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CONCEPTUAL PEARLS

- ▶ As more physicians prescribe opioid analgesics to treat a variety of pain syndromes, an understanding of the role of active metabolites becomes increasingly relevant clinically.
- ▶ Active metabolites of opioid drugs can be a major source of adverse effects.
- ▶ Metabolites and their parent compounds may have different pharmacokinetics.
- ▶ Pharmacogenetic differences in drug metabolism can cause wide variability in response to opioid drugs.
- ▶ The efficacy and tolerability of an opioid analgesic are the net result of the parent drug *and* its active metabolites.

Looking beyond the administered drug: Metabolites of opioid analgesics

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Pain continues to be a primary reason that patients seek medical attention.¹ Guidance provided by the World Health Organization's "analgesic ladder," as well as recommendations from several professional medical societies, can help physicians select the proper analgesics for pain management.²⁻⁵ Opioids are an important analgesic option for many patients with moderate to severe pain. They provide effective analgesia for a wide variety of acute and chronic pain types, are generally well tolerated, and are not typically associated with organ toxicity.³⁻⁵ However, the undesirable side effects of opioids can temper their therapeutic benefits for many patients. Among the most common adverse effects (AEs) associated with opioid analgesics are gastrointestinal (GI) effects (eg, nausea, vomiting, constipation), but more serious AEs (eg, seizures) can also occur.⁶

The therapeutic efficacy and tolerability of an opioid analgesic are usually not mediated solely by the parent drug itself. The natural metabolism of most opioids leads to production of pharmacologically active metabolites.⁷ These active metabolites can evoke a significant proportion of the AEs associated

with the parent drug. With most opioids, any contribution by active metabolites to the parent drug's therapeutic efficacy would have to be weighed against the possibility of a less predictable side-effect profile.⁸

As more physicians prescribe opioid analgesics to treat a variety of pain syndromes, an understanding of the role of active metabolites becomes increasingly relevant clinically. This article explores the role that active metabolites play in the therapeutic efficacy and tolerability profiles of frequently prescribed opioid analgesics. The goal is to provide physicians with an overview of the effects of metabolic mechanisms to help inform the opioid selection process.

■ Opioids

Opioids are endogenous or exogenous substances that produce effects similar to those produced by morphine.⁶ Three opioid receptor subtypes—mu (μ), delta (δ), and kappa (κ)—have been identified.⁹ Most of the current commonly used opioid analgesic drugs bind primarily to, or produce their analgesic effects primarily through, the μ subtype of opioid receptor. These receptors

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are located throughout the brain, spinal cord, and periphery, including the GI tract.⁶ Binding to opioid receptors in the central nervous system (CNS) primarily mediates analgesia and has the potential to cause such AEs as dizziness, nausea, and vomiting, whereas binding to receptors in both the CNS and gut mediates constipation.¹⁰

Drug metabolism and pharmacokinetics

The major site of drug metabolism (biotransformation) for most opioid drugs is the liver, but metabolism also occurs in extrahepatic tissues such as the small intestine, lung, and kidney.¹¹ Most drugs are catabolized into multiple metabolites of differing activity and toxicity, and transformation of the parent drug molecule is catalyzed via numerous enzyme superfamilies. Phase I metabolism includes oxidation-reduction-type chemical reactions, whereas phase II metabolism involves conjugation-type reactions (ie, linking of the drug molecule with some endogenous substrate). Members of the cytochrome P450 (CYP) family are the key enzymes that catalyze phase I reactions. In humans, the major conjugation reaction involves the addition of glucuronic acid to the drug (glucuronidation), a reaction that is catalyzed by uridine diphosphate glucuronosyltransferases (UGTs).¹²

Some opioid drugs (eg, oxycodone) are subject to extensive metabolism by enzymes in the liver and the small intestine following oral dosing.^{6,13} Further, the activity of a given opioid can differ between individuals due to genetic variability in metabolism (pharmacogenetics), drug-drug interactions, and other variables (eg, diet, smoking status, disease state).¹⁴

Metabolism is a critical aspect of a drug's pharmacokinetic (PK) profile. For opioids that are metabolized—especially those that give rise to active metabolites (ie, most currently available opioids)—it is critical to characterize the PK profile of the metabolite in addition to that of the parent drug, since this better relates to the drug effect (pharmacodynamics [PD]) than does the PK profile of the parent drug alone.^{7,14}

After undergoing metabolism, usually in the liver and GI tract, most opioids are eliminated principally in the urine as a mixture of the parent drug and multiple metabolites. With most oral opioids, there can be significant but variable first-pass metabolism in the liver. This can result in lower bioavailability of oral vs intravenous opioids.¹⁴

The time course of the analgesic effect following administration is comparable for most opioid analgesics, which have serum half-lives of about 2 to 3 hours.⁶

Importantly, the half-lives of active metabolites can be significantly longer than those of the parent drug, resulting in their accumulation over time. For example, normeperidine, the demethylated neurotoxic metabolite of meperidine hydrochloride that can cause seizures, has a substantially longer half-life than meperidine (15-20 hours vs 3 hours, respectively).⁶ Due to the ensuing accumulation of the metabolite, given this long half-life, meperidine should not be used for more than 48 hours.⁶ The same is true for propoxyphene hydrochloride, which has a half-life of 6 to 12 hours, whereas its demethylated metabolite, norpropoxyphene, has a half-life of 30 hours and is cardiotoxic.^{6,15}

Enterohepatic recycling

Some opioids form glucuronidated metabolites, which involves an additional metabolic pathway. Normal flora within the GI tract convert certain metabolites back to the parent drug. Recirculation may occur due to deconjugation of the metabolite in the gut lumen.¹⁴ The drug is therefore available for enterohepatic recirculation, which typically results in a second peak in its plasma-concentration/time profile. If the drug has active metabolites, enterohepatic recycling can produce a “depot” effect, with prolonged exposure to both the parent drug and the active metabolites; this can potentially result in a delayed but strong pharmacologic response. Morphine and buprenorphine are 2 opioids that are known to undergo enterohepatic recirculation.^{14,16}

Pharmacogenetic variability in drug response

Genetic variability is now recognized as critical to understanding differences in drug response (efficacy and tolerability) between individuals.¹⁷ Variability in drug-metabolizing enzymes or transporter genes, as well as target receptor genes, can contribute to PK/PD differences.⁸ Due to these differences, some patients may be poor metabolizers of certain opioids and derive little analgesia from them. For example, due to genetic variability in the CYP2D6 enzyme, patients can be poor, intermediate, or fast metabolizers of codeine into its active metabolite, morphine. Given the same dose, poor metabolizers may receive minimal relief, whereas fast metabolizers may experience a morphine overdose.¹⁸⁻²⁰

Patients who are poor metabolizers of codeine may have their pain undermedicated, or they may be incorrectly identified as underreporting pain relief to gain access to larger drug quantities for the purpose of abuse. Prescribers should be aware that about

TABLE 1

Summary of Opioid Metabolites

Opioid analgesic	Trade name(s)	Key metabolizing enzyme(s)	Major metabolites
Buprenorphine	Subutex®	CYP3A4	Norbuprenorphine, glucuronides
Codeine	N/A	CYP3A4, 2D6	Morphine, glucuronides
Fentanyl	Actiq®, Duragesic®, Fentora	CYP3A4	Norfentanyl
Hydrocodone	Vicodin®, Lortab® (hydrocodone bitartrate and acetaminophen)	CYP3A4, 2D6	Hydromorphone, norhydrocodone
Hydromorphone	Dilaudid®	UGT1A3, 2B7	Glucuronides
Meperidine	Demerol®	CYP3A4, 2B6, 2C19	Normeperidine
Methadone	Dolophine®	CYP2B6	EDDP
Morphine	MS Contin®, Oramorph®, Kadian®	UGT2B7	Glucuronides
Oxycodone	OxyIR®, OxyContin®	CYP3A4, 2D6	Noroxycodone, oxymorphone
Oxymorphone	Opana®, Numorphan®	UGT2B7	6-OH-oxymorphone, oxymorphone-3-glucuronide
Propoxyphene	Darvon®	CYP3A4	Norpropoxyphene
Tramadol	Ultram®	CYP2D6	O-desmethyl tramadol

EDDP = 2-Ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium.
Source: References 7, 8, 15, 16, 24-30.

1% of East Asians and 7% to 10% of Caucasians are poor metabolizers of codeine.^{19,21} Similarly, persons with CYP-family enzyme variants have been found to differentially metabolize other agents, including fentanyl and tramadol, leading to differences in toxicity and efficacy between patients.^{22,23}

■ Opioids, active metabolites, and adverse effects

Nausea, constipation, and diminished acuity are among the most commonly encountered AEs associated with opioid analgesic use.⁶ Typically, these AEs are partly attributable to both the parent drug and one or more of the drug's active metabolites. **TABLE 1** lists the active metabolites of the opioid analgesics discussed in this article.^{7,8,15,16,24-30} Serious AEs arising from meperidine (seizures) and propoxyphene (cardiotoxicity) are primarily attributable to their respective metabolites, normeperidine and norpropoxyphene.^{6,7,15,31}

Likewise, the major glucuronidation metabolite of hydromorphone, hydromorphone-3-glucuronide, is suspected of causing the psychotomimetic reactions associated with the parent drug's use.^{7,32} Opioid permeability of the blood-brain barrier is usually quite high;

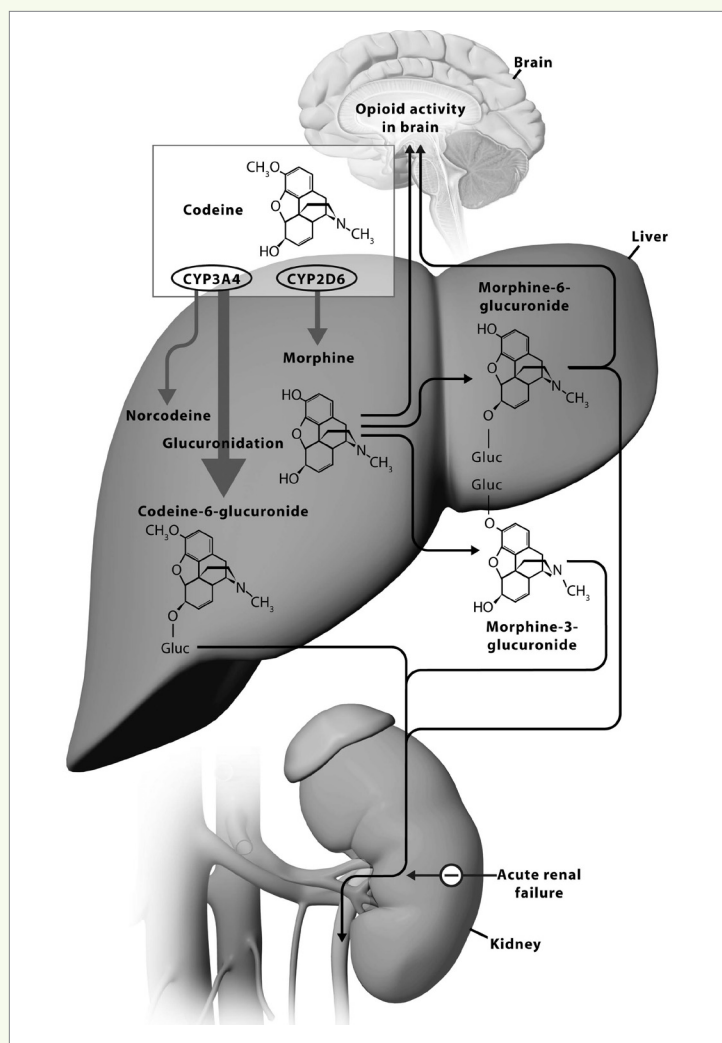
however, the variable extent to which different drug metabolites cross the blood-brain barrier may affect their relative contribution to the parent drug's clinical effects.³³ A brief summary of relevant opioid metabolites and their common AEs follows.

Morphine

Morphine is converted by the liver primarily into morphine-3-glucuronide (M3G).^{15,34} M3G elicits no analgesic activity but is believed to cause neuroexcitatory effects such as allodynia, myoclonus, and seizures.³² The active minor metabolite morphine-6-glucuronide (M6G) has received more research attention, as it may provide some proportion of the analgesia in patients treated with morphine.^{7,15,35} M6G has also been associated with respiratory depression, particularly in patients with renal failure.⁷ M3G and M6G are converted back to morphine in the GI tract. This enterohepatic recirculation results in the continued presence of morphine and its metabolites in the feces and urine days after the last dose, even in healthy individuals without liver or kidney disease. Since both M3G and M6G can accumulate in patients experiencing kidney failure, such patients should be monitored carefully for toxic reactions when administered morphine.³⁶

FIGURE 1

Pathways of Codeine Metabolism



About 80% of administered codeine is either converted by CYP3A4 into norcodeine or glucuronidated into codeine-6-glucuronide. Conversion of codeine into morphine by CYP2D6 represents about 10% of codeine metabolism. Morphine is further glucuronidated into morphine-3-glucuronide and morphine-6-glucuronide. Morphine and morphine-6-glucuronide exert opioid analgesic activity within the central nervous system. Glucuronides are eliminated by the kidney and are thus susceptible to accumulation in cases of acute renal failure.

Adapted with permission from Gasche Y, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med.* 2004;351:2827-2831. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

susceptible to accumulation in cases of acute renal failure (FIGURE 1).¹⁹ Individuals with CYP2D6 genetic variants that lead to low enzyme activity (poor metabolizers) convert less codeine to morphine and thus derive less analgesic effect.^{18,32} Conversely, persons with duplicated or amplified CYP2D6 can convert more codeine into morphine, risking the possibility of morphine overdose and even death. Such an outcome was observed in the recent case of morphine poisoning of a male infant. The infant's mother, who was an ultrarapid metabolizer of codeine, had been prescribed codeine and acetaminophen for episiotomy pain. The child demonstrated lethargy and difficulty feeding on postnatal day 7 and died on day 13. The mother's breast milk was found to have dramatically elevated concentrations of morphine (87 ng/mL) compared with typical concentrations in the milk of nursing mothers administered codeine (1.9-20.5 ng/mL), and the infant's blood concentrations of morphine were found to be similarly elevated.²⁰

Hydromorphone

Like its structural analogue, morphine, hydromorphone is primarily metabolized to its inactive 3-glucuronide metabolite, hydromorphone-3-glucuronide (H3G).^{7,32} Although H3G lacks analgesic activity, several lines of evidence suggest that it elicits neuroexcitatory effects such as allodynia, myoclonus, seizures, chewing, ataxia, and convulsions.^{7,32} H3G may accumulate when not eliminated normally by the kidneys.⁷

Hydrocodone

Hydrocodone is primarily metabolized to another active opioid, hydromorphone, by the CYP2D6 enzyme or to norhydrocodone by the CYP3A4 enzyme.^{25,37} Similar to poor metabolizers of codeine, poor metabolizers of hydrocodone may experience little to no analgesia.³⁸ As with morphine, hydrocodone may carry a greater risk of toxic reaction in patients with renal impairment.³⁹ Following metabolism of hydrocodone to hydromorphone, further metabolism can give rise to neuroexcitatory H3G.

Codeine

The analgesic effects of codeine depend on its metabolism to morphine in the liver by the CYP2D6 enzyme. In most individuals, about 10% of administered codeine is converted to morphine; the other main metabolites are codeine-6-glucuronide, which has pain-relieving effects in rats, and norcodeine.^{7,15} Because the glucuronide metabolites of codeine (and ultimately of morphine) are eliminated by the kidney, they are

Meperidine

Meperidine is metabolized in the liver to the inactive metabolite meperidinic acid and the active metabolite normeperidine.^{15,31} Normeperidine has about half the analgesic potency of meperidine but several times the neurotoxicity.⁴⁰ Normeperidine accumulation has been associated with irritability, seizures, myoclonus, tremors, and prolonged lethargy.^{7,31} Accumulation is facilitated by the much longer half-life of normeperidine compared with the parent drug (FIGURE 2).³¹ Patients with renal dysfunction may be especially susceptible to the neurotoxicity associated with this metabolite.^{7,15} Meperidine is not recommended for general use because of the serious AEs associated with its metabolites and the resulting poor benefit-risk ratio.⁴¹

Propoxyphene

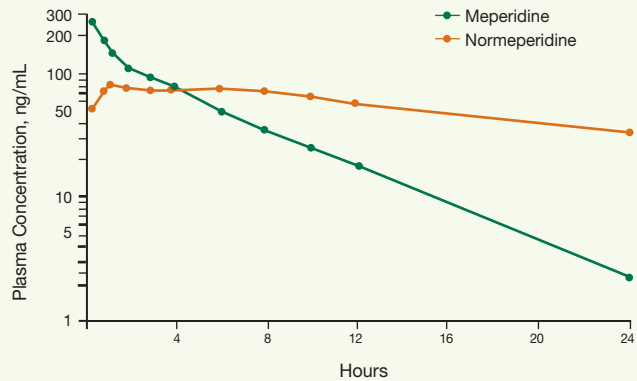
Propoxyphene undergoes extensive first-pass metabolism in the liver to norpropoxyphene, the main form in which it is eliminated.¹⁵ Similar to meperidine, the primary metabolite of propoxyphene has a much longer half-life than the parent drug. As a result, plasma concentrations of norpropoxyphene are generally much higher than concentrations of propoxyphene. This is of particular concern, since high doses of norpropoxyphene are associated with cardiotoxicity.¹⁵ Although the usual opioid AEs of propoxyphene are readily reversed by naloxone, treatment of the drug's high-dose cardiotoxicity is more complicated.⁴² Some experts consider propoxyphene to be contraindicated for use in the elderly, whereas some are adamant that the benefit-risk ratio of propoxyphene argues against even its general use.^{43,44}

Oxymorphone

Oxymorphone undergoes extensive metabolism in the liver, with less than 1% being excreted as unchanged drug. However, it has relatively straightforward metabolism (via phase I and phase II reactions) that results in 2 major metabolites: 6-OH-oxymorphone (6-OH-OXM) and oxymorphone-3-glucuronide (OXM-3-G). In animal models, 6-OH-OXM has analgesic activity; the activity of OXM-3-G has not been evaluated.²⁹ There is no literature to suggest that either metabolite is notably toxic, nor that either accumulates to induce seizures in neurologically healthy patients as do some other opioids. Unfortunately, the oral bioavailability

FIGURE 2

Concentrations of Meperidine and Normeperidine in Plasma of a Normal Subject After a Single Oral Dose of Meperidine (1.6 mg/kg)



Elimination of normeperidine is slower than that of meperidine, resulting in accumulation of the metabolite in patients receiving repeated doses of meperidine.

Reprinted from Pond SM, et al. Presystemic metabolism of meperidine to normeperidine in normal and cirrhotic subjects. *Clin Pharmacol Ther.* 1981;30:183-188, with permission from Blackwell Publishing.

of immediate-release oxymorphone is extremely low (10%).⁴⁵ Steady-state concentrations are achieved after 3 days of multiple-dose administration. The steady-state plasma concentrations of oxymorphone, 6-OH-OXM, and OXM-3-G are approximately 40% higher in elderly patients compared with younger individuals.²⁹

Methadone

Methadone has long been used in the treatment of opiate abuse but is now receiving attention for its analgesic properties, particularly for the treatment of cancer pain and other chronic pain.⁴⁶ Methadone undergoes extensive metabolism in the liver, forming pyrrolidine and pyrroline metabolites, which are not notably active.^{15,47} However, a concern is that its rate of metabolism varies greatly among individuals, as clearance rates vary by as much as 100-fold.⁴⁷ Although elimination half-lives typically vary over a broad range of 9 to 47 hours (mean of about 28 hours), reports span from as few as 4 hours to as many as 91 hours.⁴⁷ Methadone can produce prolonged QT intervals by inhibiting cardiac potassium channels, and cases of QT interval prolongation and severe ventricular arrhythmias (*torsades de pointes*) have been reported in patients receiving large, multiple daily doses of methadone for pain relief.⁴⁸ However, methadone's

TABLE 2

Potential Benefits of an Opioid Analgesic Devoid of Active Metabolites

Absorption	Bioavailability would not rely on metabolism to the active form and would not be affected by the pharmacogenetics of this conversion.
Distribution	The relationship between plasma concentration of drug and its analgesic effect would be less complicated.
Metabolism	Pharmacogenetic variability would primarily impact the parent drug, not the conversion to active metabolites.
Toxicity	It is simpler to treat toxicity caused by one active molecule than by multiple metabolites.
Drug interactions	Fewer active molecules means fewer possibilities of problematic drug-drug interactions.
Prescribing	Chronic treatment will not lead to accumulation of active metabolites, as can occur with many currently available opioids.
Compliance	Compliance is best when the dosing regimen is simple and constant over time; this is most likely to occur when there is no accumulation of active metabolites.

pyrrolidine and pyrroline metabolites have not demonstrated significant inhibition of cardiac potassium channels and are not believed to contribute to the cardiovascular side effects associated with methadone treatment.⁴⁸

Buprenorphine

A significant proportion of buprenorphine undergoes first-pass metabolism in the GI tract and liver, accompanied by marked enterohepatic recycling.¹⁶ The 3 major metabolites are buprenorphine glucuronide, norbuprenorphine, and norbuprenorphine glucuronide, which accumulate with chronic dosing to concentrations that can exceed those of the parent drug.¹⁶ Norbuprenorphine is the only biologically active metabolite, and its contribution to the clinical effects of buprenorphine is currently under investigation.

Tramadol

The CYP2D6 enzyme converts tramadol into its principal metabolite, O-desmethyl tramadol, which is

known as the “M1 metabolite.”⁷ The analgesic effect of tramadol is not mediated solely by opioid receptor agonism; inhibition of both noradrenaline and serotonin reuptake also contributes.²⁴ The relative contributions of the parent compound and the M1 metabolite in the analgesic effect of tramadol can vary. Because of its multimodal analgesic action, the effects of CYP2D6 pharmacogenetic variability on efficacy and tolerability are less predictable. Reduced analgesic efficacy of high-dose tramadol has been reported in individuals with decreased CYP2D6 function.⁷

Oxycodone

Oxycodone undergoes extensive metabolism in the liver, principally through the CYP3A4 enzyme family, which converts it to the major circulating metabolite noroxycodone. Additionally, oxycodone is converted by the CYP2D6 isozyme to oxymorphone.¹³ The mean half-lives of the metabolites noroxycodone and oxymorphone (5.8 hours and 8.8 hours, respectively) are longer than that of oxycodone (3.5 hours) following oral administration.³³ Data from a recent, single-dose study of oxycodone suggest that the central opioid effects (as assessed by time course of pupil constriction relative to drug and metabolite PK/PD profiles) appear to be mediated primarily by the parent drug, with only a small contribution from its metabolites.³³ It has been hypothesized that this difference in activity may be due to the lower permeability of the blood-brain barrier to the metabolites compared with the parent compound.³³ It should be noted, however, that most investigations of the pharmacologic activity of oxycodone’s metabolites have consisted of single-dose studies.^{33,49-51} If the drug had been dosed to steady-state concentrations with repeated administration, it is likely that higher concentrations of its metabolites would have been produced. Additional studies that adequately reflect conditions observed in clinical practice are needed to fully determine the role of oxycodone’s metabolites in this drug’s effects.

Fentanyl

Fentanyl is rapidly and extensively metabolized by the liver, mostly into norfentanyl by the CYP3A4 enzyme, though several other minor metabolites have been reported, including despropionylfentanyl, hydroxyfentanyl, hydroxynorfentanyl, and N-phenylpropionamide.⁵² These metabolites do not appear to contribute to the parent drug’s activity and have not been shown to be pharmacologically active in animal models.²⁶⁻²⁸

■ Potential benefits of opioid analgesics with no active metabolites

When prescribing opioids for pain management, physicians need to consider not only the activity of the parent drug, but also the added contribution of any pharmacologically active metabolites to an opioid's clinical effects. The relationship between a drug's plasma concentration and its clinical effects is made more complex in the presence of active metabolites. Enterohepatic recycling of the parent drug and active metabolites can result in prolonged exposure to both, potentially resulting in a delayed but amplified pharmacologic response. This could impact both analgesic efficacy as well as the AEs associated with opioid use. The presence of metabolites that have substantially longer half-lives than their parent opioids further complicates the PD of the agent used. Furthermore, interpatient variability in the metabolism of the parent drug based on pharmacogenetic differences can affect analgesia, as has been observed in patients administered codeine, hydrocodone, and oxycodone. Pharmacogenetic variability extends to the conversion of active metabolites themselves, as well as to the parent drugs, adding further complexity.

Conversely, opioids that are not converted into active metabolites could simplify prescribing and patient monitoring issues (TABLE 2). The metabolites of certain opioid analgesics such as fentanyl and methadone have not demonstrated pharmacologic activity.^{28,47} Furthermore, novel analgesic agents are currently in development that may offer an improved balance between analgesic efficacy and tolerability, and that lack pharmacologically active metabolites. A lack of active metabolites may benefit drug safety; monitoring or managing drug toxicity associated with the parent agent would be simpler than managing toxicity that arises from multiple active molecules, as observed with meperidine and propoxyphene. Fewer active metabolites would also reduce the number of possible drug-drug interactions. Chronic pain management could be simplified because accumulation of active metabolites over time could be avoided. These benefits may extend to patient compliance, due to the absence of prolonged side effects mediated by active metabolites with longer half-lives. Although not guaranteed, the simplest course of pain management, therefore, might be expected from an opioid analgesic that is not metabolized into an active form. Opioids that lack

an active metabolite could offer physicians a therapeutic option with a more predictable adverse event profile, simplifying care.

■ Conclusion

Opioid analgesics are being increasingly used for the treatment of a variety of pain syndromes, including acute and chronic nonmalignant pain. Oral opioid administration is convenient and generally provides pain relief within an acceptable interval but is associated with characteristic side effects that may limit its utility, particularly in more vulnerable populations such as older patients. Many physicians may underappreciate the effects of active metabolites produced from opioid breakdown on both drug efficacy and, more importantly, tolerability. The exact extent to which different pharmacologically active metabolites mediate opioid-associated side effects requires further research. Still, there is considerable evidence that active metabolites do evoke their own side effects, which may be typically attributed to the parent drug. Additionally, pharmacogenetic variability can result in unique differences in patients' ability to metabolize a drug, especially in those receiving multiple drugs concomitantly, thus impacting drug efficacy and toxicity. In selecting an appropriate opioid analgesic, physicians should consider the possible effect of any active metabolites and the role of pharmacogenetic variability in metabolism when assessing the drug's risk-benefit relationship. Prescribing opioids that lack active metabolites could be a simpler approach to managing pain. Agents that are not extensively metabolized or that do not produce active metabolites would offer an attractive analgesic option due to the reduced potential for metabolite-mediated AEs. ■

Drug Brand Names

Buprenorphine • Subutex
Fentanyl • Actiq, Duragesic, Fentora
Hydrocodone • Vicodin, Lortab
Hydromorphone • Dilaudid
Meperidine • Demerol
Methadone • Dolophine
Morphine • MS Contin, Oramorph, Kadian
Oxycodone • OxyIR, OxyContin
Oxymorphone • Opana, Numorphan
Propoxyphene • Darvon
Tramadol • Ultram

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