyContin controlled-release tablets contain oxycodone HCl and are prepared using the AcroContin delivery system, which is an improvement upon the Contin system. The AcroContin system provides a biphasic absorption profile due to both an immediate release of drug within one hour, which cannot be achieved using the Contin system, and a prolonged release over 12 hours. This system uses a dual-controlled matrix consisting of 2 hydrophobic polymers (ammonio methacrylate copolymer). After ingestion, the GI fluid dissolves the tablet coating, exposing the hydrophobic acrylic matrix. An initial amount of oxycodone (~30–40% of the respective dose) is immediately released upon contact with the GI fluid, which begins channeling into the pores of the tablet matrix. This immediate-release component is much greater than that of Avinza (~10% of the respective dose). As GI fluid enters the tablet matrix, it dissolves the entrapped drug, which slowly diffuses out of the matrix pores. Oxycodone release from the tablets is pH independent, which allows for a uniform release throughout the GI tract. Since the matrix is hydrophobic and does not dissolve, patients should be advised that they may pass empty tablets or “ghosts” in the stool or via colostomy, and that this is not a concern since the active ingredient has already been released from the tablet.

**PALLADONE EXTENDED-RELEASE CAPSULES**

Palladone extended-release capsules were launched in February 2005 and marketed to a limited number of medical practitioners. The capsules were the first oral modified-release opioid product that contained hydromorphone HCl. The product used an ATC (Around The Clock) matrix pellet formulation to achieve a biphasic release of drug that resulted in a relatively rapid rise to an initial peak concentration, followed by a second broad peak with therapeutic plasma concentrations maintained over the 24 hour dosing interval. During product development, results indicated that consuming ethanol while taking Palladone disrupted the modified-release mechanism of the product and resulted in the absorption of a potentially fatal dose of hydromorphone. Peak blood concentrations increased approximately 6 times with the consumption of 8 ounces of a 40% (80 proof) ethanol solution, and approximately 2 times with the consumption of 8 ounces of a 4% ethanol solution. These results were disclosed to the Food and Drug Administration (FDA), and Purdue had developed professional prescribing information and a patient medication guide with strong warnings, including a boxed warning that clearly stated the risks of consuming alcohol while taking Palladone.

**OTHER MODIFIED-RELEASE PRODUCTS**

ALZA is developing an oral hydromorphone controlled-release product that uses the OROS delivery system (Dilaudid CR) for once-daily dosing. The product is currently in Phase III clinical trials. Endo has recently received approval from the FDA for an oral oxymorphone extended-release formulation that is to be dosed every 12 hours. Also, slow-release morphine sulfate or oxycodone HCl
capsules that use a drug/Methocel hypromellose matrix are often compounded by pharmacists in certain settings.\textsuperscript{28-30}

**Clinical and Comparative Issues**

The goal of managing chronic pain is to provide sufficient relief with minimal ADEs so that patients can function at a desirable level.\textsuperscript{1} Short-acting opioid products are used to rapidly titrate patients to an adequate dose or as breakthrough pain management if the patient is initiated on modified-release opioids.\textsuperscript{31} Patients may be converted to a long-acting opioid product to prevent baseline pain, with additional dosing of a short-acting product to treat breakthrough pain.\textsuperscript{1} Many of the available clinical trials involving oral modified-release opioid products included a small number of patients, an open-label study, or sponsorship by pharmaceutical companies.

The American Pain Society states that the choice of opioid is based on the clinician’s experience with an agent, since there are few data indicating a preferred agent. Clinicians also base their choice of opioid on a patient’s previous experience, since some patients will tolerate or respond to particular agents better than others.\textsuperscript{15} Because there is also a great deal of interpatient variability that may be due to genetic polymorphism, some patients may need longer or shorter dosing intervals of a modified-release opioid. This may increase costs to the patient if the interval must be decreased, resulting in more doses each day. In such cases, it may be prudent to switch the opioid to use tolerance or agents with longer half-lives (Avinza or Kadian) to decrease the pill burden and cost to the patient.

There are 3 commonly used modified-release formulations of morphine (MS Contin, Kadian, and Avinza). Kadian and Avinza have smaller trough to peak fluctuations compared with MS Contin.\textsuperscript{13,17} This means these agents have lower maximum and higher minimum concentrations than MS Contin. The clinical benefit of these pharmacokinetic differences has not correlated with higher efficacy or safety in clinical studies when Kadian or Avinza has been compared with MS Contin.\textsuperscript{32,33} It has been hypothesized that reduced fluctuations in blood morphine concentrations may influence the rate of opioid tolerance. The trough to peak fluctuation hypothesis has not been confirmed by controlled trials and should not be the reason for choosing one morphine formulation over another.

**Special Population Considerations**

**PEDIATRIC PATIENTS**

The safety of oral modified-release opioid products has not been established in children younger than 18 years of age. Therefore, these products should not be used in this group of patients. These products cannot be divided or crushed and are not available in liquid formulations. It is not

The safety of oral modified-release opioid products has not been established in children younger than 18 years of age. Therefore, these products should not be used in this group of patients. These products cannot be divided or crushed and are not available in liquid formulations. It is not recommended that Avinza and Kadian capsules be opened and sprinkled onto applesauce for children even though it is an appropriate administration technique for adults.\textsuperscript{13}

**PREGNANT AND BREAST-FEEDING WOMEN**

All opioid analgesics reviewed here are pregnancy category C. Opioid analgesic concentrations have been found in breast milk; therefore, the risk/benefit of using these agents in nursing women should be considered. If patients require chronic opioid therapy, the cessation of breast feeding may be necessary to reduce the risk to the neonate or infant. The amount of systemic absorption of the recipients used in preparing the modified-release products has not been formally evaluated. Therefore, the risk of these agents to the breast-feeding infant cannot be determined.

**ELDERLY PATIENTS**

Elderly patients (aged ≥65 y) were incorporated into the clinical studies of the oral modified-release opioid products. However, subgroup analysis was not possible in these trials due to small sample sizes. It is recommended that conservative doses be initiated in these patients due to their metabolism differences, their sensitivity to CNS active agents, and the potential for decreased renal elimination of metabolites compared with that of younger patients. The use of these agents is not contraindicated in this population if appropriate monitoring and slow-dose titration are practiced.

**PATIENTS WITH PAST OR CURRENT SUBSTANCE ABUSE**

Opioid products are not contraindicated in patients experiencing past or current substance abuse if they are prescribed with the intention of treating pain. Boundary setting, frequent assessment, and treatment plan development are key components of opioid therapy in these patients. Boundary setting methods include medication therapy agreements (opioid contracts) and developing clear goals for the reduction of pain. Patients with an addictive disorder who are experiencing chronic pain should be referred to a specialist in pain management or addiction medicine. Opioids are used in detoxification and maintenance programs within facilities licensed to administer these agents to patients. All of the labeling for the oral modified-release opioid products contains warnings and information about drug abuse and dependence.

**Summary**

Oral modified-release opioid products have enabled patients to better maintain pain control due to convenient dosing intervals and sustained blood concentrations. The consistent blood concentration reduces the peaks and
troughs of the drug and, therefore, can decrease ADEs and periods of inadequate pain control. The differences between available oral modified-release products are half-life, cost, and formulation (excipients and drug-release properties). Since there are no data supporting superior efficacy of any one of these opioids compared with the others, selection should be based on other features. Initiating the opioid with which the clinician is most comfortable or the opioid to which the patient has responded in the past should be the first step in drug selection. Cost should also be a consideration in the choice, since most of these products are expensive. Patients will respond differently to opioids due to differences in pain tolerance, drug metabolism, and control of ADEs. The oral modified-release opioid products have been an innovative addition to the treatment of chronic pain.

**References**

CONCLUSIONES: Los productos de liberación modificada han permitido a los pacientes mantener un mejor control del dolor ya que permiten ajustar los intervalos de dosificación y mantener las concentraciones plasmáticas. Las diferencias entre los distintos productos son: vida media, coste y formulación (los excipientes y las propiedades de liberación del medicamento).

Juan del Arco

RÉSUMÉ

OBJECTIF: Évaluer les différences pharmaceutiques et pharmacothérapeutiques des préparations orales d’opioïdes utilisées dans le traitement de douleur chronique.


SÉLECTION DES ÉTUDES ET DE L’INFORMATION: Tous les articles identifiés à partir de la revue de littérature furent évalués. L’information jugée pertinente fut inclue si elle apportait de nouveaux concepts ou supportait des concepts connus ou finalement si elle clarifiait des éléments cliniques importants.

Marc M Perreault

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