Drug interactions between antidepressants and selective MAO-B inhibitors: Understanding and communicating safety considerations

Stephen M. Setter and Lauren Cerruto

Parkinson disease, depression, and MAO-B inhibitors

Although Parkinson disease (PD) is typically thought of as a motor disease, it is also characterized by a number of nonmotor features. These include psychiatric symptoms such as depression. One-quarter to nearly three-quarters of patients with PD also suffer from depression.1–3 Depression is not just a reaction to PD, it is also part of the illness because PD causes dysfunction in dopaminergic, noradrenergic, and serotonergic neurotransmission.1 Depression is associated with worse motor function, greater impairment in activities of daily living, and an earlier need for symptomatic therapy for PD.1 However, depression often goes undiagnosed in patients with PD because clinical symptoms of depression (e.g., flat affect, inability to work, fatigue, loss of desire, preoccupation with illness) can overlap with and even be mistaken for PD.3

Selective serotonin reuptake inhibitors (SSRIs) are the treatment of choice for managing depression in patients with PD.5 However, their use in PD patients is complicated by their ability to exacerbate parkinsonian symptoms and by a potential, albeit rare, drug interaction with one class of PD medications, selective monoamine oxidase (MAO) type B (MAO-B) inhibitors.5

MAO inhibitors can be classified according to their selectivity for the two subtypes of MAO (type A and type B). Nonselective MAO inhibitors block both type A and type B activity. Selective MAO inhibitors block only MAO-B or only MAO-A activity. Nonselective MAO inhibitors used in the United States are antidepressants and include isocarboxazid (Marplan—Validus), phenelzine (Nardil—Pfizer), and tranylcyromine (Transton—GlaxoSmithKline). Outside of the United States, therapies selective for MAO-A (e.g., moclobemide) are also used in the treatment of depression. Selegiline (Emsam—Bristol-Myers Squibb) and rasagiline (Azilect—Teva), at FDA-approved doses, are selective MAO-B inhibitors indicated for use in the treatment of PD.5–8 A transdermal formulation of selegiline is also approved to treat depression.9

Learning objectives

At the completion of this activity, the pharmacist will be able to:
- Describe the causes, clinical features, and treatment of serotonin syndrome.
- Recognize the potential for, and clinical significance of, drug interactions with the coadministration of antidepressants and MAO-B inhibitors in Parkinson disease.
- List tips for counseling patients and caregivers and communicating with physicians regarding this potential interaction.
Drug interactions associated with MAO inhibitors are largely attributable to inhibition of MAO-A and are therefore less common with the selective MAO-B inhibitors.

Concurrent use of any antidepressant that affects serotonin levels with any MAO inhibitor potentially increases the risk of serotonin syndrome. The most serious reactions have occurred with therapies that inhibit MAO-A, including nonselective MAO inhibitors. The risk remains theoretical with MAO-B inhibitors. However, most drug interaction screens do not differentiate between MAO inhibitor classes and “flag” any use of an MAO inhibitor and antidepressant as a potential drug interaction. Pharmacists have a unique knowledge base and therefore are in a primary position to determine clinical significance of drug interactions and work with prescribers on these issues.

Serotonin syndrome
Serotonin syndrome is caused by excessive activation of serotonin receptors in the central nervous system. Clinical manifestations (Table 1) represent a concentration-dependent spectrum of toxicity ranging from barely noticeable to seizures, coma, and death. Early recognition and treatment are therefore essential. Serotonin syndrome is usually precipitated or suddenly exacerbated when a new serotonergic medication is added to ongoing serotonergic medications, when doses are increased, or after an overdose of a serotonergic medication. Onset can be rapid, within minutes to hours of ingestion.

<table>
<thead>
<tr>
<th>Behavioral/cognitive symptoms</th>
<th>Autonomic effects</th>
<th>Somatic effects</th>
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<tbody>
<tr>
<td>Confusion</td>
<td>Syncope</td>
<td>Muscular rigidity</td>
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<tr>
<td>Hypomania</td>
<td>Shivering</td>
<td>Myoclonus</td>
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<tr>
<td>Hallucinations</td>
<td>Sweating</td>
<td>Muscle twitching</td>
</tr>
<tr>
<td>Agitation/hypervigilance</td>
<td>High fever/hyperthermia</td>
<td>Hyperreflexia manifested by clonus, either inducible or sustained, typically greater in lower versus upper extremities</td>
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<tr>
<td>Slightly slurred speech</td>
<td>Hypertension</td>
<td>Horizontal ocular clonus</td>
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<tr>
<td>Headache</td>
<td>Tachycardia</td>
<td>Tremor</td>
</tr>
<tr>
<td>Delirium</td>
<td>Nausea</td>
<td>Repetitive head turning with neck moderately extended</td>
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<tr>
<td>Coma</td>
<td>Increased bowel sounds/diarrhea</td>
<td>Akathisia</td>
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Source: References 6 and 10.

No laboratory test exists that can confirm high levels of serotonin; therefore, serotonin syndrome must be diagnosed clinically based on history and symptoms. Multiple diagnostic criteria have been proposed, but the Hunter Serotonin Toxicity Criteria are the most sensitive and specific. According to Hunter’s criteria, serotonin syndrome is diagnosed in the presence of any one of the following in a patient taking a serotonergic agent:
- Spontaneous clonus (rhythmic muscular contractions)
- Inducible clonus and either agitation or diaphoresis (excessive sweating)
- Ocular clonus and either agitation or diaphoresis
- Tremor and hyperreflexia (overactive reflexes)
- Hypertonia (increased muscle tone) and temperature greater than 38°C and either ocular clonus or inducible clonus

Most cases of serotonin syndrome are mild and can be managed by discontinuing the precipitating drugs and providing supportive care. Supportive measures may include hemodynamic stabilization, sedation, cooling, hydration, and monitoring for complications. Benzodiazepines (e.g., diazepam) may help relieve agitation and tremor, regardless of syndrome severity. After treatment is instituted and the offending drugs withdrawn, mild serotonin syndrome typically resolves within 24 to 72 hours. Drugs with longer half-lives, active metabolites, or long durations of action may result in more persistent symptoms.

Patients with moderate to severe cases in which they also have hypertonicity, hyperthermia, autonomic instability, or progressive cognitive changes should be hospitalized and may require neuromuscular paralysis, external cooling, sedation, and intubation. For these cases, therapies with antiserotogenic activity can be beneficial and cyproheptadine is the most commonly used. (This use of cyproheptadine is not approved by FDA, and no prospective controlled trials exist.) Cyproheptadine is usually given as an initial 12-mg dose followed by 2 mg every 2 hours to a maximum 32 mg in 24 hours if symptoms continue, then a maintenance dose of 8 mg every 6 hours. Sedation as a potential adverse effect of cyproheptadine is not undesirable because it may aid in relieving some of the symptoms of serotonin syndrome. Antipyretics do not have a role because hyperthermia associated with serotonin syndrome results from increased muscle activity rather than central nervous system activity.

MAO-B inhibitors and antidepressants: Potential drug interaction
A theoretical risk of serotonin syndrome exists when selective MAO-B inhibitors are used in combination with drugs that have serotonergic activity (e.g., SSRIs, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, tryptophan, dextromethorphan, meperidine). In theory, select antidepressants with low serotonergic potential (e.g., bupropion, nortriptyline, desipramine, doxepin, amoxapine) might have a lower risk of serotonin syndrome. Risk of serotonin syndrome is also increased if MAO-B inhibitors are used in combination with tricyclic antidepressants, tryptophan, dextromethorphan, meperidine.
with cytochrome P450 (CYP) enzyme inhibitors or at doses greater than 10 mg/day for selegiline or greater than 1 mg/day for rasagiline. Rasagiline is a substrate of CYP1A2, and selegiline is a substrate of CYP2B6 and CYP3A4. Concurrent use of rasagiline or selegiline with inhibitors of these enzymes may increase the rasagiline or selegiline concentration, which theoretically may increase the risk of serotonin syndrome.

Serotonin syndrome resulting from the combination of MAO-B inhibitors and antidepressants is rare. The Parkinson Study Group found that of 4,568 PD patients treated with an antidepressant and selegiline, only 11 (0.24%) reported symptoms consistent with serotonin syndrome. Only two patients (0.04%) experienced serious symptoms, and no fatalities occurred. In a recent study of 12 healthy male volunteers, 1 week of combination rasagiline 1 mg/day and escitalopram 10 mg/day was well tolerated, without evidence of serotonin syndrome.

Many pharmacy drug database systems do not differentiate between contraindications and warnings/precautions listed in product labeling. A drug is labeled as concomitantonly if a known (not theoretical) hazard exists and the risk from use clearly outweighs potential benefit. A warning/precaution describes a potential adverse reaction or drug interaction, giving clinicians information about the risk, risk factors, and steps to take to reduce the risk or manage the reaction if it occurs. FDA labeling for rasagiline and selegiline contains a warning/precaution informing health professionals about the potential for severe central nervous system toxicity with concurrent use of antidepressants and selective or nonselective MAO inhibitors. The warning/precaution states that, in general, avoiding the combination of MAO-B inhibitors and any antidepressant is prudent and that a reasonable washout period should occur between them; however, this is not labeled as an absolute contraindication to concurrent use. In routine practice, MAO-B inhibitors and antidepressants, including SSRIs, are commonly used together. Use of meperidine, tramadol, methadone, propoxyphene, dextromethorphan, St. John’s wort, and other MAO inhibitors (selective or nonselective) concurrent with MAO-B inhibitors is contraindicated, however. In clinical trials of rasagiline, fluoxetine and fluvoxamine were not permitted, but the following antidepressants and doses were allowed: amitriptyline 50 mg or less per day, trazodone 100 mg or less per day, citalopram 20 mg or less per day, sertraline 100 mg or less per day, and paroxetine 30 mg or less per day. No cases of serotonin syndrome have been reported in rasagiline clinical trials to date. A subgroup analysis of patients from a clinical trial of rasagiline as adjunct to carbidopa/levodopa reported that no increase in the prevalence of adverse effects occurred when rasagiline and an SSRI were used concurrently. Pharmacists should discuss with prescribers the risks and benefits of concomitant administration of MAO-B inhibitors and antidepressants for specific patients. If a decision is made to use these agents in combination, pharmacists and prescribers should be aware of the potential for serotonin syndrome and monitor accordingly.

**Discussion with patients and prescribers**

Ultimately, as the medication expert, the role of the pharmacist is to ensure that patients receive safe and effective medication therapy, get the most benefit from the medication that is prescribed, and achieve optimal outcomes related to their medication therapy. A key element of the pharmacist’s responsibility in safe medication use is to identify drug interactions and determine the potential severity and clinical significance of the interaction. Pharmacists should identify situations in which a selective MAO-B inhibitor is being prescribed concurrently with an antidepressant that may increase serotonin levels. When this situation arises, pharmacists must determine whether patients need to be counseled or whether the interaction requires physician notification. Pharmacists can ask patients what they were told by their physician and then provide reinforcement—a strategy that is usually much appreciated by both patients and physicians.

Pharmacists can make physicians aware when an interaction potentially exists between an MAO-B inhibitor and an antidepressant and assist physicians in determining the clinical significance and whether medication and/or dosage adjustments are needed or whether monitoring patients is adequate. Pharmacists may suggest changing to an antidepressant with lower serotonergic potential (e.g., bupropion, amoxapine, doxepin, desipramine, nortriptyline), adjusting the dose of the antidepressant, changing PD therapy, or initiating active monitoring for patients remaining on the combination. Pharmacists and prescribers should discuss these options in the context of the individual patient’s needs. Pharmacists should approach

**Want to know more?**

Drugs and combination regimens that have been associated with serotonin syndrome are not limited to MAO-B inhibitors. In fact, many other single therapies, drug combinations, dietary supplements, and illicit substances also have been implicated. More information can be found in Boyer and Shannon.

**Reflect: To what extent do you rely on computerized pharmacy alert systems? In what situations do you override the alerts?**

Dispensing systems and electronic drug interaction databases are important pharmacy tools but can be limited in relaying clinical significance. Recent investigations have shown that prescribers frequently ignore these alerts. In fact, in one survey, 40% of prescribers said they override alerts about drug–drug interactions most of the time or always when using electronic prescribing systems. The most common reasons prescribers ignored the alerts were that many were considered trivial or not clinically relevant, the alerts often involved drugs that patients were no longer taking, or the potential interaction was known but the benefits of the drugs were considered to outweigh the risks. These findings suggest a need for refinements to drug alert systems to reduce “alert overload,” to differentiate between warnings/precautions and contraindications, and to focus on critical interactions. In the meantime, pharmacists and prescribers should take computerized alerts into consideration while using their own judgment based on knowledge of the medical literature, product labeling, and specific patient needs.
Table 2. Discussing concomitant use of MAO-B inhibitors and antidepressants

<table>
<thead>
<tr>
<th>Tips for counseling patients</th>
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<tr>
<td><strong>Tips for communicating with prescribers</strong></td>
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<tr>
<td>Be aware of the prescriber’s specialty. Most movement disorder specialists and neurologists have considerable experience using selective MAO-B inhibitors and antidepressants in combination, whereas internists and family practice physicians may have less experience with this patient population and these combinations of medications.</td>
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<td>Phone or type messages directly to the prescriber; avoid handwritten notes and messages conveyed through others.</td>
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<td>Confirm that the prescriber is aware of the potential drug interaction, citing or providing clinical references as support if necessary.</td>
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<td>Keep the focus on the patient’s welfare.</td>
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<td>Initiate discussion of the risk-to-benefit ratio of the two therapies, actively listening to and showing respect for the prescriber’s perspective.</td>
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<td>When pointing out a potential problem, describe the problem succinctly and provide potential solutions.</td>
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<tr>
<td>Pay attention to word choice, maintain a nonconfrontational tone. Avoid escalating the conversation into an exchange of who is “right” or “wrong.”</td>
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<td>Be clear on what the prescriber’s final decision is: what, if any, change is needed to the patient’s medications?</td>
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<tr>
<td>If the decision is made to continue with both MAO-B inhibitor and antidepressant, discuss a plan for monitoring the patient.</td>
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Prescribers tactfully, showing respect for their medical opinion and expertise, while collaborating to achieve what is in the patient’s best interest. The role of pharmacists as patient care collaborators may be new to some prescribers, who may react with bewilderment or irritation when they are approached by a pharmacist who questions their prescription. Table 2 provides tips for communicating with both patients and prescribers about potential drug interactions.

Assessing your communication skills
Reflect on the last few conversations you have had with patients and prescribers regarding potential drug interactions. How well did they go? What could you have done to improve communication?

Conclusion
Selective MAO-B inhibitors and antidepressants theoretically increase the risk of serotonin syndrome when used concurrently. Although serotonin syndrome is potentially serious, it is an extremely rare occurrence and often mild. When serotonin syndrome is recognized promptly and managed appropriately, prognosis is favorable. Pharmacists should discuss with the patient’s provider the risks and benefits of combined selective MAO-B inhibitor and antidepressant therapy for individual PD patients. Pharmacists should provide counseling to patients taking these combinations so that they can be alert to and report the onset of any symptoms, but should also help patients keep the risks in perspective.

References


Inpatient to outpatient: The pharmacist’s role in improving patient outcomes in venous thromboembolism
American Pharmacists Association

Introduction
In the fall of 2008, the Office of the U.S. Surgeon General issued a call for a coordinated, multifaceted plan to reduce the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) in the United States. Noting that many of the estimated 100,000 deaths each year from these conditions can be avoided, the report emphasized the need for raising awareness about DVT and PE and increasing the use of evidence-based practices for preventing DVT.¹

Although proven, effective measures are available to prevent DVT and PE in high-risk individuals, a significant proportion of people who could benefit from such services do not receive them. According to the Surgeon General’s report, too few health care professionals are aware of the evidence-based practices for identifying high-risk patients and providing preventive, diagnostic, or therapeutic services. There is a clear need to disseminate information more widely about the availability of effective interventions to prevent and treat DVT and PE.¹

The American Pharmacists Association is responding to this call to action by educating its members through programs offered at its Annual Meetings and this edition of Topics in Patient Care. Pharmacists have a tremendous opportunity to educate both patients and other health care providers about these important conditions.

Venous thromboembolism
Venous thromboembolism (VTE) is a disorder with two primary components: (1) DVT is the formation of a thrombus, or blood clot, in a deep vein, usually in the calf or thigh, which partially or completely obstructs blood flow; (2) PE occurs when a por-

Learning objectives
At the completion of this activity, the pharmacist will be able to:
- Describe the clinical presentation of venous thromboembolism (VTE) and differentiate deep vein thrombosis from pulmonary embolism.
- Summarize the latest guidelines for prevention and treatment of venous thromboembolic disorders.
- Review both the inpatient and ambulatory treatment approaches for VTE, including appropriate VTE prophylaxis in surgical patients.
- Identify opportunities for the pharmacist to optimize outcomes in patients receiving anticoagulation therapy.
- Provide patient education for outpatient anticoagulant management of VTE.

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How risky are long flights?
Prolonged air travel appears to be a risk factor for VTE. However, the risk for most people is very small: the rate of symptomatic VTE within 30 days of a long flight has been estimated to be approximately one in 2 million, and the estimated risk of dying from the VTE event is 2%. The association between VTE and air travel is strongest for flights that last more than 8 hours.1 The risk increases with the number of flights taken in a short time span. Prolonged immobility appears to be the “biggest culprit,” as the incidence is higher among those who are not seated on an aisle.2

Whether the passenger travels in economy class or business/first class does not affect the risk.3,4 Hence, the name “economy-class syndrome” is a misnomer.5

Passengers on long flights who are obese or pregnant, have large varicose veins, use estrogens or tobacco, or are relatively immobile are at moderate risk for VTE. Those with previous VTE, who suffer from hypercoagulable state, had major surgery within 6 weeks of air travel, or have cancer are at high risk.5,6 Most individuals with travel-associated VTE have one or more risk factors for thrombosis.5

Travelers taking long flights should be advised to use precautions such as: maintain hydration, reduce alcohol and caffeine consumption, change positions, and walk through the cabin periodically (every 60 to 90 minutes). If unable to walk around frequently, patients should exercise their legs by curling or pressing their toes down, which causes the calf muscles to contract, improving venous blood flow. They should wear loose-fitting clothing and avoid socks with tight elastic bands at the top. They also should avoid sitting with legs crossed for long periods of time.7

Long-distance travelers who are considered to be at high risk should wear properly fitted graduated compression stockings providing 15 to 30 mm Hg of pressure at the ankle or have a single prophylactic injection of low-molecular-weight heparin prior to departure. Aspirin is not effective for VTE prevention.4,5

What causes DVT?
DVT is caused by the interaction of several factors: inherited, acquired, behavioral, and/or environmental. The pathogenesis of VTE typically involves one or more factors: damage to the vessel wall, slow or obstructed venous blood flow, and hypercoagulability.3 Inherited abnormalities of the coagulation system, including variants in factor V Leiden, prothrombin gene mutations, and deficiencies in anticoagulant proteins, lead to hypercoagulability (also called thrombophilia), whereby the patient has an increased tendency to develop venous blood clots.1

Circumstances that cause immobilization of the extremities, such as paralysis, prolonged bed rest, and hospitalization increase risk for DVT. People taking long airline flights are also at increased risk of developing a DVT (see “How risky are long flights?”).4

The majority of DVTs and PEs are related to specific, identifiable triggering events or risk factors such as hospitalization, major surgery, trauma, and prolonged periods of immobility. Often, DVT occurs in an individual with genetic and/or acquired risk factors who also experiences one of these precipitating events.1

More than half of diagnosed DVT cases are asymptomatic, including some that progress to PE. Symptoms of DVT typically include leg swelling, redness or discoloration, pain, and increased warmth of the skin near the clot. Common symptoms of PE are substernal chest pain, shortness of breath, dizziness, fainting, anxiety, and rapid pulse. Because these are similar to symptoms of many other common conditions, it can be difficult to distinguish DVT symptoms from those of an injury, muscle strain, or skin infection; differentiating PE symptoms from those of stroke or heart attack may also be challenging. Specialized imaging studies are usually required to make a definitive diagnosis of DVT and PE. Therefore, individuals who experience these symptoms should seek prompt medical attention.

DVTs are often categorized as proximal DVTs (located above the knee) or distal DVTs (below the knee). One quarter of postoperative DVT cases involve proximal deep veins, which are more likely to cause symptoms and result in PE. Between 10% and 20% of distal DVT cases extend into a proximal DVT.3

What is the impact of DVT?
An estimated 350,000 to 600,000 Americans suffer from symptomatic DVT or PE each year, and at least 100,000 deaths may be directly or indirectly related to these conditions.1 The American Heart Association estimates that more than 250,000 individuals are hospitalized with VTE each year and approximately one third of patients with symptomatic DVT develop PE.6 Of all patients with VTE each year, almost one-third die within 30 days, one-fifth suffer sudden death due to PE, and about one-third develop another VTE within 10 years.8 Many patients who survive a PE episode die within 90 days of hospital discharge due to recurrent VTE, lung damage, or other causes.3 Increasing age, obesity, malignant neoplasm, and extremity paresis are predictors for recurrent VTE.8

While nearly half of the approximately 100,000 annual deaths from VTE could not have been predicted based on known risk factors, the other half could have been predicted based on risk factors present at the time of hospitalization. Appropriate and effective prevention measures could save an estimated 40,000 lives each year.2

The cost of care related to VTE in the United States has been estimated at $1.5 billion per year.9 Postoperative VTE is the second most common medical complication among hospitalized patients, the second most common cause of excess length of stay, and the third most common cause of excess mortality and excess charges.3 An analysis of cost data from a large private-sector medical center in 2001–2002 found that postoperative thromboembolic complications added an average of $18,310 to total hospital costs for each patient who experienced VTE.9

What is the long-term prognosis for VTE?
In addition to PE, potential complications of DVT include worsening symptoms, with venous inflammation (phlebitis) and potential limb loss, recurrent thromboembolic events, and
chronic venous insufficiency leading to the postthrombotic syndrome. Chronic venous insufficiency occurs when the thrombus injures or destroys one or more of the venous valves located in the deep veins of the leg. Damaged veins cannot efficiently pump blood back to the heart, leading to leg pain and swelling. Approximately one-third of those who experience DVT will develop postthrombotic syndrome within 8 years. Postthrombotic syndrome can be extremely debilitating, causing chronic leg symptoms including swelling, chronic pain, skin ulceration, altered sensation, cramps, and itching. These symptoms tend to be permanent and irreversible and cause a significant reduction in the quality of life.

Management of VTE
The American College of Chest Physicians (ACCP) published updated guidelines for management of thromboembolic disorders in 2008 (hereafter called “the ACCP guidelines”). The 850-page document includes chapters on the prevention and treatment of a variety of thrombotic disorders in various patient populations, including those with atrial fibrillation and other cardiovascular disorders, pregnant women, and children. This monograph will focus on those sections covering prevention of VTEs in surgical patients and treatment of patients who develop DVT or PE. As more is learned about how to prevent DVT and PE and evidence has accumulated on the effectiveness of various strategies, a number of organizations have created clinical practice guidelines. The areas of greatest agreement among these guidelines are the need to (1) screen all hospitalized patients at the time of admission to identify risk factors for DVT and PE, and (2) implement preventive measures to mitigate the risk. Preventing VTE in surgical patients
It is estimated that more than half of diagnosed DVTs begin intraoperatively. Without appropriate prophylaxis, DVT occurs after approximately 20% of all major surgical procedures and PE occurs after 1% to 2% of such surgeries. The prevalence of DVT is higher among patients who undergo an orthopedic procedure: more than 50% of major orthopedic surgeries of the lower extremity are complicated by DVT and up to 30% by PE. Without prophylaxis, fatal postoperative PE occurs in up to 5% of patients undergoing hip or knee surgery. (See “Orthopedic surgery = highest VTE risk” for more on VTE prophylaxis for orthopedic surgical patients.) According to the ACCP, almost all hospitalized patients have at least one risk factor for VTE, and approximately 40% have three or more risk factors (Table 1).

Research has demonstrated conclusively that thromboprophylaxis reduces DVT and PE, including fatal PE. The ACCP Guidelines state, “Routine use of thromboprophylaxis reduces adverse patient outcomes while at the same time decreasing overall costs.”

The ACCP guidelines recommend that every hospital develop a formal strategy to prevent VTE and that most hospitalized patients should receive routine thromboprophylaxis—not only to improve patient outcomes, but also to protect health care providers and hospitals from legal liability. The Joint Commission has included in its National Patient Safety Goals a requirement that hospitals and health systems “reduce the likelihood of patient harm associated with the use of anticoagulant therapy.” (The requirement does not apply to short-term

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**Table 1. Risk factors for deep vein thrombosis/pulmonary embolism**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Low risk</strong></td>
<td>Surgery duration less than 30 minutes, age less than 40 years, repair of small fractures</td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td>Age 40 to 60 years, arthroscopy or repair of lower leg fractures, postoperative plaster cast</td>
</tr>
<tr>
<td><strong>High risk</strong></td>
<td>Age greater than 60 years, or age 40 to 60 years with additional VTE risk factors, or immobilization for more than 4 days</td>
</tr>
<tr>
<td><strong>Highest risk</strong></td>
<td>Hip or knee arthroplasty, hip fracture repair, repair of open lower leg fractures, surgery after major trauma or spinal cord injury, or multiple risk factors for VTE</td>
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Orthopedic surgery = highest VTE risk
Patients undergoing hip or knee arthroplasty or hip fracture repair are in the highest risk category for VTE. However, nearly half of such patients do not receive optimal prophylaxis, often because of clinicians’ concerns over bleeding complications. Orthopedic surgical patients may be stratified into the following four VTE risk levels based on patient and surgical characteristics:

- **Low risk**: Surgery duration less than 30 minutes, age less than 40 years, repair of small fractures
- **Moderate risk**: Age 40 to 60 years, arthroscopy or repair of lower leg fractures, postoperative plaster cast
- **High risk**: Age greater than 60 years, or age 40 to 60 years with additional VTE risk factors, or immobilization for more than 4 days
- **Highest risk**: Hip or knee arthroplasty, hip fracture repair, repair of open lower leg fractures, surgery after major trauma or spinal cord injury, or multiple risk factors for VTE

No specific prophylaxis is indicated beyond early and aggressive ambulation for patients in the low-risk category. Patients in the other categories should receive VTE prophylaxis with anticoagulants and/or mechanical devices. Recommended agents and duration of use vary according to the type of surgery.

Concerns about bleeding caused by anticoagulant drugs used after surgery must be kept in perspective. The risk of major bleeding attributable to pharmacologic prophylaxis was considerably lower than the risk of VTE in the absence of prophylaxis in a study of patients undergoing major orthopedic surgery; bleeding associated with heparin ranged from 0.2% to 1.7%, compared with a 10% to 20% risk of proximal DVT.
prophylactic anticoagulation for VTE prevention at this time.)\(^{12}\) ACCP favors routine thromboprophylaxis for all surgical patients in the following major target groups\(^{5}\):

- Major general surgery
- Major gynecologic surgery or major, open urologic procedures
- Elective hip or knee arthroplasty
- Hip fracture surgery
- Major trauma and spinal cord injury

The following four agents are widely used for thromboprophylaxis in hospitalized patients:

- Low–molecular-weight heparin (LMWH)
- Low-dose unfractionated heparin (UFH)
- Fondaparinux, a selective factor Xa inhibitor
- Warfarin (after elective hip and knee surgeries)

The ACCP guidelines stipulate that patients under-going hip or knee surgery should continue to receive anticoagulants for a minimum of 10 days and up to 35 days for those undergoing hip procedures. The general approach to thromboprophylaxis is to implement a strategy based on the patient’s level of risk (Table 2).\(^5\)

Up to 16% of hospitalized patients with acute medical illness develop DVT without appropriate VTE prophylaxis. Therefore, such patients should routinely receive thromboprophylaxis. Patients admitted to an intensive care unit should be assessed for VTE risk; most should receive thromboprophylaxis. Aspirin alone is not recommended for prophylaxis for any patient group.\(^5\)

### Treating existing DVTs

The goals of DVT treatment are to arrest thrombus growth, prevent embolization and postphlebitic syndrome, minimize limb symptoms, and prevent recurrence.\(^{13}\) VTE treatment is usually provided in two stages: (1) rapid initial anticoagulation with parenteral anticoagulants such as heparin, LMWH, or fondaparinux to minimize the risk of thrombus extension and subsequent PE; and (2) extended anticoagulation to prevent recurrent VTE and reduce the risk of the postthrombotic syndrome.\(^{14,15}\) The oral anticoagulant warfarin is usually used for this extended stage, however parenteral anticoagulants may also be appropriate.

Historically, patients were hospitalized for administration and monitoring of intravenous UFH for any VTE. However, with the availability of subcutaneous LMWH and fondaparinux, which require less monitoring, more patients are being treated as outpatients. The American Society of Health-System Pharmacists encourages health care professionals to become involved in the development and documentation of innovative outpatient DVT treatment programs, which offer the opportunity “to dramatically reduce the cost of treating DVT and improve the quality of life without compromising clinical outcomes.”\(^{13}\) Similarly, the ACCP guidelines recommend that patients with acute DVT receive LMWH “as an outpatient if possible or as an inpatient if necessary.”\(^{16}\)

Patient selection is important: the ideal candidate for outpatient treatment is one who is willing and able to self-inject LMWH and to adhere to intensive monitoring of oral warfarin therapy until the goal international normalized ratio (INR) range is reached, permitting transition to oral warfarin only. Pharmacists have assumed lead roles in developing and implementing successful anticoagulation management services, which have a proven track record in improving outcomes and reducing costs in the management of patients with VTE.\(^{13}\)
Pharmacologic agents for anticoagulation

Rapidly acting parenteral anticoagulants are used for initial treatment of VTE, with oral agents used for long-term therapy in most cases. The various anticoagulants target different clotting factors and enzymes in the clotting cascade, thereby preventing the interactions that are necessary for clot formation. For example, heparin binds to antithrombin, which accelerates the inactivation of factor Xa and thrombin. The final step in blood clot formation relies on thrombin to convert fibrinogen to fibrin. Hence, inactivation of thrombin disrupts the formation of a clot. Newer agents under development and in clinical testing target thrombin generation directly or indirectly (Table 3).

Parenteral anticoagulants

UFH has been used for many years and has been shown to be an effective anticoagulant for a wide variety of indications. However, treatment response with UFH is unpredictable, requiring frequent monitoring of either the activated partial thromboplastin time or anti-Xa levels and dosage adjustment as needed. Because of intravenous administration and the need for frequent monitoring, patients must be hospitalized for UFH treatment. Complications that can occur due to UFH include heparin-induced thrombocytopenia (HIT), hemorrhage, osteoporosis.

Standard treatment options changed significantly with the development of the LMWHs—in the United States as enoxaparin, dalteparin, and tinzaparin. Similar to UFH, the LMWHs work by binding to and markedly enhancing the activity of antithrombin. Derived from standard heparin, the LMWHs consist of polysaccharide fragments about one third the size of those found in UFH. This change results in more selective anticoagulant activity, improved bioavailability, a longer half-life, and a lower incidence of HIT. Unlike UFH, the LMWHs are not associated with bone loss with prolonged use. Their bioavailability and longer half-life result in a more predictable response and enable daily weight-based dosing without laboratory monitoring. The LMWHs are administered subcutaneously for both the prevention and treatment of VTE.

Are we ready for pharmacogenetic dosing?

The International Warfarin Pharmacogenetics Consortium (IWPC) reported in early 2009 on the use of an algorithm for estimating the initial maintenance dose of warfarin based on both clinical and genetic data. IWPC tested this algorithm against one that used clinical data only as well as against a fixed-dose approach.

The researchers demonstrated that the use of the IWPC algorithm predicted the initial maintenance dose of warfarin better than either the clinical data–only algorithm or a fixed-dose approach. In addition to clinical information, the IWPC algorithm included data regarding the patient’s genotype for the cytochrome P450 2C9 and vitamin K epoxide reductase (VKORC1) enzymes, both of which are known to contribute to the variability in warfarin dose requirements. Patients with certain variants may require lower or higher doses than individuals who have the wild-type (or “normal”) variant of these genes. An algorithm for warfarin dosing that incorporates both clinical factors and genetic information is available at www.warfarindosing.org.

In an editorial accompanying publication of the IWPC report in the New England Journal of Medicine, representatives of the Food and Drug Administration Center for Drug Evaluation and Research noted that using the IWPC algorithm benefited only the outliers and that the study did not evaluate clinical outcomes. Future clinical trials will help determine whether outcomes would be improved by the use of pharmacogenetic testing. Given the expected volume of genetic information, the lack of clinical trial data, they urged “clear thinking about what is required for the adoption of pharmacogenetic testing.”

Similarly, the ACCP guidelines recommend against the routine use of pharmacogenetic testing to guide warfarin dosing at this time and state that additional randomized data are needed to determine the benefit of pharmacogenetic dosing.

Table 3. Anticoagulant mechanisms of action

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Enhances antithrombin activity, inhibits factor Xa and factor IIa</td>
</tr>
<tr>
<td>Low–molecular-weight heparin</td>
<td>Enhances antithrombin activity, inhibits factor Xa more than factor IIa</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Enhances antithrombin activity, inhibits factor Xa</td>
</tr>
<tr>
<td>Idraparinux</td>
<td>Enhances antithrombin activity, inhibits factor Xa</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Darabigratin</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Inhibits production of prothrombin; factors II (prothrombin), VII, IX, and X, and anticoagulant proteins C and S</td>
</tr>
</tbody>
</table>

* Investigational drugs; not available in the United States. Source: References 3 and 8.
Oral anticoagulants

In most cases, oral agents are preferred over parenteral drugs for long-term anticoagulation. (The exception is patients with cancer, who are at high risk for bleeding and do better on LMWH.) Vitamin K antagonists (VKA), such as warfarin, have been the only oral anticoagulants available for the past 65 years.¹⁷

Warfarin competitively inhibits production of vitamin K–dependent proteins (factors II, VII, IX, and X, and anticoagulant proteins C and S). While warfarin’s anticoagulation effect generally begins within 24 hours and peak plasma concentrations are achieved in 72 to 96 hours, 7 to 10 days of therapy generally begins within 24 hours and peak plasma concentrations are achieved in 72 to 96 hours, 7 to 10 days of therapy are needed for the full anticoagulant effects to be achieved.³,¹⁸

It takes several days for the concentration of circulating factors to decline. The slow onset of action of warfarin necessitates overlap with a parenteral anticoagulant for at least 5 days. The therapeutic dose of warfarin varies from patient to patient based on age, nutritional status, differences in dietary vitamin K intake, genetic differences in enzymes involved in warfarin and vitamin K metabolism, and concomitant use of medications that suppress or enhance the anticoagulant effects of warfarin.¹⁴

Hence, the dose of warfarin must be monitored frequently to ensure that a therapeutic response is achieved and maintained over time. A subtherapeutic response is associated with an increased risk of thrombosis extension or recurrence, while excessive anticoagulation increases the risk of hemorrhage.³,¹⁴

The dose must be adjusted according to the prothrombin time—also known as protime—a laboratory blood test that measures the length of time it takes for clotting to begin after thromboplastin is added to the blood sample. This test is standardized to account for variations in the thromboplastins used to conduct the test. The INR is a standardized way of reporting the prothrombin time. When warfarin treatment is initiated, the INR must be obtained several times weekly. Once a stable INR and warfarin dose are achieved, the frequency of INR testing is gradually decreased, but is recommended to be no less often than every 4 weeks.¹⁰,²²

When a rapid anticoagulant effect is required, UFH, LMWH, or fondaparinux should be administered and overlapped with warfarin for at least 5 days and until the INR has been in the therapeutic range for at least 2 days.²² Once these criteria have been met, the rapid anticoagulant can be discontinued.

Complications of anticoagulant therapy

Bleeding is the most common complication of antithrombotic therapy. The risk of bleeding is influenced by both agent- and patient-related factors such as intensity of dosing, drug–drug interactions, and recent surgery or trauma. Other characteristics that increase the risk of bleeding are older age, recent stroke, generalized hemostatic defect, history of gastrointestinal hemorrhage, and serious comorbid conditions. Bleeding associated with warfarin is related to the intensity of the therapy; the risk can be reduced to about one-third if the targeted INR range is lowered from between 3 and 4.5 to between 2 and 3. Concomitant use of aspirin increases heparin- and warfarin-induced bleeding.³

Nonhemorrhagic adverse effects of heparin include urticaria at the site of subcutaneous injection; thrombocytopenia (occurs in 2% to 4% of patients treated with higher doses of UFH); osteoporosis and osteopenia; and, rarely, alopecia, adrenal insufficiency, and skin necrosis.³

In the new drug pipeline

The ACCP guidelines note that “the greatest unmet need in anticoagulation therapy” is an orally active agent that produces a predictable anticoagulation response and may be given in fixed doses without routine monitoring of coagulation.¹⁷

Better understanding of coagulation has led to the development of new agents that inhibit specific coagulation factors, including thrombin and factor X. New oral agents in the most advanced stages of development include direct thrombin inhibitors (e.g., dabigatran) and direct factor Xa inhibitors (e.g., rivaroxaban, apixaban). Direct thrombin inhibitors, as their name implies, directly inhibit the actions of thrombin, thereby attenuating the formation of fibrin and thrombin-mediated platelet activation. Factor Xa inhibitors also modulate these
processes by impairing thrombin generation. The net effect of both types of coagulation modifiers is to reduce fibrin formation.14,17

Idraparinux, a new indirect factor Xa inhibitor similar to fondaparinux, offers the advantages of subcutaneous administration and once-weekly dosing. This would benefit patients who must now self-inject LMWH while waiting for a therapeutic response with warfarin.14 The new oral direct factor Xa and thrombin inhibitors have a rapid onset of action, with peak plasma levels achieved within 2 to 4 hours. Since this is the same time frame as subcutaneously injected LMWH or fondaparinux, the new agents would obviate the need for a parenteral anticoagulant for the initial management of VTE. They also offer advantages over warfarin: fixed dosing and no need for routine coagulation monitoring.14 Table 4 provides a comparison of the new oral and parenteral agents.

Currently, the main drawback to all of the new agents is that they lack a rapidly acting antidote to reverse their anticoagulant effects.14

Clinical trials have shown that several of the new agents are safe and effective at preventing and treating thrombosis.14-17 In March 2009, an FDA advisory panel recommended approval of rivaroxaban to prevent DVT and PE in patients undergoing hip or knee replacement surgery.23

Nonpharmacologic treatment
Mechanical thromboprophylaxis is recommended primarily for patients at high risk of bleeding and for hospitalized patients who are not fully ambulatory. Mechanical modalities of thromboprophylaxis such as intermittent pneumatic compression, venous foot pump, and/or graduated compression stockings increase venous blood flow. These methods also may reduce leg swelling, and the routine use of graduated compression stockings after DVT can reduce the risk of developing postthrombotic syndrome.3

Patients who cannot tolerate anticoagulation may receive an inferior vena cava (IVC) filter to prevent PE. The filters are also used in patients who develop recurrent VTE despite adequate anticoagulation therapy and those requiring pulmonary embolectomy. While IVC filters should not be routinely used, this option should be considered in patients with large, free-floating DVT; problems with adherence to anticoagulation therapy and monitoring; and limited cardiopulmonary reserve. Usage has increased since retrievable IVC filters became available.3

The pharmacist’s role in improving VTE outcomes
Pharmacists who are up to date on the prevention and treatment of thromboembolic disorders can confidently interact with patients and other health care providers in the management of anticoagulant therapies, particularly with regard to new therapies and clinical practice recommendations. Pharmacists can play an important role in achieving the National Patient Safety Goal related to VTE and anticoagulation drug use in the hospital and ambulatory care settings.

Table 5. Reasons for routine use of thromboprophylaxis in hospitalized patients

<table>
<thead>
<tr>
<th>Benefits of thromboprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High prevalence of VTE</td>
</tr>
<tr>
<td>• Most patients have one or more risk factors</td>
</tr>
<tr>
<td>• Hospital-acquired DVT and PE are often clinically silent but may have long-term consequences</td>
</tr>
<tr>
<td>• Predicting which patients will die from PE is difficult</td>
</tr>
<tr>
<td>• Screening patients using physical examination or noninvasive testing is not effective or cost-effective</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse consequences of not preventing VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptomatic DVT and PE</td>
</tr>
<tr>
<td>• Fatal PE</td>
</tr>
<tr>
<td>• Cost of investigating symptomatic patients</td>
</tr>
<tr>
<td>• Risks and costs of treating VTE</td>
</tr>
<tr>
<td>• Increased future risk of recurrent VTE</td>
</tr>
<tr>
<td>• Chronic postthrombotic syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In the hospital or health system</th>
</tr>
</thead>
<tbody>
<tr>
<td>The importance of evaluating hospitalized patients for risk of VTE has received considerable attention and will continue to be a major area of focus for the health care system in the coming decades.24 Table 5 summarizes the importance of routine thromboprophylaxis in the hospital setting. This focus offers pharmacists a number of opportunities to contribute to patient care.</td>
</tr>
</tbody>
</table>

For example, health-system pharmacists are in a unique position to help in the VTE challenge by identifying hospitalized patients at risk.2 The U.S. Surgeon General’s report suggests that a nurse, physician, or pharmacist could conduct patient rounds on all overnight admissions, review those patients’ charts, and determine whether specific patients are at moderate or high risk for developing DVT and/or PE during hospitalization. Pharmacists can review written physician orders to determine whether prophylaxis had been instituted. For high-risk patients not receiving prophylaxis, the pharmacist could contact the appropriate physician, discuss the patient’s risk factors for VTE, and recommend implementation of preventive measures.1

The American Society of Health-System Pharmacists advises pharmacists to check that their hospital routinely assesses all patients for their risk of DVT, provides appropriate prevention therapy for those who are at high risk, and gives anticoagulants in accordance with the evidence-based guidelines, such as those from ACCP.25
Numerous published reports have documented improved outcomes following implementation of a variety of pharmacist-directed models.\textsuperscript{26,27} For example, in a retrospective analysis of 717,396 Medicare recipients who were hospitalized for various conditions in 955 hospitals, those hospitals with pharmacist-provided heparin management services had significantly lower mortality rates and significant reductions in hospital lengths of stay, Medicare costs, frequency of bleeding complications, and percentage of patients requiring blood transfusion when compared with hospitals that did not have such services.\textsuperscript{28}

For pharmacists interested in developing VTE prevention and treatment programs at their institution, numerous guides and protocols are suggested in the “Tell me more” section of this monograph.

**In the community**

As the use of extended VTE prophylaxis following hospital discharge increases and as more health systems implement outpatient DVT treatment programs, pharmacists in the ambulatory care setting will see a significant rise in the number of outpatients receiving anticoagulant therapy.\textsuperscript{24} Also, the availability of newer, longer-acting anticoagulants administered subcutaneously has shifted the treatment of VTE to the outpatient setting.

Over the last two decades, the benefits of pharmacist-managed anticoagulant therapy have been well established.\textsuperscript{21,29,30} Anticoagulant therapy management services by pharmacists have resulted in documented improvements in the percentage of INRs in the therapeutic range and a reduction in hospitalization for thromboembolic or bleeding events. Anticoagulation clinics have been found to have a favorable cost-to-benefit ratio.\textsuperscript{24} Articles in the medical literature have described the success of many kinds of programs, ranging from a case management approach in a rural physician’s office to statewide clinical pharmacy anticoagulation services in a large health enterprise.\textsuperscript{31,32}

ACCP reports that patients experience better outcomes

<table>
<thead>
<tr>
<th>Table 6. Educating patients about anticoagulant medication use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Issue</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Low–molecular-weight heparin or fondaparinux</strong></td>
</tr>
<tr>
<td>Injection technique</td>
</tr>
<tr>
<td>Pain medication</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Foods to avoid</td>
</tr>
<tr>
<td>Change in medications</td>
</tr>
<tr>
<td>OTC and herbal products</td>
</tr>
<tr>
<td>Emergencies</td>
</tr>
<tr>
<td>Missed dose</td>
</tr>
<tr>
<td>Duration of treatment</td>
</tr>
</tbody>
</table>

Abbreviation used: OTC = Over-the-counter.
Source: References 18 and 33.
when their anticoagulant therapy is managed by an anticoagulation management service or anticoagulation clinic than when they receive usual care from their personal physician. The ACCP guidelines recommend that health care providers who manage oral anticoagulant therapy do so in a "systematic and coordinated fashion," incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication.

In carefully selected and trained individuals, self-testing and self-management of warfarin dosing are effective patient management strategies. These models of care have shown to improve the quality of anticoagulation management, increase the time spent in the therapeutic range, and reduce adverse events. ACCP recommends that such management strategies be implemented in suitable patients.

Pharmacists who work in an ambulatory setting have a range of options—from establishing an anticoagulation management service or anticoagulation clinic to providing one-on-one patient education regarding anticoagulant therapy. Pharmacists can help patients understand that anticoagulants prevent the formation of additional clots and permit the body's natural clot-dissolving activity to break down an existing clot. Patient education should include instruction on the signs and symptoms of DVT and bleeding, their personal risk factors for DVT and bleeding, and how to appropriately use their anticoagulant medications, including a list of the foods and other medications or nutritional supplements that may interact with warfarin therapy. Pharmacists can teach patients how to properly self-inject LMWH or fondaparinux and educate them to remain vigilant about managing the potential impact of other risk fac-

### Table 7. Interactions with warfarin

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Supplements</th>
<th>Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin or aspirin-containing products</td>
<td>Fish oil and omega-3 supplements</td>
<td>Spinach and other dark green, leafy vegetables</td>
</tr>
<tr>
<td>Ibuprofen, naproxen, and other nonsteroidal anti-inflammatory drugs</td>
<td>Vitamin E (high doses)</td>
<td>Broccoli</td>
</tr>
<tr>
<td>Acetaminophen-containing products (in doses &gt;1500 mg/d for &gt;7 d)</td>
<td>Vitamin K</td>
<td>Soybean and canola oils</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Bromelains</td>
<td>Licorice</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Coenzyme Q10</td>
<td>Cranberries, cranberry juice</td>
</tr>
<tr>
<td>Fluoroquinolone antibiotics</td>
<td>Cranberry extracts</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Danshen</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Dong quai</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Garlic</td>
<td></td>
</tr>
<tr>
<td>Azole antifungal agents</td>
<td>Ginkgo</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Ginseng</td>
<td></td>
</tr>
<tr>
<td>Statins, particularly lovastatin and simvastatin</td>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Estrogen-containing contraceptives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Consult the warfarin (Coumadin) package insert for a complete list of interactions.

Source: References 19 and 34.

### Topic tips

**Tip 1**
Venous thromboembolism (VTE) is manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE). While both cause serious complications, PE is potentially fatal. More than half of DVTs are asymptomatic.

**Tip 2**
VTE can occur in individuals with damage to the wall of a vein, slow venous blood flow, or inherited or acquired hypercoagulability. VTE is often triggered by an inciting event such as surgery or trauma.

**Tip 3**
Factors such as older age, obesity, use of estrogen-containing medications, cancer and cancer treatment, previous VTE, immobility, acute medical illness, and recent surgery or trauma put an individual at risk for VTE.

**Tip 4**
Routine thromboprophylaxis in hospitalized patients is advised because most patients have at least one risk factor and the consequences of VTE can be devastating.

**Tip 5**
DVT treatment typically involves unfractionated heparin, low–molecular-weight heparin, or fondaparinux to achieve a rapid anticoagulation response, followed by long-term use of oral warfarin. Patients on warfarin require frequent monitoring and periodic dosage adjustments.
Practical pointers

Case #1

JT is a 55-year-old woman who is admitted to the hospital for knee replacement surgery. She is obese and on hormone replacement therapy. JT has no past medical history of DVT and no contraindications to anticoagulation.

1. Should this patient receive thromboprophylaxis?
2. What is the preferred regimen for this patient?
Following her knee surgery, JT is discharged from the hospital on warfarin and enoxaparin. Her INR is 1.6.
3. What kind of follow-up should be scheduled?

Case #2

ZB is a 71-year-old man admitted to the general medical floor of the hospital with pneumonia. He has chronic obstructive pulmonary disease, coronary artery disease, hypertension, dyslipidemia, and chronic kidney disease. He is given antibiotics and improves. However, on the day ZB is supposed to be discharged, his condition declines; he experiences increased shortness of breath and chest pain. A Doppler study is done, which reveals DVT in his left leg. Because of his symptoms, it is assumed he has PE. He is given 100 mg enoxaparin subcutaneously daily and 10 mg oral warfarin once daily. After 2 days of this treatment, ZB is discharged with prescriptions for warfarin and enoxaparin and given an appointment at the outpatient anticoagulation clinic in 1 week.

1. Is this course of action the best approach for this patient?
When ZB takes his prescriptions to the pharmacy to be filled, the pharmacist asks if he has any questions about his medications. ZB says he does not. When he goes to his appointment at the anticoagulation clinic 1 week later, he says he has been feeling weak and dizzy and has had dark, tarry stools for the past 3 days. A bleed is suspected, and the pharmacist arranges for him to be taken to the emergency department, where his INR is checked (INR 11.5).
2. Could this outcome have been prevented?

Responses are provided on page 68.

tors they may encounter, such as prolonged air travel, surgery, or trauma.1 See Table 6 for a summary of important information that patients taking anticoagulants should know.

Pharmacists can also identify patients who are at risk for DVT (Table 1). If patients older than 60 years with atrial fibrillation or younger patients with diabetes, hypertension, congestive heart failure, or a history of thromboembolism are not receiving warfarin, pharmacists can refer them to their physicians.30

Because warfarin has numerous drug–drug interactions that can increase the risk of bleeding, pharmacists should carefully review patients’ medication profiles and ask questions about new medications and herbal product use at every encounter. A summary of some of the more important interactions appears in Table 7. (A comprehensive list of interactions may be found in the warfarin [Coumadin] package insert.)

To avoid some of the adverse events associated with warfarin use, pharmacists can advise patients to take certain precautions. Patients should be counseled to take the following steps:

- Inform all health care providers of their warfarin use, particularly if they are undergoing dental or medical procedures, including vaccinations.
- Avoid situations that increase the risk of injury, such as contact sports or activities that could result in head injury.
- Carry a card or wear a bracelet so emergency medical personnel know of their use of warfarin.

Finally, to help improve adherence to warfarin therapy, pharmacists should remind patients about the need for ongoing INR monitoring and inquire about their most recent test results.

Summary

Recommendations from professional and governmental organizations are driving the increased use of thromboprophylaxis in hospitalized patients and the outpatient treatment of VTE. Pharmacists have a major opportunity to assist in preventive approaches in the hospital by identifying patients at risk for VTE and educating hospital staff about the importance of prevention and the safe use of anticoagulant therapies. In the ambulatory setting, pharmacists can help to improve outcomes by helping to manage anticoagulation therapies and ensuring that patients understand how to appropriately use their anticoagulant medications.

References

Tell me more

**For health professionals**

**Agency for Healthcare Research and Quality**
Preventing Hospital-Acquired Venous Thromboembolism: A Guide for Effective Quality Improvement
www.ahrq.gov/qual/vtguide/

**American College of Chest Physicians**
Antithrombotic and Thrombolytic Therapy Guidelines
www.chestjournal.org/content/133/6_suppl.full.html

**Anticoagulation Forum**
Consensus Statement: Delivery of Optimized Anticoagulant Therapy

**ClotCare**
An interactive site for health professionals with links to the latest information and online resources on anticoagulation and antithrombotic therapy
www.clotcare.com

**Joint Commission**
(Formerly Joint Commission on Accreditation of Healthcare Organizations)
National Patient Safety Goals: Anticoagulation Therapy
(NPSG.03.05.01)
www.jointcommission.org

**Society of Hospital Medicine**
Venous Thromboembolism Resource Room: including sample protocols, an implementation guide, and other tools.
www.hospitalmedicine.org/ResourceRoomRedesign/RR_VTE/VTE_Home.cfm

**University of Washington Medical Center**
VTE Safety Toolkit: including prophylaxis guidelines.
http://vte.washington.edu

**U.S. Surgeon General**
The Surgeon General’s Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism—2008
www.surgeongeneral.gov/topics/deepvein/

**For patients**

**Agency for Healthcare Research and Quality**
Your Guide to Preventing and Treating Blood Clots
www.ahrq.gov/consumer/bloodclots.pdf

Your Guide to Coumadin/Warfarin Therapy
www.ahrq.gov/consumer/coumadin.htm

**National Alliance for Thrombosis and Thrombophilia**
Stop the Clot Website
http://stoptheclot.org

**National Heart, Lung, and Blood Institute**
Deep Vein Thrombosis

Pulmonary Embolism

**Venous Disease Coalition**
Deep Vein Thrombosis
www.venousdiseasecoalition.org/diseaseinfo/dvt/


Practical pointers responses

Responses To Case #1

1. Yes, JT’s combination of knee surgery and additional risk factors (age, obesity, hormone therapy) put her in the high-risk category for DVT—40% to 80%.

2. The recommended prophylactic regimen for this patient is to administer either dalteparin 5,000 U subcutaneously every 24 hours, enoxaparin 40 mg subcutaneously every 24 hours, enoxaparin 30 mg subcutaneously every 12 hours, fondaparinux 2.5 mg subcutaneously every 24 hours, or warfarin orally once daily to achieve a target INR between 2 and 3.

3. Because this patient has been prescribed warfarin, she should get INR testing within a few days of discharge and have her coagulation status measured frequently until her INR stabilizes in the target range, between 2 and 3.

Responses To Case #2

1. No, this was not the optimal approach. ZB was not screened for risk factors for VTE at the time of admission. If he had been, it would have been noted that this patient is at moderate risk owing to his age, acute respiratory illness, and the presence of several chronic medical problems and he would have been placed on thromboprophylaxis. After the patient was diagnosed with DVT, INR testing should have been done in the hospital and again within 2 days after hospital discharge, not 1 week later. The warfarin dosing should have been reduced because of his older age.

2. Yes, this outcome could have been prevented if the community pharmacist reviewed the anticoagulant treatment with ZB to make sure he understood what to expect and how to take his medications. The patient was receiving a large dose of warfarin and enoxaparin with no instructions for monitoring. The pharmacist should have educated him about the importance of monitoring and checked to see if the dose was appropriate for a man his age and with his comorbidities. The pharmacist should have advised ZB when to call his physician (e.g., if he had signs of bleeding such as black, tarry stools).

In this patient case, both the hospital pharmacist and the community pharmacist missed opportunities to provide better care. Simple interventions could have significantly improved ZB’s outcome.

CPE Information

To obtain 2.0 contact hours of CPE credit (0.2 CEUs) for this activity, complete and submit the CPE exam online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You will have two opportunities to successfully complete the CPE exam. Pharmacists who successfully complete this activity before July 1, 2011, can receive credit.

Your Statement of Credit will be available online immediately upon successful completion of the CPE exam.

CPE instructions: Get your documentation of credit now! Completing a posttest at www.pharmacist.com/education is as easy as 1-2-3.

1. Go to Online CPE Quick List and click on the title of this activity.

2. Log in. APhA members enter your user name and password. Not an APhA member? Just click “Create one now” to open an account. No fee is required to register.

3. Successfully complete the CPE exam and evaluation form to gain immediate access to your documentation of credit.

Live step-by-step assistance is available Monday through Friday 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing InfoCenter@pharmacist.com.


