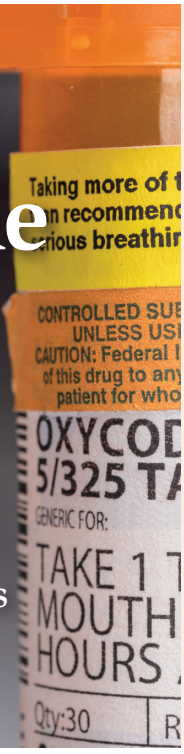
The Podiatric Physician's Guide to Prescribing Opioids



Here's how to identify, assess, and respond to patient groups who may have changes in opioid pharmacokinetics and pharmacodynamics.

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Learning Objectives

Completion of this course will better enable the course participant to perform the following:

1) Describe the types of possible opioid drug interactions that exist within the context of patient demographics and disease states;

2) Recognize and identify both pharmacokinetic and pharmacodynamics changes of opioid agents within certain patient demographics; and

3) Explain the art of clinical coping mechanisms to prescribe opioids to patients who may be elderly or presenting with disease states that may alter opioid pharmacokinetics.

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*Following this article, an answer sheet and full set of instructions are provided (pg. 138).—**Editor***

Note: *The purpose of this article is to provide podiatric physicians with strategies for identifying, assessing, and responding to patients who may have changes in opioid pharmacokinetics and pharmacodynamics due to sex and age differences and disease states.*

Introduction

Podiatric physicians frequently prescribe opioids for pain management. Podiatrists have an ethical obligation to prescribe responsibly yet cautiously to diminish the potential for opioid diversion and help minimize the growth of the current epidemic of opioid abuse.[1] Analgesic-opioid therapy has been the cornerstone of pharmacotherapeutic management of acute and chronic pain. Ideally, opioid analgesics are prescribed by balancing beneficial and adverse effects. Further, the foot and ankle specialist must remember that comfort is the ultimate goal when using any medication, including opioids, to manage pain.[1,2] Opioid selections are based on patient-specific factors such as age, renal function, and sex differences. The use of an opioid agent requires a practitioner to be comfortable with its use, especially in the presence of demographic or disease states like age, obesity, diabetes mellitus, kidney disease, congestive heart disease, and sex differences. When selecting an opioid, immediate-release formulations are safer than extended-release or long-acting opioids, re-

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gardless of whether the drug is used for acute or long-term treatment.

Due to a medication's pharmacodynamic and pharmacokinetic profile or a patient's response to an opioid agent, no single opioid analgesic product may be a perfect choice for a clinician to rely on, in order to treat all types of pain. Although no opioid seems to be superior in relieving pain, certain products are clearly inferior because of increased risks of toxic effects.[1-3] Opioid pharmacologic regimens must be individualized based on subjective, objective, and clinical findings.

As part of opioid stewardship, this review highlights and describes opioid pharmacodynamics and pharmacokinetics, especially in the presence of disease states like diabetes mellitus, kidney disease, congestive heart disease, and sex differences to assist and empower the podiatric physician to prescribe an opioid agent for maximizing opioid analgesic effects and decrease opioid possible adverse effects. First of all, alterations in pharmacokinetics and pharmacodynamics due to age, illnesses, and sex will be presented as a foundation. Finally, methods of clinical coping centered on opioid prescribing will be applied to patients who may present with alterations in pharmacokinetics secondary to age, illness, or sex.

Pharmacokinetic Changes

Pain in the elderly population is especially difficult to treat, given the myriad physiological, pharmacological, and psychological aspects of caring for the geriatric patient. Opiates are the mainstay of pain treatment throughout all age groups, but special attention must be paid to the efficacy and side-effects of these powerful drugs when prescribing to a population with impaired metabolism, excretion, and physical reserve.[4]

In the elderly, important age-related changes might alter opioid drug pharmacokinetics and result in unwanted side effects. The process of aging is characterized by structural and functional changes affecting all organ systems, which results in reduced homeostatic capacity over time.[4]

Although the function of a particular system may be maintained during resting conditions, the reduction of functional reserve is responsible for an increased vulnerability to stress.[5] Changes in body composition and in hepatic and renal function are responsible for an increase in the volume of distribution of lipid-soluble drugs and reduced clearance of lipid-soluble and water-soluble drugs.[5]

All these changes lead to a prolonged plasma elimination half-life, leading to greater drug plasma levels. Moreover, significant pharmacodynamic changes occur that cause an increased sensitivity to many drugs.[5] Finally, a reduced body functional reserve itself also leads to an increase in sensitivity by impairing homeostatic compensatory mechanisms.[5]

Obesity affects all four aspects of pharmacokinetics.

Opioids are highly varied and generally thought to possess similar pharmacokinetic activity. Opioids are rapidly absorbed in the gut, have a high rate of first pass in the liver, are conjugated in the liver, have metabolites, and vary in distribution based on their differing protein affinity, and then they are excreted via bile to feces or via kidneys. Opioid pharmacodynamic effects are complex and depend upon poorly measured variables such as receptor function and intracellular response, which can alter drug action.[5,6]

Pharmacokinetic actions of drug absorption, distribution, and elimination are more measurable. In general, the rate at which certain drugs are absorbed can be altered in older patients because of decreased gastrointestinal transit time and increased gastric pH secondary to the use of proton pump inhibitors, H2 receptor antagonists, or antacids.

With aging, there are changes in body composition, such as increase in adipose tissue, decrease in lean body mass, and decrease in total body water. These changes can affect drug distribution. Therefore, lipophilic drugs tend to have greater volume of distribution and can take more time to be eliminated from the body.[5,7]

Aging can also bring reduction in hepatic blood flow and volume, which can decrease metabolism of drugs.[5,8] Additional impairments in drug metabolism can occur with impaired Phase I reactions, which include oxidation, hydroxylation, and dealkylation.[5,8] This can specifically reduce the first pass effect of opiates in the elderly.[5,8] Elimination of drugs can be altered with age-related reductions in renal blood flow and glomerular filtration rate (GFR). For opiates that have primary renal clearance, such as morphine and hydromorphone, decreases in GFR lead to more side effects.[5,9]

Obesity affects all four aspects of pharmacokinetics. Weight-based dosing scalars must be considered as drug administration based on total body weight can result in underdosing or overdosing, depending on the characteristics of the drug. The pharmacodynamic profile of drugs may also be affected, e.g., the risk of respiratory depression and loss of airway patency is greater with sedatives and narcotics. Careful therapeutic drug monitoring is important in obese patients.

Morbidly obese people are often excluded from clinical trials during the drug development process, so data is limited on the correct dosing of many drugs. Obesity induces pharmacokinetic change in the absorption of oral medications as well as an increase in gastric emptying. Therefore, using clinical judgment, combined with interpretation of drug pharmacokinetics, is often required by the podiatric physician who prescribes a medication.

Decreased subcutaneous absorption is due to poor subcutaneous blood supply. Intramuscular administration may fail if needles are too short to pierce the skin. Opioid distribution is markedly affected by ratio of adipose tissue to lean body mass; if a drug has a high lipid solubility then its volume and distribution will result in an accumulation in fat stores.[10]

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Diabetes Mellitus

Diabetes mellitus affects protein, lipid and carbohydrate metabolism, and the biochemical pathways that are involved in drug biotransformation.[11] The principles of pharmacokinetics that may be influenced by diabetes mellitus include absorption, distribution, biotransformation, and excretion.[11,12] Diabetic changes in subcutaneous and muscle blood flow and delayed gastric emptying may influence the way a drug is absorbed.[11,12]

Non-enzymatic glycation of albumin secondary to diabetes mellitus

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TABLE 1:

Interactions of Opioid Analgesic Drugs Commonly Used in a Podiatry Practice

Prescribed Opioids	Substance Causing Drug Interactions	Explanation or Effect of Drug Interaction
Opioid Analgesic Class	Sedatives Barbituates-Anxiolytics-Benzodiazepines	Profound sedation and respiratory depression may occur with any class of drug with sedative effect
Codeine	SSRIs Antidepressants Bupropion	Inhibit the prodrug conversion to active morphine derivative; thus decrease and reduce analgesic effects
	Cabamazepine-Oxcarbazepine-Phenytoin-Primidone-Rifampin-HAARTs*	Reduce analgesic effects and may cause withdrawal symptoms
	Ciprofloxacin-Clarithromycin-Clotrimazole-Erythromycin-Fluconazole-Itraconazole-Ketoconazole-Quinupristin	Excessive opioid effects by causing reduced elimination of opioids
	Amiodarone-Cimetidine-Cyclosporin-Diltiazem-Dronedarone Fluvoxamine-Imatnib-Nefazodone-Verapamil-HAARTs*	Excessive opioid effects by causing reduced elimination of opioids
Fentanyl	Cabamazepine-Oxcarbazepine-Phenytoin-Primidone-Rifampin-HAARTs*	Reduce analgesic effects and may cause withdrawal symptoms
	Ciprofloxacin-Clarithromycin-Clotrimazole-Erythromycin-Fluconazole-Itraconazole-Ketoconazole-Quinupristin	Excessive opioid effects by causing reduced elimination of opioids
	Amiodarone-Cimetidine-Cyclosporin-Diltiazem-Dronedarone Fluvoxamine-Imatnib-Nefazodone-Verapamil-HAARTs*	Excessive opioid effects by causing reduced elimination of opioids
Hydrocodone	SSRIs Antidepressants Bupropion	Inhibit the prodrug conversion to active morphine derivative; thus decrease and reduce analgesic effects
Morphine	Cabamazepine-Oxcarbazepine-Phenytoin-Primidone-Rifampin-HAARTs*	Reduce analgesic effects and may cause withdrawal symptoms
Meperidine	MAO Inhibitors Phenelzine (Nardil) Selegiline (Eldepryl)	Mechanism of interaction is unclear, but hypertensive crisis, seizures, coma have been reported with this combination
Oxycodone	Cabamazepine-Oxcarbazepine-Phenytoin-Primidone-Rifampin-HAARTs*	Reduce analgesic effects and may cause withdrawal symptoms
	Ciprofloxacin-Clarithromycin-Clotrimazole-Erythromycin-Fluconazole-Itraconazole-Ketoconazole-Quinupristin	Excessive opioid effects by causing reduced elimination of opioids
	Amiodarone-Cimetidine-Cyclosporin-Diltiazem-Dronedarone Fluvoxamine-Imatnib-Nefazodone-Verapamil-HAARTs*	Excessive opioid effects by causing reduced elimination of opioids
Tapentadol	MAO Inhibitors, SSRIs, SNRIs	Contraindicated—Number of cases of Serotonin Syndrome and inhibitation opioid metabolism
Tramadol	MAO Inhibitors, SSRIs, SNRIs, Amitriptyline	Contraindicated—Number of cases of Serotonin Syndrome and inhibitation opioid metabolism

HAART	Highly Active Antiretroviral Therapy
MAO Inhibitors	Monoamine Oxidase Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
SNRIs	Selective Serotonin–Norepinephrine Reuptake Inhibitors

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may affect a medication's distribution within the body.[11,12] Gastric emptying is frequently abnormal in patients with long-standing type 1 and type 2 diabetes mellitus.[13] Symptoms commonly associated with delayed gastric emptying include nausea, vomiting, bloating, and epigastric pain. These patients are also at risk of malnutrition, weight loss, impaired drug absorption, disordered glycemic control, and having a poor quality of life.[13]

Gastric emptying is frequently abnormal in patients with long-standing type 1 and type 2 diabetes mellitus.

Although many studies have reported diabetes-mediated changes in gastric emptying time, the magnitude of the delay is modest, and at this time, some authors may not consider it clinically important.[11-13] Drug metabolism is enzyme-mediated structural modification to a drug that changes its biological activity and/or water solubility. These enzymatic reactions result in metabolites that may be active or rendered inactive. The gastrointestinal wall, lungs, liver, and blood possess enzymes that metabolize drugs.[14-16]

Drug metabolism by the liver occurs through one or both biotransformation reactions classified as either Phase I or Phase II reactions.[15] Building on the assertion centered on the direct relationship between diabetes mellitus and obesity, the effect of obesity on cytochrome P450 appears to be isozyme-specific with the activity of cytochrome P450 3A4 decreasing.[16] The clearance of cytochrome P450 (CYP) 3A4 substrates is lower in obese patients in comparison with non-obese patients. Conversely, researchers saw trends indicating higher clearance values via the following cytochrome P450 isoenzymes: CYP1A2, CYP2C9, CYP2C19 and CYP2D6.[16] Opioid drug-drug interactions are presented in Table 1.

There are complex interactions within the body's neuroendocrine systems in response to opioids which include alterations in the autonomic nervous system (sympathetic and parasympathetic nervous system), the renin–angiotensin–aldosterone system, and anti-diuretic hormone.[17] In addition, other mechanisms are also involved, including dehydration, rhabdomyolysis, and urinary retention.[17]

Changes in the sympathetic and parasympathetic nervous systems affect the kidney by altering renal blood flow and glomerular filtration rate. These changes occur at several levels including the heart and kidney. Usually the autonomic nervous system controls vital body functions with the sympathetic and parasympathetic innervation acting antagonistically based on need.

In the cardiovascular system, the sympathetic nervous system (SNS) increases heart rate and myocardial contractility as well as raises peripheral vascular resistance and arterial blood pressure via vasoconstriction.[17]

In chronic kidney diseases, there is an increase in morphine in the mean peak concentration and the area under the concentration-time curve for both active and principle metabolites. With chronic kidney diseases, the metabolites of merperidine are present for longer, can decrease the seizure threshold, and should be avoided for chronic use. Extended effects of codeine and dihydrocodeine with chronic kidney disease have been reported.[17]

Morphine has long been considered the gold standard of opioid agents.

Gender Differences

Specific drug pharmacokinetics and pharmacodynamics may differ between men and women.[18] Soldin and Mattison report that reviews of the Food and Drug Administration's Adverse Events Reporting System (AERS) suggest that women experience more drug-related adverse events, and often these adverse events are described as more serious.[18] Physiological differences between males and females have been observed in plasma volume, body mass index, plasma proteins, body fat, cardiac output, liver blood flow, and hepatic enzyme activity, thus influencing the hepatic clearance of drugs.[18]

Further, there are known sex differences with all three major renal functions: glomerular filtration, tubular secretion, and tubular re-absorption.[18]

Morphine the Gold Standard

Morphine has long been considered the gold standard of opioid agents.[19] Morphine has been shown to be more potent and exhibiting a slower onset and offset in women.[20,21] It has been established that women perceive more pain and require greater dosages of morphine to achieve the same antinociceptive effect as in men.[21-23] Soldin, et al. offer an explanation for this as higher mu-receptor binding in various cortical and subcortical brain regions exhibited in women than in men.[21]

Fillingim, et al. highlight the data collected in a 2009 comprehensive review on sex-specific influences on pain, which reveals that women appear to be more sensitive to pain and are more vulnerable to chronic, widespread, and post-procedural pain conditions.[24] Finally, Averitt, et al. present evidence that demonstrates a neural basis implicating sex differences in opioid metabolism and neuro-immune signaling with a focus on the periaqueductal gray as a sexual dimorphic core of descending opioid-induced inhibition.[25] They summarize the data to state that both pre-clinical and clinical research indicates that opioids are less effective in females to explain why women are more likely to be prescribed opioids at higher doses and for longer periods of time than men.[25]

Clinical Coping and Opioid Dosing

In the context of opioid stewardship, clinical coping is expending conscious effort to solve potential opioid dosing problems due to the impact of presenting demographics and disease

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states that may cause opioid adverse effects, opioid misuse, or opioid abuse disorder, thus seeking to master, minimize, or tolerate these possible issues or conflicts. The effectiveness of this clinical coping effort depends on the type of opioid issue and/or conflict, the particular individual, and the particular circumstances. Clinical coping suggestions with regard to dosing opioids in the context of demographics and disease states are summarized and presented in Table 2.

In the management of chronic pain in the elderly, podiatric physicians should consider a multimodal therapy approach to include non-pharmacologic therapy and non-opioid pharmacologic therapy before initiating opioids.[26] Opioid use should be implemented only when alleviation of pain and improvement of function outweigh the risks to the patient.[26]

When selecting non-opioid pharmacologic therapies that may include antidepressants, anti-arrhythmics, anticonvulsants, tranquilizers, and regional anesthesia, the podiatric physician should be aware of the possibility of drug-drug interactions as well as patient demographic interactions that may result with co-administration of these agents.

As always, goals of chronic pain therapy in the elderly are to decrease pain, increase function, and improve overall quality of life. It is recommended that opioids be prescribed at the lowest effective dose, which is approximately 25% to 50% of the starting dose recommended for adults, and then it must be slowly titrated to minimize adverse effects for patients older than age 70 years.[27] The dosage should be re-assessed one to four weeks after initiation or dose escalation. Immediate-release formulations of opioids should be initiated before extended-release or long-acting opioids are attempted.[26]

When podiatric physicians prescribe opioids to patients with renal or hepatic dysfunction, it is essential to understand and consider how opioid pharmacokinetics can be altered. This is necessary to ensure appropriate pain relief for the patient while limiting serious and potentially preventable adverse effects, such as respiratory depression, hypotension, or central nervous system toxicity from either the parent drug or its metabolites.

Patients with severe liver disease should be prescribed lower doses of opioids, with extended dosing intervals when multiple daily doses of opioids are needed to relieve pain. Opioids should be used cautiously in patients with severe renal and hepatic dysfunction because of the possible accumulation of the parent drug and/or metabolites. Usual or adjusted

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TABLE 2:
Clinical Coping with Prescribing Opioid Analgesics and Disease States

Prescribed Opioids	Presenting Demographics and Disease State	Recommendations for Opioid Prescribing
Opioid Analgesic Class	Elderly—Greater than 70 years old	Approximately 25% to 50% of the adult recommended starting dose, and then slowly titrated to pain relief
Opioid Analgesic Class	Obesity	Lean body weight is the optimal dosing for opioids agents
Opioid Analgesic Class	Female Sex	Use a minimal dose for a short period of time
Codeine	Not recommended in patients with renal insufficiency Not recommended in patients with liver insufficiency	Accumulation of active metabolites in renal failure Impaired conversion of codeine to morphine (active metabolite)
Fentanyl	Parent compound may accumulate with renal insufficiency Pharmacokinetics were not altered in patients with cirrhosis	No increase in adverse effects have been reported
Hydromorphone	Hydromorphone-3-glucuronide can accumulate and cause CNS toxicity	Avoid use in patients on dialysis and patients with GFR less than 30 ml/min
	Risk accumulation of parent drug due to decrease conversion	Recommend to decrease dose by 50% of usual dose in liver dysfunction
Morphine	Morphine-6-glucuronide may accumulate causing increase sedation	Adjust dose appropriate in patients with renal dysfunction Decrease frequency and dosage with liver dysfunction
Meperidine	Accumulation of Normeperidine causing CNS toxicity	Not recommended in renal and liver insufficiency
Oxycodone	Accumulation of parent and active metobilite oxymorphone	Use with caution with renal insufficiency Reduce dose by 1/3 or 1/2 with severe liver dysfunction and cirrhosis

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doses may be appropriate for patients prescribed morphine, hydromorphone, and hydrocodone.

Oxycodone should not be used in hemodialysis patients, and codeine and meperidine should be avoided at all times. Methadone and fentanyl can be carefully used in patients with renal dysfunction or on dialysis, and methadone is not advised in severe liver failure. For most patients with renal or hepatic dysfunction, either morphine or hydromorphone should be the opioid agents prescribed.

Patients with severe liver disease should be prescribed lower doses of opioids, with extended dosing intervals when multiple daily doses of opioids are needed to relieve pain.

Awareness of the pharmacology of the commonly used opioids is necessary for safe and effective care of morbidly obese patients. Changes in cardiac output and alterations in body composition affect the distribution of numerous opioid drugs. The podiatric physician should use a patient's lean body weight as the most optimal method to dose opioid agents.[10]

The increased incidence of obstructive sleep apnea and fat deposition in the pharynx and chest wall places the morbidly obese at increased risk for adverse respiratory events secondary to opioid agents, thus altering the pharmacokinetic and pharmcodynamic properties of opioid agents.[10]

Acute foot and ankle pain may often be managed with non-opioid medication. If opioids are used, prescribe the lowest dose for the shortest duration and avoid prescribing refills to reduce the risk for dependency. Literature sources have found that greater use and misuse of prescription medications among older women may be connected to the loss of a partner, low income, mental health issues, or poor overall health.[28]

Clinical recommendations for prescribing opioids to women of child-bearing age include the following: assess pregnancy risk in all women of childbearing age prior to prescribing an opioid, avoid prescribing opioids to pregnant women, and educate pregnant women about the known risks of opioids to both the mother and the fetus.[29]

If opioids must be prescribed to a pregnant woman for acute pain, prescribe the lowest dose and duration appropriate. Provide proper pain control and education to lactating women experiencing acute pain following birth and surgical procedures to avoid opioid adverse effects to the mother and the child.[29]

Oxycodone should not be used in hemodialysis patients, and codeine and meperidine should be avoided at all times.

Conclusions

Opioid stewardship requires the podiatric physician to acknowledge that opioid pharmacodynamic and pharmacokinetic parameters may be altered in the presence of the following age or disease states: diabetes mellitus, kidney disease, obesity, and sex differences that may impact opioid's beneficial and possible adverse effects.

As a foundation, alterations in opioid pharmacokinetics and pharmacodynamics due to age, illnesses, and sex differences were presented. Second, building on these clinical alterations in pharmacokinetics and pharmacodynamics were applied to opioid pharmacology to describe possible adverse effects. Finally, methods of clinical coping centered on opioid prescribing were presented and applied to patients who may present with alterations in pharmacokinetics secondary to age, illness, or sex. **PM**

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CME EXAMINATION

SEE ANSWER SHEET ON PAGE 139.

1) Obesity affects all _____ aspects of pharmacokinetics

- **A) four**
- **B) five**
- **C) seven**
- **D) ten**

2) Which agent of the following opioids can be used in hemodialysis patients?

- **A) Oxycodone**
- **B) Morphine**
- **C) Codeine**
- **D) Meperidine**

3) It is recommended that opioids be prescribed at the lowest effective dose, which is approximately _____ of the adult recommended starting dose and then slowly titrated to minimize adverse effects for patients older than age 70 years.

- **A) 10–20%**
- **B) 1–8%**
- **C) 9–17%**
- **D) 25–50%**

4) _____ has long been considered the gold standard of opioid agents

- **A) Codeine**
- **B) Fentanyl**
- **C) Morphine**
- **D) Hydrocodone**

5) In which body functions that influence the hepatic clearance of drugs have differences been observed between males and females?

- **A) Plasma volume**
- **B) Body mass index**
- **C) Hepatic enzyme activity**
- **D) All the above answers are correct**

6) Patients with severe liver disease should be prescribed _____ doses of opioids, with _____ dosing intervals when multiple daily doses of opioids are needed to relieve pain.

- **A) higher, shorter**
- **B) lower, extended**
- **C) higher, extended**
- **D) lower, shorter**

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7) Gastric _____ is frequently abnormal in patients with long-standing type 1 and type 2 diabetes mellitus.

A) microbacteria production
B) bicarbonate production
C) acid production
D) emptying

8) _____ can accumulate and cause CNS toxicity secondary to renal dysfunction.

A) Hydromorphone-3-glucuronide
B) Hydromorphone-4-glucuronide
C) Hydromorphone-9-glucuronide
D) Hydromorphone-12-glucuronide

9) In the presence of severe liver dysfunction and cirrhosis Oxycodone should be reduced by _____?

A) One eighth to one quarter
B) One twenty-fifth to one fiftieth
C) One third-to one half
D) One fourteenth to one sixteenth

10) With which opioid does the accumulation of normeperidine causing CNS toxicity due to renal and liver dysfunction occur?

A) Oxycodone
B) Morphine
C) Codeine
D) Meperidine

SEE ANSWER SHEET ON PAGE 139.

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Enrollment/Testing Information and Answer Sheet

Note: If you are mailing your answer sheet, you must complete all info. on the front and back of this page and mail with your credit card information to: **Program Management Services, P.O. Box 490, East Islip, NY 11730.**

TESTING, GRADING AND PAYMENT INSTRUCTIONS

(1) Each participant achieving a passing grade of 70% or higher on any examination will receive an official computer form stating the number of CE credits earned. This form should be safeguarded and may be used as documentation of credits earned.

(2) Participants receiving a failing grade on any exam will be notified and permitted to take one re-examination at no extra cost.

(3) All answers should be recorded on the answer form below. For each question, decide which choice is the best answer, and circle the letter representing your choice.

(4) Complete all other information on the front and back of this page.

(5) Choose one out of the 3 options for testgrading: mail-in, fax, or phone. To select the type of service that best suits your needs, please read the following section, "Test Grading Options".

TEST GRADING OPTIONS

Mail-In Grading

To receive your CME certificate, complete all information and mail with your credit card information to: **Program Management Services, P.O. Box 490, East Islip, NY 11730. PLEASE DO NOT SEND WITH SIGNATURE REQUIRED, AS THESE WILL NOT BE ACCEPTED.**

There is **no charge** for the mail-in service if you have already enrolled in the annual exam CME program, and we receive this exam during your current enrollment period. If you are not enrolled, please send $29.00 per exam, or $249 to cover all 10 exams (thus saving $41 over the cost of 10 individual exam fees).

Facsimile Grading

To receive your CME certificate, complete all information and fax 24 hours a day to 1631-532-1964. Your CME certificate will be dated and mailed within 48 hours. This service is available for $2.95 per exam if you are currently enrolled in the annual 10-exam CME program (and this exam falls within your enrollment period), and can be charged to your Visa, MasterCard, or American Express.

If you are *not* enrolled in the annual 10-exam CME program, the fee is $29 per exam.

Phone-In Grading

You may also complete your exam by using the toll-free service. Call 1-800-232-4422 from 10 a.m. to 5 p.m. EST, Monday through Friday. Your CME certificate will be dated the same day you call and mailed within 48 hours. There is a $2.95 charge for this service if you are currently enrolled in the annual 10-exam CME program (and this exam falls within your enrollment period), and this fee can be charged to your Visa, Mastercard, American Express, or Discover. If you are not currently enrolled, the fee is $29 per exam. When you call, please have ready:

1. Program number (Month and Year)
2. The answers to the test
3. Credit card information

In the event you require additional CME information, please contact PMS, Inc., at **1-631-563-1604**.

ENROLLMENT FORM & ANSWER SHEET

Please print clearly...Certificate will be issued from information below.

Name _____ Email Address _____
Please Print: FIRST MI LAST

Address _____

City _____ State _____ Zip _____

Charge to: _____Visa _____ MasterCard _____ American Express

Card # _____ Exp. Date _____ Zip for credit card _____

Note: Credit card is the only method of payment. Checks are no longer accepted.

Signature _____ Email Address _____ Daytime Phone _____

State License(s) _____ Is this a new address? Yes _____ No _____

Check one:

_____ I am currently enrolled. (If faxing or phoning in your answer form please note that $2.95 will be charged to your credit card.)

_____ I am not enrolled. Enclosed is my credit card information. Please charge my credit card $29.00 for each exam submitted. (plus $2.95 for each exam if submitting by fax or phone).

_____ I am not enrolled and I wish to enroll for 10 courses at $249.00 (thus saving me $41 over the cost of 10 individual exam fees). I understand there will be an additional fee of $2.95 for any exam I wish to submit via fax or phone.

Over, please

ENROLLMENT FORM & ANSWER SHEET *(continued)*

EXAM #1/20
The Podiatric Physician's Guide to Prescribing Opioids
(Smith)

Circle:

1.	A	B	C	D	6.	A	B	C	D
2.	A	B	C	D	7.	A	B	C	D
3.	A	B	C	D	8.	A	B	C	D
4.	A	B	C	D	9.	A	B	C	D
5.	A	B	C	D	10.	A	B	C	D

Medical Education Lesson Evaluation

Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]

1) This CME lesson was helpful to my practice ____

2) The educational objectives were accomplished ____

3) I will apply the knowledge I learned from this lesson ____

4) I will makes changes in my practice behavior based on this lesson ____

5) This lesson presented quality information with adequate current references ____

6) What overall grade would you assign this lesson?

A B C D

7) This activity was balanced and free of commercial bias.

Yes _____ No _____

8) What overall grade would you assign to the overall management of this activity?

A B C D

How long did it take you to complete this lesson?

_____hour _____minutes

What topics would you like to see in future CME lessons ? Please list :

_____

_____

_____

_____

_____