CHRONIC PAIN PERSPECTIVES™

A SUPPLEMENT TO THE JOURNAL OF FAMILY PRACTICE

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What to do when pain and addiction coexist

Polymyalgia rheumatica and giant cell arteritis: How best to approach these related diseases

OxyContin® CII
(oxycodone HCl controlled-release) tablets

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

OxyContin® contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit *[see Warnings and Precautions (5.1)]*. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving OxyContin for signs of misuse, abuse, and addiction during treatment *[see Drug Abuse and Dependence (9)]*.

Life-Threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of OxyContin, even when the drug has been used as recommended and not misused or abused *[see Warnings and Precautions (5.2)]*. Proper dosing and titration are essential and OxyContin should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of OxyContin or following a dose increase. Instruct patients to swallow OxyContin tablets intact. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental Exposure

Accidental ingestion of OxyContin, especially in children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)]*.

Indications and Usage

OxyContin is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

OxyContin is not for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- In the immediate postoperative period (the first 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time

OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

Contraindications

OxyContin is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus and gastrointestinal obstruction
- Hypersensitivity (e.g., anaphylaxis) to oxycodone

Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.

For appropriate patients

Medicare Part D coverage can help you meet your patients' individual needs

Not actual patients

To confirm coverage on patients' individual plans, visit PurdueHCP.com/MedD

OxyContin is covered* for the majority† of Medicare Part D patients nationally, including major Part D plans such as:

- UnitedHealthcare/AARP/ Medicare Rx Preferred
- Express Scripts Part D
- Medco Part D
- Prime Therapeutics Part D

The preferred branded tier status of OxyContin may enable patients to obtain OxyContin at the lowest available branded co-pay‡

Inclusion on formulary does not imply superior clinical efficacy or safety.

**Covered* represents on formulary (on any tier, with or without restrictions) and may include quantity limits, prior authorizations, and/or step edit restrictions.

†*Majority* is based on data indicating that OxyContin is covered for 63% of Medicare Part D lives nationally. Source: Fingertip Formulary®–database represents 95%-98% of commercial, Medicare, and Medicaid covered lives in the U.S. (4/1/13). Please check with the health plan directly to confirm coverage for individual patients. Patient costs may vary among plans.

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OxyContin® CII
(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

OxyContin® CII

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg | 15 mg | 20 mg | 30 mg

40 mg | 60 mg* | 80 mg*

***60 mg and 80 mg tablets for use in opioid-tolerant patients only**

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details please see the Full Prescribing Information and Medication Guide.)

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, and ACCIDENTAL EXPOSURE

Abuse Potential

OxyContin® contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit *[see Warnings and Precautions (5.1)]*. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving OxyContin for signs of misuse, abuse, and addiction during treatment *[see Drug Abuse and Dependence (9)]*.

Life-Threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of OxyContin, even when the drug has been used as recommended and not misused or abused *[see Warnings and Precautions (5.2)]*. Proper dosing and titration are essential and OxyContin should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of OxyContin or following a dose increase. Instruct patients to swallow OxyContin tablets intact. Crushing, dissolving, or chewing the tablet can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental Exposure

Accidental ingestion of OxyContin, especially in children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE OxyContin is indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. *Limitations of Use* OxyContin is not for use: • As an as-needed (prn) analgesic • For pain that is mild or not expected to persist for an extended period of time • For acute pain • In the immediate postoperative period (the first 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established. • For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. OxyContin 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for patients in whom tolerance to an opioid of comparable potency is established. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

4 CONTRAINDICATIONS OxyContin is contraindicated in patients with: • Significant respiratory depression • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected paralytic ileus and gastrointestinal obstruction • Hypersensitivity (e.g., anaphylaxis) to oxycodone *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS **5.1 Abuse Potential** OxyContin contains oxycodone, an opioid agonist and a Schedule II controlled substance. Oxycodone can be abused in a manner similar to other opioid agonists legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OxyContin in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain. Assess each patient's risk for opioid abuse or addiction prior to prescribing OxyContin. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use. Misuse or abuse of OxyContin by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death *[see Drug Abuse and Dependence (9), and Overdosage (10)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product. **5.2 Life-Threatening Respiratory Depression** Respiratory depression is the chief hazard of opioid agonists, including OxyContin. Respiratory depression if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OxyContin, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with OxyContin and following dose increases. Instruct patients against use by individuals other than the patient for whom OxyContin was prescribed and to keep OxyContin out of the reach of children, as such inappropriate use may result in fatal respiratory depression. To reduce the risk of respiratory depression, proper dosing and titration of OxyContin are essential *[see Dosage and Administration (2)]*. Overestimating the OxyContin dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused. To further reduce the risk of respiratory depression, consider the following: • Proper dosing and titration are essential and OxyContin should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. • OxyContin 60 mg and 80 mg tablets are for use in opioid-tolerant patients only. Ingestion of these strengths of OxyContin tablets may cause fatal respiratory depression when administered to patients not already tolerant to high doses of opioids. • Instruct patients to swallow OxyContin tablets intact. The tablets are not to be crushed, dissolved, or chewed. The resulting oxycodone dose may be fatal, particularly in opioid-naïve individuals. • OxyContin is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression *[see Contraindications (4)]*. **5.3 Accidental Exposure** Accidental ingestion of OxyContin, especially in children, can result in a fatal overdose of oxycodone. **5.4 Elderly, Cachectic, and Debilitated Patients** Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Therefore, monitor such patients closely, particularly when initiating and titrating OxyContin and when OxyContin is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. **5.5 Use in Patients with Chronic Pulmonary Disease** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with OxyContin, as in these patients, even usual therapeutic doses of OxyContin may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible. **5.6 Interactions with Alcohol, CNS Depressants, and Illicit Drugs** Hypotension, and profound sedation, coma or respiratory depression may result if OxyContin is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, muscle relaxants, other opioids). When considering the use of OxyContin in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient's use, if any, of alcohol and/or illicit drugs that can cause CNS depression. If OxyContin therapy is to be initiated in a patient taking a CNS depressant, start with a lower OxyContin dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.1)]*. **5.7 Hypotensive Effects** OxyContin may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7.1)]*. Monitor these patients for signs of hypotension after initiating or titrating the dose of OxyContin. In patients with circulatory shock, OxyContin may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OxyContin in patients with circulatory shock. **5.8 Use in Patients with Head Injury or Increased Intracranial Pressure** Monitor patients taking OxyContin who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with OxyContin. OxyContin may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of OxyContin in patients with impaired consciousness or coma. **5.9 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen** There have been post-marketing reports of difficulty in swallowing OxyContin tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet OxyContin tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth. There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen. **5.10 Use in Patients with Gastrointestinal Conditions** OxyContin is contraindicated in patients with GI obstruction, including paralytic ileus. The oxycodone in OxyContin may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms. Opioids may cause increases in the serum amylase. **5.11 Use in Patients with Convulsive or Seizure Disorders** The oxycodone in OxyContin may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during OxyContin therapy. **5.12 Avoidance of Withdrawal** Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including OxyContin. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing OxyContin, gradually taper the dose *[see Dosage and Administration (2.4)]*. Do not abruptly discontinue OxyContin. **5.13 Driving and Operating Machinery** OxyContin may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OxyContin and know how they will react to the medication. **5.14 Cytochrome P450 3A4 Inhibitors and Inducers** Since the CYP3A4 isoenzyme plays a major role in the metabolism of OxyContin, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations. Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid effects. CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration is necessary, caution is advised when initiating OxyContin treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.3), and Clinical Pharmacology (12.3)]*. **5.15 Laboratory Monitoring** Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

6 ADVERSE REACTIONS The following adverse reactions described elsewhere in the labeling include: • Respiratory depression *[see Boxed Warning, Warnings and Precautions (5.2, 5.5), and Overdosage (10)]* • CNS depression *[see Drug Interactions (7.1), and Overdosage (10)]* • Hypotensive effects *[see Warnings and Precautions (5.7), and Overdosage (10)]* • Drug abuse, addiction, and dependence *[see Drug Abuse and Dependence (9.2, 9.3)]* • Gastrointestinal Effects *[see Warnings and Precautions (5.9, 5.10)]* • Seizures *[see Warnings and Precautions (5.11)]* **6.1 Clinical Trial Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of OxyContin was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day. OxyContin may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*. The most common adverse reactions (>5%) reported by patients in clinical trials comparing OxyContin with placebo are shown in Table 1 below:

TABLE 1: Common Adverse Reactions (>5%)

Adverse Reaction	OxyContin (n=227)	Placebo (n=45)
	(%)	(%)
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	—
Sweating	(5)	(2)

In clinical trials, the following adverse reactions were reported in patients treated with OxyContin with an incidence between 1% and 5%: **Gastrointestinal disorders:** abdominal pain, diarrhea, dyspepsia, gastritis **General disorders and administration site conditions:** chills, fever **Metabolism and nutrition disorders:** anorexia **Musculoskeletal and connective tissue disorders:** twitching **Psychiatric disorders:** abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities **Respiratory, thoracic and mediastinal disorders:** dyspnea, hiccups **Skin and subcutaneous tissue disorders:** rash **Vascular disorders:** postural hypotension The following adverse reactions occurred **in less than 1% of patients** involved in clinical trials: **Blood and lymphatic system disorders:** lymphadenopathy **Ear and labyrinth disorders:** tinnitus **Eye disorders:** abnormal vision **Gastrointestinal disorders:** dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis **General disorders and administration site conditions:** withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema **Injury, poisoning and procedural complications:** accidental injury **Investigations:** ST depression **Metabolism and nutrition disorders:** dehydration **Nervous system disorders:** syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion **Psychiatric disorders:** depression, agitation, depersonalization, emotional lability, hallucination **Renal and urinary disorders:** dysuria, hematuria, polyuria, urinary retention **Reproductive system and breast disorders:** impotence **Respiratory, thoracic and mediastinal disorders:** cough increased, voice alteration **Skin and subcutaneous tissue disorders:** dry skin, exfoliative dermatitis **6.2 Postmarketing Experience** The following adverse reactions have been identified during post-approval use of controlled-release oxycodone: abuse, addiction, amenorrhea, cholestasis, death, dental caries, increased hepatic enzymes, hyperalgesia, hyponatremia, ileus, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, syndrome of inappropriate antidiuretic hormone secretion, and urticaria. Anaphylaxis has been reported with ingredients contained in OxyContin. Advise patients how to recognize such a reaction and when to seek medical attention. In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

7 DRUG INTERACTIONS **7.1 CNS Depressants** Concurrent use of OxyContin and other central nervous system (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol can increase the risk of respiratory depression, hypotension, profound sedation or coma. Monitor patients receiving CNS depressants and OxyContin for signs of respiratory depression and hypotension. When such combined therapy is contemplated, start OxyContin at 1/3 to 1/2 of the usual dosage and consider using a lower dose of the concomitant CNS depressant. **7.2 Muscle Relaxants** Oxycodone may enhance the neuromuscular blocking action of true skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and OxyContin for signs of respiratory depression that may be greater than otherwise expected. **7.3 Agents Affecting Cytochrome P450 Isoenzymes** *Inhibitors of CYP3A4* Co-administration of a strong CYP3A4 inhibitor ketoconazole, with OxyContin, significantly increased the plasma concentrations of oxycodone. Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. *Inducers of CYP3A4* A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, significantly decreased plasma oxycodone concentrations. CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of oxycodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration with OxyContin is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. *Inhibitors of CYP2D6* Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance during oxycodone treatment. However, clinicians should be aware of this possible interaction. **7.4 Mixed Agonist/Antagonist Opioid Analgesics** Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should generally not be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as OxyContin. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and may precipitate withdrawal symptoms in these patients. **7.5 Diuretics** Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Opioids may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates. **7.6 Anticholinergics** Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastric motility when OxyContin is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** *Pregnancy Category B* There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. In animal reproduction and developmental toxicology studies, no evidence of fetal harm was observed. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed. *Teratogenic Effects* The effect of oxycodone in human reproduction has not been adequately studied. Studies with oral doses of oxycodone hydrochloride in rats up to 8 mg/kg/day and rabbits up to 125 mg/kg/day, equivalent to 0.5 and 2.0 times an adult human dose of 160 mg/day, respectively on a mg/m^2 basis, did not reveal evidence of harm to the fetus due to oxycodone. In a pre- and postnatal toxicity study, female rats received oxycodone during gestation and lactation. There were no long-term developmental or reproductive effects in the pups *[see Nonclinical Toxicology (13.1)]*. *Non-Teratogenic Effects* Oxycodone hydrochloride was administered orally to female rats during gestation and lactation in a pre- and postnatal toxicity study. There were no drug-related effects on reproductive performance in these females or any long-term developmental or reproductive effects in pups born to these rats. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to approximately 0.4-times an adult human dose of 160 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered. **8.2 Labor and Delivery** Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. OxyContin is not recommended for use in women immediately prior to and during labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. Have a specific opioid antagonist, such as naloxone or nalmefene, available for reversal of opioid-induced respiratory depression in the neonate. **8.3 Nursing Mothers** Oxycodone has been detected in breast milk. Instruct patients not to undertake nursing while receiving OxyContin. Do not initiate OxyContin therapy while nursing because of the possibility of sedation or respiratory depression in the infant. Withdrawal signs can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped. **8.4 Pediatric Use** Safety and effectiveness of OxyContin in pediatric patients below the age of 18 years have not been established. **8.5 Geriatric Use** In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, reduce the starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients. Respiratory depression is the chief risk in elderly or debilitated patients, usually the result of large initial doses in patients who are not tolerant to opioids, or when opioids are given in conjunction with other agents that depress respiration. Titrate the dose of OxyContin cautiously in these patients. **8.6 Hepatic Impairment** A study of OxyContin in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function. Therefore, in the setting of hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration *[see Clinical Pharmacology (12.3)]*. **8.7 Renal Impairment** In patients with renal impairment, as evidenced by decreased creatinine clearance (< 60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Follow a conservative approach to dose initiation and adjust according to the clinical situation *[see Clinical Pharmacology (12.3)]*. **8.8 Gender Differences** In pharmacokinetic studies with OxyContin, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials. **8.9 Neonatal Opioid Withdrawal Syndrome** Chronic maternal use of oxycodone during pregnancy can affect the fetus with subsequent withdrawal signs. Neonatal withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration and severity of neonatal withdrawal syndrome vary based on the drug used, duration of use, the dose of last maternal use, and rate of elimination of drug by the newborn. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts.

9 DRUG ABUSE AND DEPENDENCE **9.1 Controlled Substance** OxyContin contains oxycodone, a Schedule II controlled substance with a high potential for abuse similar to other opioids including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*. The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse. **9.2 Abuse** Abuse of OxyContin poses a hazard of overdose and death. This risk is increased with compromising the tablet and with concurrent abuse of alcohol or other substances. All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over-the-counter drug to get "high", or the use of steroids for performance enhancement and muscle build up. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. "Drug-seeking" behavior is very common to addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction. OxyContin, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests as required by state law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to reduce abuse of opioid drugs. *Risks Specific to Abuse of OxyContin* OxyContin is for oral use only. Abuse of OxyContin poses a risk of overdose and death. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk of overdose or death is increased with concurrent use of OxyContin with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OxyContin enhances drug release and increases the risk of overdose and death. With parenteral abuse, the inactive ingredients in OxyContin can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV. *Summary* The *in vitro* data demonstrate that OxyContin has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OxyContin by these routes, as well as by the oral route is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OxyContin on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate. OxyContin contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1), and Drug Abuse and Dependence (9.1)]*. **9.3 Dependence** Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects. Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. OxyContin should not be abruptly discontinued *[see Dosage and Administration (2.4)]*. If OxyContin is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.9)]*.

10 OVERDOSAGE ***Clinical Presentation*** Acute overdosage with OxyContin can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations. ***Treatment of Overdose*** In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques. The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Such agents should be administered cautiously to persons who are known, or suspected to be physically dependent on OxyContin. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome. Because the duration of reversal would be expected to be less than the duration of action of oxycodone in OxyContin, carefully monitor the patient until spontaneous respiration is reliably reestablished. OxyContin will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be administered as directed in the product's prescribing information. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

CAUTION
DEA FORM REQUIRED

17 PATIENT COUNSELING INFORMATION *See FDA-approved patient labeling (Medication Guide)* *Abuse Potential* Inform patients that OxyContin contains oxycodone, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share OxyContin with others and to take steps to protect OxyContin from theft or misuse. *Life-Threatening Respiratory Depression* Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting OxyContin or when the dose is increased. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties. *Accidental Exposure* Instruct patients to take steps to store OxyContin securely. Accidental exposure, especially in children, may result in serious harm or death. Advise patients to dispose of unused OxyContin by flushing the tablets down the toilet. *Risks from Concomitant Use of Alcohol and other CNS Depressants* Inform patients that the concomitant use of alcohol with OxyContin can increase the risk of life-threatening respiratory depression. Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter drug products that contain alcohol, during treatment with OxyContin. Inform patients that potentially serious additive effects may occur if OxyContin is used with other CNS depressants, and not to use such drugs unless supervised by a health care provider. *Important Administration Instructions* Instruct patients how to properly take OxyContin, including the following: • OxyContin is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OxyContin tablets can result in a fatal overdose. • OxyContin tablets should be taken one tablet at a time. • Do not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth. • Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth. *Hypotension* Inform patients that OxyContin may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position). *Driving or Operating Heavy Machinery* Inform patients that OxyContin may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication. *Constipation* Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention. *Anaphylaxis* Inform patients that anaphylaxis has been reported with ingredients contained in OxyContin. Advise patients how to recognize such a reaction and when to seek medical attention. *Pregnancy* Advise female patients that OxyContin can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant. Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

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June 2013

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FEATURE ARTICLES

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Polymyalgia rheumatica and giant cell arteritis: How best to approach these related diseases

Each of these painful disorders can be challenging to diagnose, and many patients have both. Adequate glucocorticoid dosing and gradual tapering are key to treatment success.

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Polymyalgia rheumatica (PMR) is a relatively common inflammatory rheumatic disease occurring most often in the elderly population.[1,2] It usually causes pain and stiffness in the shoulders, pelvic girdle, and neck. Up to 15% of individuals with PMR also have giant cell arteritis (GCA),[2] a vasculitis of medium-size and large arteries that typically occurs in patients >50 years. Headache, jaw claudication, and visual abnormalities characterize GCA. Up to 50% of patients with GCA have PMR.[2] (See "A trip to the eye doctor yields more than this patient bargained for" on page S7.) With both conditions, there are usually elevations in the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, although the ESR in some cases can be normal.[3]

Office-based primary care physicians are

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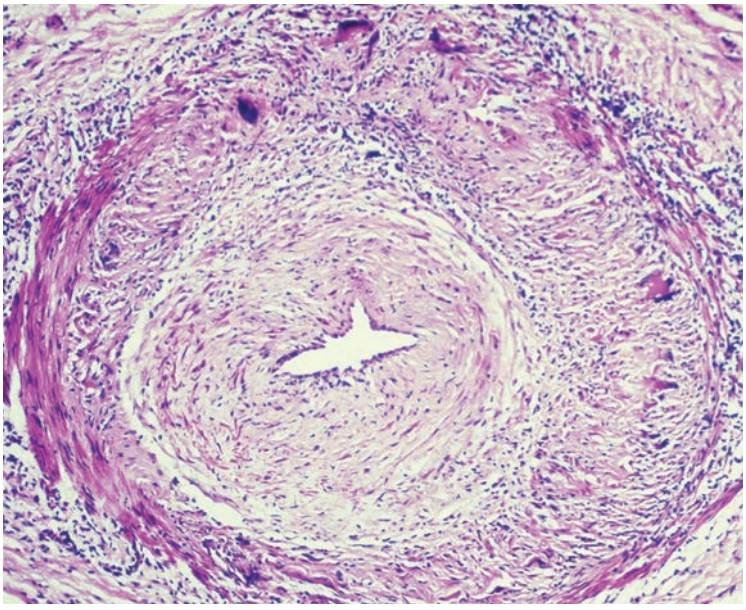

Cross-section of a temporal artery biopsy specimen from a patient with giant cell arteritis.

Photo: Biophoto Associates / Science Source

often the first to encounter these diseases. Symptoms can vary among patients and presentations can be vague, making the diagnoses of PMR and GCA challenging. This article can assist you in recognizing the signs and symptoms of PMR and GCA, and in developing and executing an appropriate plan of care.

Polymyalgia rheumatica

The cause of PMR is unknown, and the disease is often self-limited.[4] Average patient age at diagnosis is 70 years, though onset does occur in individuals in their 50s and 60s. PMR may arise abruptly, causing increasing pain and stiffness in the neck, shoulder, or pelvic girdle, which often lead to impairment of activities of daily living. Patients may complain of difficulty lifting their arms above the shoulders, an inability to comb their hair, or trouble simply getting in and out of a chair. Up to 40% of patients have associated fever, malaise, weight loss, depression, and joint swelling—most commonly in the hands.[3,5] The myalgias and stiffness are typically symmetrical; they tend to be worse in the morning and improve later in the day. However, prolonged inactivity may cause the stiffness to return. A duration of symptoms lasting more than 2 weeks is part of the core inclusion criteria for diagnosis recommended by the British Society for Rheumatology and the British Health Professionals in Rheumatology (BSR-BHPR).[6]

Myalgias and stiffness of polymyalgia rheumatica are typically symmetrical and tend to be worse in the morning and improve during the day.

Other diagnoses to consider. The differential diagnosis includes bacterial and viral infections, rheumatoid arthritis, malignancy, osteoarthritis, hypothyroidism, amyloidosis, vasculitis, inflammatory myopathy, fibromyalgia, iatrogenic causes, and, of course, GCA.[7,8] In many cases, patients live with their symptoms for weeks or longer, often attributing them to arthritis or just getting old, and do not seek medical attention until the symptoms become significant and debilitating.

Physical exam clues. Limitation in a patient's range of motion—eg, difficulty lifting arms or standing from a sitting position—is attributable primarily to pain, not muscular weakness. Hands may be swollen. Rarely, with longer durations of illness, PMR can cause muscle atrophy and proximal muscle tenderness.[2]

No pathognomonic test. Although acute phase reactants are typically elevated in PMR, a pathognomonic test for the disorder does not exist. A diagnosis of PMR therefore depends on clinical presentation and ruling out other diagnoses. Serum ESR levels that support a diagnosis of PMR typically are >40 to 50 mm/h.[9] However, in up to 20% of patients, ESR can be normal.[10] Other lab findings may include elevated CRP and normocytic anemia, as well as negative results for antinuclear antibody, rheumatoid factor, and anti-cyclic citrullinated antibody.

Radiographs rarely aid in diagnosis, and magnetic resonance imaging (MRI) can detect abnormalities but is usually not necessary for diagnosis.

Treat with glucocorticoids

While the mainstay of PMR treatment is oral glucocorticoids, data are limited on optimal dosing to achieve remission.[11] There is no universally accepted approach for initiating, tapering, or maintaining therapy. Available studies suggest that prednisone be started at between 10 and 20 mg/d.[6,8,11] Symptoms should resolve in a week.[12] Most patients require up to 2 years of tapering glucocorticoid treatment, and relapses occur in 23% to 29% of patients using prednisone, prompting the need for a dose adjustment.[11] In one study, 55% of PMR patients taking prednisolone relapsed.[5]

A reasonable approach. A systematic review of the treatment of PMR found that prednisone given at 15 mg/d for 4 weeks is most effective. After that, the suggested rate of tapering is 1 mg each month to reach a dose of 8 to 10 mg/d. Further tapering should proceed by 1 mg every 2 months to discontinuation. The review also noted that initiating prednisone doses at <10 mg/d and tapering at a rate >1 mg/mo were associated with higher relapse rates and a need for longer glucocorticoid therapy.[11]

BSR-BHPR guidelines recommend initiating prednisolone at 15 mg/d for 3 weeks, reducing the dose to 12.5 mg/d for 3 weeks, then 10 mg/d for 4 to 6 weeks, and then reducing the dose by 1 mg every 4 to 8 weeks until completion.[6] However, a lack of controlled studies means no consistent evidence supports any advocated treatment plan.

Let the patient's clinical course guide you. Tailor the steroid regimen to a patient's regression of symptoms and normalization of inflammatory markers. Keep in mind that there is some benefit in gradual tapers to avoid relapses. Consider dose adjustments if symptoms resurface.[6] Persistent or recurrent

elevation of ESR or CRP may suggest an alternate diagnosis of malignancy or GCA. Also recommend regular exercise and, as needed, adequate intake of calcium, vitamin D, and bisphosphonates to prevent glucocorticoid-induced osteoporosis.[6]

Treatments of unlikely or uncertain benefit. PMR studies have looked at different glucocorticoid routes of administration, corticosteroid-sparing drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Various glucocorticoids have been given intramuscularly, but oral glucocorticoid agents have shown greater consistency in treatment effects and control of symptoms.[11,13,14]

As for corticosteroid-sparing drugs, methotrexate and anti-tumor necrosis factor (anti-TNF) agents have yielded mixed results.[15] Unfortunately, a lack of controlled studies and long-term follow-up data make it difficult to safely recommend these agents.[8,11,15] Methotrexate used with prednisone has shown some promise in studies—less so in clinical practice—for reducing the duration of relapses and the need for upward titration of prednisone, and for reducing prednisone-related adverse effects such as osteoporosis.[11] Lastly, adding NSAIDs to glucocorticoid therapy has shown no advantage over using glucocorticoids alone. And they increase the number of adverse effects.

Following up the PMR-GCA connection

Given the strong clinical association between PMR and GCA, even if a patient's presentation suggests isolated PMR, it might be prudent to consider a rheumatology consultation to rule out the possibility of silent GCA.

Giant cell arteritis

GCA, also known as temporal arteritis, is a systemic vasculitis that affects medium-size and large cranial arteries originating from the aortic arch. It tends to involve the extracranial branches of the carotid artery.[16]

Visual disturbance is the most dire symptom. Presenting symptoms can vary but classically include headache, scalp tenderness/sensitivity, jaw claudication, and visual changes. Nonvascular symptoms usually mimic the vague symptoms of PMR: fever, malaise, aching joints, and weight loss.[2,7] Due to the risk of abrupt visual loss with GCA, promptly evaluate any patient complaining of visual disturbances. If appropriate treatment is not initiated at onset of symptoms, irreversible visual loss may ensue. An important distinction between PMR and GCA is that PMR alone does not cause blindness.[8,10] Less common manifestations of GCA are cough and other upper-respiratory symptoms, arm claudication, aneurysm, and aortic dissection.[3,14]

First steps in the work-up. Physical exam findings are usually normal, but patients may

A TRIP TO THE EYE DOCTOR YIELDS MORE THAN THIS PATIENT BARGAINED FOR

MJ visits his ophthalmologist because he had recently noticed blurry vision in his right eye. While waiting to see the doctor, the 68-year-old patient experiences chest pain and is immediately transported to the hospital.

Cardiac catheterization reveals an occluded distal left anterior descending (LAD) artery, and the patient undergoes angioplasty. Other lesions of concern involve the mid LAD and right circumflex arteries. MJ is considered a good candidate for further surgery, but he suddenly loses vision in his right eye. In addition, visual acuity testing reveals decreased acuity in the left eye. You, along with his surgeon, decide that a stat biopsy of his right temporal artery is in order. The biospy results come back positive for giant cell arteritis.

Tipoffs to associated polymyalgia rheumatica

While talking with the patient, you learn that, for the past month, he'd been experiencing right-sided facial cramping when chewing food, left-sided headaches, increasing pain with attempted shoulder movement, and hip discomfort when getting out of bed in the morning. MJ says he thought this was his arthritis acting up and indicates that he'd been taking ibuprofen to get some relief.

Limited range of motion on examination

A musculoskeletal examination reveals decreased range of motion in both shoulders, with the left side more limited than the right. The patient's hip range of motion is decreased bilaterally and, due to the pain, he has difficulty standing from the side of the bed. Palpation of the joints and muscles reveals no tenderness.

Elevated lab values

MJ's erythrocyte sedimentation rate (ESR) is 78 mm/h; C-reactive protein level is 5 mg/dL; the alkaline phosphatase level is mildly elevated at 134 U/L; and the complete blood count is within normal limits without evidence of anemia or an altered platelet count.

Treatment and follow-up

You order IV methylprednisolone 1 g/d for 3 days, and then oral prednisone 60 mg/d. After discharge, MJ's ophthalmologist and rheumatologist monitor his progress. At 2 weeks, MJ's ESR normalizes to 3 mm/h.

After 1 month, there is neither improvement nor deterioration in either visual field—that is, the patient can't see out of his right eye and his left eye remains blurry. The rheumatologist tapers the oral prednisone to 20 mg twice daily. The patient's hip and shoulder pain resolve, with a return of full range of motion. He no longer has headaches or cramping with chewing. His chief complaint is his weight gain and Cushingoid appearance. He does well with a continued taper of the prednisone, and after 2.5 years is down to 2.5 mg/d. The vision in his left eye returns to baseline acuity, and vision in his right eye improves enough to let him read large print and watch television.

have a large tender, nodular, or pulseless temporal artery.[3] With a complaint of visual disturbances, conduct a visual acuity exam to assess for monocular or binocular visual aberrations and to identify any decrease in visual fields. Additional physical exam findings may be related to PMR.[3] In up to 50% of GCA cases, PMR symptoms may be the presenting clinical features.[10,16]

Lab findings are nonspecific. The ESR is usually >50 mm/h and is the most consistently elevated laboratory test in GCA. However, a recent study showed that 25% of patients who tested positive for GCA on biopsy had a normal ESR.[10] Elevated CRP and alkaline-phosphatase levels and platelet count are often noted.[10] Normochromic or hypochromic anemia is also a common finding, and it occurs in PMR, as well.[2]

Other conditions to consider include polyarteritis nodosa and Takayasu arteritis. The temporal arteries are rarely abnormal on examination, and unaffected vision helps with the differentiation.[2] Takayasu arteritis is pathologically similar to GCA but tends to target large elastic arteries such as the aorta and its main branches. And it occurs predominantly in individuals younger than 40 years of age.[10]

Hospitalize a patient with suspected giant cell arteritis and visual disturbances, and start high-dose IV glucocorticoid therapy immediately to prevent blindness.

If vision is affected, take immediate steps

There is no time to waste if you suspect GCA in a patient with visual disturbances. Hospitalize the patient and initiate high-dose intravenous (IV) glucocorticoid therapy immediately to prevent permanent blindness. Normal vision returns in one-third of patients who receive IV therapy within 24 hours.[14] Treatment provides no benefit if delayed for more than 48 hours after the onset of visual disturbances.[16]

Give IV methylprednisolone 1 g/d for 3 to 5 days,[10,16] then switch to oral prednisone starting at 60 mg/d and tapering the dose gradually as you would in PMR, according to the patient's clinical course.[3,10,16] If treatment does not diminish the visual disturbance, it's time to investigate other possible causes.[10]

No emergency? Consider biopsy

Unlike PMR, GCA can be diagnosed definitively, with a temporal artery biopsy. With suspicion of this diagnosis, immediately refer the patient to a surgeon for biopsy. Sliced segments of the artery are sampled at intervals of 1 to 2 mm.[2] Positive histologic evidence reveals granulomatous lesions on multiple levels, usually with giant cells and often in close proximity to disrupted, internal elastic lamina.[17] Biopsy of the contralateral temporal artery may increase yield, but it is seldom necessary and not often done. Should biopsy results be negative on both sides, consider other diagnoses. However, 15.3% of GCA patients with a negative biopsy result meet other diagnostic criteria.[17]

Exploration of other artery involvement may be prudent. Consider involvement of large vessels such as the aorta and subclavian artery. MRI or angiography would be a study of choice, especially in cases where the patient complains of arm claudication or other systemic symptoms.[3]

Treat with oral prednisone

In patients without risk of visual loss, an initial daily dose of oral prednisone, 40 to 60 mg, is sufficient to suppress symptoms and normalize inflammatory factors.[18] Continue at this dose until clinical and laboratory markers show that the inflammatory process has subsided. Although systemic symptoms may reduce dramatically within 72 hours, it may take 2 to 4 weeks for them to reach a level (in conjunction with improving lab values) that allows steroid tapering to begin.[2-4,10,16]

Associated manifestations such as headache, scalp tenderness, and jaw claudication may take longer to improve. As in the case of PMR, a slow gradual taper based on the patient's clinical response is prudent to reduce the risk of relapse. Do not be concerned if increased dose adjustments by 15 to 25 mg/d are required before attempting further reductions. The disease course is generally less than 2 years.[2-4] However, relapses occur in 30% to 50% of patients.[4] It has been recommended that patients receive follow-up evaluation as long as 6 to 12 years after corticosteroids are withdrawn.[2,4]

Steroid-sparing agents have not necessarily shown benefit in this group of patients, but newer agents are being investigated.

Unless contraindicated, consider antiplatelet therapy with aspirin at 81 mg/d to reduce the risk of visual loss, transient ischemic attack, or stroke. As with PMR management, take steps to prevent glucocorticoid-induced osteoporosis, since corticosteroid therapy will continue for at least 1 to 2 years. Up to 25% of

patients with GCA have large-vessel involvement, making it prudent to monitor for aortic aneurysm, which is 17 times more likely in patients with GCA than among the general population.[3]

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What to do when pain and addiction coexist

A multidimensional approach to pain treatment will serve all patients with chronic pain well and is especially important for those who misuse alcohol, street drugs, or prescribed medications.

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Illustration: Steve Dininno

Chronic pain and addictive disorders are each distinct clinical conditions that can be expressed in unique ways in different individuals. Similar to other chronic conditions such as diabetes, hypertension, or asthma, both pain and addictive disease often have biological as well psychobehavioral contributors that may shape clinical expression.[1]

As with these other illnesses, it is helpful for clinicians to engage the patient in a consistent process of self-care and to provide long-term clinical care while at the same time coordinating the care of other providers and specialists.[2,3] In some cases a definitive cure for pain may be possible, but more often, chronic pain, like addiction, is a persistent condition requiring treatment over many years.

It will come as no surprise to learn that the convergence of pain and addiction can complicate recovery from both problems.[4] Pain or its associated symptoms may prompt continuing

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The author reported no potential conflict of interest relevant to this article.

use of substances that provide transient relief, but which sometimes perpetuate distress and reduce quality of life. And addiction may drive the experience of pain and seem to justify use of an addictive substance that the patient craves.

It is also important to recognize that pain and addiction frequently share a number of similar clinical features—including sleep and mood disturbances, substance use, deconditioning, functional losses, and high levels of stress—such that the conditions can reinforce one another. Full evaluation and comprehensive treatment of the biopsychosocial components of both conditions can improve outcomes.

The purpose of this article is to explore a model of multidimensional care that will serve all patients with chronic pain well, including those with addiction disorders.

What drives substance use? How common is it?

Patients with chronic pain may use alcohol, street drugs, or prescribed medications for diverse reasons. Many are self-medicating pain, sleep difficulties, mood fluctuations, or painful, intrusive memories. Others use these psychoactive agents as a form of recreation, as a compulsive act due to addiction, or to avoid withdrawal symptoms when physically dependent. And still others use these agents for diversion and profit.

Sometimes only one motive drives their behavior, but often several are present. As a physician, your goal is to identify the substances being used and the motivators of use (when possible) to better address the underlying causes.

The lifetime prevalence of addictive disorders among US adults is about 12.5% for alcohol dependence, 17.8% for alcohol abuse, 2.6% for drug dependence, and 7.7% for drug abuse.[5,6]

Research also suggests that there is a relatively high rate of chronic pain among individuals with addiction disorders.[7] Many factors may contribute to pain in people with addictions, including injuries[8] and traumatic childhood experiences. The latter appears to increase the risk of developing addiction and/or chronic pain later in life.[9,10]

Conducting a thorough assessment

In addition to a careful assessment of pain and its consequences for the patient, it is important to conduct a thorough assessment of current and past use of alcohol, street drugs, tobacco, and controlled prescription drugs in a nonjudgmental manner. A number of validated screening tools are available that may help identify substance abuse.

Consider using NIDA-Modified ASSIST (http://www.drugabuse.gov/sites/default/files/pdf/nmassist.pdf), an excellent assessment tool for primary care providers that inventories substance use and helps monitor it on an ongoing basis. If the patient does not misuse substances, the screen is very brief. If he or she misuses them and acknowledges it, NIDA-Modified ASSIST will provide a comprehensive picture of the nature of the problem. Other assessment tools—including those specifically geared to opioid misuse[11]—are listed in the TABLE.

If you are considering the use of opioids to treat a patient's chronic pain, urine drug testing can provide objective information regarding current substance use and is especially important in patients with known addictive disorders or substance misuse.

A 24-hour inventory of substance and medications use, identifying exactly when and for what symptoms each was used, can reveal important clinical information. It is not unusual, for instance, to identify a pain patient using alcohol at bedtime to induce sleep (although alcohol actually disrupts sleep architecture) or using opioids for stress or anxiety even when pain is not anticipated or present.

Multidimensional treatment approach

Your goals in treating chronic pain include reduction in pain and associated symptoms, enhanced functioning, and a return to a high quality of life with meaning and purpose. The goals of addiction or substance misuse recovery usually include avoiding harmful use of substances and similarly achieving physical, psychological, and spiritual well-being. These goals are entirely compatible.

Unless specific surgeries, procedures, or other interventions are able to eliminate a patient's pain, treatment usually must address not only the pain, but also coexisting mental health or medical issues, as well as pain sequelae that may increase pain. An interdisciplinary approach often offers the best opportunity for success.[12]

To effectively address substance misuse in the context of chronic pain requires an understanding of what is driving the misuse and

Research suggests that there is a relatively high rate of chronic pain among individuals with addiction disorders.

TABLE
Screens for addictive disorders

Instrument	Screening target	What's involved
Addiction Behaviors Checklist http://dsibmeetings.westat.com/SBIRT/Wu%20addiction%20behaviors%20checklist.pdf	Tracks behaviors of patients who have been prescribed opioids	20 observations
CAGE-AID http://www.ncdhhs.gov/mhddsas/providers/DWI/dualdiagnosis/CAGE-AID.pdf	Alcohol, drugs	4 questions
Cyr Wartman screen http://www.ama-cmeonline.com/pain_mgmt/tables/table_cage.htm	Alcohol, drugs	2 questions
DAST (Drug Abuse Screening Test) http://www.emcdda.europa.eu/attachements.cfm/att_61480_EN_DAST%202008.pdf	Drugs	20 questions
DIRE (Diagnosis, Intractability, Risk, Efficacy) http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=5&ved=0CEgQFjAE&url=http%3A%2F%2Fwww.fmdrl.org%2Findex.cfm%3Fevent%3Dc.getAttachment%26riid%3D6613&ei=vJ7lULDHFqKc2AWCilGwAQ&usg=AFQjCNECSYFnam9UATA-Xm_JQ0cjm6Xdiw&bvm=bv.1355534169,d.b2I	Opioid risk specific	Scoring of 4 factors
NIDA-Modified ASSIST http://www.drugabuse.gov/sites/default/files/pdf/nmassist.pdf	Alcohol, tobacco, drugs	Short to comprehensive, depending on use
ORT (Opioid Risk Tool) http://www.partnersagainstpain.com/printouts/Opioid_Risk_Tool.pdf	Opioid risk specific	5 questions
PMQ (Pain Medication Questionnaire) http://download.journals.elsevierhealth.com/pdfs/journals/0885-3924/PIIS0885392404001010.pdf	Opioid risk specific	26 questions
SOAPP (Screener and Opioid Assessment for Patients with Pain) http://www.painedu.org/soapp.asp	Opioid risk specific	3 versions: 24,14, and 5 questions
Urine drug screening	Objective information on drug/medication use	Objective lab test

again must address coexisting mental health or other medical issues, as well as the sequelae of the substance problem. A biopsychosocial approach to treatment of both pain and addiction that actively engages the patient in self-management is ***critical*** to recovery from both chronic conditions.[13] (See "Self-care options for patients with chronic pain and addiction" on page S14.)

Such treatment ideally involves the primary care physician, psychologist or counselor, and physical or occupational therapist—with support from pain or addiction providers. The medical home can play important roles in coordination of care, facilitation of self-management, and promotion of recovery from both conditions.[14]

The structure of our health care system, however, favors payment for short clinic visits and procedures and may limit access to mental health and substance services. It may be more expedient to prescribe a medication or refer for a pain block than to explore things like stress, diet, exercise, sleep, mood, substance use, and

the ability to function at work and home. The "quick solution" approach often omits the development of a foundation of self-care that is important to long-term success.

While patients without co-occurring substance use disorders may get by with this approach, patients with co-occurring addiction-related disorders can be hurt by reliance on medications and other passive therapies.

Finding the best treatment approaches

Effective treatment of chronic pain may draw from 4 broad categories: psychobehavioral, physical therapeutic, and interventionalist approaches, as well as medications.

Psychobehavioral and physical therapeutic approaches can provide a foundation for recovery from chronic pain and a context in which strategic use of interventionalist procedures and medications may be more effective. Fortunately, many self-management strategies that have been shown to be effective in pain management are also effective in the treatment of addiction. Among these are: cognitive-behavioral therapy, meditation, emerging 12-step programs for pain, and physical reconditioning.

As you plan out each patient's therapeutic regimen, consider these options:

Cognitive-behavioral therapy (CBT) aims to change behaviors and thought patterns to help patients gain control over their condition. It has been shown to be effective in improving outcomes in chronic pain and substance abuse treatment.[15,16] In the treatment of chronic pain, patients often identify negative self-talk that is impeding their recovery—"My pain is killing me. I'll never be able to work." They are encouraged to substitute more positive thoughts that favor recovery, eg, "My pain is hurtful but not harmful. My pain will lead me to new and more meaningful work."

Patients also examine physical activities, stress, sleep challenges, and mood fluctuations that can increase pain and engage in approaches such as activity pacing, stretching, and relaxation that may mitigate their pain. When CBT is used in addiction treatment, patients similarly explore triggers for drug use (often people, places, and things), and they substitute alternatives that support abstinence and recovery.

For example, patients may elect social opportunities with friends who do not get high, participate in valued activities that don't involve alcohol or drugs, and frequent places not associated with old drug use patterns. They reframe negative thinking to gain a more positive perspective that favors recovery and prevents relapse. "I can't live without alcohol forever" becomes "I can enjoy today without alcohol." They also apply relaxation or meditation skills to reduce stress, and they develop coping skills to address high-risk situations.[17]

Meditation-relaxation. Despite some scientific debate about the relative merits of different relaxation approaches, such as hypnosis, guided imagery, progressive muscle relaxation, and meditation, there is clear evidence that deep relaxation practices can play an important role in pain management. Recent studies have shown benefit for mindfulness meditation in the treatment of pain.[18] Other studies suggest various forms of meditation may help patients recover from addiction.[19] The physiologic basis of pain relief associated with meditation or deep relaxation has been variously attributed to muscular relaxation, reduction in sympathetic arousal, and changes in activity of different brain centers that process pain and pain inhibition. Effects on sleep enhancement and reduction in anxiety may also contribute to recovery from pain and substance abuse.

One simple approach to meditation is for the patient to sit comfortably for 10 to 20 minutes while focusing awareness on the natural flow of his or her breath going in and out. The patient is instructed to note thoughts, sounds, and sensations as they pass by and gently bring attention back to the flow of breath. A word or phrase can be silently thought on the outbreath to enhance focus.

12-step programs. Twelve-step programs such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) have been a key element of self-management of recovery from addiction for at least 7 decades. AA and similar meetings engage attendees in a process of self-reflection, reframing of perspectives, interpersonal sharing, and acceptance that for many are powerful supports for substance abuse recovery.[20]

12-step programs for pain. Recently 12-step programs for chronic pain that use the same basic strategies and paradigm to engage individuals in a process of recovery have begun to proliferate; these meetings are open to people both with pain alone and those with pain and addiction.[21] And when pain-specific 12-step groups are not available, many patients find they can adapt the steps in an AA or NA meeting to address their pain.

There are now 12-step programs for chronic pain that use the same basic strategies as Alcoholics Anonymous and Narcotics Anonymous to engage in the process of recovery.

SELF-CARE OPTIONS FOR PATIENTS WITH CHRONIC PAIN AND ADDICTION

Consider suggesting that your patient:

- Participate in a cognitive-behavioral therapy (CBT) pain and addiction recovery group to learn skills for pain and substance recovery. (Ideally, 8-10 sessions plus a periodic refresher.)
  Two resources for identifying CBT therapists are the Association for Behavioral and Cognitive Therapies (www.abct.org) and the National Association of Cognitive-Behavioral Therapists (www.nacbt.org).
- Practice deep relaxation/meditation one to 2 times daily on a regular basis.
  One widely available, evidence-based approach is mindfulness-based stress reduction (MBSR); certified instructors can be found online.
- Engage in comfortable aerobic exercise on a regular basis, gently stretching before and after.
  Initial guidance from a physical therapist or trainer experienced with chronic pain may be helpful.
- Work with an addictions counselor to explore substance use and support recovery.
- Attend Chronic Pain Anonymous or another chronic pain peer-support group.
  Information on face-to-face, phone, and Internet groups can be found on the Web sites of the American Chronic Pain Association (www.theacpa.org) and Chronic Pain Anonymous (www.chronicpainanonymous.org).
- Participate in a substance self-help group regularly. (Alcoholics Anonymous and Narcotics Anonymous are the most common. Alternative programs include Smart Recovery and Rational Recovery.)
  Meeting information for these groups can be found at: www.aa.org, www.na.org, www.smartrecovery.org, and www.rational.org.
- Identify a sponsor (a support person experienced in successful recovery in the 12-step world).
  Sponsors are usually identified at self-help group meetings.
- Engage in meaningful and/or pleasurable activities that focus attention away from pain.
  Activities can include things like art, crafts, gardening, outdoor activities, or volunteer work.

Remember that chronic pain and addiction are chronic conditions, so it is important to check on self-care at each visit and revise the plan as helpful to the patient. Use selected treatments, such as targeted physical therapy, medications, procedures, or other approaches when appropriate.

Some studies suggest that exercise can improve outcomes in addiction treatment.

The strengths of 12-step groups are that they are free and widely available. Patients may need to try different groups, however, to find one at which they feel comfortable.

Physical reconditioning. The benefits of exercise and movement therapies in chronic pain management are well documented. Exercise activates central endorphin release and descending pain inhibition. Aerobic exercise, such as cycling, using an elliptical machine, or walking, may improve circulation and tissue oxygenation, which in turn can improve healing. Stretching can relieve muscular tension and normalize joint motion; however, stretches must be tailored to the condition of the particular patient. Improved posture and proper biomechanics during movement reduce physical stress. Similarly, toning or strengthening can provide support for spinal and other joints and reduce propensity for spasm. It is usually important for a patient to initiate exercise under the guidance of a physical therapist.

Clinicians should advise patients with pain to exercise in a manner that is gentle, gradually progressive, and avoids significantly increasing the patient's pain.[22] Some studies suggest exercise can improve outcomes in addiction treatment; it is speculated that enhanced self-esteem and the increase in endogenous endorphins may contribute.[23]

Adding active treatments to the platform of self-care

Selection of specific procedures and medications for different pain problems is beyond the scope of this article, but it is worth noting that engagement in a biobehavioral self-care

program provides a context that supports successful use of procedures and medication. For example, improved posture, muscular support of the spine, and proper biomechanics may reduce disc stresses that can produce recurrent pain after a successful epidural injection of steroids. Similarly, muscular trigger point injections are more likely to result in protracted muscular relaxation if a patient is engaged in regular stress management and stretching.

Similarly, when withdrawal-producing medications are eliminated, when stress, anxiety, and depression are addressed, and when the patient is physically conditioned, he or she may respond better to nonopioid pain medications.

Opioids for pain in substance use disorders

Opioids are rarely first-line medications for chronic pain treatment but they can be valuable components of care for some who have not responded to self-management, interventionalist procedures, and nonopioid medications. But use of opioids in chronic pain patients with addictive disorders requires ***exceptional*** care.

As you might expect, the risk of opioid misuse is higher in individuals with a prior history of substance use when compared with a person without this history. But the relative risk for people with different types of addiction is unknown. There's the potential to become addicted to opioids, for instance, when an individual is in recovery from addiction to alcohol or marijuana. However, observation suggests the risk of addiction to prescribed opioids is more likely in patients with a past history of opioid addiction than other addictions. Duration of recovery is generally inversely related to the risk of relapse, so longer term recovery presents less risk than recent recovery.

Whenever possible, engage any patient with a history of addiction in an active addiction recovery program and have him or her co-managed by an addiction specialist if you plan to prescribe opioids. Patients in recovery from nonopioid addiction who require opioids for pain may benefit from tightening the structure of care. This may include:

- providing a smaller supply of medications at more frequent intervals;
- increasing supports for recovery from pain, addiction, and co-occurring disorders;
- increasing supervision including office visits, urine drug screens, and pill counts;
- selecting treatments carefully to limit reward (euphoria) when possible, as reward can trigger misuse; and
- assuring that the setting of care can provide optimal care coordination.[24]

For those with a history of opioid addiction, the safest option for opioid therapy is engagement in an addiction treatment paradigm of opioid therapy. This will mean either buprenorphine/naloxone with a registered provider or methadone maintenance treatment through a licensed clinic in which medications will be tightly supervised and the patient engaged in psychosocial addiction treatment. Both types of opioid agonist therapy may provide some pain relief while providing pharmacologic treatment of opioid addiction and minimizing the risk of misuse and associated harm (such as overdose).

What's your role?

The key roles of the primary care physician in managing chronic pain and coexisting substance use disorders are to (1) identify the variables that contribute to the patient's experience of pain and use of substances, (2) encourage and support the patient as he or she tries to develop a self-care program, (3) strategically implement or refer for active treatment of the various contributing factors, and (4) see the patient regularly to monitor engagement in both self-care and active treatments and to revise the plan as needed.

Coexisting pain and addiction are among the most challenging scenarios encountered in primary care. Recovery is possible, but patience, time, flexibility, and consistent motivational support are critical**.** The process is often 2 steps forward, one step back, so clinicians and patients need to celebrate small victories.

The process is often 2 steps forward, one step back, so clinicians and patients need to celebrate small victories.

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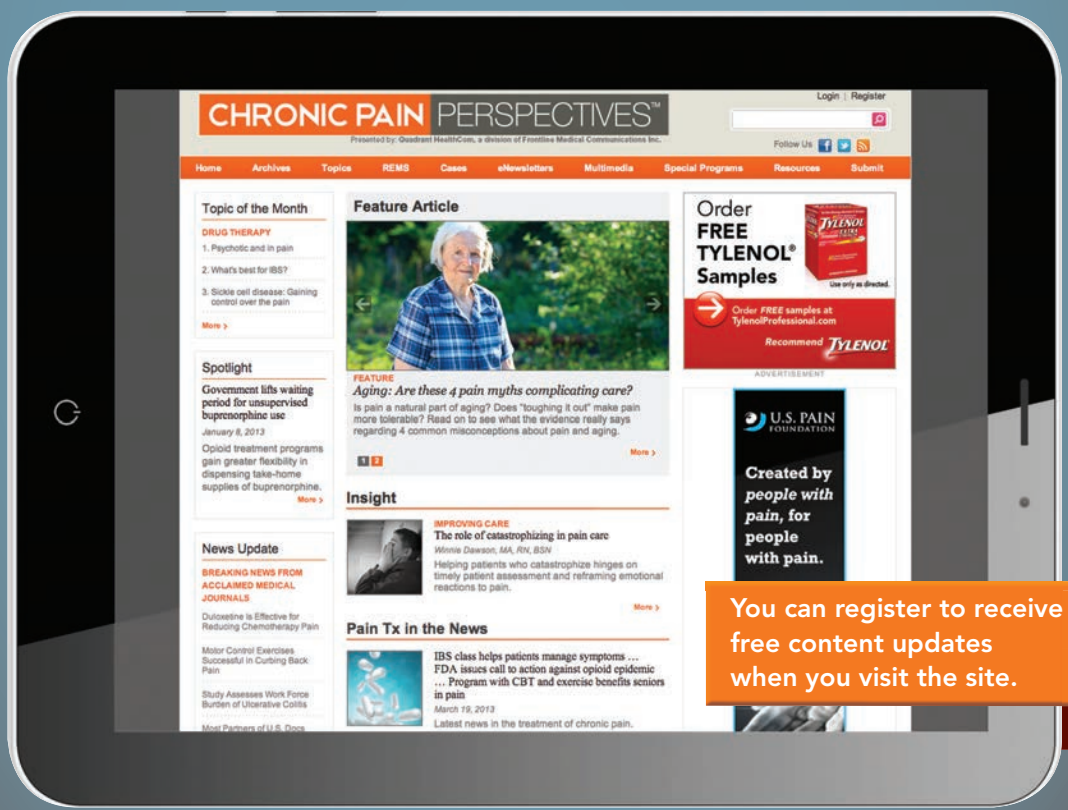

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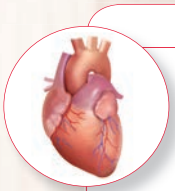

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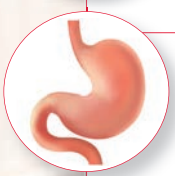

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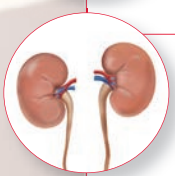

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