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## Contents

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Introduction

The information contained in this training module is for your educational purposes only. This training piece is designed to provide you with information you need on the product, the disease, and the competitive environment. It is not to be used in detailing or distributed to any third parties.

LYRICA® (pregabalin), an anticonvulsant with analgesic properties, binds with high affinity to the alpha2-delta (α2-δ) site, an auxiliary subunit of voltage-gated calcium channels, in central nervous system tissues. This binding is thought to produce the analgesic and antiseizure effects of LYRICA. Key features of LYRICA include its ability to get to an effective starting dose quickly, rapid onset of action, powerful and sustained efficacy, well-studied safety profile and tolerability profile, linear pharmacokinetics, high bioavailability, low potential for pharmacokinetic drug interactions, and a newly elucidated mechanism of action.

In the United States, LYRICA is FDA-approved for:

• management of neuropathic pain associated with diabetic peripheral neuropathy (DPN)
• management of postherpetic neuralgia (PHN)
• management of fibromyalgia
• adjunctive therapy for adult patients with partial seizures

This module provides the information that you will need in order to effectively discuss LYRICA and its indications with healthcare professionals.

Section 1 presents an overview of LYRICA, including its indications; dosing and administration for painful diabetic peripheral neuropathy (pDPN), PHN, fibromyalgia, epilepsy; dosage and strength forms; mechanism of action; relevance of the mechanism of action in treating pDPN, PHN, fibromyalgia, and epilepsy; and pharmacokinetic profile.

Section 2 describes the safety profile of LYRICA, including contraindications; warnings and precautions; adverse events associated with LYRICA; drug interactions associated with LYRICA; use of LYRICA in specific populations; the risk of drug abuse and dependence; and experience of overdosage with LYRICA.

The module concludes with a summary, glossary of medical terms, and bibliography.
Section 1: Introduction to LYRICA®

Objectives

- State the indications for LYRICA
- Describe the dosing and administration of LYRICA in painful DPN and PHN
- Describe the dosing and administration of LYRICA in fibromyalgia
- Describe the dosing and administration of LYRICA in epilepsy
- Describe the LYRICA dosing recommendations for special populations
- State the dosage and strength forms of LYRICA
- Describe the mechanism of action of pregabalin
- Discuss the pharmacokinetic profile of LYRICA

This section presents information about LYRICA and its active ingredient pregabalin. This information includes indications for LYRICA and how it is dosed and administered for each FDA-approved disease state. Also reviewed in this section is the mechanism of action for pregabalin, and its relevance in treating painful diabetic peripheral neuropathy (pDPN), postherpetic neuralgia (PHN), fibromyalgia, and epilepsy. The section ends with a discussion of the pharmacokinetic profile for LYRICA.
State the indications for LYRICA®

Indications for LYRICA®

LYRICA is also FDA-approved for:

- the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN)
- the management of postherpetic neuralgia (PHN)
- management of fibromyalgia
- adjunctive therapy for adult patients with partial seizures

Click on the icon to reinforce what you have learned about the FDA-approved indications for LYRICA.
Progress Check

There may be more than one correct answer to each question.

1. Which of the following is an indication for LYRICA for pain in the US?
   A management of fibromyalgia
   B management of chronic, widespread pain of neuropathic origin
   C management of neuropathic pain associated with DPN
   D management of PHN

2. Which of the following is an indication for LYRICA for epilepsy?
   A first-line therapy for patients with partial seizures
   B emergency management of acute seizures and long-term control of partial seizures
   C adjunctive therapy for adult patients with partial seizures
   D management of partial onset and generalized seizures
Describe the dosing and administration of LYRICA® in painful DPN and PHN

**Dosing and Administration of LYRICA® in pDPN and PHN**

LYRICA is given orally with or without food. When discontinuing LYRICA, taper gradually over a minimum of 1 week.

**Dosing for Neuropathic Pain Associated With pDPN**

For neuropathic pain associated with DPN, the maximum recommended dose of LYRICA is 100 mg 3 times a day (300 mg/day) in patients with creatinine clearance (CLcr) of at least 60 mL/min (normal renal function) (LYRICA PI, 2009, p. 3C). Dosing should begin at 50 mg 3 times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability.

Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. Since dose-dependent adverse effects may occur, treatment with doses above 300 mg/day is not recommended.

**Oral Solution Concentration and Dispensing**

The oral solution consists of 20 mg pregabalin per mL. Prescriptions should be written in milligrams, and the pharmacist should calculate the approximate dose in mL for dispensing (eg, 150 mg equals 7.5 mL of the oral solution).
Describe the dosing and administration of LYRICA® in painful DPN and PHN

Click on the icon to read about Rodney, a patient with pDPN, and to answer 2 questions about his treatment with LYRICA.

CASE STUDY
Rodney — A Patient with pDPN

Dr. Holmes has diagnosed 66-year-old Rodney with pDPN based on Rodney’s patient history and physical exam. During his discussion with Rodney about treatment options, Dr. Holmes explains that the primary goal of treatment is to meaningfully reduce the intense pain that he’s experiencing.

After testing Rodney’s renal function to ensure that his kidneys are functioning normally, Dr. Holmes prescribes LYRICA to manage the neuropathic pain that’s associated with Rodney’s pDPN.

Dosing for PHN

For PHN, the recommended dose of LYRICA is 75 mg to 150 mg 2 times a day or 50 mg to 100 mg 3 times a day (150 mg/day to 300 mg/day) in patients with creatinine clearance of at least 60 mL/min (normal renal function). Dosing should begin at 75 mg 2 times a day or 50 mg 3 times a day (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability.

Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate LYRICA may be treated with up to 300 mg 2 times a day or 200 mg 3 times a day (600 mg/day). Since dose-dependent adverse events and a higher rate of treatment discontinuation due to adverse events may occur, dosing above 300 mg/day should be reserved only for those patients who have ongoing pain and are tolerating 300 mg daily.

Oral Solution Concentration and Dispensing

The oral solution consists of 20 mg pregabalin per mL. Prescriptions should be written in milligrams, and the pharmacist should calculate the approximate dose in mL for dispensing (eg, 150 mg equals 7.5 mL of the oral solution).
Describe the dosing and administration of LYRICA® in painful DPN and PHN

Click on the icon to read about Jennifer, a patient with PHN, and to answer 2 questions about her treatment with LYRICA.

CASE STUDY

Jennifer — A Patient with PHN

Dr. Wagner has diagnosed 68-year-old Jennifer with PHN based on Jennifer’s recent history with herpes zoster lesions and her physical exam. When Dr. Wagner tells Jennifer that they can begin treatment of her pain right away, Jennifer is relieved. The persistent, throbbing pain in her right chest wall that extends to her back and her nipple line has made wearing clothes difficult for her to tolerate and has affected her state of mind.

After testing Jennifer’s renal function to ensure that her kidneys are functioning normally, Dr. Wagner prescribes LYRICA at a starting dose of 150 mg/day to manage Jennifer’s PHN.

Summary of Dosing for pDPN and PHN

Figure 1A summarizes the dosing for LYRICA in painful DPN and PHN. As described previously, this figure notes that LYRICA is only approved for TID dosing in painful DPN, while it is approved for BID and TID dosing for PHN.

Figure 1A: LYRICA Dosing in Painful DPN and PHN

Adjust the dose within the approved dosage range for optimal efficacy and tolerability

Adapted from LYRICA Product Information, 2009
Progress Check

There may be more than one correct answer to each question.

1. Which of the following statements about the dosing and administration of LYRICA is (are) true?
   A The maximum recommended dose for LYRICA in painful DPN is 300 mg/day.
   B The recommended dose for LYRICA in PHN ranges from 150 mg/day to 600 mg/day.
   C If LYRICA has to be discontinued, it is not necessary to withdraw it gradually.
Describe the dosing and administration of LYRICA® in fibromyalgia

**Dosing and Administration of LYRICA® in Fibromyalgia**

LYRICA is given orally with or without food. When discontinuing LYRICA, taper gradually over a minimum of 1 week.

The recommended dose of LYRICA for fibromyalgia is 300 mg/day to 450 mg/day:

- dosing should begin at 75 mg 2 times daily (150 mg/day)
- the dose should be increased to 150 mg 2 times daily (300 mg/day) within 1 week based on efficacy and tolerability
- patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg 2 times daily (450 mg/day)

Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended.

Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function.

**Oral Solution Concentration and Dispensing**

The oral solution consists of 20 mg pregabalin per mL. Prescriptions should be written in milligrams, and the pharmacist should calculate the approximate dose in mL for dispensing (eg, 150 mg equals 7.5 mL of the oral solution).
Describe the dosing and administration of LYRICA® in fibromyalgia

Click on the icon to read about Amy, a 41-year-old woman with fibromyalgia, and to answer 2 questions about her treatment with LYRICA.

CASE STUDY

Amy — A Patient with Fibromyalgia

After he tells Amy what her diagnosis is, Dr. Harris gives her some educational materials about fibromyalgia and recommends that Amy check out some of the national fibromyalgia Web sites for more information. He also suggests she consider joining a fibromyalgia support group and starting an exercise program under the supervision of her PCP.

In addition to these nonpharmacological approaches, Dr. Harris prescribes LYRICA to manage Amy’s fibromyalgia.
Progress Check

There may be more than one correct answer to each question.

1. Which of the following statements is (are) true regarding the dosing and administration of LYRICA for fibromyalgia?
   A The recommended dose of LYRICA is 300 mg/day to 450 mg/day.
   B Dosing should begin at 100 mg 2 times daily.
   C When discontinuing LYRICA, the dose should be tapered gradually over a minimum of 2 weeks.
   D Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 450 mg/day based on efficacy and tolerability.
Describe the dosing and administration of LYRICA® in epilepsy

Dosing and Administration of LYRICA® in Epilepsy

LYRICA is given orally with or without food. When discontinuing LYRICA, taper gradually over a minimum of 1 week.

LYRICA doses of 150 mg/day to 600 mg/day have been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. The total daily dose should be divided and administered either BID or TID.

In general, it is recommended that patients be started with a total daily dose no greater than 150 mg/day (75 mg BID or 50 mg TID). Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day. The efficacy and adverse event profiles of LYRICA have been shown to be dose-related. The effect of dose escalation rate on the tolerability of LYRICA has not been formally studied.

The efficacy of add-on LYRICA in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of LYRICA with gabapentin cannot be offered.

Figure 1B summarizes LYRICA dosing for adult epilepsy patients with partial onset seizures.

**Figure 1B: LYRICA Dosing in Partial Onset Seizures in Adults**

Oral Solution Concentration and Dispensing

The oral solution consists of 20 mg pregabalin per mL. Prescriptions should be written in milligrams, and the pharmacist should calculate the approximate dose in mL for dispensing (eg, 150 mg equals 7.5 mL of the oral solution).
Describe the dosing and administration of LYRICA® in epilepsy

Click on the icon to read about Mark, a 41-year-old man with epilepsy experiencing simple partial seizures, and to answer 2 questions about his treatment with LYRICA.

**CASE STUDY**

**Mark — A Patient with Epilepsy**

Neurologist Dr. Idira has diagnosed 41-year-old Mark with epilepsy based on his presentation, medical and family history, the physical exam, and results from the functional EEG. She further believes that Mark is having idiopathic simple partial seizures.

Mark is concerned about the diagnosis and the impact it may have on his quality of life. He is relieved when Dr. Idira assures him that medication could treat the symptoms and reduce his risk of experiencing another seizure.

When Mark is unable to gain adequate control over his seizures after trying 2 different AEDs as monotherapy, Dr. Idira decides to prescribe LYRICA as adjunctive therapy to Mark’s existing treatment regimen.
Progress Check

There may be **more than one** correct answer to each question.

1. Which of the following statements about the dosing and administration of LYRICA as adjunctive therapy in adult patients with partial onset seizures is (are) **true**?
   
   A. The recommended starting dose for LYRICA is 75 mg/day (25 mg TID).
   
   **B.** LYRICA doses of 150 mg/day (75 mg BID or 50 mg TID) to 600 mg/day (300 mg BID or 200 mg TID) have been shown to be effective.
   
   C. If LYRICA has to be discontinued, it is not necessary to withdraw it gradually.
Describe the LYRICA® dosing recommendations for special populations

LYRICA® Dosing Recommendations for Special Populations

Dosage Adjustments for Patients with Renal Impairment

Dosage adjustment in patients with renal impairment should be based on creatinine clearance, as illustrated in the following table. The first step in using this table is to determine a patient's creatinine clearance in mL/min from the patient's serum creatinine using the Cockcroft and Gault equation.

Table 1A shows the Cockcroft and Gault equation.

Table 1A: Cockcroft and Gault Equation for Determining Creatinine Clearance Based on Serum Creatinine

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Total LYRICA Daily Dose (mg/day)*</th>
<th>Dose Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>150</td>
<td>300</td>
</tr>
<tr>
<td>30 to 60</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>15 to 30</td>
<td>25 to 50</td>
<td>75</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25</td>
<td>25 to 50</td>
</tr>
</tbody>
</table>

Supplementary dosage following hemodialysis**

- Patients on the 25 mg QD regimen: take 1 supplemental dose of 25 mg or 50 mg
- Patients on the 25 mg QD to 50 mg QD regimen: take 1 supplemental dose of 50 mg or 75 mg
- Patients on the 75 mg QD regimen: take 1 supplemental dose of 100 mg or 150 mg

TID = 3 divided doses; BID = 2 divided doses; QD = single daily dose
* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
** Supplementary dose is a single additional dose.

As noted in Table 1B, in patients undergoing hemodialysis, the LYRICA daily dose should be adjusted based on renal function. In addition, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment.
Progress Check

There may be more than one correct answer to each question.

1. Dosing of pregabalin should be adjusted in:
   A all elderly patients.
   B patients receiving hemodialysis.
   C patients with impaired renal function.
   D patients who have age-related renal insufficiency.

2. Patients with a creatinine clearance rate of 30 to 60 mL/min should:
   A receive the same dose as patients with a creatinine clearance rate of >60 mL/min.
   B receive one-half of the dose (eg, 150 mg/day instead of 300 mg/day).
   C receive one-quarter the dose (eg, 75 mg/day instead of 300 mg/day).
   D not receive LYRICA.
Available Dosage and Strength Forms of LYRICA®

Capsules

LYRICA is available as 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg capsules.

LYRICA is supplied in the following manner:

- bottles of 90: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg capsules
- unit-dose blister packages of 100: 50 mg, 75 mg, 100 mg, and 150 mg capsules

Oral Solution

LYRICA oral solution is available as 20 mg/mL. It is supplied in the following manner:

- bottles of 90: 16 fluid ounce white, high-density polyethylene bottle with a polyethylene-lined closure

Storage

LYRICA should be stored at 25°C (77°F), but may be stored within a range of 15°C to 30°C (59°F to 86°F).
Progress Check

There may be more than one correct answer to each question.

1. LYRICA is available in capsules that increase at 25 mg intervals between 75 mg and 300 mg.
   A true
   B false

2. All LYRICA capsule sizes are available in bottles of 90 and blister-packs of 100.
   A true
   B false

3. LYRICA should be stored at 25°C (77°F), but may be stored within a range of:
   A 0°C to 15°C (32°F to 59°F).
   B 5°C to 20°C (41°F to 68°F).
   C 10°C to 25°C (50°F to 77°F).
   D 15°C to 30°C (59°F to 86°F).
Describe the mechanism of action of pregabalin

Product Description and Mechanism of Action of Pregabalin

The active ingredient in LYRICA is pregabalin. Before discussing the mechanism of action of pregabalin, it is important to note that LYRICA and gabapentin are the only FDA-approved, prescription agents with this mechanism.

Figure 1C illustrates the chemical structure of pregabalin, the active ingredient in LYRICA.

![Figure 1C: Structure of Pregabalin](Adapted from LYRICA Product Information, 2009)

**Mechanism of Action**

The mechanism of action of LYRICA is unknown in humans. LYRICA binds with high affinity to the alpha_2-delta (\(\alpha_2-\delta\)) site, an auxiliary subunit of **voltage-gated calcium channels**, in central nervous system tissues such as the dorsal horn of the spinal cord and the brain.
Describe the mechanism of action of pregabalin

Figure 1D illustrates the binding site of LYRICA.

Figure 1D: Pregabalin Binding to Alpha2-delta Subunit of Voltage-Gated Calcium Channels

These calcium channels regulate the movement of calcium (as calcium ions, or Ca\(^{2+}\)) into cells, and calcium influx is needed to trigger the release of several neurotransmitters from presynaptic neurons. Recall that the mechanism of action of LYRICA is unknown and that LYRICA binds with high affinity to the alpha2-delta site. Data from preclinical and animal models indicate that:

- binding at the alpha2-delta subunit modulates calcium influx in hyperexcited neurons
- this reduces the release of calcium-dependent excitatory neurotransmitters, including glutamate and substance P
- this is believed to be responsible for the analgesic and anticonvulsive effects of LYRICA

The clinical significance in humans is not known.

Click on the icon to view a video that illustrates the mechanism of action of LYRICA.

Click on the icon to reinforce what you have learned about the mechanism of action of pregabalin.
Describe the mechanism of action of pregabalin

**Pregabalin Is NOT a Vascular Calcium Channel Blocker**

While the alpha_2_-delta binding site is on voltage-gated calcium channels, it is important to note that pregabalin is *not* a vascular calcium channel blocker (CCB). Vascular calcium channel blockers (for example, such as amlodipine):

- bind to the alpha_1_ subunit of L-type calcium channels
- directly block the channel pore, preventing the movement of calcium ions
- produce their effects in the peripheral vascular smooth muscle, and their actions result in a decrease in blood pressure

In contrast, pregabalin binds to the alpha_2_-delta subunit (a different protein). Instead of blocking the channel pore and calcium ion movement, pregabalin modulates (reduces) calcium ion influx into hyperexcited neurons. Furthermore, pregabalin does not affect blood pressure or heart rate.

These differences are illustrated in the following animation.

Click on the icon to reinforce what you have learned about the binding site for pregabalin.
What Pregabalin Does Not Do

It is important to understand how the mechanism of action of pregabalin differs from those of other agents used to treat chronic pain conditions and epilepsy. Although pregabalin has some structural similarities to gamma (γ)-aminobutyric acid (GABA), pregabalin does not act like GABA, and it acts differently than agents that affect GABA and its responses:

- pregabalin does not bind directly to GABA_A, GABA_B, or benzodiazepine receptors
- pregabalin does not augment GABA_A responses (differentiating it from benzodiazepines and barbiturates)
- pregabalin does not act like GABA uptake inhibitors (unlike tiagabine) or GABA transaminase inhibitors (unlike vigabatrin)
- as noted previously, pregabalin does not block calcium channels and does not block sodium channels (unlike phenytoin, carbamazepine, lamotrigine, and TCAs)
- pregabalin is not active at opiate receptors (unlike morphine)
- pregabalin does not alter cyclooxygenase activity (unlike nonsteroidal anti-inflammatory drugs [NSAIDs])
- pregabalin is inactive at serotonin receptors (unlike buspirone) and dopamine receptors (unlike haloperidol and other antipsychotics)
- pregabalin does not inhibit dopamine, serotonin, or norepinephrine reuptake (unlike TCAs, selective serotonin reuptake inhibitors [SSRIs], or serotonin norepinephrine reuptake inhibitors [SNRIs])
Progress Check

There may be more than one correct answer to each question.

1. Pregabalin:
   A does not bind to the alpha_2-delta site.
   B binds with low affinity to the alpha_2-delta site.
   C binds with high affinity to the alpha_2-delta site.

2. Data from preclinical and animal models show that pregabalin:
   A reduces the release of calcium-dependent excitatory neurotransmitters.
   B increases the sodium-dependent release of neurotransmitters in hyperexcited neurons.
   C modulates calcium influx in hyperexcited neurons.
   D is a vascular calcium channel blocker.

3. In animal models, in terms of mechanism of action:
   A LYRICA blocks the action of neurotransmitters at specific types of calcium channels.
   B LYRICA increases the release of inhibitory neurotransmitters by binding to the alpha_2-
      delta subunit of voltage-gated calcium channels.
   C LYRICA binds to the alpha_2-delta site, an auxiliary subunit of voltage-gated 
      calcium channels.
   D The action of LYRICA is believed to result in a reduction in the release of 
      glutamate and substance P.
   E LYRICA is thought to act similarly to compounds that inhibit gamma-aminobutyric acid.

4. Pregabalin has ________ effects.
   A analgesic
   B antiseizure

5. Which of the following statements is (are) true?
   A Pregabalin does not bind to GABA_A or GABA_B receptors.
   B Pregabalin does not bind to benzodiazepine receptors.
   C Pregabalin does not block sodium or calcium channels.
   D Pregabalin is inactive at serotonin and dopamine receptors.
Discuss the pharmacokinetic profile of LYRICA®

**Pharmacokinetic Profile**

LYRICA is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours. The following paragraphs describe its pharmacokinetics in greater detail.

**Absorption and Distribution**

After oral administration of LYRICA under fasting conditions, peak plasma concentrations occurred within 1.5 hours. The oral bioavailability of LYRICA is ≥90% and is independent of dose (no saturable absorption).

As shown in Figure 1E, the $C_{\text{max}}$ of LYRICA increases proportionally with increasing dose, as does area under the time/concentration curve. Multiple-dose pharmacokinetics can be predicted from single-dose data.

![Figure 1E: $C_{\text{max}}$ Increases Proportionally With Increasing Doses](image)

LYRICA was given under fasting conditions in healthy normal volunteers. Multiple-dose pharmacokinetics can be predicted from single-dose data.

As can be seen from this figure, the peak plasma concentration ($C_{\text{max}}$) of pregabalin increases proportionally as the dose increases.

*Adapted from Pfizer Data on File [3]*
Following repeated administration, plasma concentration reaches **steady state** within 24 to 48 hours.

The rate of absorption is decreased when LYRICA is given with food, which results in a decrease in $C_{\text{max}}$ by approximately 25% to 30% and an increase in the time to $C_{\text{max}}$ to approximately 3 hours. However, because there is no clinically relevant effect on the amount of LYRICA that is absorbed, LYRICA can be taken with or without food.

Animal studies have shown that LYRICA readily crosses the **blood-brain barrier**. These studies also show that LYRICA crosses the placenta and is present in the milk of lactating rats.

LYRICA is not bound to plasma proteins.

**Metabolism and Elimination**

LYRICA undergoes negligible hepatic metabolism in humans. LYRICA is eliminated primarily by renal excretion as unchanged drug, and elimination is nearly proportional to creatinine clearance. Elimination is thought to involve **renal tubular reabsorption**.

The **mean** elimination half-life is 6.3 hours.

**Pharmacokinetics in Special Populations as Seen in the Pivotal LYRICA® Clinical Trials**

Table 1C describes the pharmacokinetics of LYRICA in special populations, as seen in the pivotal LYRICA clinical trials.

<table>
<thead>
<tr>
<th>Population</th>
<th>Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>• no differences have been observed among Caucasians, Blacks, and Hispanics</td>
</tr>
<tr>
<td>Gender</td>
<td>• no differences have been observed</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>• clearance is nearly proportional to creatinine clearance</td>
</tr>
<tr>
<td></td>
<td>• dosage reduction in patients with renal dysfunction is necessary</td>
</tr>
<tr>
<td></td>
<td>• because LYRICA is removed by hemodialysis, dosing must be modified for patients on hemodialysis</td>
</tr>
<tr>
<td>Elderly</td>
<td>• oral clearance of LYRICA tends to decrease with increasing age, consistent with age-related decreases in creatinine clearance</td>
</tr>
<tr>
<td></td>
<td>• dosage should be adjusted in patients who have age-related renal insufficiency</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>• pharmacokinetics of LYRICA have not been adequately studied in pediatric patients</td>
</tr>
</tbody>
</table>
Progress Check

There may be more than one correct answer to each question.

1. Which of the following is (are) true regarding the pharmacokinetics of LYRICA?
   A  The mean elimination half-life is 12 hours.
   B  While the rate of absorption is decreased with food, LYRICA can be taken with or without food.
   C  LYRICA is not bound to plasma proteins.
   D  The cytochrome P-450 system, specifically CYP3A4, metabolizes LYRICA.
   E  LYRICA undergoes negligible hepatic metabolism.
   F  LYRICA crosses the blood-brain barrier.
   G  The oral bioavailability of pregabalin is dependent on dose.
   H  In studies in rats, pregabalin did not cross the placenta.

2. When LYRICA is administered with food:
   A  the rate of absorption does not change.
   B  there is an increase in $C_{\text{max}}$ by approximately 25% to 30%.
   C  there is no clinically relevant effect on the amount of LYRICA that is absorbed.
   D  there is a decrease in the time to $C_{\text{max}}$. 

LYRICA has been evaluated in an extensive clinical trial program that shows its well-studied safety profile and tolerability profile. This section discusses this profile, describing the contraindications, warnings and precautions, adverse events, drug interactions, and other safety profile topics associated with its use for the management of fibromyalgia.

Upon completion of this section, you should be able to describe the safety profile of LYRICA, including:

- contraindications
- warnings and precautions
- adverse reactions
- drug interactions
- use in specific populations
- risk of drug abuse and dependence
- experience with overdosage

It is important that you familiarize yourself with aspects of the package insert related to safety. Additional training pieces provide you with more information so that you will be able to effectively handle objections that may arise from these issues; these pieces will address physician questions and help you handle them by putting safety issues into context.
State the contraindications for LYRICA®

Contraindications for LYRICA®

LYRICA is contraindicated in patients with known hypersensitivity to pregabalin or any of its components.
Progress Check

There may be more than one correct answer to each question.

1. LYRICA is contraindicated in:
   A patients with any degree of renal impairment.
   B patients with known hypersensitivity to pregabalin or any of its components.
   C patients with moderate to severe hepatic impairment.
Discuss the warnings and precautions contained in the LYRICA® prescribing information

**Warnings and Precautions Contained in the LYRICA® Prescribing Information**

**Angioedema**

There have been postmarketing reports of **angioedema** in patients during initial and chronic treatment with LYRICA. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. LYRICA should be discontinued immediately in patients with these symptoms.

Caution should be exercised when prescribing LYRICA to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (eg, angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema.

**Hypersensitivity**

There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with LYRICA. Adverse reactions included skin redness, blisters, hives, rash, **dyspnea**, and wheezing. LYRICA should be discontinued immediately in patients with these symptoms.

**Withdrawal of Antiepileptic Drugs**

The product information discusses withdrawal of LYRICA therapy twice. The second time is in the Warnings and Precautions section, and this is specific to use in patients with partial onset seizures. However, because all CNS drugs need to be withdrawn slowly — regardless of what they have been prescribed for — this information is also discussed in the Dosing and Administration section, which can be found near the beginning of the LYRICA product information.

The Warnings and Precautions section notes the need for all antiepileptic drugs (AEDs) to be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If LYRICA is discontinued, this should be done gradually over a minimum of 1 week.
Suicidal Behavior and Ideation

The product information for LYRICA notes that antiepileptic drugs (AEDs) carry a class warning about the increased risk of suicidal thoughts or behaviors in patients taking AEDs for any indication. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Clinical Trials Showing Increased Risk of Suicidal Behavior and Ideation

Pooled analysis of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5–100 years) in the clinical trials analyzed.

Table 2A shows the absolute and relative risk by indication for all evaluated AEDs.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events per 1,000 Patients</th>
<th>Drug Patients with Events per 1,000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events per 1,000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.4</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.7</td>
<td>8.5</td>
<td>1.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Other</td>
<td>1.0</td>
<td>1.8</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>
Discuss the warnings and precautions contained in the LYRICA® prescribing information

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Clinical Implications

Anyone considering prescribing LYRICA or any other AEDs must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Peripheral Edema

LYRICA treatment may cause peripheral edema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

In controlled trials, the incidence of peripheral edema was:

- 6% in the LYRICA group
- 2% in the placebo group

In controlled clinical trials, 0.5% of patients receiving LYRICA and 0.2% patients receiving placebo withdrew due to peripheral edema.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with DPN. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only; 8% (69/859) of patients who were treated with LYRICA only; and 19% (23/120) of patients who were on both LYRICA and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on LYRICA only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when coadministering LYRICA and these agents.
Because there are limited data on patients with congestive heart failure with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients.

**Clinical Implications**

It is important to remember that:
- only 0.5% of patients withdrew due to peripheral edema
- peripheral edema was dose-related but was not associated with cardiovascular complications or lab changes suggestive of deterioration in renal or hepatic function

Care should be taken when coadministering LYRICA with thiazolidinediones

**Dizziness and Somnolence**

LYRICA may cause dizziness and somnolence. Patients should be informed that LYRICA-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery.

In the LYRICA controlled trials, dizziness was experienced by:
- 31% of LYRICA-treated patients
- 9% of placebo-treated patients

In those same controlled trials, somnolence was experienced by:
- 22% of LYRICA-treated patients
- 7% of placebo-treated patients

Dizziness and somnolence generally began shortly after the initiation of LYRICA therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal (4% each) from controlled studies. In LYRICA-treated patients reporting these adverse reactions in short-term, controlled studies, dizziness persisted until the last dose in 30% of patients, and somnolence persisted until the last dose in 42% of patients.

**Weight Gain**

LYRICA treatment may cause weight gain. In LYRICA controlled trials of up to 14 weeks, a gain of ≥7% over baseline weight was observed in 9% of LYRICA-treated patients, and 2% in placebo-treated patients. Few patients treated with LYRICA (0.3%) withdrew from the controlled trials due to weight gain. LYRICA-associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema.

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled trials, the long-term cardiovascular effects of LYRICA-associated weight gain are unknown.
Among diabetic patients, LYRICA-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received LYRICA for at least 2 years, the average weight gain was 5.2 kg.

While the effects of LYRICA-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term, open-label clinical trials with diabetic patients, LYRICA treatment does not appear to be associated with loss of glycemic control (as measured by \textit{HbA1C}).

\textbf{Clinical Implications}

Although a $\geq 7\%$ increase in weight from baseline may be clinically relevant, it is important to remember that:

\begin{itemize}
  \item weight gain was reported in 1 or 2 ways:
    \begin{itemize}
      \item as a patient's increase in body weight of $\geq 7\%$ over baseline
      \item as an adverse event in clinical trials
    \end{itemize}
  \item in controlled trials, weight gain $\geq 7\%$ was not associated with clinically important changes in systolic or diastolic blood pressure
  \item although the effects of LYRICA-associated weight gain on glycemic control have not been systematically assessed, LYRICA treatment does not appear to be associated with loss of glycemic control
\end{itemize}

\textbf{Abrupt or Rapid Discontinuation}

Following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms that included insomnia, nausea, headache, and diarrhea. LYRICA should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

\textbf{Tumorigenic Potential}

In standard preclinical in vivo lifetime carcinogenicity studies of LYRICA, an unexpectedly high incidence of \textit{hemangiosarcoma} was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during premarketing development provides no direct means to assess its potential for introducing more tumors in humans.

In clinical studies across various patient populations, comprising 6,396 patient-years of exposure in patients $>12$ years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.
Discuss the warnings and precautions contained in the LYRICA® prescribing information

**Ophthalmologic Effects**

In controlled studies, a higher proportion of patients receiving LYRICA reported blurred vision (7%) than did patients receiving placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1% of patients discontinued LYRICA treatment due to vision-related adverse events (primarily blurred vision).

Table 2B shows the results of prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing, and dilated funduscopic examination, was performed in over 3,600 patients.

![Table 2B: Ophthalmologic Testing](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LYRICA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced visual acuity</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Visual field changes</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Funduscopic changes</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision occur, they should notify their physician. If the visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions.

**Creatine Kinase**

LYRICA treatment was associated with creatine kinase (CK) (also called creatine phosphokinase) elevations. Mean changes in CK from baseline to the maximum value were:

- 60 U/L for patients treated with LYRICA
- 28 U/L for patients treated with placebo

In all controlled trials across multiple patient populations, the following percentage of patients had a value of CK ≥3X the upper limit of normal (ULN):

- 1.5% who received LYRICA
- 0.7% who received placebo

Three LYRICA-treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and LYRICA is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. LYRICA treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated CK levels occur.
Clinical Implications

Creatine kinase is an enzyme involved in muscle activities. Its level is increased after vigorous exercise (eg, weight lifting), and in specific cardiovascular conditions (eg, myocardial infarction) or disease of the musculoskeletal system (eg, rhabdomyolysis, myopathy). The normal range of CK levels is 30 U/L to 130 U/L.

When considering the changes in CK levels in trials of LYRICA, it is important to remember that:

- prescribers should instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever
- although these changes were noted, the package insert does not recommend routine monitoring prior to the administration of LYRICA; however, the physician's clinical judgment should prevail

Decreased Platelet Count

LYRICA treatment was associated with a decrease in platelet count. Patients treated with LYRICA experienced a mean maximal decrease in platelet count of 20 x 10^3/mL, compared to 11 x 10^3/mL in patients treated with placebo. In the overall database of controlled trials, 2% of patients treated with placebo and 3% of patients treated with LYRICA experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 x 10^3/mL. A single LYRICA-treated subject developed severe thrombocytopenia with a platelet count less than 20 x 10^3/mL. In randomized controlled trials, LYRICA was not associated with an increase in bleeding-related adverse events.

Clinical Implications

Although these changes were noted, the package insert does not recommend routine monitoring prior to the administration of LYRICA. However, the physician's clinical judgment should prevail.

PR Interval Prolongation

Treatment with LYRICA was associated with PR interval prolongation. In analysis of clinical trial ECG data, the mean PR interval increase was 3 msec to 6 msec at LYRICA doses ≥300 mg/day. This mean change difference did not lead to an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or to an increased risk of adverse events of second or third degree AV block.

Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR-prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

Click on the icon to reinforce what you have learned about the Warnings and Precautions for LYRICA.
Progress Check

There may be more than one correct answer to each question.

1. In all controlled studies, the incidence of peripheral edema was 6% with LYRICA and 2% with placebo; this event led to ________ of patients taking LYRICA discontinuing from the study.
   A 0.5%
   B 2.1%
   C 8%

2. In all controlled studies, the incidence of weight gain ≥7% of baseline was ________ with LYRICA and ________ with placebo.
   A 12%; 4%
   B 9%; 2%
   C 4%; 0%

3. Which of the following statements about LYRICA is (are) true?
   A LYRICA should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.
   B Patients treated with LYRICA should notify their physician if changes in vision occur.
Discuss the adverse events associated with LYRICA® in all controlled clinical trials

Adverse Events Associated with LYRICA® in All Controlled Clinical Trials

In all controlled and uncontrolled trials across various patient populations during the premarketing development of LYRICA, more than 10,000 patients have received LYRICA. Approximately 5,000 patients were treated for 6 months or more; over 3,100 patients were treated for 1 year or longer; and over 1,400 patients were treated for at least 2 years.

Discontinuations Due to Adverse Events

In controlled trials of all populations combined, the following percentages of patients discontinued due to adverse reactions:

- LYRICA: 14%
- placebo: 7%

In the LYRICA group, the adverse reactions most frequently leading to discontinuation of LYRICA were dizziness (4%) and somnolence (3%). Other adverse reactions that led to discontinuation from controlled trials more frequently in the LYRICA group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema.

Most Common Adverse Events

The most common adverse reactions (≥5% and twice the rate seen with placebo) for LYRICA in all trials combined were:

- dizziness
- somnolence
- dry mouth
- edema
- blurred vision
- weight gain
- “thinking abnormal” (primarily difficulty with concentration/attention)

Click on the icon to reinforce what you have learned about discontinuations due to adverse events in controlled trials of all populations combined.
Progress Check

There may be more than one correct answer to each question.

1. Which of the following are among the most common (≥5% and twice placebo) adverse events seen with LYRICA in all controlled clinical trials?
   A. dizziness, somnolence, dry mouth
   B. edema, blurred vision, weight gain, “thinking abnormal”
Discuss the adverse events associated with LYRICA® in clinical trials in patients with pDPN

Adverse Events Associated with LYRICA® in Clinical Trials in Patients with pDPN

Discontinuations Due to Adverse Events

In clinical trials in patients with neuropathic pain associated with DPN, 9% of patients treated with LYRICA and 4% of patients treated with placebo discontinued prematurely due to adverse events. In the LYRICA group, the most common reasons for discontinuation due to adverse events were:

- dizziness (3%)
- somnolence (2%)

In comparison, less than 1% of patients receiving placebo withdrew due to dizziness or somnolence.
Most Common Adverse Events

Table 2C lists all adverse events occurring in ≥5% of patients with neuropathic pain associated with DPN receiving LYRICA, and for which the incidence was greater than in the placebo group. Please note that the LYRICA package insert uses a cutoff of ≥1%. A majority of patients treated with LYRICA in clinical trials had adverse events with a maximum intensity of mild or moderate.

### Table 2C: Treatment-Emergent Adverse Events in Controlled Trials in Painful DPN (≥25% of All Patients Treated With LYRICA in at Least One Dose Group and Overall Numerically More Than in the Placebo Group)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>LYRICA 75 mg/day (n = 77)</th>
<th>LYRICA 150 mg/day (n = 212)</th>
<th>LYRICA 300 mg/day (n = 321)</th>
<th>LYRICA 600 mg/day (n = 369)</th>
<th>All LYRICA (n = 979)</th>
<th>Placebo (n = 459)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>4%</td>
<td>2%</td>
<td>4%</td>
<td>7%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>5%</td>
<td>2%</td>
<td>2%</td>
<td>6%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3%</td>
<td>2%</td>
<td>5%</td>
<td>7%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>0%</td>
<td>2%</td>
<td>4%</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Metabolic and Nutritional Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>4%</td>
<td>6%</td>
<td>9%</td>
<td>12%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0%</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>9%</td>
<td>23%</td>
<td>29%</td>
<td>21%</td>
<td>5%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4%</td>
<td>6%</td>
<td>13%</td>
<td>16%</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9%</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6%</td>
<td>1%</td>
<td>2%</td>
<td>4%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurry vision*</td>
<td>3%</td>
<td>1%</td>
<td>3%</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Investigator term; summary level term is amblyopia.
Progress Check

There may be **more than one** correct answer to each question.

1. In clinical trials in patients with pDPN, what were the most common reasons for discontinuation due to adverse events?
   - A. somnolence
   - B. constipation
   - C. dizziness
   - D. dry mouth
Discuss the adverse events associated with LYRICA® in clinical trials in patients with PHN

Adverse Events Associated with LYRICA® in Clinical Trials in Patients with PHN

Discontinuations Due to Adverse Events

In clinical trials in patients with neuropathic pain associated with PHN, 14% of patients treated with LYRICA and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the LYRICA treatment group, the most common reasons for discontinuation due to adverse events were:

- dizziness (4%)
- somnolence (3%)

In comparison, less than 1% of patients receiving placebo withdrew due to dizziness or somnolence.
Most Common Adverse Events

Table 2D lists all adverse events that occurred in ≥5% of patients with neuropathic pain associated with PHN receiving LYRICA, and for which the incidence was greater than in the placebo group. Please note that the LYRICA package insert uses a cutoff of >1%. A majority of patients treated with LYRICA in clinical trials had adverse events with a maximum intensity of mild or moderate.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>LYRICA 75 mg/day (n = 84)</th>
<th>LYRICA 150 mg/day (n = 302)</th>
<th>LYRICA 300 mg/day (n = 312)</th>
<th>LYRICA 600 mg/day (n = 154)</th>
<th>All LYRICA (n = 852)</th>
<th>Placebo (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>14%</td>
<td>8%</td>
<td>6%</td>
<td>3%</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
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<td>9%</td>
<td>5%</td>
<td>8%</td>
<td>7%</td>
<td>5%</td>
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<tr>
<td>Pain</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7%</td>
<td>7%</td>
<td>6%</td>
<td>15%</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Metabolic and Nutritional Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0%</td>
<td>8%</td>
<td>16%</td>
<td>16%</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>1%</td>
<td>2%</td>
<td>5%</td>
<td>7%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Edema</td>
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<td>1%</td>
<td>2%</td>
<td>6%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11%</td>
<td>18%</td>
<td>31%</td>
<td>37%</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8%</td>
<td>12%</td>
<td>18%</td>
<td>25%</td>
<td>16%</td>
<td>5%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1%</td>
<td>2%</td>
<td>5%</td>
<td>9%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>0%</td>
<td>2%</td>
<td>4%</td>
<td>8%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Confusion</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
<td>7%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Thinking abnormal*</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
<td>6%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurry vision**</td>
<td>1%</td>
<td>5%</td>
<td>5%</td>
<td>9%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
<td>5%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking

** Investigator term; summery level term is amblyopia
Progress Check

There may be more than one correct answer to each question.

1. In clinical trials in patients with PHN, __________ of all patients treated with LYRICA experienced dizziness?
   A  6%
   B  16%
   C  26%
   D  36%
Discuss the adverse events associated with LYRICA® in clinical trials in patients with fibromyalgia

Adverse Events Associated with LYRICA® in Clinical Trials in Patients with Fibromyalgia

Discontinuations Due to Adverse Events

In clinical trials of fibromyalgia, approximately 19% of patients receiving LYRICA and 10% receiving placebo discontinued prematurely due to adverse events. In the LYRICA group, the adverse events most frequently leading to discontinuation were:

- dizziness (6%)
- somnolence (3%)

In comparison, less than 1% of patients receiving placebo withdrew due to each of these events.
Discuss the adverse events associated with LYRICA® in clinical trials in patients with fibromyalgia

**Most Common Adverse Events**

Table 2E lists all dose-related adverse events occurring in ≥5% of patients with fibromyalgia receiving LYRICA. Please note that the LYRICA package insert uses a cutoff of ≥2%. A majority of patients treated with LYRICA in clinical studies had adverse events with a maximum intensity of mild or moderate.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>LYRICA 150 mg/day (n = 132)</th>
<th>LYRICA 300 mg/day (n = 502)</th>
<th>LYRICA 450 mg/day (n = 505)</th>
<th>LYRICA 600 mg/day (n = 378)</th>
<th>All LYRICA (n = 1751)</th>
<th>Placebo (n = 505)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td>8%</td>
<td>7%</td>
<td>7%</td>
<td>12%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7%</td>
<td>6%</td>
<td>9%</td>
<td>9%</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>4%</td>
<td>7%</td>
<td>10%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>General Disorders and Administrative Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>5%</td>
<td>7%</td>
<td>6%</td>
<td>8%</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>5%</td>
<td>5%</td>
<td>6%</td>
<td>9%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4%</td>
<td>5%</td>
<td>7%</td>
<td>5%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>8%</td>
<td>10%</td>
<td>10%</td>
<td>14%</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased appetite</td>
<td>4%</td>
<td>3%</td>
<td>5%</td>
<td>7%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>23%</td>
<td>31%</td>
<td>43%</td>
<td>45%</td>
<td>38%</td>
<td>9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13%</td>
<td>18%</td>
<td>22%</td>
<td>22%</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>11%</td>
<td>12%</td>
<td>14%</td>
<td>10%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
<td>6%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>2%</td>
<td>3%</td>
<td>6%</td>
<td>9%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>2%</td>
<td>5%</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Progress Check

There may be **more than one** correct answer to each question.

1. In the fibromyalgia trials, _____ of patients receiving LYRICA and ______ patients receiving placebo discontinued due to adverse events.
   - A 22%; 7%
   - B **19%; 10%**
   - C 12%; 4%
   - D 9%; 3%
Discuss the adverse events associated with LYRICA® in clinical trials in patients with epilepsy

Adverse Events Associated with LYRICA® in Add-On Clinical Trials in Patients with Epilepsy

Discontinuations Due to Adverse Events

In controlled add-on studies in epilepsy, approximately 15% of patients receiving LYRICA and 6% receiving placebo discontinued prematurely due to adverse events. In the LYRICA group, the adverse events most frequently leading to discontinuation were:

- dizziness (6%)
- ataxia (4%)
- somnolence (3%)

In comparison, less than 1% of patients receiving placebo withdrew due to each of these events.
Discuss the adverse events associated with LYRICA® in clinical trials in patients with epilepsy

Section 2: Safety Profile of LYRICA®

Most Common Adverse Events

Table 2F lists all dose-related adverse events occurring in ≥5% of patients with epilepsy receiving LYRICA, and for which the incidence in the 600 mg/day group was at least 2% greater than the rate in both the 150 mg/day and placebo groups. Please note that the LYRICA package insert uses a cutoff of ≥2%. A majority of patients treated with LYRICA in clinical studies had adverse events with a maximum intensity of mild or moderate.

**Table 2F: Incidence of Dose-Related Treatment-Emergent Adverse Events in Controlled Studies in Adjunctive Therapy for Adult Patients with Partial Onset Seizures (Events in ≥5% of Patients Treated With LYRICA, With an Incidence in the 600 mg/day Group >2% the Incidence in Both the 150 mg/day and Placebo Groups)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>LYRICA 150 mg/day (n = 185)</th>
<th>LYRICA 300 mg/day (n = 90)</th>
<th>LYRICA 600 mg/day (n = 395)</th>
<th>All LYRICA (n = 670)</th>
<th>Placebo (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental injury</td>
<td>7%</td>
<td>11%</td>
<td>10%</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Pain</td>
<td>3%</td>
<td>2%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased appetite</td>
<td>2%</td>
<td>3%</td>
<td>6%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1%</td>
<td>2%</td>
<td>6%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1%</td>
<td>1%</td>
<td>7%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Metabolic and Nutritional Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>5%</td>
<td>7%</td>
<td>16%</td>
<td>12%</td>
<td>1%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>3%</td>
<td>3%</td>
<td>6%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>18%</td>
<td>31%</td>
<td>38%</td>
<td>32%</td>
<td>11%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11%</td>
<td>18%</td>
<td>28%</td>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6%</td>
<td>10%</td>
<td>20%</td>
<td>15%</td>
<td>4%</td>
</tr>
<tr>
<td>Tremor</td>
<td>3%</td>
<td>7%</td>
<td>11%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Thinking abnormal*</td>
<td>4%</td>
<td>8%</td>
<td>9%</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Amnesia</td>
<td>3%</td>
<td>2%</td>
<td>6%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Speech disorder</td>
<td>1%</td>
<td>2%</td>
<td>7%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Incoordination</td>
<td>1%</td>
<td>3%</td>
<td>6%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>1%</td>
<td>3%</td>
<td>5%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Twitching</td>
<td>0%</td>
<td>4%</td>
<td>5%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Confusion</td>
<td>1%</td>
<td>2%</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred vision**</td>
<td>5%</td>
<td>8%</td>
<td>12%</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>5%</td>
<td>7%</td>
<td>12%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>3%</td>
<td>1%</td>
<td>5%</td>
<td>4%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* “Thinking abnormal” primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.

** Investigator term; summary level term is amblyopia
Progress Check

There may be more than one correct answer to each question.

1. The 2 most common adverse events (≥5%) occurring in patients with epilepsy who received LYRICA (all LYRICA doses) and for which the incidence was ≥2% greater than in the 150 mg/day and placebo groups were:
   A. dizziness and blurred vision.
   B. ataxia and somnolence.
   C. somnolence and peripheral edema.
   D. dizziness and somnolence.
Discuss drug interactions associated with LYRICA®

Drug Interactions Associated with LYRICA®

Drug interactions are an important topic when prescribing medications for patients with fibromyalgia. These patients are frequently taking multiple medications. For example, market data show that patients with fibromyalgia take, on average, 3 prescriptions to manage their symptoms, with 33% of patients taking 4 or more medications.

Drug interactions that can occur with a compound can be classified as:

- **pharmacokinetic drug interactions**: those caused when one drug affects the absorption, distribution, metabolism, or elimination of another drug; these changes may cause increased or decreased concentrations of the drug and/or its metabolites, potentially resulting in increased or decreased therapeutic or toxic effects

- **pharmacodynamic drug interactions**: those caused when one drug changes the tissue sensitivity/reactivity of another drug at the intended receptor site or end organ, or when the drugs produce additive effects through different mechanisms

Pharmacokinetic Drug Interactions

Drugs that are metabolized by the cytochrome P-450 (CYP450) enzyme system or that are highly protein bound have a greater potential for drug-drug interactions than drugs that are not metabolized by CYP450 or that have a low protein binding.

LYRICA is unlikely to be affected by other agents through metabolic interactions or protein binding displacement because LYRICA:

- is predominantly excreted unchanged in the urine
- undergoes negligible metabolism (<2% of a dose is recovered in urine as metabolites)
- does not bind to plasma proteins

In vitro and in vivo studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, no pharmacokinetic interactions have been identified in population pharmacokinetic analyses between pregabalin and the following AEDs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between LYRICA and commonly used AEDs.

In Vitro Studies

Pregabalin, at concentrations that were generally 10 times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 enzyme systems. In addition, pregabalin does not induce CYP1A2 or CYP3A4 activity. Therefore, an increase in the metabolism of coadministered CYP1A2 substrates (eg, theophylline, caffeine) or CYP3A4 substrates (eg, midazolam, testosterone) is not anticipated.
Discuss drug interactions associated with LYRICA®

In Vivo Studies

Table 2G summarizes information on the drug interactions studied with LYRICA.

**Table 2G:** No Clinically Significant Pharmacokinetic Interactions Based on Pharmacokinetic Studies or Population Analyses

<table>
<thead>
<tr>
<th>LYRICA Interactions</th>
<th>Other Drugs Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin*</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Hypoglycemics:* glyburide, metformin</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Diuretics:* furosemide</td>
<td>Phenobarbital*</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Tiagabine*</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Topiramate*</td>
</tr>
<tr>
<td>Ethanol (alcohol)</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Oral contraceptives: ethinyl estradiol, norethindrone</td>
<td></td>
</tr>
</tbody>
</table>

*Based on a pharmacokinetic population analysis

Pharmacodynamic Drug Interactions

Multiple oral doses of LYRICA were coadministered with oxycodone, lorazepam, and ethanol. Although no pharmacokinetic interactions were seen, LYRICA appears to be additive in the impairment of cognitive and gross motor functioning, which were seen when LYRICA was coadministered with these drugs. No clinically important effects on respiration were seen.

Click on the icon to reinforce what you have learned about the drug interactions associated with LYRICA.
Progress Check

There may be more than one correct answer to each question.

1. Which of the following is (are) true regarding LYRICA and the potential for drug interactions?
   A  Because of the potential for drug-drug interactions, LYRICA should not be administered with lorazepam or oxycodone.
   B  LYRICA is unlikely to be affected by other agents through metabolic interactions or protein binding displacement.
   C  In in vitro studies, LYRICA did not inhibit CYP2D6 or CYP3A4.
   D  No clinically significant drug interactions have been seen between LYRICA and oral contraceptives (ethinyl estradiol, norethindrone).

2. Which of the following statements about drug interactions with LYRICA is (are) true?
   A  Additive effects on cognitive and gross motor function were seen when LYRICA was coadministered with ethanol and lorazepam.
   B  Pregabalin is bound to plasma proteins.
   C  Pregabalin has been shown to interact with diuretics and hypoglycemics.
Discuss the use of LYRICA® in specific populations

Use of LYRICA® in Specific Patient Populations

Table 2H presents precautions associated with special populations.

<table>
<thead>
<tr>
<th>Population</th>
<th>Precautions</th>
</tr>
</thead>
</table>
| Pregnant women      | • LYRICA is pregnancy category C  
                     • effects of LYRICA on labor and delivery are unknown                                                                                     |
| Nursing mothers     | • it is not known if LYRICA is excreted in human milk, but it is present in the milk of rats  
                     • because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother |
| Pediatric patients  | • safety and efficacy in pediatric patients have not been established                                                                          |
| Geriatric patients  | • no overall differences in efficacy and safety were observed between these patients and younger patients  
                     • although the adverse reaction profile was similar between the 2 age groups, the following neurologic adverse reactions were more frequent in patients ≥65 years: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy  
                     • LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function  
                     – because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment |

Click on the icon to reinforce what you have learned about the use of LYRICA in special populations.
Progress Check

There may be more than one correct answer to each question.

1. Which of the following statements regarding LYRICA use in special populations is (are) true?
   A. LYRICA is pregnancy category B.
   B. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

2. ________ were observed between geriatric patients and younger patients enrolled in clinical studies.
   A. Significant differences in efficacy and safety
   B. No overall differences in efficacy and safety
Discuss the risk of drug abuse and dependence for LYRICA®

Risk of Drug Abuse and Dependence for LYRICA®

LYRICA is a schedule V controlled substance. It is important that you understand what constitutes a scheduled drug and what data are available for LYRICA.

The Federal Controlled Substances Act regulates the prescribing, dispensing, manufacturing, storage, sale, and distribution of controlled substances — that is, drugs that may have a potential for abuse or misuse. Potential for abuse or misuse is not the same as addiction or physical tolerance:

- addiction is defined as cluster of symptoms indicating that the individual continues to use the substance despite significant substance-related problems
- addiction can include tolerance, which is when a higher dose is needed to produce the same effect, and physical dependence, which is when the body requires continued administration of a substance to maintain normal function, but tolerance and physical dependence can also occur without addiction

The prescription of controlled substances is more regulated than that of other prescription drugs. In many cases, state laws are more restrictive than federal laws and impose additional requirements.

Controlled substances are assigned to 1 of 5 schedules (I to V):

- schedule I is reserved for drugs with the highest potential of abuse and no recognized medical use
- schedule V is for agents with lower potential for abuse or misuse relative to other scheduled drugs, and these drugs have clear medical value; in certain states, some products may be sold in limited amounts without a prescription
Table 21 presents common examples of drugs in these 5 classifications.

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>heroin</td>
</tr>
<tr>
<td>II</td>
<td>morphine, OxyContin®, Ritalin®</td>
</tr>
<tr>
<td>III</td>
<td>Tylenol® with Codeine, Vicodin®</td>
</tr>
<tr>
<td>IV</td>
<td>phenobarbital, benzodiazepines (XANAX®, Valium®, Ambien®</td>
</tr>
<tr>
<td>V</td>
<td>Robitussin AC®, LOMOTIL®</td>
</tr>
</tbody>
</table>

OxyContin® is a registered trademark of Purdue Pharma.  
Ritalin® is a registered trademark of Novartis.  
Tylenol® with Codeine is a registered trademark of Ortho-McNeil.  
Vicodin® is a registered trademark of Abbott.  
Valium® is a registered trademark of Roche.  
Ambien® is a registered trademark of sanofi-aventis (formerly Sanofi-Synthelabo).  
Robitussin AC® is a registered trademark of Wyeth Consumer Healthcare.

The FDA submits its recommendation for the schedule of a controlled substance to the Drug Enforcement Administration (DEA), which ultimately determines the classification of the drug. LYRICA is a schedule V drug, which has lower potential for misuse and abuse relative to other scheduled drugs.

Today, all drugs with new mechanisms of action and CNS activity must go through a battery of tests for abuse potential. By scheduling a drug, the DEA hopes to limit misuse or abuse and ensure that only patients with a legitimate medical need receive the agent.

Selected data considered by the FDA and DEA in scheduling LYRICA included the following 3 sets of data:

- a study in nondependent recreational drug or alcohol users
- reports of euphoria in clinical trials
- adverse events following abrupt discontinuation

LYRICA was compared with the benzodiazepine diazepam in a study of nondependent recreational users of sedative/hypnotic drugs (including alcohol) — that is, individuals who regularly take these drugs. In this study (N = 15), a single dose of LYRICA 450 mg was associated with descriptions such as "good drug effect," "high," and "liking" to a degree that was similar to a single dose of diazepam 30 mg.

Data examined by the FDA and DEA also included euphoria rates. In controlled clinical studies in over 5,500 patients, euphoria was reported in:

- 4% of patients treated with LYRICA
- 1% of patients treated with placebo
Discuss the risk of drug abuse and dependence for LYRICA®

And finally, data considered by the FDA and DEA included adverse events after abrupt discontinuation. After abrupt or rapid discontinuation of LYRICA in clinical studies, some patients reported symptoms such as:

- insomnia
- headache
- nausea
- diarrhea

LYRICA is not known to be active at receptor sites associated with drugs of abuse such as opioids and benzodiazepines.

Based on these findings, the FDA could not exclude a low risk for misuse or abuse, and LYRICA was designated schedule V, which has lower potential for abuse relative to schedules I through IV. Recall from Table 2I that the following are also schedule V agents: diphenoxylate/atropine (eg, LOMOTIL®) and cough syrup with codeine (eg, Robitussin AC®).

Physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (eg, development of tolerance, dose escalation, drug-seeking behavior).

Click on the icon to reinforce what you have learned about how drugs, including LYRICA, are scheduled.
Progress Check

There may be more than one correct answer to each question.

1. LYRICA is a schedule _____ controlled substance.
   - A II
   - B III
   - C IV
   - D V
Experience of Overdosage with LYRICA®

Signs, Symptoms, and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (≥900 mg) were not clinically different from those of patients administered recommended doses of LYRICA.

Treatment or Management of Overdose

There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage. General supportive care of the patient is indicated, including monitoring of vital signs and observation of the clinical status of the patient. A Certified Point Control Center should be contacted for up-to-date information on the management of overdose with LYRICA.

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).
Progress Check

There may be more than one correct answer to each question.

1. What are the signs and symptoms of an overdose of LYRICA?
   - A nausea and diarrhea
   - B excessive somnolence and dizziness
   - C increased blood glucose levels that could lead to loss of consciousness, coma, and death
   - D no notable clinical consequences
Module Summary

(1) LYRICA is FDA-approved for:
   - the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN)
   - the management of PHN
   - management of fibromyalgia
   - adjunctive therapy for adult patients with partial seizures

LYRICA can be administered with or without food. When discontinuing treatment, LYRICA should be tapered gradually over a minimum of 1 week.

**Dosing for patients with pDPN:**
   - maximum recommended dose is 100 mg 3 times daily (300 mg/day) in patients with a creatinine clearance of at least 60 mL/min
   - dosing should begin at 50 mg 3 times a day (150 mg/day) and may be increased to 100 mg 3 times a day (300 mg/day) within 1 week

**Dosing for patients with PHN:**
   - recommended dose of LYRICA is 75 mg to 150 mg 2 times a day, or 50 mg to 100 mg 3 times a day (150 mg/day to 300 mg/day) in patients with a creatinine clearance of at least 60 mL/min
   - dosing should begin at 75 mg 2 times daily or 50 mg 3 times daily (150 mg/day) and may be increased to 300 mg/day within 1 week
   - patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate LYRICA, may be treated with up to 600 mg/day (300 mg 2 times daily, or 200 mg 3 times daily)

**Dosing for Fibromyalgia:** The recommended dose of LYRICA for fibromyalgia is 300 mg/day to 450 mg/day:
   - dosing should begin at 75 mg 2 times daily (150 mg/day)
   - the dose should be increased to 150 mg 2 times daily (300 mg/day) within 1 week based on efficacy and tolerability
   - patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg 2 times daily (450 mg/day)

**Dosing for Epilepsy:** LYRICA is administered either BID or TID in epilepsy. LYRICA doses of 150 mg/day to 600 mg/day have been shown to be effective as adjunctive therapy in the treatment of partial onset seizures in adults. The recommended starting dose for LYRICA in patients with epilepsy is 150 mg/day. Based on patient response and tolerability, the dose may be increased to a maximum dose of 600 mg/day.

**Oral Solution:** The oral solution consists of 20 mg pregabalin per mL. Prescriptions should be written in milligrams, and the pharmacist should calculate the approximate dose in mL for dispensing (eg, 150 mg equals 7.5 mL of the oral solution).
Dosing Recommendations for Special Populations: Dosing in patients with compromised renal function should be adjusted based on creatinine clearance. A supplemental dose should be given immediately following every 4-hour hemodialysis treatment.

LYRICA is available as 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg capsules, and as a 20 mg/mL oral solution. LYRICA should be stored at 25°C (77°F), but may be stored within a range of 15°C to 30°C (59°F to 86°F).

The active ingredient in LYRICA is pregabalin. The mechanism of action of LYRICA is unknown in humans. Data from preclinical and animal models indicate that LYRICA binds with high affinity to the alpha2-delta site, an auxiliary subunit of voltage-gated calcium channels, in central nervous system tissues. LYRICA binding modulates calcium ion influx in hyperexcited neurons. This is believed to reduce the calcium-dependent release of excitatory neurotransmitters, such as glutamate and substance P, which is thought to be responsible for the analgesic and anticonvulsive effects of LYRICA. The clinical significance in humans is not known. Pregabalin is not a vascular calcium channel blocker.

Pregabalin differs from other agents that are sometimes used for treatment of neuropathic pain associated with pDPN and PHN, management of fibromyalgia, and adjunctive therapy in adult patients with partial onset seizures. For example, although pregabalin has some structural similarities to gamma-aminobutyric acid, pregabalin does not act like GABA, and it acts differently than agents that affect GABA and its responses.

Key pharmacokinetic information regarding LYRICA includes the following:

- $C_{\text{max}}$ within 1.5 hours; $C_{\text{max}}$ increases proportionally with increasing dose
- oral bioavailability $\geq 90\%$
- reaches steady state within 24 to 48 hours
- food has no clinically relevant effect on amount absorbed
- is not bound to plasma proteins
- undergoes negligible hepatic metabolism; excreted as unchanged compound in the urine; elimination nearly proportional to creatinine clearance
- mean elimination half-life is 6.3 hours
- special populations: as seen in pivotal LYRICA clinical trials, no differences by gender or race; dosage reduction required in patients with impaired renal function and those undergoing hemodialysis
(2) The following is a summary of the safety profile of LYRICA.

**Contraindications:** LYRICA is contraindicated in patients with known hypersensitivity to LYRICA or any of its components.

**Warnings and precautions:** The following warnings and precautions are listed in the labeling for LYRICA:

- there have been postmarketing reports of angioedema (specific symptoms included swelling of the face, mouth, and neck) in patients during initial and chronic treatment with LYRICA; there were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment
- there have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with LYRICA; adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing
- LYRICA should be discontinued gradually over a minimum of 1 week
- antiepileptic drugs (AEDs) carry a class warning about the increased risk of suicidal thoughts or behaviors in patients taking AEDs for any indication; patients taking LYRICA should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior
- incidence of peripheral edema in controlled trials was 6% with LYRICA and 2% with placebo; <1% withdrew due to peripheral edema
- dizziness and somnolence reported by patients in controlled studies; events began shortly after the initiation of therapy and generally occurred more frequently at higher doses
- incidence of weight gain ≥7% baseline in all controlled trials was 9% with LYRICA versus 2% with placebo; only 0.3% withdrew due to weight gain
- following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms that included insomnia, nausea, headache, and diarrhea; LYRICA should be tapered gradually over a minimum of 1 week
- some preclinical studies in mice show an unexpectedly high incidence of hemangiosarcoma
- in controlled studies, a higher proportion of patients receiving LYRICA rather than placebo reported blurred vision; patients should have their visual acuity and field of vision routinely monitored
- in all controlled trials, 1.5% of patients on LYRICA and 0.7% of patients on placebo had an increase in creatine kinase ≥3X ULN
- LYRICA was associated with decrease in platelet count
- LYRICA was associated with PR interval prolongation

**Adverse reactions:** In all controlled trials, discontinuation due to adverse reactions was 14% for LYRICA and 7% for placebo. The most common adverse reactions (≥5% and at least twice placebo) were dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and thinking abnormal. In the LYRICA group, the adverse reactions most frequently leading to discontinuation of LYRICA were dizziness (4%) and somnolence (3%).
In painful DPN trials, discontinuation due to adverse events was 9% for LYRICA and 4% for placebo. Discontinuation due to dizziness was 6% (<1% for placebo) and discontinuation due to somnolence was 2% (<1% for placebo). The most common adverse events (≥5% for all LYRICA doses) in pDPN studies were dizziness (21%), somnolence (12%), peripheral edema (9%), asthenia (5%), and dry mouth (5%). Most patients treated with LYRICA reported adverse events with a maximum intensity of mild or moderate.

In PHN trials, discontinuation due to adverse events was 14% for LYRICA and 7% for placebo. Discontinuation due to dizziness was 4% (<1% for placebo) and discontinuation due to somnolence was 3% (<1% for placebo). The most common adverse events (≥5% for all LYRICA doses) in PHN studies were dizziness (26%), somnolence (16%), peripheral edema (12%), headache (7%), pain (5%), constipation (5%), ataxia (5%), and blurry vision (5%). Most patients treated with LYRICA reported adverse events with a maximum intensity of mild or moderate.

In fibromyalgia trials, discontinuation due to adverse reactions was 19% for LYRICA and 10% for placebo. Discontinuation due to dizziness was 6% (<1% for placebo) and discontinuation due to somnolence was 3% (<1% for placebo). The most common adverse reactions (≥5% for all LYRICA doses) in fibromyalgia studies were dizziness (38%), somnolence (20%), headache (12%), weight increased (11%), vision blurred (8%), dry mouth (8%), constipation (7%), fatigue (7%), peripheral edema (6%), euphoric mood (6%), balance disorder (5%), increased appetite (5%), sinusitis (5%), and disturbance in attention (5%). Most patients treated with LYRICA reported adverse events with a maximum intensity of mild or moderate.

In controlled add-on epilepsy studies, adverse events led to discontinuation in 15% of patients taking LYRICA and 6% taking placebo. Discontinuation due to dizziness was 6% (<1% for placebo), ataxia was 4% (<1% for placebo), and somnolence was 3% (<1% for placebo). The most common adverse events (≥5% for all LYRICA doses) in epilepsy studies were dizziness (32%), somnolence (22%), ataxia (15%), weight gain (12%), blurred vision (10%), accidental injury (9%), diplopia (9%), tremor (8%), thinking abnormal (8%), increased appetite (5%), peripheral edema (5%), amnesia (5%), and speech disorder (5%). Most patients treated with LYRICA reported adverse events with a maximum intensity of mild or moderate.

Drug interactions: As shown in both in vivo and in vitro studies, LYRICA is unlikely to produce or be subject to pharmacokinetic interactions because it is predominantly excreted unchanged in the urine, undergoes negligible metabolism, and is not bound to plasma proteins. LYRICA does not inhibit major CYP enzymes. Specifically, no pharmacokinetic interactions have been identified in population pharmacokinetic analyses between commonly used AEDs, oral contraceptives (ethinyl estradiol, norethindrone), lorazepam, oxycodone, diuretics, and hypoglycemics. LYRICA administered with oxycodone, ethanol, or lorazepam had no clinically important effects on respiration; however, LYRICA may exacerbate effects of these other agents on cognitive and gross motor function.
Use in special populations:

- pregnancy category C; a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother
- safety and efficacy in pediatric patients have not been established
- although in clinical studies, the adverse reaction profile was similar between patients ≥65 years and patients <65 years, the following neurologic adverse reactions were more frequent in patients ≥65 years: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy
- because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment

Drug abuse and dependence: LYRICA is a schedule V controlled substance

Overdosage: The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses. Emesis or gastric lavage, or hemodialysis may be used; general supportive care is recommended.
Glossary

**alpha2-delta (α2-δ)**
an auxiliary subunit of voltage-gated calcium channels in central nervous system tissues that can be involved in the treatment of epilepsy and neuropathic pain

**amlodipine**
a calcium channel blocker and antihypertensive that is FDA-approved for the treatment of hypertension, chronic stable angina, and vasospastic angina

**analgesic**
a compound capable of relieving pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness

**angioedema**
swelling under the skin that is acute, painless, and of short duration; may occur in the face, neck, lips, larynx, hands, feet, genitalia, or viscera; may be hereditary, or the result of allergies caused by food or drugs, infection, emotional stress, or blood products

**asthenia**
weakness or debility

**ataxia**
loss of coordination

**BID**
twice a day; abbreviation for the Latin *bis in die*

**bioavailability**
the physiologic availability of a given amount of a drug; proportion of the administered dose that is absorbed into the bloodstream

**blood-brain barrier**
a selective mechanism opposing the passage of most ions and large-molecular weight compounds from the blood to brain tissue located in a continuous layer of endothelial cells connected by tight junctions

**calcium channel blocker (CCB)**
a class of drugs with the capacity to prevent calcium ions from passing through biologic membranes; used to treat hypertension, angina pectoris, and cardiac arrhythmias; examples include nifedipine, diltiazem, verapamil, and amlodipine

**Cmax**
peak plasma concentration

**creatine kinase (CK)**
an enzyme in muscle, brain, and other tissues; can be elevated following a heart attack

**creatine**
a component of urine and the final product of creatine catabolism

**creatine clearance (CLcr)**
measurement of the clearance of endogenous creatinine, used for evaluating the glomerular filtration rate (GFR)

**cyclooxygenase**
the enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and thromboxane A2
cytochrome P-450 (CYP450) enzyme system
the enzyme system in the liver that is responsible for the metabolism of many drugs

diabetic peripheral neuropathy (DPN)
diabetes mellitus-related damage of the peripheral nervous system; can result in neuropathic pain

diplopia
double vision

dopamine
an intermediate in tyrosine metabolism and precursor of norepinephrine and epinephrine; depletion of dopamine produces Parkinson's disease

dyspnea
shortness of breath

epilepsy
a chronic brain disorder characterized by the predisposition to the occurrence of unprovoked recurrent seizures

fibromyalgia
a common condition characterized by the hallmark symptom of chronic, widespread pain; patients may also present with a wide range of symptoms, including tenderness, sleep disturbances, fatigue, and morning stiffness

gamma (γ)-aminobutyric acid (GABA)
the major inhibitory neurotransmitter in the central nervous system

half-life
time necessary for the blood concentration of a drug to be reduced by one-half

HbA1C
glycosylated hemoglobin, the fraction of hemoglobin that is bound to glucose in the blood; represents the patient's overall glycemic control for the past 3 to 4 months; normal range is 4% to 6%; values over 6% are abnormal

hemangiosarcoma
a rare malignant tumor characterized by rapidly proliferating, extensively infiltrating cells derived from blood vessels and lining irregular blood-filled or lumpy spaces

hemodialysis
dialysis of soluble substances and water from the blood by diffusion through a semipermeable membrane

L-type calcium channel
long-lasting voltage-gated calcium channel responsible for normal myocardial and vascular smooth muscle contractility

mean
the average; usually assumed to be the arithmetic mean (sum of all values divided by number of values) unless otherwise specified

median
the middle value in a set of measurements

myopathy
any abnormal condition or disease of the muscular tissues; commonly designates a disorder involving skeletal muscle

neuropathic pain
pain that is initiated or caused by a primary lesion or dysfunction in the nervous system; has no protective function; pain is generally chronic and does not respond to standard analgesic treatment
neuropathy
inflammation or degeneration of the peripheral nerves

norepinephrine
a catecholamine hormone secreted in response to hypotension and physical stress that has strong vasoconstrictive effects

open-label
a study in which both investigators and patients know the identity of the medication

painful diabetic peripheral neuropathy (pDPN)
diabetes mellitus-related damage of the peripheral nervous system; can result in neuropathic pain

partial seizure
a seizure characterized by localized cerebral ictal onset, also called focal or localization-related seizure

peripheral edema
abnormal buildup of fluid in the ankles, feet, and legs

pharmacokinetics
movements of drugs within biologic systems, as affected by uptake, distribution, binding, elimination, and biotransformation; particularly the rates of such movements

platelet
a cell fragment in the blood that aids in blood clotting

postherpetic neuralgia (PHN)
chronic severe, stabbing, or throbbing pain that continues after the visible evidence of an episode of shingles (herpes zoster) has resolved

PR interval
the portion of the ECG that corresponds to the depolarization of the atria and then the ventricles

renal tubular reabsorption
the process that actively transfers substances out of the blood in capillaries across the cells lining the renal tubules into the tubular fluid for elimination in the urine

rhabdomyolysis
an acute, potentially fatal disease that involves destruction of skeletal muscle

seizure
a paroxysmal episode of brain dysfunction, usually leading to sudden stereotyped changes in behavior

serotonin
a chemical messenger (neurotransmitter) that has a variety of roles in regulating mood, behavior, and perception of pain

somnolence
an inclination to sleep

steady state
the point at which the introduction of a drug to the body just keeps pace with its removal so that all volumes, concentrations, pressures, and flows remain constant

substance P
a protein involved in nervous system function; stimulates smooth muscle contraction and the dilation of blood vessels; active in inflammation and pain transmission
**TID**
3 times a day; abbreviation for the Latin *ter in die*

**voltage-gated calcium channel**
a calcium ion channel that opens and closes in response to change in the electrical potential across the plasma membrane of the cell
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